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Title	Catalyst and substrate effects in enantioselective C–H insertion reactions of α-diazosulfones
Authors	Clarke, Leslie-Ann
Publication date	2015
Original Citation	Clarke, L .A. 2015. Catalyst and substrate effects in enantioselective C–H insertion reactions of α-diazosulfones. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
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Catalyst and substrate effects in enantioselective C–H insertion reactions of α-diazosulfones



Leslie Ann Clarke, B.Sc.

A thesis presented for the degree of

Doctor of Philosophy

to

THE NATIONAL UNIVERSITY OF IRELAND, CORK

Department of Chemistry

University College Cork

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January 2015

Acknowledgements

To begin with I would like to extend my sincerest gratitude to Prof. Anita Maguire for her constant guidance and support throughout this project. I am especially grateful for all the help that she provided throughout the writing of this thesis. I would also like to thank Dr. Dan McCarthy and Dr. Lorraine Bateman for the extensive NMR work conducted. I would like to express appreciation to Dr. Florence McCarthy and to Mick O' Shea for mass spectrometry services and to Dr. Simon Lawrence and Dr. Abhijeet Sinha for X-ray crystallography data. I would also like to extend my sincerest thanks to all the technical staff at UCC for providing invaluable services and support, in particular Noel Browne, Tina Kent, Terry Horgan, Pat O' Connell, Donnacha O' Connell, Dr. Matthias Jauch, Chrissie O' Flaherty, Dr. Ken Divine and Dr. Tom O' Mahony. I would like to thank Dr. Nuala Maguire for all her help with HPLC analysis and for her constant encouragement. I want to sincerely thank Dr. Alan Ford and Dr. Francis Harrington for the running of lab 2.34; for their constant patience, supervision and for never refusing to any answer question and for always being available to help in any way possible; this thesis would not be possible without either of you. I am grateful to Debbie Curran for all her help over the years and for her patience and friendship. Thank you to the Irish Research Council for funding. Thank you to Dr. Alan Ford, Dr. Denis Lynch and Ms Aoife Ring for proof reading this thesis.

I would like to thank all the members of the ARM group both past and present and all the researchers of the organic chemistry department that I have had the pleasure of working with over the past number of years. I would like to thank all my work colleagues, friends and family members for their constant support throughout this PhD, without which I would not have been able to complete this work.

I would like to dedicate this thesis to the following people who have offered me friendship, support and guidance over the past number of years; Mary Regan Noone, Brid O' Connor, Stuart Collins, Jim O' Neill, Caoimhe Whelan, Úna Barrett, Rebecca Deasy, Deirdre Kelleher, Debbie Curran, Niki Mullins, Liam Greaney, Rosemary Walsh, Mary Clarke, Leti Pardo, Stephen Stokes, Marie Kissane, Denis Lynch, Abhi Sinha, Kay Foley, Sinead Milner, Sally O' Neill, Brian Feerick, Brian O' Neill, Shane O'Neill, Sarah Clarke, James Clarke, Graham O' Mahony, Tom O' Neill, Amy Shiely, Francis Harrington, Aoife Ring, Anne Breen, Harry Moloney, Kevin O' Shea, Kevin Eccles, Anita Maguire, Thomas O'Neill, Pat O' Connell, Tracy O' Neill, Chris Flynn, Ben Deadman, Agnes Fitzgerald, Frank Clarke, Aoife Buckley, Denis Beecher, Chloe Murphy, Patrick McCaw, Nuala Maguire, Elaine Stack, Kevin O' Neill, Veronica Clarke, Deirdre O' Neill, Catherine Slattery, Lorraine Bateman, Vera Foley, Patrick O' Sullivan, Tomas O' Neill, Declan Gavin, Orla McNamara, Naomi Buckley, Carla Daly, Alan Ford, Amy Nagle, Eoin Mc Gillicuddy, Fiona Neville, Ted Foley, Annie Clarke, Viv Gough, Muireann Costello, Paul McDowell, Jonathan Quille, Niamh O'Connell, Valérie Cacheux, Bobbie Clarke, John O' Neill and Aoife Foley.

Abstract

This thesis describes a systematic investigation of the mechanistic and synthetic aspects of intramolecular reactions of a series of α-diazo-β-oxo sulfone derivatives using copper and, to a lesser extent, rhodium catalysts. The key reaction pathways explored were C–H insertion and cyclopropanation, with hydride transfer competing in certain instances, especially when copper catalysts were employed. Significantly, up to 98% ee has been achieved in the C–H insertion processes using copper-NaBARF-bisoxazoline catalysts, with the presence of the additive NaBARF critical to the efficiency of the transformations. This novel synthetic methodology provides access to a diverse range of enantioenriched heterocyclic compounds including thiopyrans, sulfolanes, β- and ɣ-lactams, in addition to carbocycles such as fused cyclopropanes.

Chapter One contains a literature review of the synthesis of precursors for α-sulfonyl carbenes and α-sulfonyl nitrenes and their subsequent reactivity. While α-diazocarbonyl compounds have been widely reviewed, this review focuses specifically on the subgroup bearing a sulfonyl substituent on the diazo carbon which has a profound impact on the overall stability and reactivity of these compounds. For comparative purposes, a brief overview of the reactivity of sulfonyl nitrenes is included as there are important similarities in reactivity patterns.

Chapter Two outlines the aims and objectives of the work described in this thesis, and the rationale for the substrate design, and places this study in the context of relevant literature reports.

Chapter Three describes the synthesis of the α-diazosulfones required for the subsequent investigations. The work is structured in two sections: precursor synthesis and diazo transfer. Of the twenty seven diazo sulfones described, nineteen are novel and are fully characterised in this work.

Each of Chapters Four – Seven focus on a specific study of the copper and rhodium catalysed reactions of the α -diazosulfones with Chapter Four focused on highly enantioselective C–H insertion to form thiopyrans and sufolanes, Chapter Five focused on C–H insertion to form fused sulfolanes, Chapter Six focused on C–H insertion in sulfonyl α-diazoamides where both lactam formation and / or thiopyran / sulfolane formation can result from competing C–H insertion pathways, while Chapter Seven focuses on cyclopropanation to yield fused cyclopropane derviatives. One of the key outcomes of this work is an insight into the steric and / or electronic factors on both the substrate and the catalyst which control regio-, diastereo- and enantioselectivity patterns in these synthetically powerful transformations.

Full experimental details for the synthesis and spectral characterisation of the compounds are included at the end of each Chapter, with details of chiral stationary phase HPLC analysis and assignment of absolute stereochemistry included in the appendix.

Declaration

I hereby confirm that the body of work described within this thesis for the degree of Doctor of Philosophy, is my own research work, and has not been submitted for any other degree, either in University College Cork or elsewhere.

Leslie Ann Clarke

Date 9th January 2015

To Nana, Tom and Mam

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Chapter 1

Introduction

"If you can dream—and not make dreams your master; If you can think—and not make thoughts your aim; If you can meet with Triumph and Disaster and treat those two impostors just the same…." Rudyard Kipling

1.1 Introduction

The ability to functionalise C–H, C–X and C=C bonds in a highly regio- and enantiocontrolled manner under relatively mild reaction conditions is an attractive aim for the synthetic organic chemist, and new methods are constantly being developed and investigated to meet this objective. The use of reactive intermediates such as carbenes and nitrenes to achieve such goals has been met with a great deal of success since their discovery over a hundred years ago.[1–10] Carbenes can undergo a variety of different reaction pathways, some of the most practical being C–H insertion,[4,6,7,11] cyclopropanation,[12–14] and ylide formation;[1,5] in the same manner nitrenes have been reported to be effectively transformed *via* C–H amination[2,8,9] and aziridination reactions,[8,9] with comparatively fewer literature reports on their use in ylide reactions (**Figure 1.1**).[9,15,16]

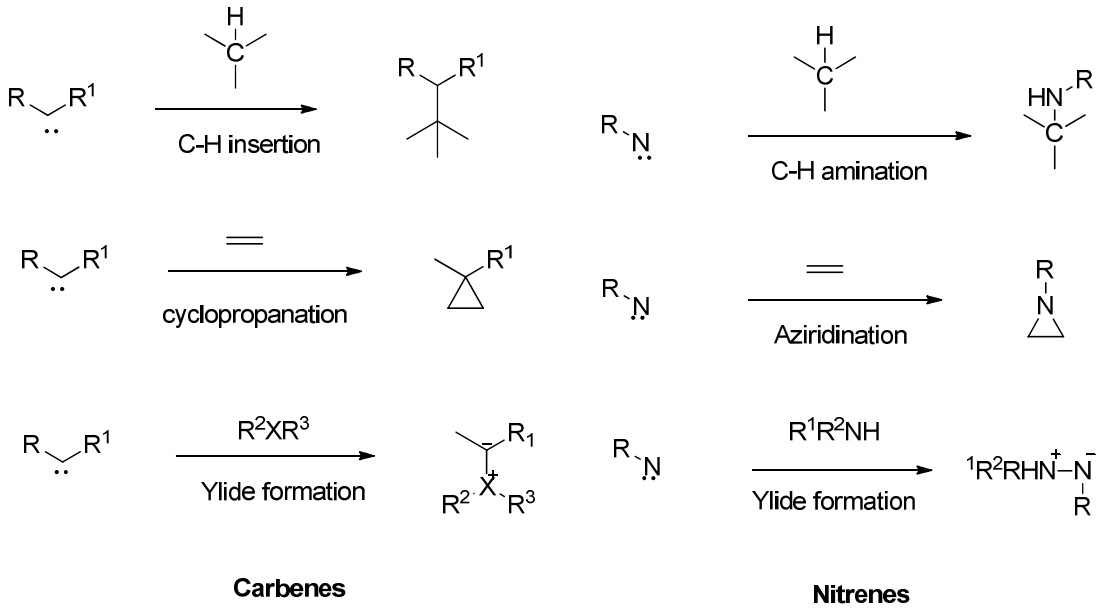


Figure 1.1

The successful application of these reactions is largely due to transition metals being employed as catalysts, for example copper, rhodium, iron, ruthenium, cobalt and iridium, have all been utilised efficiently in the aforementioned reaction pathways. In general, reactions of this type are carried out with a carbene/nitrene precursor in the presence of a transition metal, which forms a metal-carbene (carbenoid) or metal-nitrene (nitrenoid) intermediate which can subsequently undergo reaction. The transition metal confers a degree of selectivity onto the reaction of both carbenes and nitrenes which makes these

reactions synthetically viable. In addition, careful selection of these catalysts can allow enantioselective reactions to take place.[1,3,4,6–9]

In the following discussion it is the use of α-sulfonyl carbenes and α-sulfonyl nitrenes that will be considered. The use of these substrates is desirable as the sulfone group can be used as a temporary activating group which, upon removal, has the potential to lead to a number of natural products. In addition, sulfone-containing heterocycles are biologically important in their own right.[17]

1.2 Synthesis of precursors to α-sulfonyl carbenes

As both carbenes and nitrenes are highly reactive intermediates they must be generated *in situ* from a precursor. In the case of carbenes the most common precursor is an α-diazocarbonyl compound.[1] The presence of a carbonyl group stabilises the diazo functionality which upon exposure to heat, light or a transition metal catalyst generates a highly reactive carbene or carbenoid, which is subsequently capable of undergoing a variety of transformations. The structure of the initial α-diazocarbonyl compound can have a significant impact on the outcome of subsequent reactions. The structure of the carbenoid derived from these α-diazocarbonyl compounds can be broadly classed into three types, those that contain a single electron withdrawing group (acceptor), those that contain two electron withdrawing groups (acceptor-acceptor) and those that contain one electron withdrawing group and one electron donating group (acceptor-donor) (**Figure 1.2**).[4]

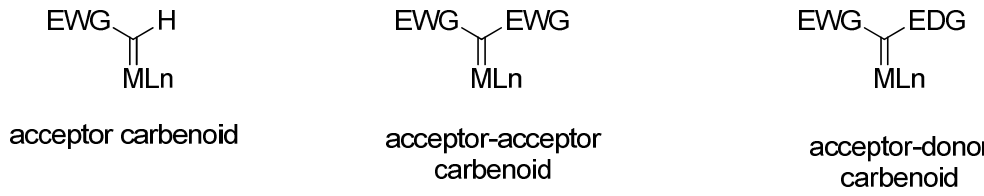


Figure 1.2[4]

Electron withdrawing groups generally stabilise the diazo functionality. Examples of electron withdrawing groups include ketones, amides, esters and sulfones, while examples of electron donating groups include vinyl and aryl groups.[4] As the main focus of the discussion in this thesis is the use of α-diazosulfones, it is their synthesis that will be subsequently described.

Of the three main classes of α-diazocarbonyl compounds that have been discussed above, examples of each class of α-diazosulfone mostly fall into two of these three categories; those containing the sulfone group as the sole electron withdrawing group (**Class A**) and those containing a sulfone group in addition to a second electron withdrawing group (**Class B**). Examples of the additional electron withdrawing groups include esters, ketones and amides (**Figure 1.3**). There are limited examples in the literature of α-diazosulfones that possess an electron donating group adjacent to the diazo functionality (**Class C**).[18,19] There are distinctively different synthetic approaches to each class of α-diazosulfones, which are discussed below. The synthesis of α-diazosulfones of the **Class C** type will not be discussed as their use for carbene reactions in the literature is relatively scarce, but the methods discussed for **Class A** and **Class B** are generally applicable to **Class C**.

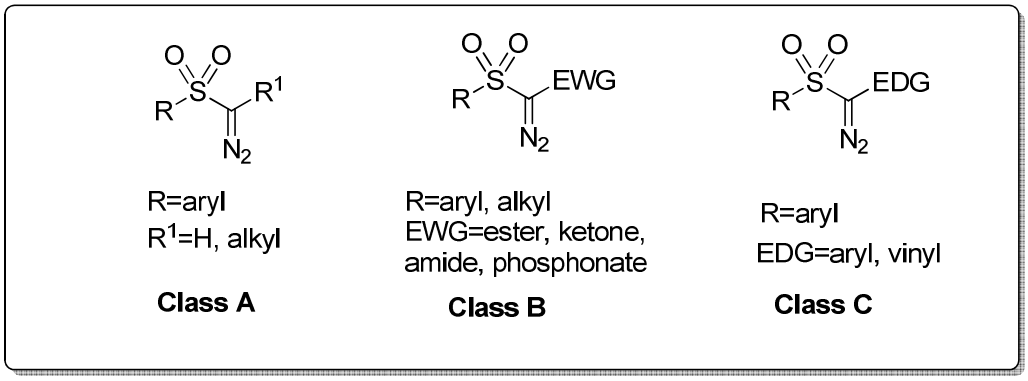
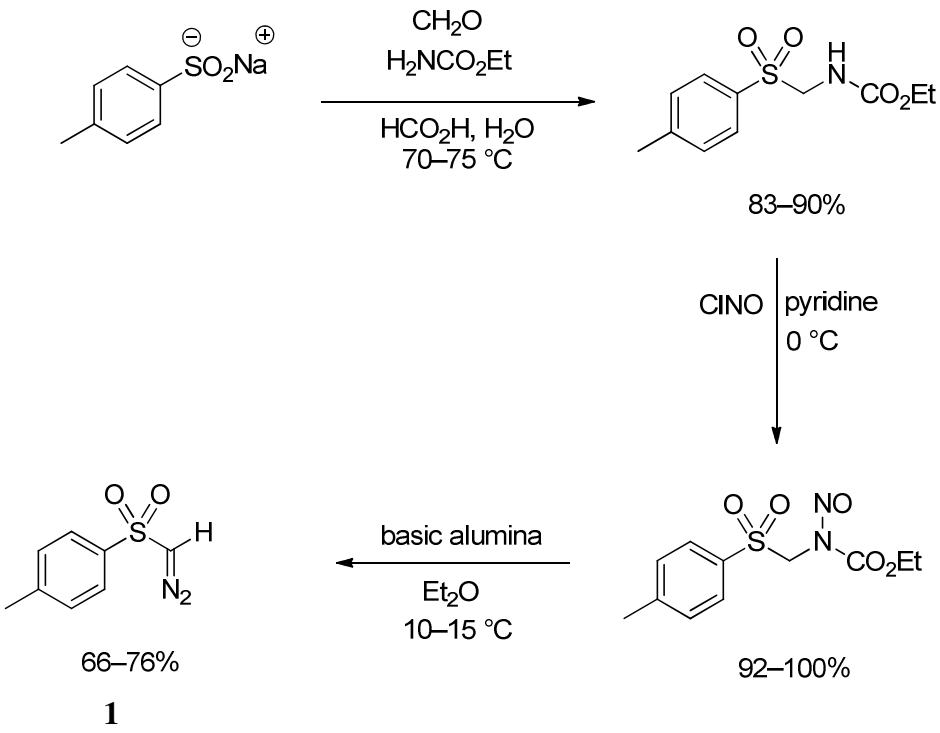


Figure 1.3

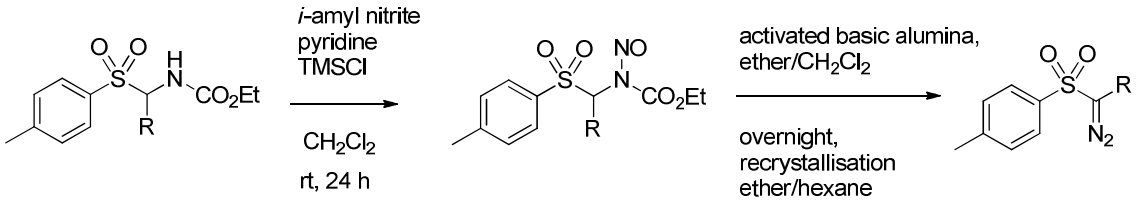
1.2.1 Synthesis of α-diazosulfones bearing the sulfone group as the sole electron withdrawing group.

As an example of the synthesis of α-diazosulfones of the **Class A** type, the synthesis of *p*-tolylsulfonyldiazomethane will be discussed. A route to *p*-tolylsulfonyldiazomethane was described by Van Leuson and Strating,[20] which involved reacting ethyl carbamate, sodium *p*-toluenesulfinate and formaldehyde in the presence of formic acid into form ethyl (tosylmethyl)carbamate, which was subsequently reacted with nitrosyl chloride in pyridine to yield ethyl nitroso(tosylmethyl)carbamate which on exposure to basic alumina in ether provided the desired α-diazosulfone **1** (**Scheme 1.1**).



Scheme 1.1[20]

In 2000,[21] an updated version of this route was published which involved the addition of excess *i*-amyl nitrite, TMSCl and pyridine to a solution of ethyl (tosylmethyl)carbamate in dichloromethane which yielded ethyl nitroso(tosylmethyl)carbamate in 90.8% yield after recrystallization. After this was exposed to activated alumina, α-diazosulfone **1** was obtained in 67.2% yield, again after recrystallisation. 1-[(1-Diazoethyl)sulfonyl]-4-methylbenzene was also synthesised in a similar manner in a good yield (**Scheme 1.2**).



2 R=H
4 R=Me

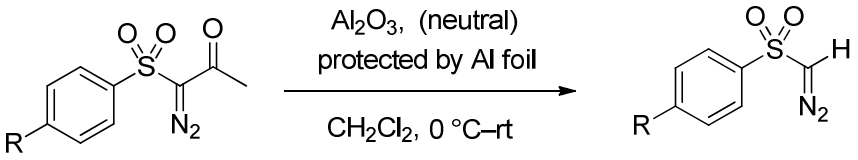
3 R=H, 90.8%
5 R=Me, 61.2 %

1 R=H, 67.2%
6 R=Me, 72.6%

Scheme 1.2

Class A type α-diazocarbonyl compounds may also be synthesised from **Class B** type substrates as demonstrated in **Table 1.1**.[22] A number of 1-diazo-1-(phenylsulfonyl)propan-2-one based substrates containing both electron donating and electron withdrawing groups at the *para* position on the benzene ring were converted to their corresponding diazomethanesulfonyl derivatives upon exposure to alumina in dry dichloromethane with yields ranging from poor (31%, **Table 1.1**, entry 3) to excellent (100%, **Table 1.1** entry 2). Notably, all three compounds listed in **Table 1.1** were stored at –20 °C in darkness.

Table 1.1 *Alternative synthesis of α-diazosulfones of the* ***Class A*** *type* [22]



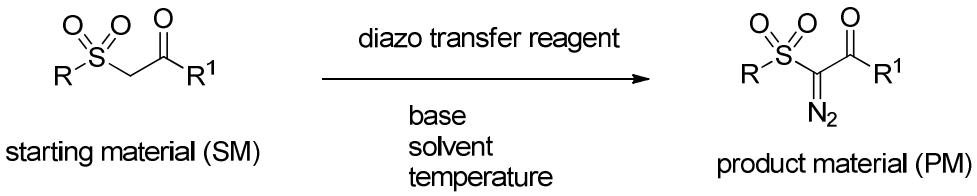
Entry	R	α-diazosulfone	α-diazosulfone	Yield (%)
1	Me	**7**	**1**	93
2	OMe	**8**	**9**	100
3	NO_2	**10**	**11**	31

The syntheses of α-diazosulfones of the **Class B** type **7**, **8**, **10** (listed in **Table 1.2**) are reported *via* diazo transfer reaction to the corresponding sulfones. This is the most commonly used method to synthesise compounds of this type, and will be discussed in **Section 1.2.2**.

1.2.2 Synthesis of α-diazosulfones bearing two electron withdrawing groups

One of the most common ways of synthesising α-diazocarbonyl compounds is by using a diazo transfer reaction, pioneered by Regitz.[1,23–25] This reaction requires the transfer of a diazo group from a diazo transfer reagent, for example *p*-tosyl azide, *p*-NBSA (nitrobenzenesulfonyl azide) or *p*-ABSA (acetamidobenzenesulfonyl azide), to an acceptor compound, which in this case is a sulfone substrate. The acceptor group must contain a methylene group that is suitably activated for deprotonation by a base of suitable strength. The most commonly used bases for this reaction include NaH, K_2CO_3, NEt_3 and DBU. It should be noted that diazo transfer reagents are generally hazardous materials and can be prone to explosion upon heating and may also be impact sensitive.[26] Suitable diazo transfer conditions for the synthesis of α-diazocarbonyl compounds are generally substrate dependant, and usually involve careful selection of the correct diazo transfer reagent/base/solvent/temperature combination.

Table 1.2 *Synthesis of α-diazosulfones (**Class B**) via diazotransfer*



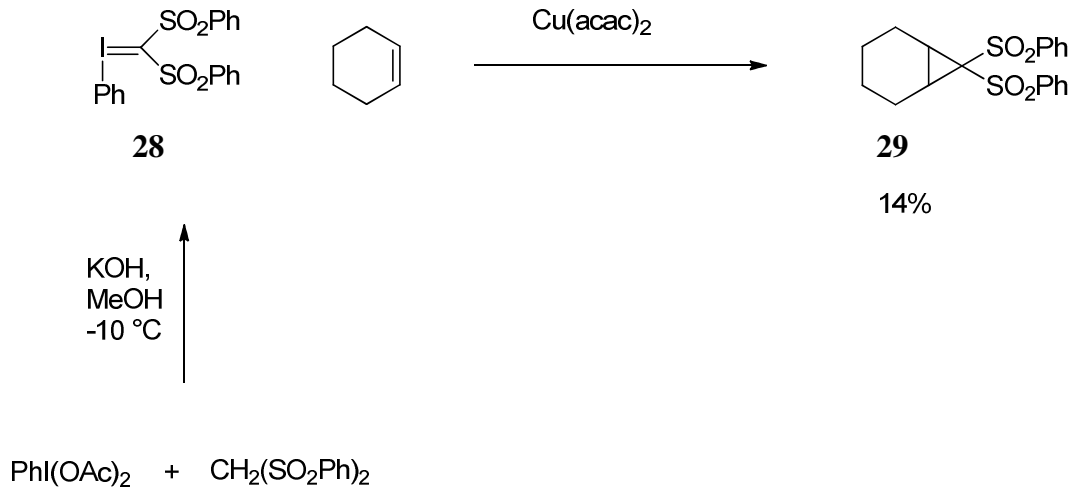
Entry	R	R^1	SM	PM	Diazo transfer	Base/Solvent/ Temp	Yield (%)
1[27,28]	$Ph(CH_2)_3$	Me	**12**	**13**	*p*-tosyl azide	K_2CO_3/CH_3CN/ 0 °C–rt	62
2[27,28]	$Ph(CH_2)_4$	OMe	**14**	**15**	*p*-tosyl azide	K_2CO_3/CH_3CN/ 0 °C–rt	94
3[29]	Me	$(CH_2)_3CH_3$	**16**	**17**	*p*-tosyl azide	K_2CO_3/CH_3CN/ 0 °C–rt	86
4[29]	Ph	$(CH_2)_4$ Ph	**18**	**19**	*p*-tosyl azide	K_2CO_3/CH_3CN/ 0 °C–rt	87
5[30]	$CH_3(CH_2)_4$	OEt	**20**	**21**	*p*-NBSA	$(i\text{-Pr})_2NEt/CH_3CN$/ −10 °C–rt	70
6[31]	*i*-$Pr(CH_2)_3O$	OEt	**22**	**23**	mesyl azide	DBU/THF/ –45 °C–rt	98
7[32]	Ph	$(CH_2)_2CH{=}CH_2$	**24**	**25**	*p*-tosyl azide	NEt_3/CH_3CN/ 0 °C–rt	85
8[33]	Ph	$N(CH_2Ph)(CH_2)_2Ph$	**26**	**27**	*p*-ABSA	DBU/CH_3CN/ 0 °C–rt	85–90

The syntheses of a number of α-diazosulfone substrates of the **Class B** type are listed in **Table 1.2**; they include both alkyl and phenyl sulfones, in addition to containing esters, ketones and amides as the second electron withdrawing group. Modification of the original Regitz procedure[23,24] by Koskinen and Muñoz[34] involved the use of *p*-tosyl azide and K_2CO_3 in acetonitrile and is a popular choice for the synthesis of α-diazosulfones as can be seen in **Table 1.2**, (entries 1–4). However, a number of other diazo transfer reagents, including *p*-NBSA, *p*-ABSA and mesyl azide have been successfully employed in the synthesis of α-diazosulfone compounds (**Table 1.2**, entries 5–6, 8), while (*i*-Pr_2)NEt, NEt_3 and DBU have been effectively utilised as bases (**Table 1.2**, entries 5–8).

1.2.3 Use of iodonium ylides as sulfone carbene precursors

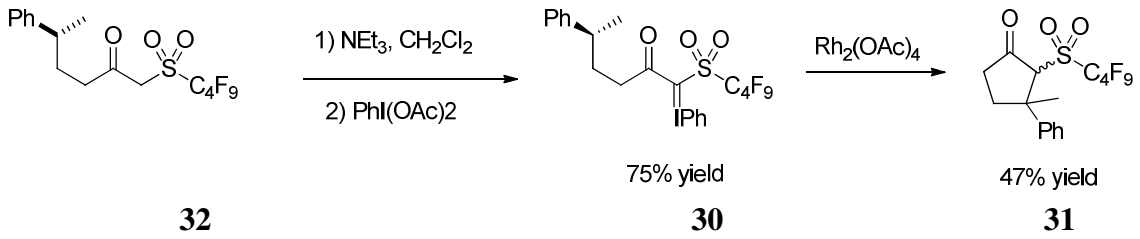
In addition to the use of α-diazocarbonyl compounds as precursors to the generation of a reactive carbene intermediate, phenyliodonium ylides may also be employed for such purposes.[35] This also applies to the specific case of the *in situ* generation of sulfonyl carbenes; α-diazosulfones and phenyliodonium ylides can potentially lead to the synthetically important sulfonyl carbene intermediate.[35] However, the use of phenyliodonium ylides in this context is the lesser utilised and explored method of the two aforementioned routes. Despite this, replacing α-diazocarbonyl compounds as a carbene precursor with the phenyliodonium ylide is a desirable aim, due to the potentially toxic and explosive nature of α-diazocarbonyl compounds.

Phenyliodonium ylides can be initially prepared or generated *in situ*. For example, the use of a pre-generated sample is illustrated in **Scheme 1.3**, where phenyliodonium ylide **28** is reported to be stable on storage at −10 °C for up to two weeks and successfully undergoes a cyclopropanation reaction to yield cyclopropane product **29**, albeit in low yields.[36]



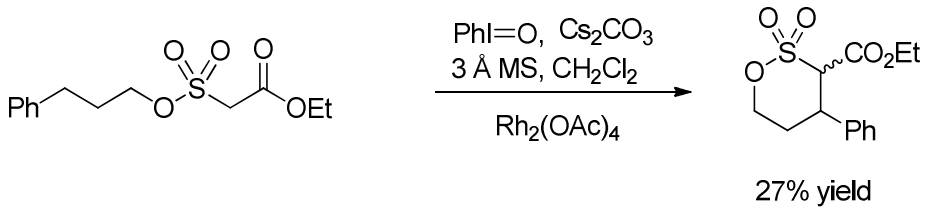
Scheme 1.3

In a similar fashion, phenyliodonium ylide **30** was prepared before undergoing a rhodium acetate catalysed intramolecular C–H insertion reaction to yield cyclopentanone **31** in a 47% yield as a mix of diastereomers, with some loss of stereochemical integrity as shown in **Scheme 1.4**.[37]



Scheme 1.4

Lastly, Du Bois and co-workers has demonstrated that phenyliodonium ylides can be generated *in situ* using PhI=O and Cs_2CO_3, which subsequently undergo C–H insertion to yield δ-sultones in the presence of rhodium acetate (**Scheme 1.5**).[31]



Scheme 1.5

1.3 Synthesis of sulfonyl nitrenes

The two most common nitrene series studied are acyl and sulfonyl nitrenes. Sulfonyl nitrenes can be generated from a variety of different sources,[38] the decomposition of sulfonyl azides and iodinanes being two of the most widely used methods. Iodinanes may be pre-formed or generated *in situ*. In addition, Lebel has reported the use of tosyloxycarbamates as nitrene precursors (**Figure 1.4**).[39]

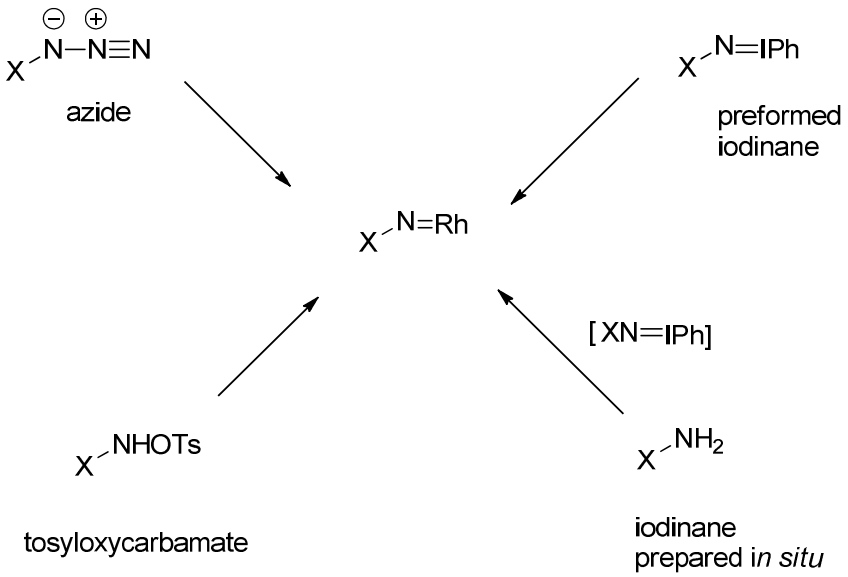
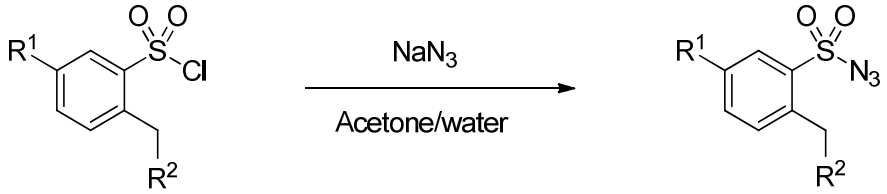


Figure 1.4[39]

1.3.1 Synthesis of azide precursors

The most traditional method of preparation of sulfonyl azides is from the corresponding sulfonyl chloride and sodium azide. For example, Katsuki and co-workers reported the synthesis of number of aryl sulfonyl nitrene precursors, with a variety of different substituents on the aryl ring using this method. With the exception of sulfonyl azide **33** (**Table 1.3**, entry 2), each of the remaining sulfonyl azides reported in **Table 1.3** was synthesised in moderate to excellent yields (**Table 1.3**, entries 1, 3–6).[40]

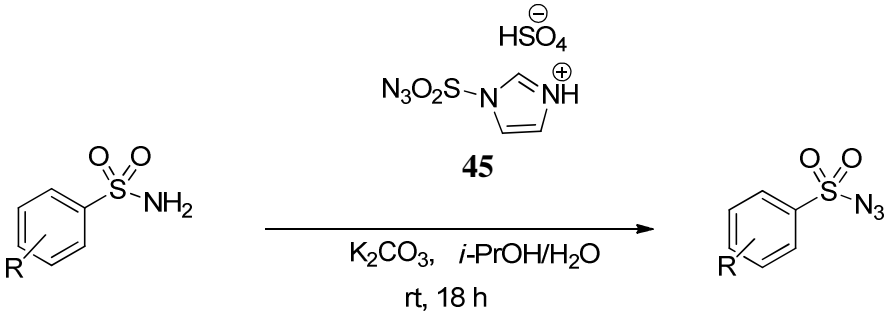
Table 1.3 *Synthesis of sulfonyl azides from sulfonyl chlorides and sodium azide*



Entry	R^1	R^2	Sulfonyl chloride	Sulfonyl azide	Yield (%)
1	H	Me	**34**	**35**	90
2	OMe	Me	**36**	**33**	35
3	NMe_2	Me	**37**	**38**	84
4	Br	Me	**39**	**40**	93
5	CO_2Me	Me	**41**	**42**	87
6	H	Bn	**43**	**44**	57

Synthesis of sulfonyl azides as nitrene precursors has also been reported *via* a diazo transfer reaction to sulfonamides. A number of diazo transfer reagents have been utilised for this purpose, for example trifluoromethanesulfonyl azide[41] and nonafluorobutanesulfonyl azide.[42] Recently, use of an imidazole-1-sulfonyl azide salt has been reported in the synthesis of a number of sulfonyl azide compounds; a select number of examples are presented in **Table 1.4**.[43]

Table 1.4 *Synthesis of sulfonyl azides via a diazo transfer reaction*[43]

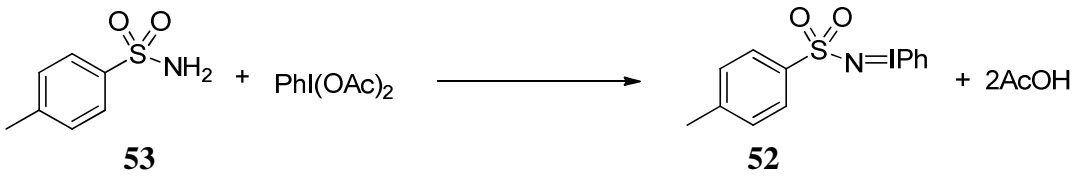


Entry	R	Sulfonyl azide	Yield (%)
1	4-Br	**46**	77
2	4-OMe	**47**	80
3	3-OMe	**48**	83
4	2-Me	**49**	80
5	4-CN	**50**	68
6	4-F	**51**	63

The authors state that the use of imidazole-1-sulfonyl azide salt **45** is advantageous over the other diazo transfer reagents previously used for this transformation, as it is prepared from cheap starting materials, has low shock sensitivity, is largely resistant to electrostatic discharge and is a solid at room temperature.[43] While nonafluorobutanesulfonylazide is shelf stable, it is an oil at room temperature.[42] ^{15}N NMR labelling studies have demonstrated that the sulfonyl amide nitrogen is retained in the sulfonyl azide.[42]

1.3.2 Iodinanes as nitrene sources

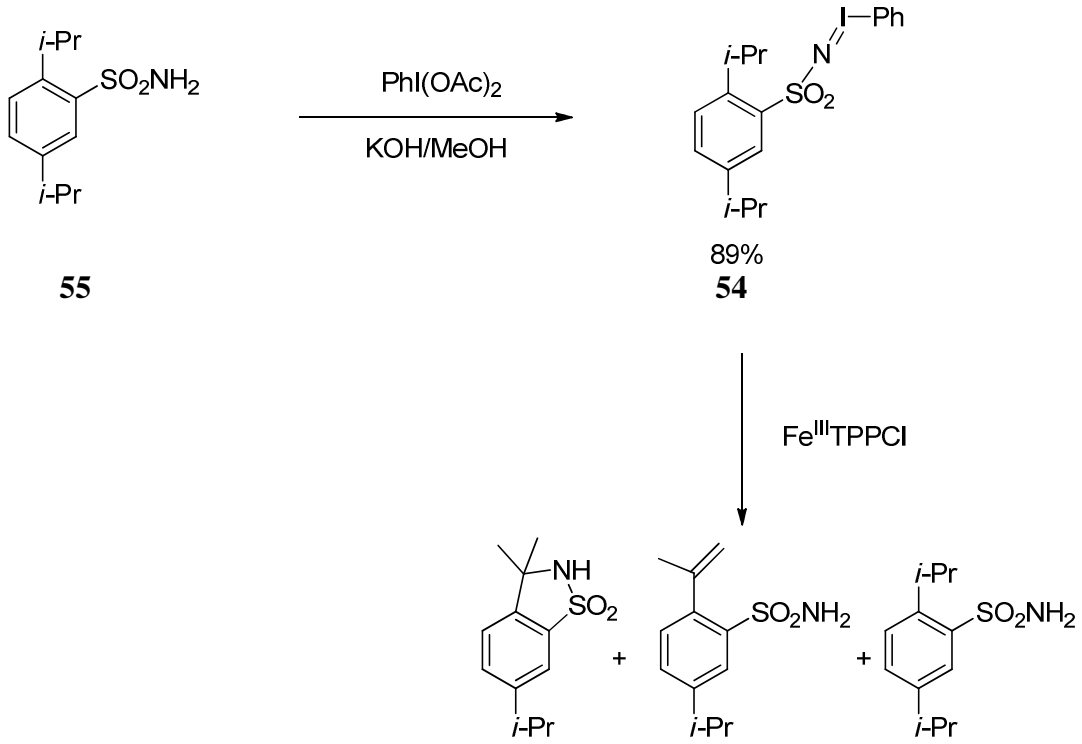
The synthesis of pre-formed iodinane **52** can be achieved by reacting *p*-toluene sulfonamide **53** with $PhI(OAc)_2$ (**Scheme 1.6**).[44]



53 **52**

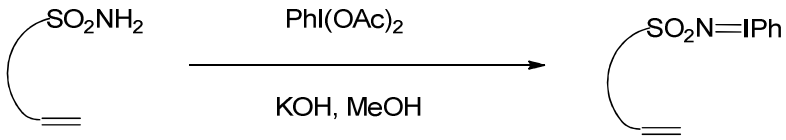
Scheme 1.6

Breslow and Gellman was the first to report the use of pre-formed iodinanes as nitrene sources.[45,46] For example 2,5-diisopropylbenzenesulfonamide was converted to the corresponding iodinane using phenyliodine diacetate in the presence of potassium carbonate using methanol as a solvent in 89% yield (**Scheme 1.7**). It was found that (imidoiodo)benzene derivative **54** did not withstand purification and was therefore carried through for C–H amination studies without purification.



Scheme 1.7

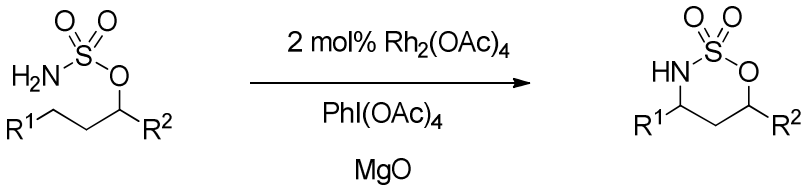
This methodology was also utilised more recently by Dauban and Dodd.[47] A range of sulfonamides were reacted to form iminoiodinanes (**Scheme 1.8**). The resulting iodinanes were isolated using a dichloromethane extraction followed by a cold aqueous wash. The authors stated that these compounds were immediately reacted with Cu(OTf).



Scheme 1.8

1.3.3 *In situ* generation of iodinanes as nitrene precursors

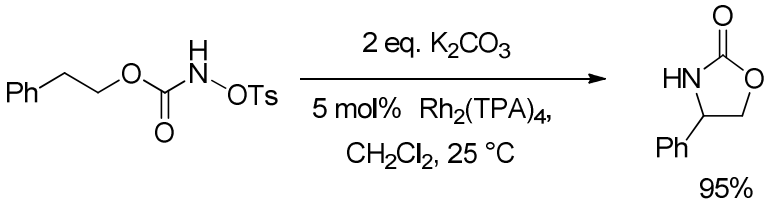
Che and co-workers[48–50] and Du Bois and co-workers[51,52] developed methods for the *in situ* generation of iodinanes, which are commonly used for the generation of nitrenes.[9] An example of the *in situ* preparation of a nitrene, which subsequently undergoes a C–H insertion reaction is illustrated in **Scheme 1.9**, where a sulfamate is exposed to $PhI(OAc)_2$, MgO, and 2 mol% $Rh_2(OAc)_4$. [51]



Scheme 1.9[51]

1.3.4 *N*-Tosyloxycarbamates as nitrene precursors

In relation to atom economy, the use of sulfonyl azides over iodinanes is preferred as the former involves the release of nitrogen gas, whereas the latter involves the formation of stoichiometric amounts of iodobenzene.[9] The generation of iodobenzene is a major drawback. Lebel and co-workers offered an alternative procedure involving the use of *N*-tosyloxycarbamates as a source of metal nitrenes for C–H insertion (**Scheme 1.10**) and aziridination reactions.[53]



Scheme 1.10[53]

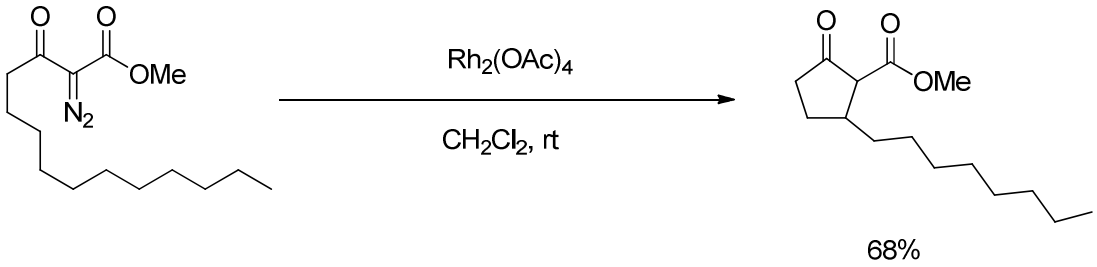
1.4 C–H insertion of carbenes and nitrenes

Catalytic C–H insertion reactions of carbenes and nitrenes into unactivated C–H bonds provide many synthetic opportunities for the construction of complex organic molecules.[3] The practical applications of these transformations can clearly be seen as carbene and nitrene insertions into C–H bonds have been used as key steps in the total synthesis of a number of important biologically active compounds.[3,54] In the following section a brief synopsis of C–H insertion reactions of α-diazocarbonyl compounds will be presented, followed by a comprehensive discussion on the intramolecular C–H insertion reactions of α-diazosulfones. Due to the large number of reports in the literature of the use of sulfonyl nitrenes in C–H insertion reactions, just a number of illustrative examples are highlighted.

1.4.1 Intramolecular C–H insertion reactions of α-diazocarbonyl compounds

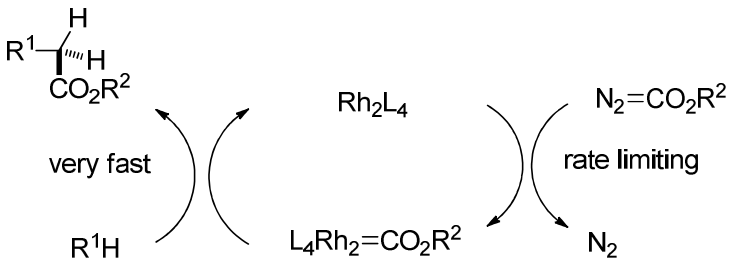
The intramolecular transition metal catalysed C–H insertion reaction of α-diazocarbonyl compounds is an extremely well-studied transformation, with high chemo-, regio- and enantioselectivity being demonstrated in the synthesis of a number of cyclic structural motifs.[1,3,4,6,7,11,55,56]

Early work carried out on the intramolecular C–H insertion reactions of α-diazocarbonyls involved the use of α-diazo-β-keto esters substrates. Taber and co-workers revealed a number of important trends (**Scheme 1.11**), namely that five-membered ring products are favoured, insertion is preferred into a methine over a methylene over a methyl group and that if insertion occurs into a stereocentre the reaction proceeds with retention of configuration at that centre.[57–60] These trends are discussed in more detail in Chapter 2.



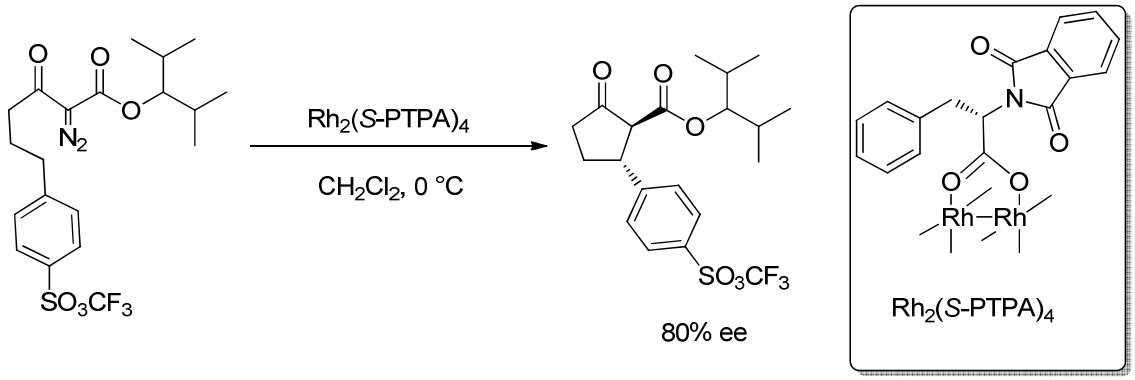
Scheme 1.11[57]

A great deal of research has been conducted into the mechanism of the C–H insertion reactions of α-diazocarbonyl compounds (**Scheme 1.12**). Doyle and co-workers proposed that C–H insertion proceeds *via* a three centred concerted transition state,[61] while Pirrung and Morehead[62] proposed a three centred stepwise mechanism. Taber co-workers [63] proposed a model in which an interaction between the hydrogen atom and the rhodium atom is present. It is now generally accepted that this mechanism occurs *via* a three centred hydride-like transition state with C–H activation and C–C bond formation occurring in a single step.[64] This is an important observation as it means that the carbenoid displays singlet carbene behaviour, which explains the observation that C–H insertion proceeds with retention of stereochemistry.[60] This mechanism will be discussed in more detail in Chapter 4.

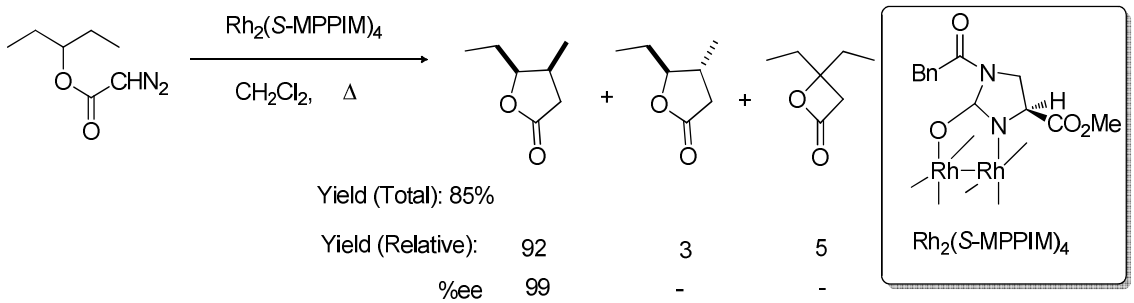


Scheme 1.12[64]

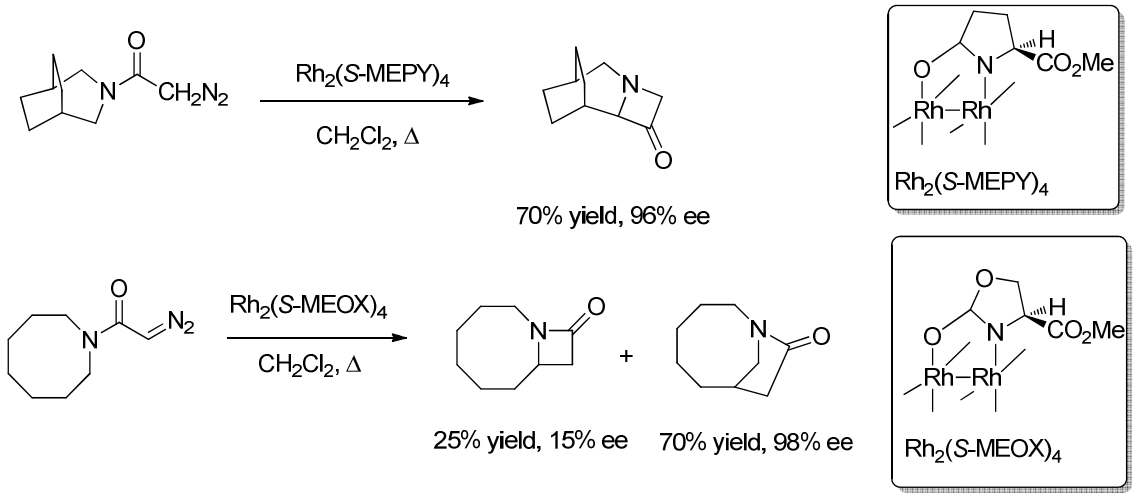
Enantioselectivities, through use of chiral catalysts,[4,6,7,11] as high as 80% ee have been reported for the synthesis of cyclopentanones,[65–67] up to 99% ee in ɣ-lactone synthesis has been achieved[68] and values in excess of 95% ee have been reported in both β- and ɣ-lactam synthesis[69] (**Scheme 1.13**).



Cyclopentanone synthesis



Lactone synthesis



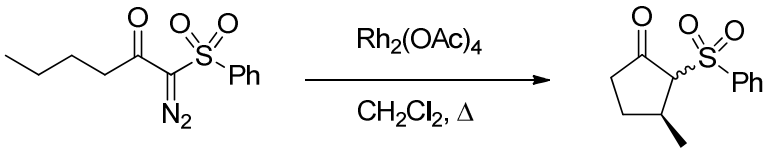
Lactam synthesis

Scheme 1.13

While rhodium(II) catalysts have been by far the most successful and widely-used of all the transition metal catalysts for C–H insertion reactions of α-diazocarbonyl compounds,[1,4,6,7] a number of other transition metal catalysts have been successfully applied to this transformation, including copper,[7,37] iron,[70] molybdenum,[71] scandium,[72] silver[73] and gold.[74] In addition, transition metal catalysed C–H insertion reactions of a number of α-diazocarbonyl compounds have been used as a key step in the total synthesis of a number of biologically active products, counting amongst them rolipram and tetrodotoxin,[3] thus demonstrating the synthetic potential of this transformation.

1.4.2 Intramolecular C–H insertion of α-diazosulfones

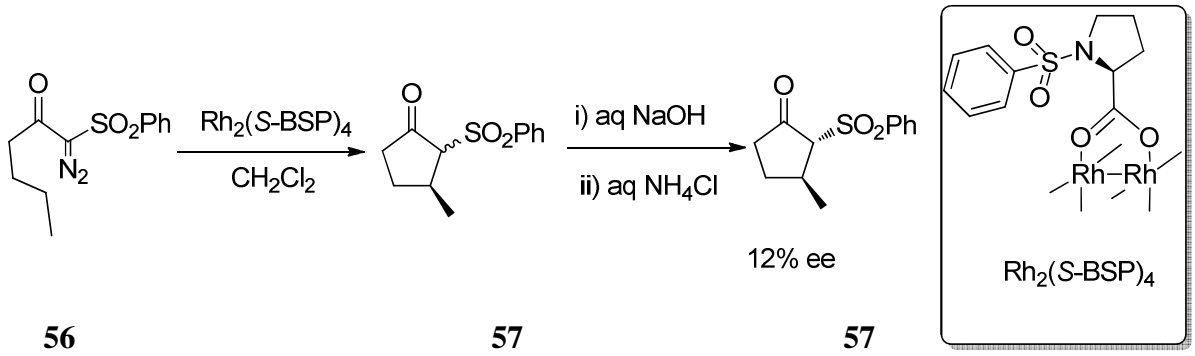
Monteiro was the first to report an intramolecular C–H insertion reaction employing α-diazo-β-keto benzenesulfones as the starting material.[75] Yields of up to 75% were reported when rhodium acetate was employed as the catalyst; these yields are comparable to those achieved when α-diazo-β-keto esters are employed (**Scheme 1.14**). The synthesis of compounds bearing a benzenesulfonyl group offers considerable potential, for further transformations, as the sulfone group can be readily removed using a reductive desulfonylation reaction, or indeed employed to effect other reactions such as alkylation.



56 **57**

Scheme 1.14

Subsequently, McKervey and co-workers exposed a similar substrate to a chiral rhodium prolinate catalyst, synthesising cyclopentanone **57** in 12% ee, marking the first report of asymmetric induction in a C–H insertion reaction (**Scheme 1.15**).[76]

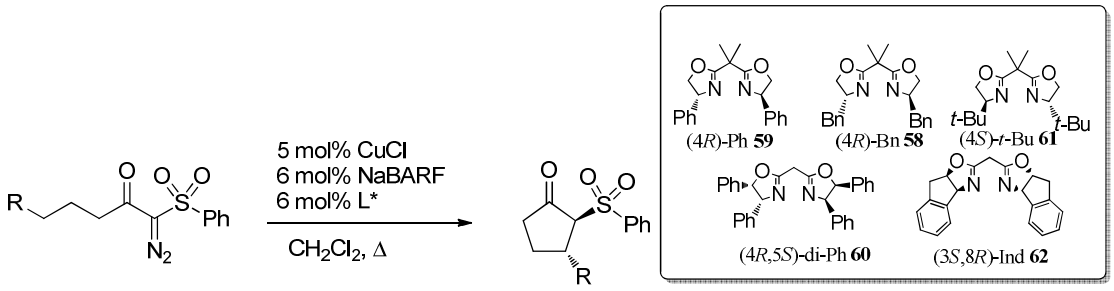


56 **57** **57**

Scheme 1.15[76]

Recently, a number of reports of asymmetric copper-bisoxazoline catalysed C–H insertion reactions of α-diazosulfones to synthesise α-sulfonyl cyclopentanones have appeared in the literature.[77–81] A range of substrates were studied, all containing the phenylsulfonyl moiety with variation in the nature of the C–H insertion site; substrates containing either benzylic or aliphatic groups adjacent to the potential C–H insertion site were investigated. Five commercially available bisoxazoline ligands **58**–**62** were utilised in this study, to explore the impact that they would have on the enantiopurity of the cyclopentanone products. The catalytic mixture consisted of a copper salt (either $CuCl_2$ or CuCl), a bisoxazoline ligand (one of **58**–**62**) and the additive NaBARF. The findings of this investigation are presented in **Table 1.5**.[77–79]

Table 1.5 *Synthesis of α-sulfonyl cyclopentanones*[77–79]



Entry	R	α-diazosulfone	L*	cyclopentanone	Yield (%)[a]	%ee [b]
1	Ph	**63**	(4*R*)-Bn **58**	**64** (2*S*,3*S*)	62	82
2[c]	Ph	**63**	(4*R*)-Bn **58**	**64** (2*S*,3*S*)	40	8
3	Ph	**63**	(4*R*)-Ph **59**	**64** (2*S*,3*S*)	68	49
4	Ph	**63**	(4*R*,5*S*)-di-Ph **60**	**64** (2*S*,3*S*)	82	58
5	Ph	**63**	(4*S*)-*t*-Bu **61**	**64** (2*R*,3*R*)	55	64
6[d]	Ph	**63**	(3*S*,8*R*)-Ind **62**	**64** (2*R*,3*R*)	87	89
7[e]	Ph	**63**	(3*S*,8*R*)-Ind **62**	**64** (2*R*,3*R*)	59	91
8	Bn	**19**	(4*R*)-Bn **58**	**65** (2*S*,3*S*)	54	57
9	*i*-Pr	**66**	(4*R*)-Bn **58**	**67** (2*S*,3*S*)	95	60
10	Et	**68**	(4*R*)-Bn **58**	**69** (2*S*,3*R*)	70	62
11	Me	**56**	(4*R*)-Bn **58**	**57** (2*S*,3*R*)	62	58

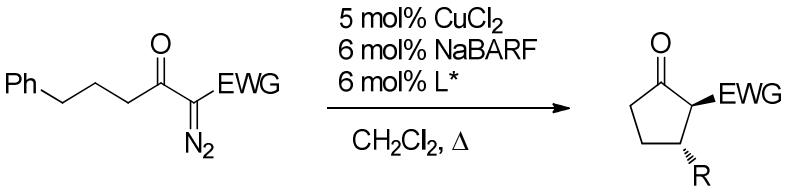
a. Yield reported after chromatography
b. Enantioselectivity measured using chiral HPLC
c. The reaction was carried out in the absence of NaBARF
d. Result obtained for $CuCl_2$, not CuCl
e. KBARF was used as an additive instead of NaBARF

Focusing initially on the outcome of the substrate investigation, it can clearly be seen in **Table 1.5**, that the nature of the site of insertion has a significant impact on the enantioselectivity of the C–H insertion reaction, with α-diazosulfone **63**, containing a benzylic site of C–H insertion giving rise to the best enantioinduction (**Table 1.5**, entries 1, 6–7). Comparing results achieved across the series with (4*R*)-Bn ligand **58**, 82% ee was the highest value attained for insertion into a benzylic C–H insertion site (**Table 1.5**, entry 1) with values decreasing for all other C–H insertion sites in the order ethyl (62% ee) > isopropyl (60% ee) > methyl (58% ee) > benzyl (57% ee) (**Table 1.5**, entries 8–11). Examining results achieved using the other four ligands for reaction with α-diazosulfone **63**, the best result achieved is for reaction with (3*S*,8*R*)-Ind **62** (89% ee), decreasing in the order (3*S*,8*R*)-Ind **62** (89% ee) > (4*R*)-Bn **58** (82% ee) > (4*S*)-*t*-Bu **61** (64% ee) >

(4*R*,5*S*)-di-Ph **60** (58% ee) > (4*R*)-Ph **59** (49% ee) (**Table 1.5**, entries 1, 3-6). Both of these trends highlight the importance of a specific substrate-ligand interaction for achieving high enantiopurity. Having investigated the roles that the substrate and the ligand play in producing cyclopentanones with high enantiopurity, the role that the counterion plays in the reaction was investigated.[78,79] For reaction of α-diazosulfone **63** with (4*R*)-Bn ligand **58**, 8% ee was obtained in the absence of NaBARF in comparison to 82% ee when the additive was present (**Table 1.5**, entries 1–2), thus demonstrating the crucial role that the additive plays in the reaction. The presence of NaCl in the reaction flask, as detected at the end of the reaction, provides evidence for the theory that the Na^+ cation abstracts the Cl^- anion leading to a catalyst with an improved geometry for high enantioinduction.[82] When KBARF was employed in the reaction instead of NaBARF an increase from 89 to 91% ee was observed (**Table 1.5**, entries 6–7), marking the highest enantioselectivity achieved to date for asymmetric copper catalysed intramolecular C–H insertion reactions leading to cyclopentanones.[78,79] In addition, it is the highest enantioselectivity achieved for the synthesis of cyclopentanones *via* a transition metal catalysed C–H insertion of an α-diazocarbonyl compound.

In a subsequent report by Maguire and Slattery, the importance of the sulfonyl group in achieving high enantioselectivity was highlighted by comparing the outcome with the sulfone group to that with other electron withdrawing groups.[83] Ester and phosphonate electron withdrawing groups were used for comparison; the results of this study are presented in **Table 1.6**.

Table 1.6 *Cyclopentanone synthesis*[83]



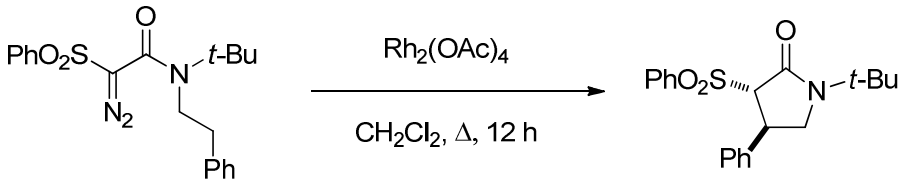
Entry	EWG	α-diazocarbonyl	L*	cyclopentanone	Yield (%)[a]	ee (%)[b]
1	$CO_2CH(i\text{-}Pr)_2$	**70**	(4*R*)-Bn **58**	**71** (+)	93	51
2	$CO_2CH(i\text{-}Pr)_2$	**70**	(3*S*,8*R*)-Ind **62**	**71** (–)	89	65
3	$CO_2CH(i\text{-}Pr)_2$	**70**	(4*R*,5*S*)-di-Ph **60**	**71** (+)	53	61
4	$PO(OMe)_2$	**72**	(4*R*)-Bn **58**	**73** (–)	71	52
5	$PO(OMe)_2$	**72**	(3*S*,8*R*)-Ind **62**	**73** (+)	77	32
6	$PO(OMe)_2$	**72**	(4*R*,5*S*)-di-Ph **60**	**73** (+)	64	45

a. Yield reported after chromatography.
b. Enantioselectivity measured using chiral HPLC.

Cyclopentanones with much lower enantiopurities were obtained when α-diazo ester **70** and α-diazo phosphonate **72** were employed as starting materials, in comparison to α-diazosulfone **63** (**Table 1.6**, *cf.* **Table 1.5**). The highest enantioselectivities reported in this study were 65% ee and 52% ee, achieved for α-diazo ester **70** and α-diazo phosphonate **72** respectively (**Table 1.6**, entries 2 and 4). Interestingly the highest enantiocontrol was achieved when (4*R*)-Bn ligand **58** or (3*S*,8*R*)-Ind ligand **62** was used for the reaction of each of the α-diazocarbonyl substrates **63**, **70** and **72**. The catalyst trends are consistent with those seen for the α-diazosulfones in terms of the optimum ligands **58** and **62**, except that the (4*R*,5*S*)-di-Ph ligand **60** proved relatively more effective with the ester and the phosphonate derivatives than seen with the sulfones.

Whereas C–H insertion reactions of α-diazo-β-keto sulfones result in the formation of cyclopentanone products, when α-diazo-α-(phenylsulfonyl)-acetamides were employed as the starting material, lactam products were formed.[33,84–86] The synthesis of β- and ɣ-lactams were of particular interest due to their biological importance.[33,84] In a preliminary report by Jung and co-workers, ɣ-lactam product **74** is formed exclusively, with no evidence for β-lactam formation when α-diazosulfone **75** undergoes a rhodium acetate catalysed intramolecular C–H insertion reaction (**Scheme 1.16**). They attribute this high regioselectivity to the use of the phenylsulfonyl moiety, which exerts both a steric effect and an electronic effect on the ensuing reaction pathway. They state that the

phenylsulfone group causes the C–H insertion reaction to proceed through a later transition state, due to a stabilisation effect that it has on the transition state.

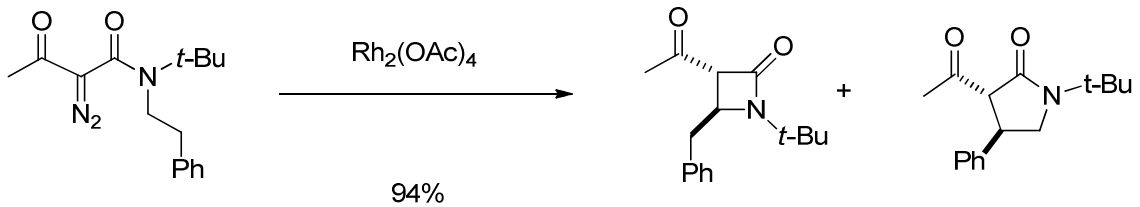


95%

75 **74**

Scheme 1.16

The importance of the phenylsulfonyl group in achieving high regioselectivity is highlighted in **Scheme 1.17**. When a methyl ketone **76** is used instead of the phenylsulfonyl moiety, approximately equal amounts of β- and ɣ-lactam **77** and **78** are formed, in comparison to the exclusive ɣ-lactam formation seen for phenylsulfonyl substrate **75** (**Scheme 1.16**).[87]

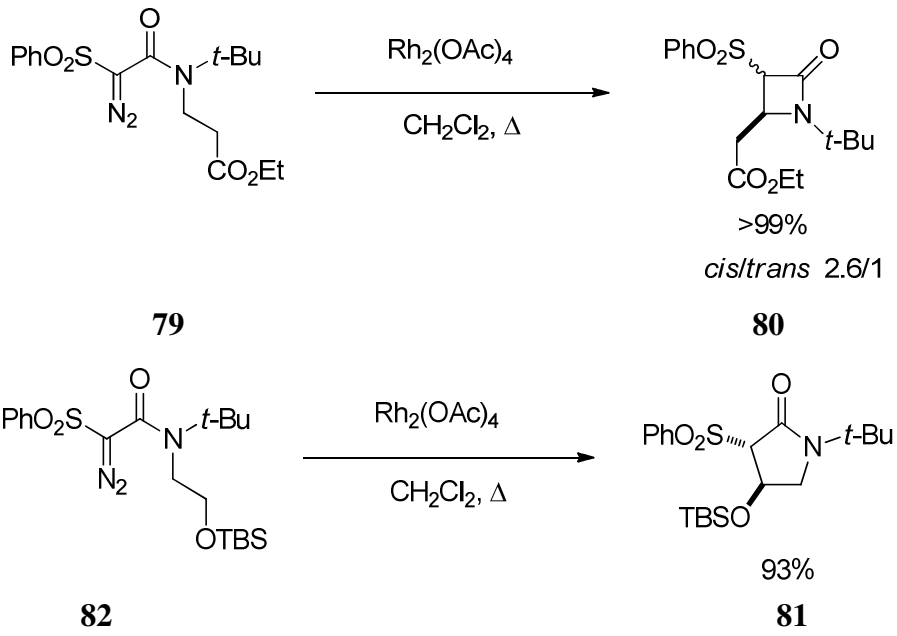


94% 49% 51%

76 **77** **78**

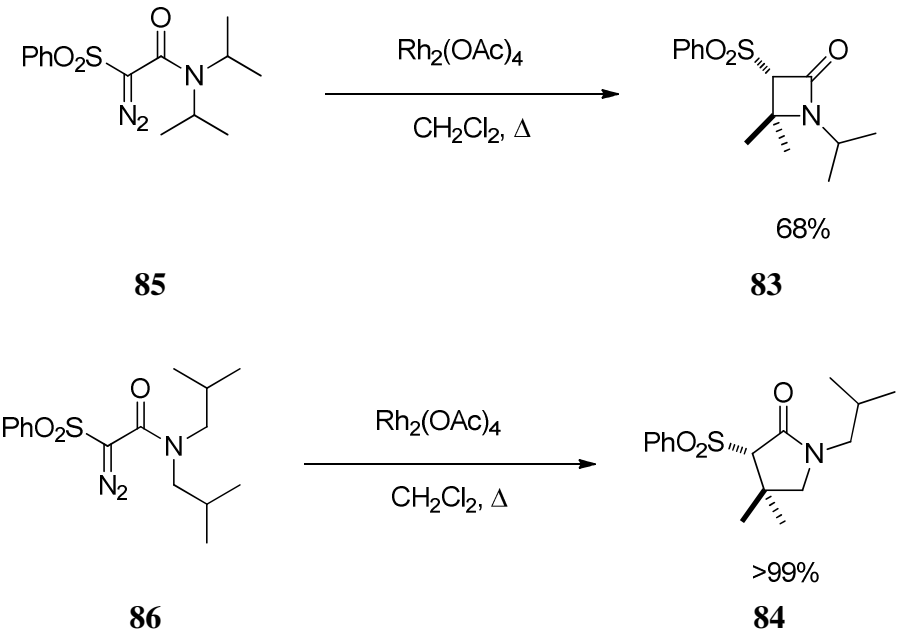
Scheme 1.17[87]

Jung and co-workers also highlighted the importance of the electronic properties at the site of C–H insertion for rhodium acetate catalysed C–H insertion reactions of α-diazo-α-(phenylsulfonyl)-acetamides (**Scheme 1.18**). The presence of the deactivating carboethoxy group in α-diazo-α-(phenylsulfonyl)-acetamide **79** resulted in β-lactam **80** as the only observable C–H insertion product, while the presence of the electron donating TBS ether yielded ɣ-lactam **81** exclusively (**Scheme 1.18**).[84]



Scheme 1.18

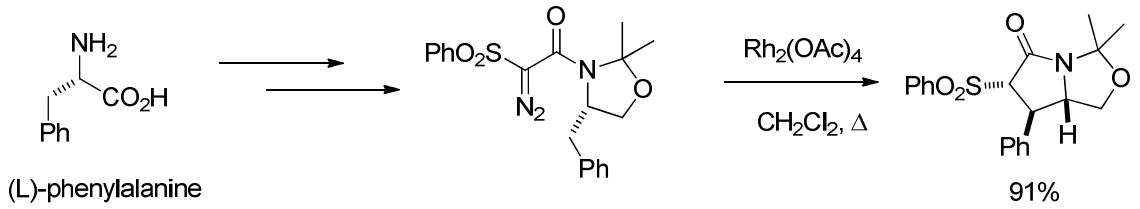
Further exploration of the site of C–H insertion revealed that insertion into a methine group is preferred where possible, resulting in β- and ɣ-lactam products **83** and **84** as depicted in **Scheme 1.19**.[84]



Scheme 1.19

In subsequent reports by Jung, it was demonstrated that chiral ɣ-lactams could be synthesised from the rhodium acetate catalysed intramolecular C–H insertion reaction of α-diazo-α-(phenylsulfonyl)-acetamides derived from chiral amino acids.[85,86] The α-diazo-α-(phenylsulfonyl)-acetamide **87** was prepared *via* a multi-step synthesis from (L)-phenylalanine (**Scheme 1.20**), and was cyclised to yield chiral ɣ-lactam **88** as the only observable C–H insertion product in 91% yield. The presence of the *gem*-dimethyl group

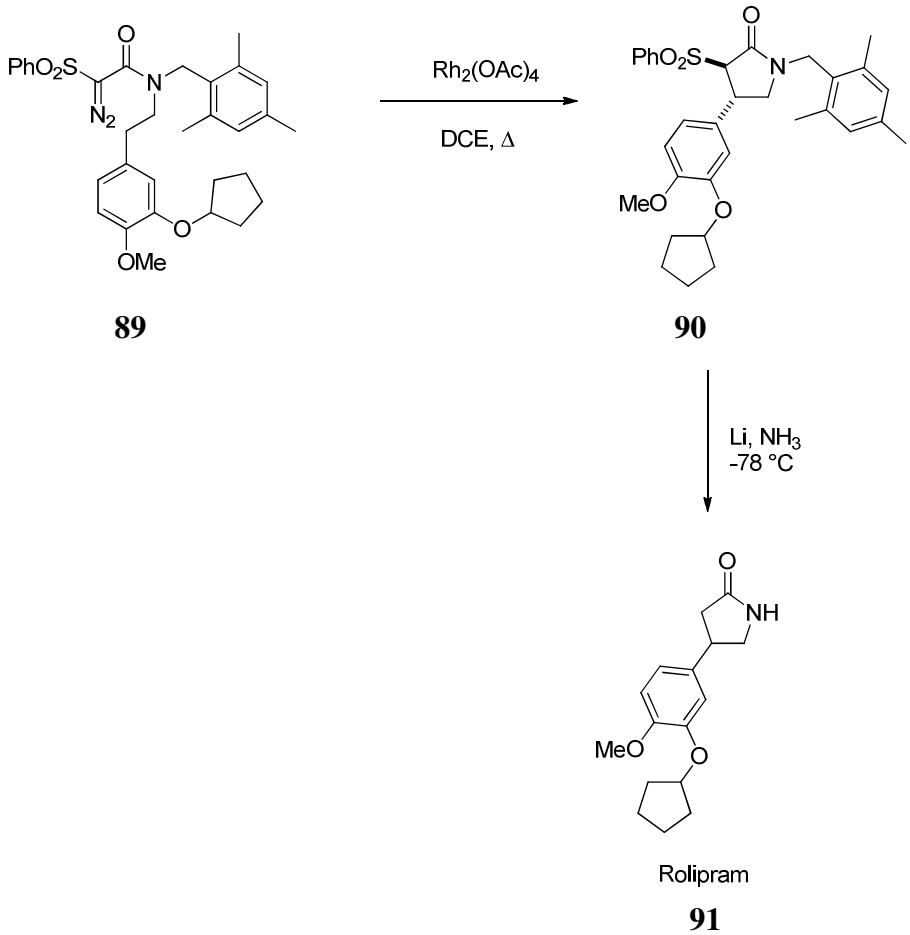
is essential for the reaction to take place, as it forces the metallocarbenoid to adopt an *s-cis* conformation which is the only conformation suitable for C–H insertion reaction. Jung confirmed this by demonstrating that in the absence of the *gem*-dimethyl group the analogous C–H insertion reaction does not take place.[85,86]



87 **88**

Scheme 1.20

The synthetic utility of this transformation was further demonstrated by Jung who used the C–H insertion of α-diazoacetamide **89** as a key step in the synthesis of rolipram (**Scheme 1.21**). Once the key intermediate **90** was accessed *via* a rhodium catalysed C–H insertion reaction, a one-pot desulfonylation/debenzylation resulted in the synthesis of rolipram **91**.[33]

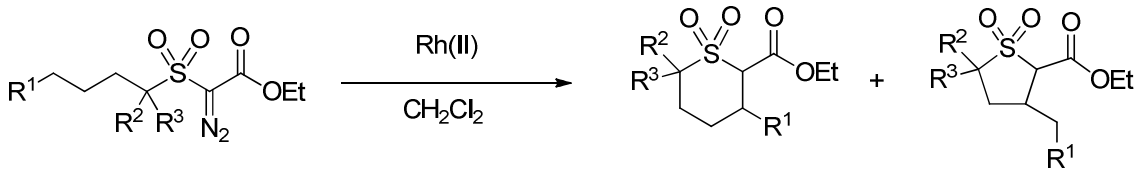


89 **90** **91**

Scheme 1.21

Intramolecular C–H insertion reactions of α-diazosulfones may also occur to afford products that contain a sulfone group in the ring. Novikov and co-workers were the first to report reactions of this nature.[88,89] A range of different α-diazo-β-oxo sulfones were exposed to a variety of achiral rhodium catalysts. One of the most significant findings presented in this publication was the overwhelming preference for the formation of six-membered ring products, which was unusual as five-membered ring products are usually preferred in intramolecular C–H insertion reactions. This was rationalised on the basis of a previous report by Du Bois and co-workers in C–H insertion reactions of nitrene derived oxosulfamides which proposed that the different geometries, in terms of bond angles and lengths around the sulfur atom relative to carbon, are the main reason for the change in this preference.[51]

Table 1.7 *Rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfones*[89]

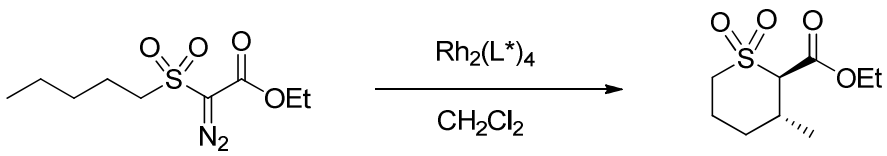


Entry	R^1	R^2	R^3	catalyst	Temperature	Yield (%) thiopyran	Yield (%) sulfolane
1	Me	Me	Me	$Rh_2(pfb)_4$	reflux	Not detected	64
2	Me	H	H	$Rh_2(OAc)_4$	rt	65	9
3	Me	H	Me	$Rh_2(OAc)_4$	rt	40	24
4	Me	H	Me	$Rh_2(pfb)_4$	rt	8	60
5	Me	Me	Me	$Rh_2(OAc)_4$	reflux	5	75

While *trans* six-membered ring formation is generally the preferred reaction outcome, five-membered ring products can also be formed in certain instances. For example, proportionately more five-membered ring products result when the more electron withdrawing $Rh_2(pfb)_4$ catalyst is used compared to $Rh_2(OAc)_4$ (**Table 1.7** entries 3 and 4, *versus* entries 1 and 5). In addition, increasing the substitution at the α-position to the sulfone also results in a relative increase in the amount of sulfolane formation (**Table 1.7**, entries 2, 3 and 5).[89]

Recently, Novikov and Jungong demonstrated that it is possible to produce enantioenriched *trans* thiopyrans employing chiral rhodium catalysts.[90] The highest enantioselectivity achieved was 50% ee, when α-diazo-β-oxo sulfone **20** was reacted with Rh_2(*S*-PTTL)$_4$ (**Table 1.8**, entries 2 and 3). The effect of variation in temperature on the reaction outcome was also investigated; it was found that decreasing the temperature from rt to 0 °C caused an increase in enantioselectivity from 45 to 50% ee. However, a further decrease in reaction temperature from 0 °C to –20 °C did not result in any further improvement in enantioselectivity. Interestingly, decreasing the reaction temperature gave rise to a drop in the isolated yield (**Table 1.8**, entries 1–3). Rh_2(*S*-PTAD)$_4$ resulted in a similar enantioselectivity of 45% ee (**Table 1.8**, entry 5), with lower values obtained for the remaining catalyst used in the study (**Table 1.8**, entry 4).

Table 1.8 *Chiral rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***20***[90]

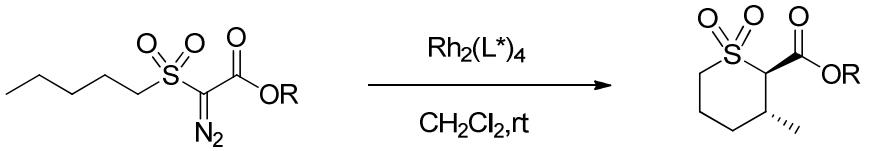


20 **92**

Entry	Catalyst	Temperature	Yield (%)	ee (%)
1	Rh_2(*S*-PTTL)$_4$	rt	85	45
2	Rh_2(*S*-PTTL)$_4$	0 °C	65	50
3	Rh_2(*S*-PTTL)$_4$	–20 °C	61	50
4	Rh_2(*S*-PTPA)$_4$	rt	70	33
5	Rh_2(*S*-PTAD)$_4$	rt	90	45

While moderate enantioselectivities were achieved for the chiral rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone **20**, excellent diastereoselectivities were reported when chiral auxiliaries were employed (**Table 1.9**).[90]

Table 1.9 *Chiral rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfones* ***93*** *and* ***94***[90]

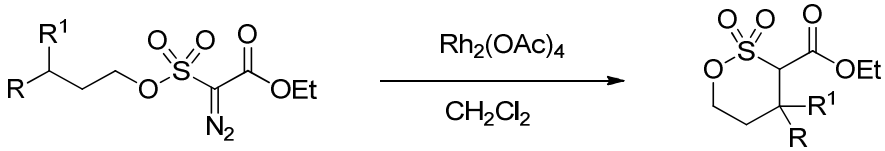


Entry	R	α-diazocarbonyl	Catalyst	*trans* thiopyran	Yield (%)	de (%)
1	(–)-Menthyl	**93**	Rh_2(*S*-PTTL)$_4$	**95**	94	90
2	(+)-Menthyl	**94**	Rh_2(*S*-PTTL)$_4$	**96**	82	–40
3	(–)-Menthyl	**93**	$Rh_2(OAc)_4$	**95**	60	0

When (–)-menthol was employed as a chiral auxiliary 90% de was achieved for reaction of α-diazo-β-oxo sulfone **93** when Rh_2(*S*-PTTL)$_4$ was employed as a catalyst (**Table 1.9**, entry 1). In an effort to understand the role that the chiral auxiliary was playing in the reaction, the reaction was carried out with the opposite enantiomer of menthol, which resulted in –40% de (**Table 1.9**, entry 2). This suggests that the menthol is playing the role of a directing chiral auxiliary rather than a sterically demanding functional group. The fact that reaction with rhodium acetate results in 0% de implies that a synergetic cooperative effect is at play in achieving the reported diastereoselectivity.

The synthesis of δ-sultones has also been reported using rhodium(II) catalysed C–H insertion reactions of α-diazocarbonyl compounds, in good to excellent yields (**Table 1.10**).[30,31] The synthetic potential of C–H insertion reaction to form δ-sultones was illustrated by Novikov and co-workers in the synthesis of Bakuchiol.[91]

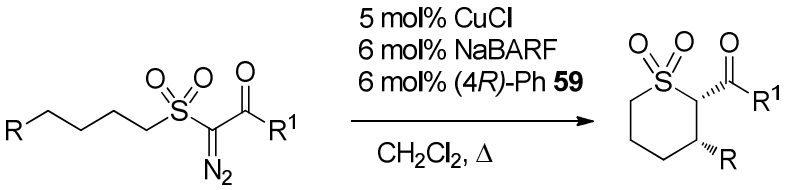
Table 1.10 *Synthesis of δ-sultones using rhodium catalysed C–H insertion reactions of α-diazocarbonyls*[30,31]



Entry	R	R^1	Temperature	α-diazocarbonyl	*δ*-sultone	Yield (%)
1[31]	Ph	H	40 °C	**97**	**98**	85
2[31]	*i*-Pr	H	40 °C	**99**	**100**	64
3[30]	Me	Me	rt	**101**	**102**	53

Maguire and Flynn demonstrated that *cis* thiopyrans could be synthesised in up to 98% ee in the copper-bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo sulfones (**Table 1.11**), marking both the highest enantioselectivity for the synthesis of a thiopyran and the highest enantioselectivity achieved for a copper catalysed C–H insertion reaction to date.[27] High enantioselectivies were achieved for a broad range of substrates with values remaining high for substrates with both benzylic (**Table 1.11**, entries 1–2, 4) and non-benzylic insertion sites (**Table 1.11**, entry 3) and for both ester (**Table 1.11**, entry 1, 3–4) and ketone derivatives (**Table 1.11**, 2). Interestingly, *cis* thiopyrans are the favoured reaction product from copper catalysed reactions, in comparison to *trans* thiopyrans for rhodium catalysed insertion reactions.[30,89]

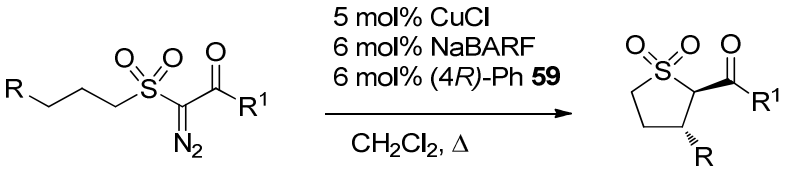
Table 1.11 *Chiral copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones*[27,78,79]



Entry	R	R^1	α-diazosulfone	thiopyran	Yield (%)	ee (%)
1	Ph	OMe	**15**	**103**	47	98
2	Ph	Ph	**104**	**105**	49	97
3	octyl	OBn	**106**	**107**	66	90
4	4-anisyl	OMe	**108**	**109**	56	91

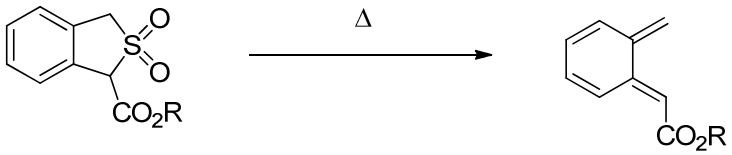
When six-membered ring formation is not possible, C–H insertion to form five-membered sulfolanes can occur. More moderate enantioselectivities were achieved for the synthesis of *trans* sulfolanes for copper catalysed C–H insertion reactions with 60% ee being the highest value attained (**Table 1.12**, entry 1).[27]

Table 1.12 *Chiral copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones* ***13*** *and* ***110***[27]



Entry	R	R^1	α-diazosulfone	sulfolane	Yield (%)	ee (%)
1	Ph	OEt	**110**	**111**	57	60
2	Ph	Me	**13**	**112**	40	40

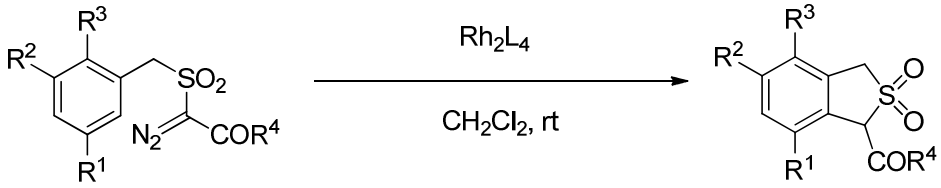
A handful of other reports exist in the literature on the use of α-diazosulfones in aromatic C–H insertion reactions. The synthesis of cyclic sulfones of the type shown in **Scheme 1.22** are desired targets as they form *o*-quinodimethanes upon extrusion of sulfur dioxide, which are important synthetic intermediates in natural product synthesis.[92]



Scheme 1.22

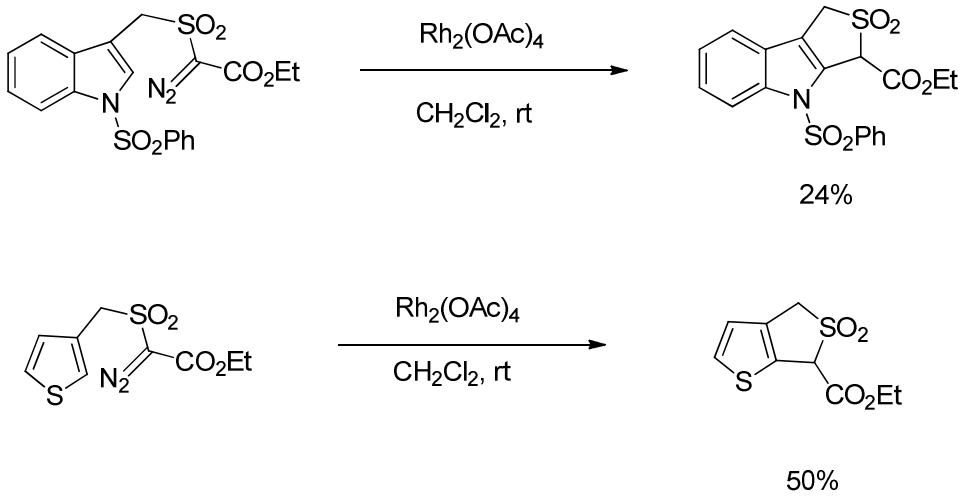
The synthesis of these cyclic sulfones has been reported in poor to moderate yields, using the rhodium catalysed aromatic C–H insertion reactions of α-diazosulfones; the results of this study are presented in **Table 1.13**. Interestingly, while the reaction tolerated a number of different functional groups at varying positions on the aromatic ring (**Table 1.13**, entries 1–5), the presence of an ortho methoxy substituent did not result in the formation of the desired C–H insertion product. The authors reported that a complex mixture of products was formed, and while it was not confirmed, it is proposed that the most likely source of these products is from the formation of an oxygen ylide.[92] Initially rhodium acetate was the catalyst employed, however, it was discovered late in the study that rhodium trifluoroacetate generally gave rise to better product yields and the yield for reaction of ketone **113** (**Table 1.13**, entry 5) is reported with rhodium trifluoracetate.

Table 1.13 *Rhodium catalysed intramolecular aromatic C–H insertion reactions of α-diazosulfones*[92]



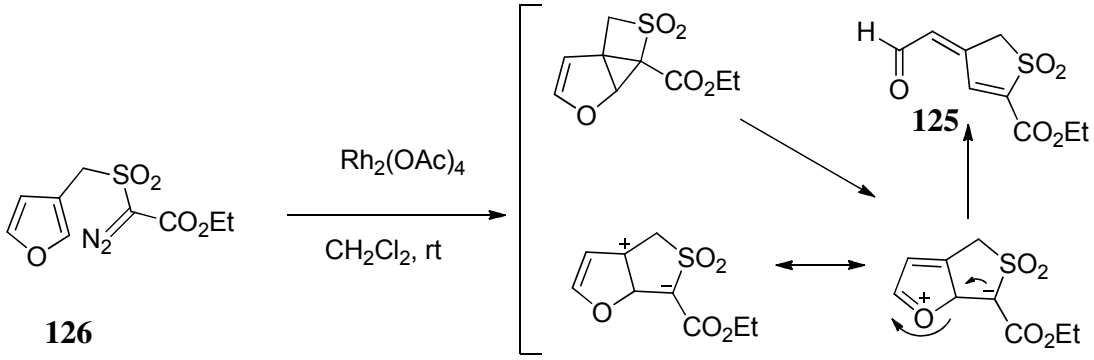
Entry	R^1	R^2	R^3	R^4	Rh_2L_4	α-diazosulfone	cyclic sulfone	Yield (%)
1	H	H	H	OMe	$Rh_2(OAc)_4$	**114**	**115**	46
2	H	H	Br	OMe	$Rh_2(OAc)_4$	**116**	**117**	48
3	H	H	Me	OMe	$Rh_2(OAc)_4$	**118**	**119**	14
4	H	OMe	H	OMe	$Rh_2(OAc)_4$	**120**	**121**	42
5	H	H	H	Me	$Rh_2(tfa)_4$	**113**	**122**	56
6	OMe	H	OMe	OMe	$Rh_2(OAc)_4$	**123**	**124**	-

Aromatic C–H insertion reactions were successfully applied to other aromatic heterocyles including indoles and thiophenes (**Scheme 1.23**).[92]



Scheme 1.23

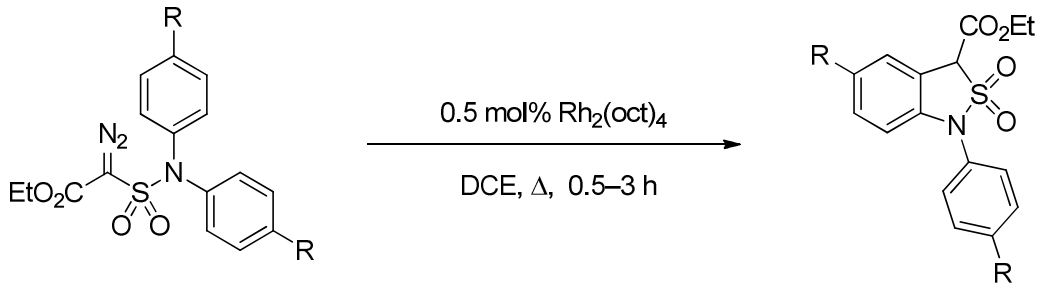
However, this could not be extended to furans, aldehyde **125** being obtained instead (**Scheme 1.24**). The appearance of this product can be rationalised by α-diazosulfone **126** initially undergoing cyclopropanation. The product is formed *via* a highly strained cyclopropane ring (which is thought to fragment either directly or *via* the formation of zwitterionic intermediate).



Scheme 1.24

Recently, Yang and Xu have reported the synthesis of benzo-ɣ-sultams in moderate to excellent yields (up to 99%, **Table 1.14**, entry 1) *via* the $Rh_2(oct)_4$ catalysed aromatic C–H insertion reactions of α-diazosulfonamides, selected results of which are presented in **Table 1.14**.[93] It is reported that this is the first instance where α-diazosulfonamides were utilised in the synthesis of benzo-ɣ-sultams. Sultams are biologically important compounds which can display antiviral and anticancer activity. The synthesis of sultams can be challenging due to fact that the S–N bond can be cleaved in the presence of a strong base/nucleophile, a problem that was largely unobserved in this report.

Table 1.14 *Rhodium catalysed aromatic C–H insertion reactions of α-diazosulfonamides in the synthesis of benzo-ɣ-sultams*[93]



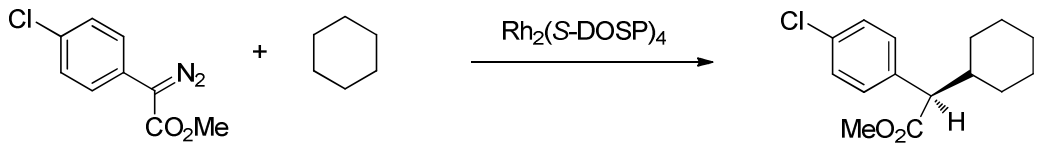
Entry	R	α-diazosulfonamide	benzo-ɣ-sultam	Yield (%)[a]
1	H	**127**	**128**	99
2	OMe	**129**	**130**	65
3	Me	**131**	**132**	94
4	F	**133**	**134**	80
5	Cl	**135**	**136**	85

a. Reported after column chromatography on silica gel.

Initially, a range of copper and rhodium catalysts and solvents were explored in the cyclisation reactions of α-diazosulfonamide **127**, with $Rh_2(oct)_4$ giving rise to the most efficient reaction and 1,2-dichloroethane (DCE) proving to be the best solvent, resulting in benzo-ɣ-sultam **128** being isolated in 99% yield (**Table 1.14**, entry 1). With optimised reaction conditions in hand, attention was subsequently focused on expanding the range of α-diazosulfonamides. It was found that the reaction tolerated both the presence of electon donating groups, such as methyl and methoxy substituents (**Table 1.14**, entries 2–3), in addition to the presence of halogen atoms, for example F and Cl (**Table 1.14**, entries 4–5) all furnished the desired benzo-ɣ-sultams products in moderate to high yields (65–94%, **Table 1.14**, entries 2–5). In this publication, a number of other substrates were investigated, with varying substitution patterns on the benzene ring, all of which were tolerated. The regioselectivity of the reaction was also investigated, using unsymmetrical *N*,*N*-diaryl groups with more limited success (the highest ratio observed was 85 : 15).

1.4.3 Intermolecular C–H insertion reactions of α-diazocarbonyl compounds

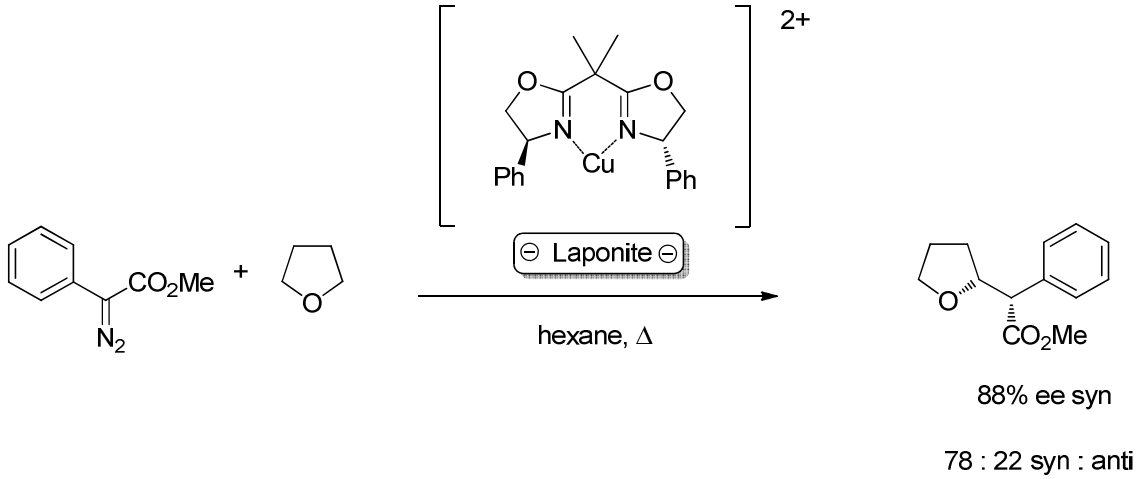
In contrast to the intramolecular C–H insertion reaction, which is characterised by excellent regio- and enantiocontrol, the intermolecular version of this reaction, until relatively recently, was thought to be a largely inefficient reaction synonymous with low regioselectivities and dimer formation.[1,94–100] However, Davies and co-workers demonstrated that this transformation could be synthetically useful if a donor/acceptor substituted carbenoid was employed, in addition establishing that high enantioselectivities could be achieved for this reaction when Rh_2(*S*-DOSP)$_4$ was employed as the catalyst (**Scheme 1.25**)[101,102] As can be seen in **Scheme 1.25**, higher enantioselectivities are achieved with lower reactions temperatures. Since these initial findings, a number of reports have emerged of the intermolecular C–H insertion reactions catalysed by Rh_2(*S*-DOSP)$_4$.[7]



Temperature °C	Yield (%)	%ee
81	91	86
25	53	93

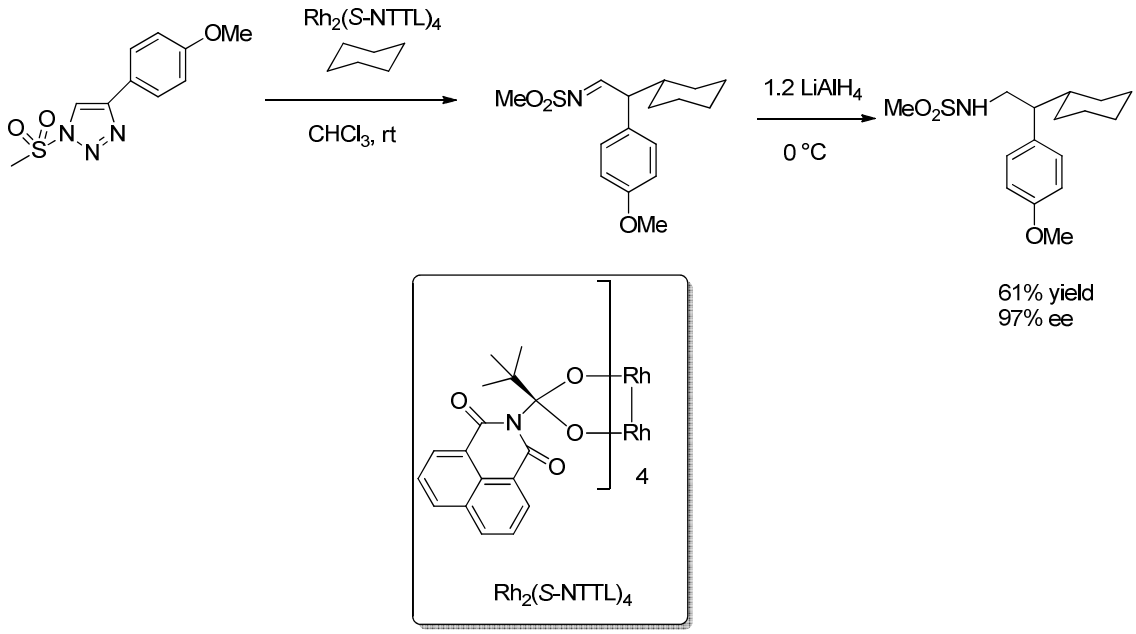
Scheme 1.25[101]

Fraile and co-workers also demonstrated that immobilised copper-bisoxazoline ligands could be used for this transformation. Enantioselectivities of up to 88% ee were achieved in the intermolecular C–H insertion reaction of methyl phenyldiazoacetate and THF, as depicted in **Scheme 1.26**. One of the main advantages of using an immobilised catalyst is that it can be recovered and re-used. Another advantage of this technique is that improved efficiencies and enantioselectivities are achieved compared to values obtained in solution, which is largely believed to be due to a "confinement effect of the bidimensional support".[103]



Scheme 1.26[103]

To the best of our knowledge, there are no literature reports of the use of sulfonyl carbenes in the intermolecular insertion reaction. However, there is a report of the use of 1-sulfonyl-1,2,3 triazoles to generate azavinyl carbenes, which in the presence of a chiral rhodium catalyst, can undergo C–H functionalisation leading to β-chiral sulfonamides with enantiopurities of up to 97% ee (**Scheme 1.27**).[104]



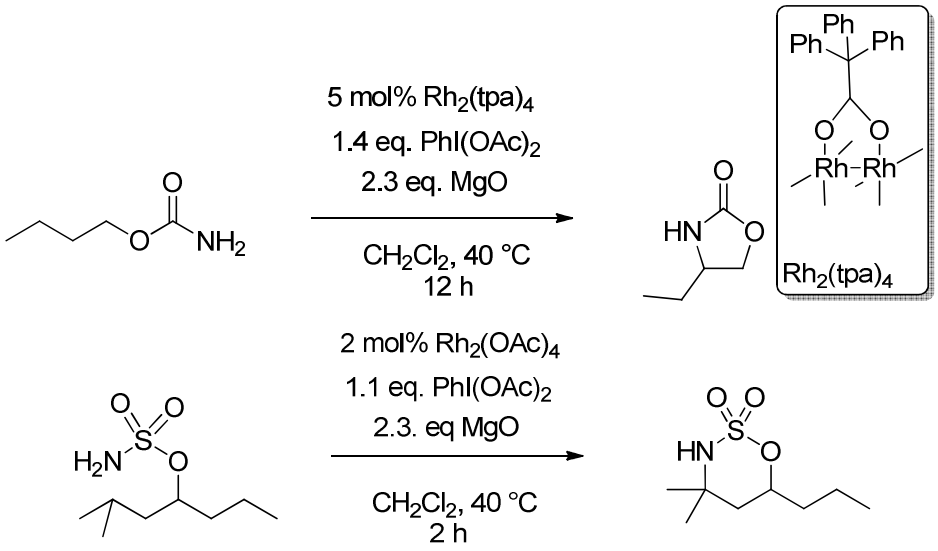
Scheme 1.27

1.4.4 Intramolecular C–H amination reactions; General remarks and trends

Catalytic inter- and intramolecular C–H amination is a powerful synthetic transformation that has a wealth of potential.[2,8–10,105–107] Pioneering work on transition metal catalysed C–H insertion reactions was carried out by Kwart and Kahn,[108,109] Breslow and Sloan[110] and Turner,[111] Abramovitch and Yamada[16,44] reported the use of sulfonyliminoiodinanes as nitrene precursors, which allowed further development of this reaction. Subsequent reports by Breslow and Gellman,[45,46] Mansuy,[112] and Müller[8,113] demonstrated that iminoiodinanes could successfully be employed in aziridination and C–H amination reactions in the presence of transition metal salts or complexes. Further developments in this field involved the discovery that C–H amination and aziridination could follow the *in situ* generation of the iminoiodinane oxidants in the presence of a transition metal.[2,8–10] This was an important development as it allowed the expansion of the substrate scope; substrates that previously would not have formed isolable iminiodinane equivalents could now be generated *in situ*. A number of transition metal catalysts have been successfully utilised for C–H amination reactions, for example, rhodium,[52,114–117] copper,[37,118,119] iron,[46,112,120] manganese,[121,122] and ruthenium.[123]

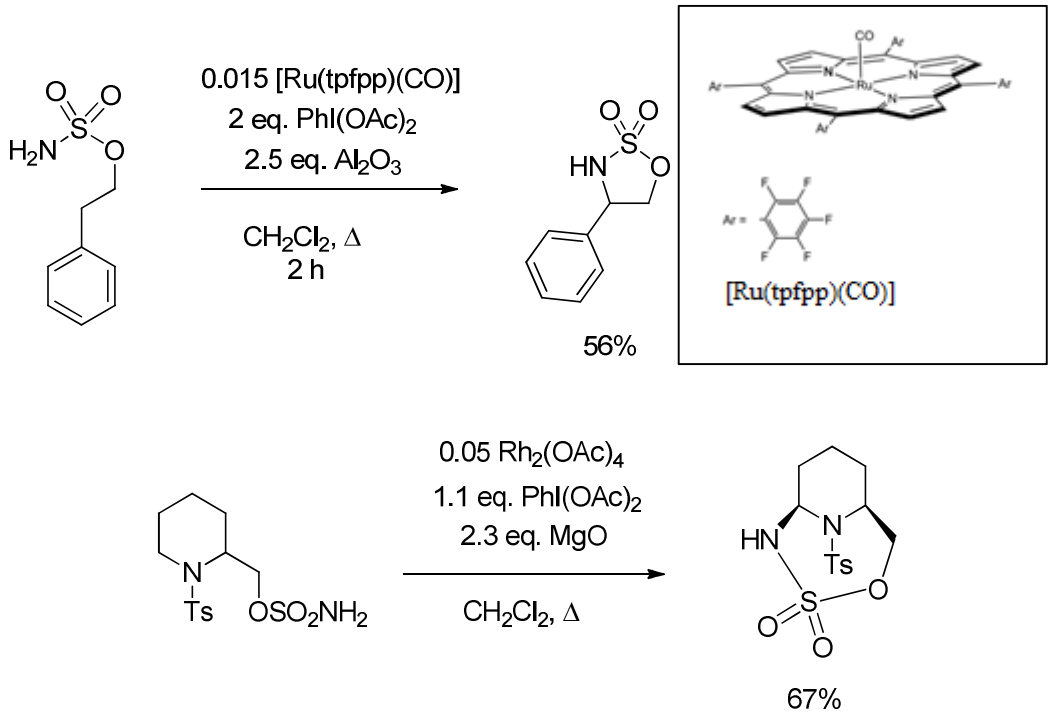
In a similar fashion to transition metal catalysed intramolecular C–H insertion reactions of α-diazocarbonyl compounds, it is possible to synthesise either five- or six-membered rings in the transition metal catalysed intramolecular C–H amination reactions of nitrenes; one of the main controlling factors is the nature of the starting material employed. In cases

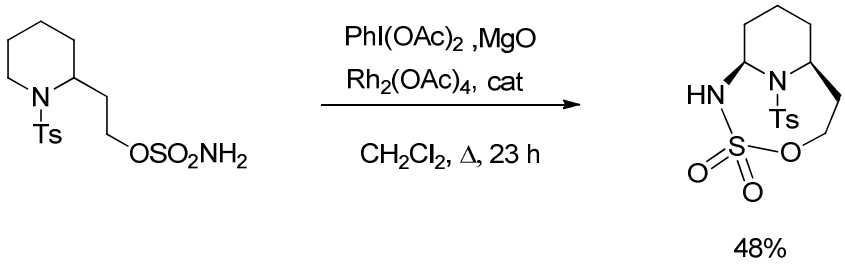
where carbamates are utilised, five-membered ring formation is generally favoured, while six-membered ring formation is the preferred reaction outcome when sulfamates undergo intramolecular C–H amination (**Scheme 1.28**).[115,116] Bond lengths and angles around the sulfone group are responsible for preferential six-membered ring formation.[115]



Scheme 1.28[115,116]

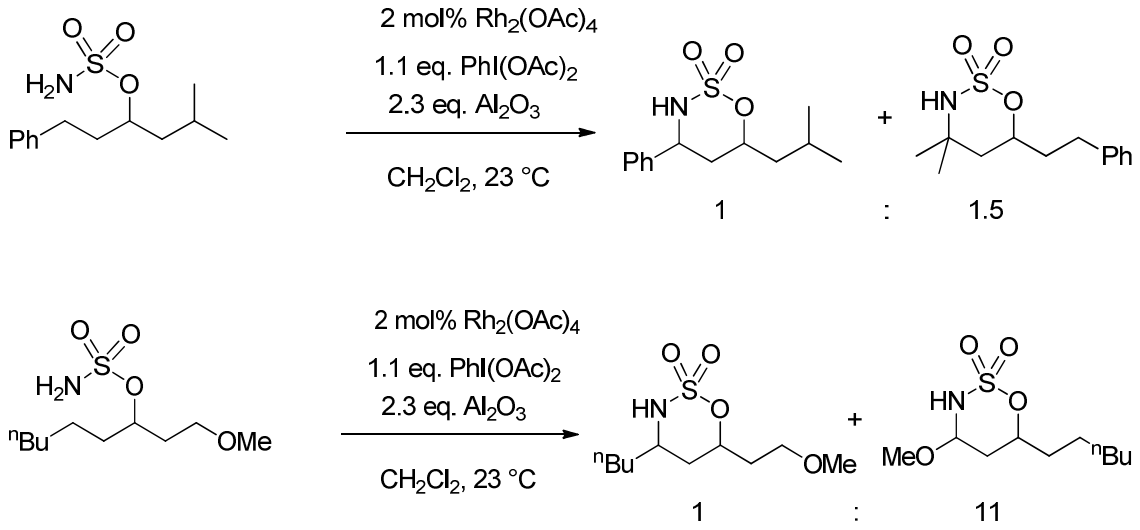
It is possible to synthesise five-,[123] seven- and even eight-[124] membered sulfone containing heterocycles using this methodology by carefully designing the substrate that is to undergo C–H amination (**Scheme 1.29**).





Scheme 1.29[123,124] (*structure of Ru[(tpfpp)(CO)] reproduced from reference*[123])

In general, amination is favoured into tertiary C–H bonds over secondary C–H bonds. In addition, it has been found that nitrene insertion is preferred into a C–H bond that is activated by an electron donating group α to the site of insertion.[52] In a study conducted by Du Bois it was discovered that for $Rh_2(OAc)_4$ catalysed reactions of sulfamate substrates C–H amination occurs preferentially into a 3° > α-ethereal, α-aminal, benzylic > 2° >> 1° (**Scheme 1.30**).[125] In this publication, Du Bois and co-workers highlights that, in general, trends observed for rhodium catalysed C–H amination reactions are analogous to many of the trends observed for rhodium catalysed carbenoid insertion reactions.

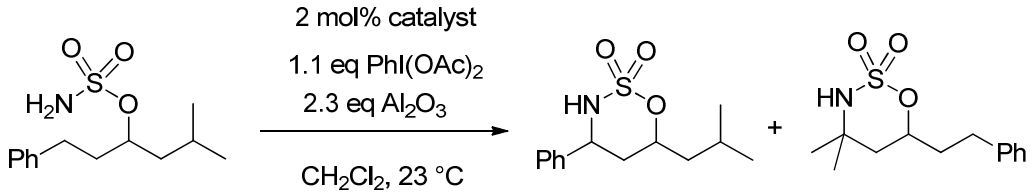


Scheme 1.30[125]

The nature of the catalyst employed can also have a significant impact on the outcome of an intramolecular C–H amination reaction. It has been found experimentally that the catalyst structure can have an effect on the selectivity of the reaction. For example, the reaction represented in **Table 1.15** demonstrates that a change in catalyst can alter the reaction product distribution. In all cases presented in **Table 1.15 product b** is the major isomer formed, however significantly more of **product b** than **product a** is formed when

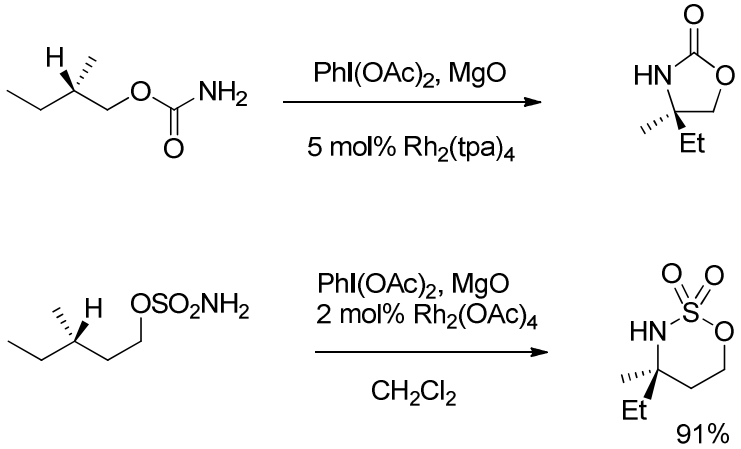
$Rh_2(tpa)_4$ is employed as a catalyst (**Table 1.15**, entry 4), which implies that steric interactions between the substrate and catalyst are one of the factors dictating the product outcome. The fact that the structure of the catalyst employed can affect the selectivity of the reaction suggests that a rhodium bound active oxidant is present.[125]

Table 1.15 *Rhodium catalysed intramolecular C–H amination reactions*[125]



Entry	Catalyst	Product a	Product b
1	$Rh_2(OAc)_4$	1	1.5
2	$Rh_2(O_2C$*t*-Bu$)_4$	1	1.5
3	$Rh_2(esp)_2$	1	7
4	$Rh_2(tpa)_4$	1	14

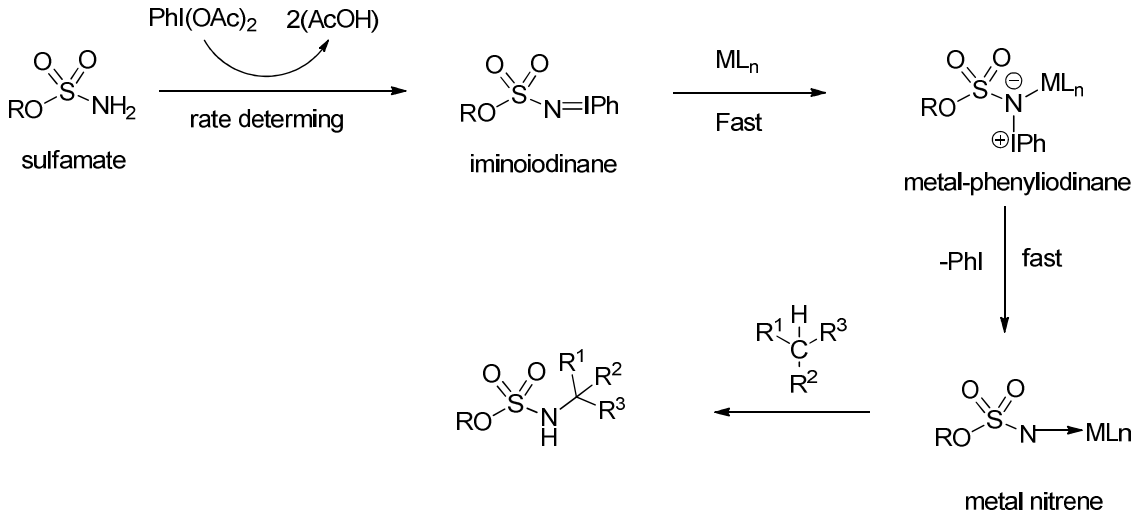
Another important aspect of rhodium catalysed C–H amination is that C–N bond formation occurs with retention of stereochemistry (**Scheme 1.31**).[115,116] This is an extremely important observation as it leads to the conclusion that a concerted asynchronous C–H insertion of a singlet nitrene is the most likely reaction pathway occurring.



Scheme 1.31[115,116]

The mechanism of intramolecular C–H amination and intramolecular aziridination has been the topic of considerable speculation and debate. The generation of a metal nitrene

is believed to occur *via* three steps; initially an iminoiodinane is formed *in situ* from the starting sulfamate, which is the rate determining step. This is subsequently followed by the generation of a metal-phenyliodinane intermediate, which upon loss of iodobenzene forms a metal nitrene intermediate (**Scheme 1.32**). Both the metal-phenyliodinane and the metal nitrene intermediates have been put forward as the species that result in nitrene delivery.[8] However, in 2007, Che and co-workers reported that the active species that is responsible for nitrene delivery is the metal nitrene species, as the metal-phenyliodinane intermediate decomposes to the metal nitrene intermediate due to an increase in entropy,[126] with Du Bois and co-workers further substantiating these claims in 2009.[125]



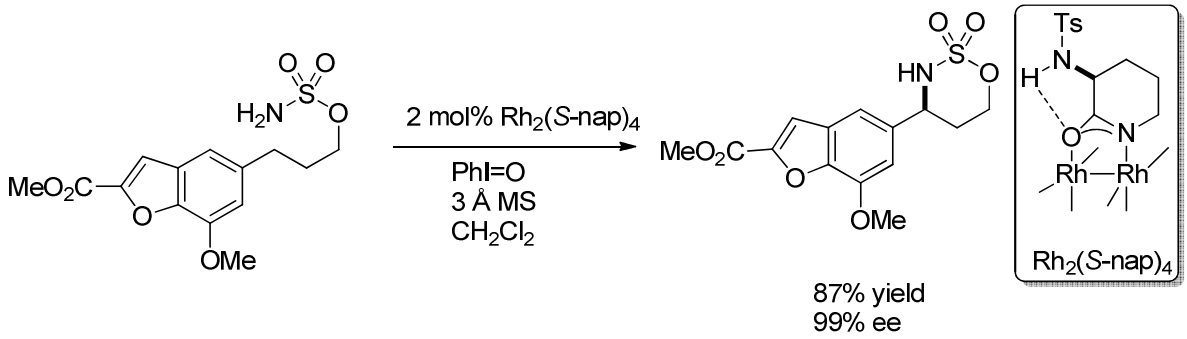
Scheme 1.32[127]

The C–H activation/ C–N bond formation steps can occur *via* two main pathways; either *via* a singlet, concerted highly asynchronous pathway or a triplet stepwise pathway. Reports in the literature exist for both pathways; a carboradical intermediate was proposed for manganese-porphyrin[128] and ruthenium-imido[121] catalysed intermolecular C–H amination reactions, whereas a concerted C–H amination process was put forward for rhodium(II) catalysed intramolecular C–H amination reactions.[116] As rhodium(II) catalysts had been shown to be the most versatile catalysts for C–H amination reactions, Che and co-workers carried out a DFT investigation into the rhodium(II) catalysed intramolecular C–H amination reactions of carbamates.[126] They reported that while the singlet and triplet states of $Rh^{II,II}$-NR^1 had similar stabilities, it was the singlet pathway that was preferred due to free energy of activation, resulting in retention of chirality at the C–H bond undergoing insertion as previously discussed. Recently, a mechanistic investigation was carried out into the Rh(II) catalysed intramolecular C–H amination and

aziridination of 4-pentenylsulfamate, suggesting that a combination of singlet and triplet nitrene species are involved in the process.[127] The mechanistic pathway of nitrene reactions are similar to carbene reactions, however, for nitrene reactions the situation is more complex; recent mechanistic studies suggest that these reactions can proceed *via* a singlet, triplet or a combination of the two.

1.4.5 Enantioselective intramolecular C–H amination reactions of α-sulfonyl nitrenes

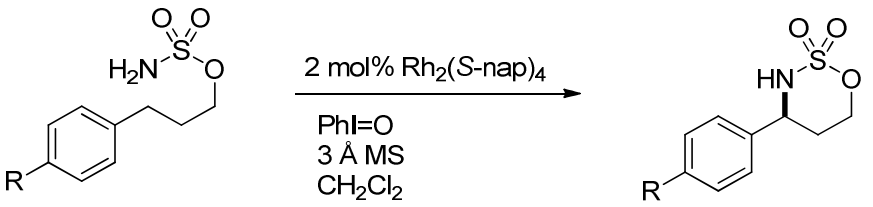
Since investigations into C–H amination reactions of α-sulfonyl nitrenes began, significant advances have been made in the enantioselectivities of these transformations, which have been the subject of a number of reviews.[2,8,10,105] In the subsequent section a number of the most significant achievements in the field will be presented. Following on from initial publications where Du Bois and co-workers reported effective intramolecular C–H amination reactions using achiral catalysts,[51,114] enantioselectivities of up to 99% ee were reported in the chiral rhodium carboxamidate catalysed intramolecular C–H amination reactions of sulfamate esters with Rh_2(*S*-nap)$_4$ as catalyst (**Scheme 1.33**).[129]



Scheme 1.33[129]

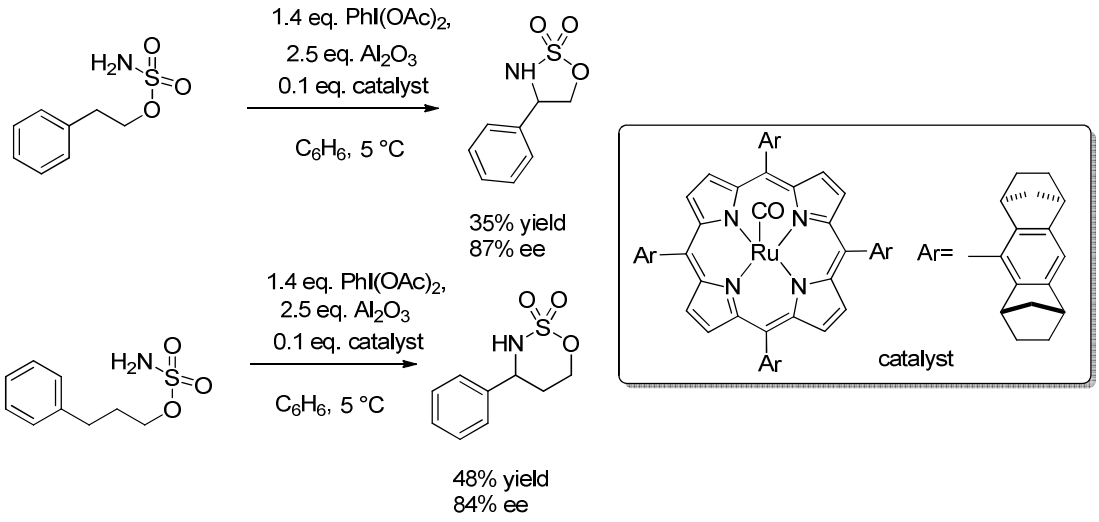
Enantioselectivities remained high when a benzene ring was present α to the C–H insertion site (**Table 1.16**, entry 1), however, substitution at the *para* position caused a decrease in enantiopurity, with *p*-CF_3 resulting in a modest 56% ee (**Table 1.16**, entry 3), highlighting the impact of electronic variation at the site of insertion.

Table 1.16 *Enantioselective C–H animation using chiral rhodium catalysts*[129]



Entry	R	α-diazosulfone	Product	Yield (%)	ee (%)
1	H	**137**	**138**	85	92
2	OMe	**139**	**140**	89	83
3	CF_3	**141**	**142**	50	56

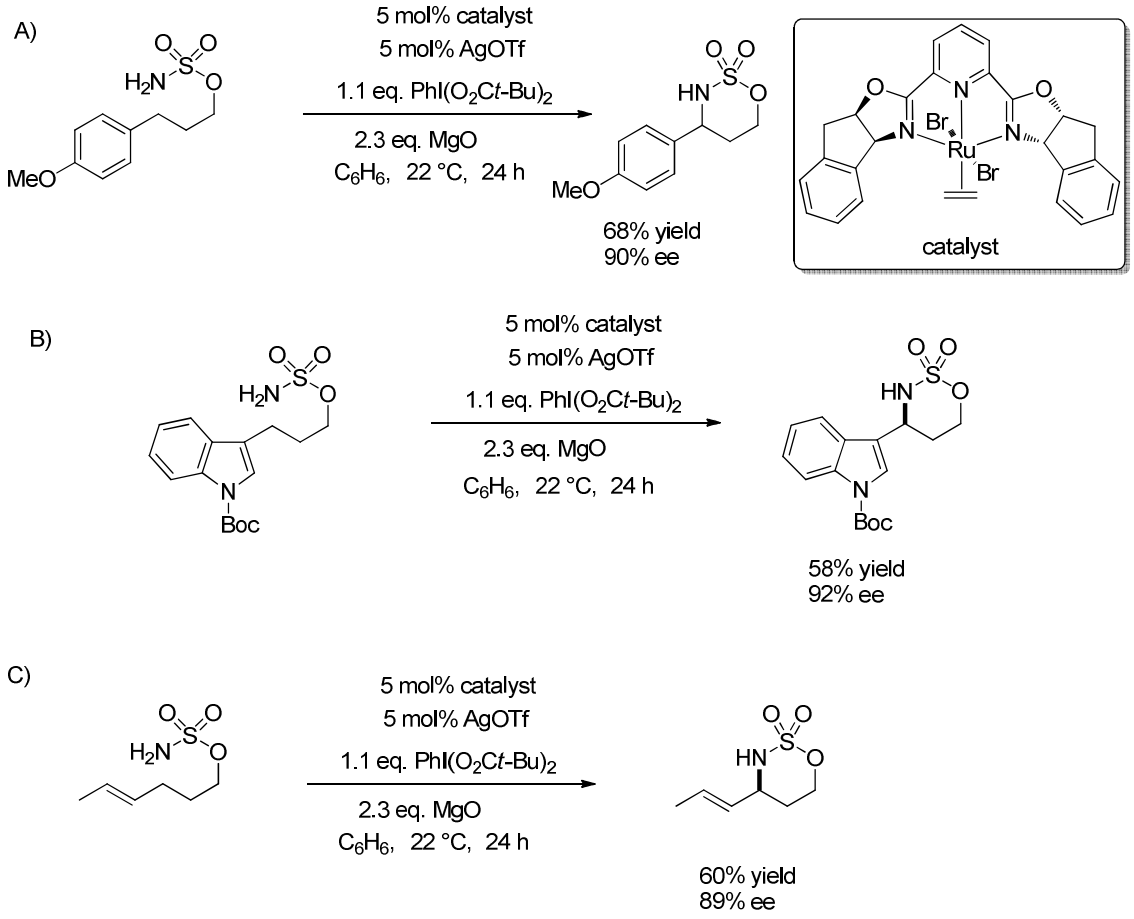
Che and co-workers examined intramolecular amidination reactions of sulfamate esters employing ruthenium porphyrins and achieved relatively high enantioselectivities for both five- and six-membered ring systems.[123] As is clearly illustrated in **Scheme 1.34**, the formation of six-membered rings is favoured, however five-membered ring syntheses will occur when the formation of the former is not possible, in line with the observation in C–H insertion of α-diazosulfones described by Flynn and Maguire.[27]



Scheme 1.34[123]

High enantioselectivities were achieved for the use of a cationic ruthenium(II)-pybox catalyst for asymmetric intramolecular benzylic and allylic amination of nitrenes. Interestingly, aziridination did not take place in the case of the reaction represented in **Scheme 1.35 (C)**: C–H insertion was the sole reaction pathway observed. This is in contrast to rhodium(II) catalysed reactions; in cases where substrates can undergo C–H

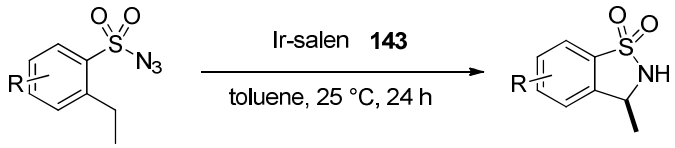
amination and aziridination, the reaction outcome is dependent on the nature of the substrate and catalyst ligand employed (See **Section 1.4.4**). Competition between cyclopropanation and C–H insertion of α-diazocarbonyl compounds is also observed, which will be discussed in **Section 1.5.3**.

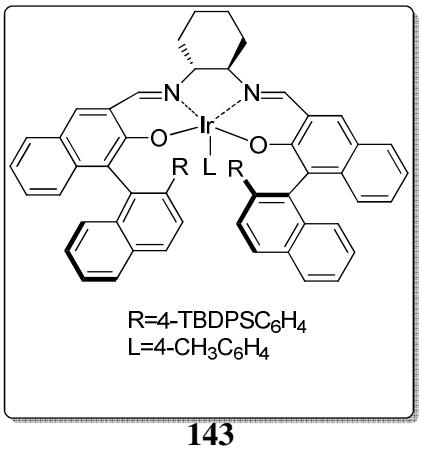


Scheme 1.35

Katsuki and co-workers reported the use of chiral iridium-salen complexes in the intramolecular C–H amination reactions of 2-ethylbenzenesulfonyl azide, and its analogues, in sultam synthesis, achieving enantiopurities of up to 92% ee in five-membered sultam synthesis. Interestingly, when these substrates underwent cyclisation with an ethyl group at the 2 position, the reaction was highly regioselective for five-membered ring synthesis and there was no evidence for six-membered ring formation (**Table 1.17**).[40]

Table 1.17 *Chiral iridium-salen* catalysed *intramolecular C–H amination reactions of 2-ethylbenzenesulfonyl azide* [40]



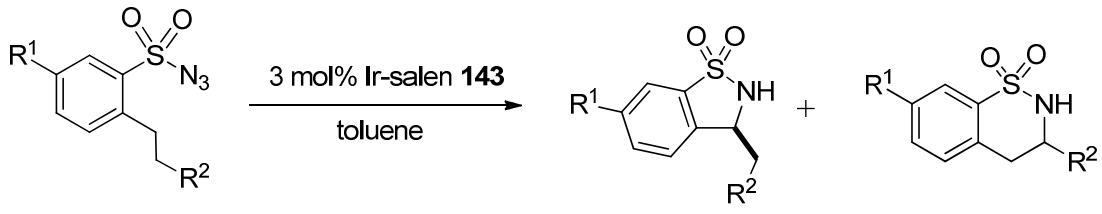


143

Entry	R	Catalyst mol%	Yield (%)	ee (%)
1	-	3	77	92
2	5-OMe	5	71	93
3	5-Br	5	63	85
4	5-NO_2	5	49	79

When the ethyl group was replaced with a propyl or an phenethyl group, the reaction was less selective for five-membered ring formation, with the major product in both cases being a six-membered ring. Enantioselectivities of up to 99% ee were achieved in six-membered ring synthesis (**Table 1.18**, entry 2).[40] Similarly high enantioselectivities were obtained for the copper-bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo sulfones in *cis* thiopyran synthesis.[27]

Table 1.18 *Chiral iridium-salen catalysed intramolecular C–H amination reactions*[40]

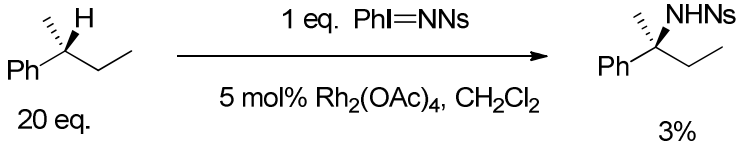


α β

Entry	R^1	R^2	Ratio α:β	ee (%)
1	Et	H	α only	91% ee (α)
2	*n*-Pr	CH_3	1 : >20	99% ee (β)
3	H	Ph	1 : 2	5% ee (α), 98% ee (β)

1.4.6 Intermolecular C–H amination reactions: Background

Many of the mechanistic features and the general trends discussed for the intramolecular C–H amination reaction (**Section 1.4.5**) also apply to the intermolecular version of the reaction.[2,125–127] For example C–H amination reactions proceed with retention of stereochemical integrity (**Scheme 1.36**).[2]



Scheme 1.36

In addition, it is also well established that intermolecular C–H amination into activated C–H bonds is preferred. The favored insertion sites for this transformation are indicated in **Figure 1.5**.[130]

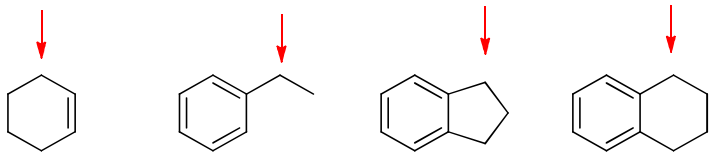
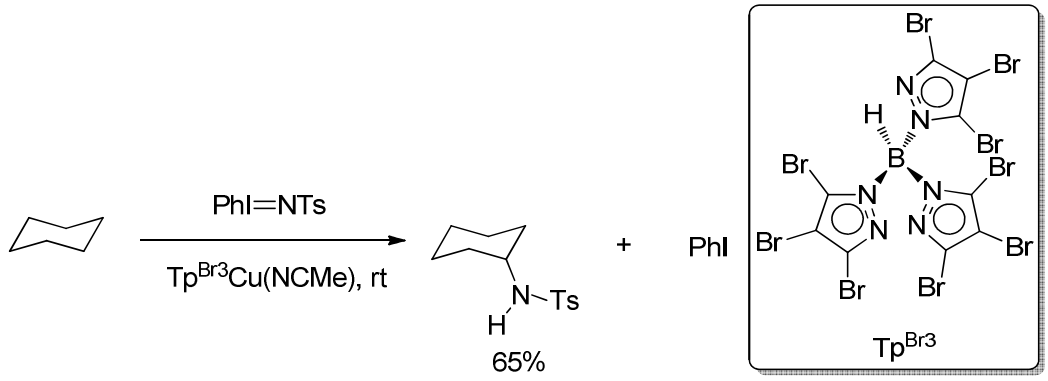


Figure 1.5[130]

However, examples of intermolecular C–H amination into unactivated C–H bonds do appear in the literature. For example, the copper-homoscorpionate catalyst

$TpBr_3Cu(NCMe)$ was reported to successfully catalyse conversion of cyclohexane into *N*-(*p*-tolylsulfo-nyl)aminocyclohexane with PhINTs in a 65% yield (**Scheme 1.37**).



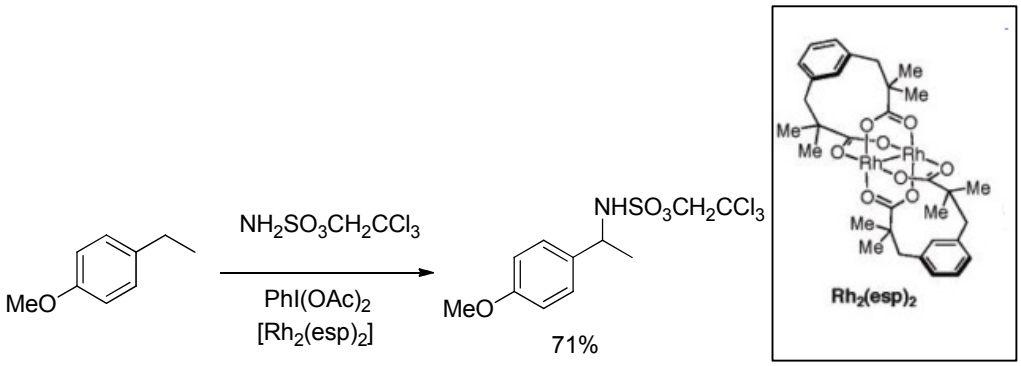
Scheme 1.37

As has already been discussed in **Section 1.4.3**, the intermolecular C–H insertion reaction of α-diazocarbonyl compounds is significantly more challenging than the intramolecular variant of the reaction, being characterized by low selectivities until relatively recently.[4,8] It was discovered that fine-tuning the structure of the metal and the carbene could lead to a selective, synthetically useful process.[4,8,131] In terms of carbene structure, the presence of an electron withdrawing substituent on the carbene is essential for reactivity. It has also been found that the same is true for nitrenes; the presence of an electron withdrawing group is needed to generate an electrophilic species capable of C–H insertion. One key difference between carbenes and nitrenes in this respect is that the presence of a second substituent on the carbene allows for further modulation of reactivity; employing an electron donating group can potentially lead to increased selectivity (**Figure 1.6**).[132]



Figure 1.6

Despite this additional limitation, significant advances have been made in the area of intermolecular C–H amination reactions. Du Bois and co-workers showed that a selective nitrene source for this transformation could be generated from trichloroethylsulfamate in the presence of phenyliodinane diacetate, with up to a 71% yield achieved, for insertion into a benzylic C–H bond (**Scheme 1.38**).[114]

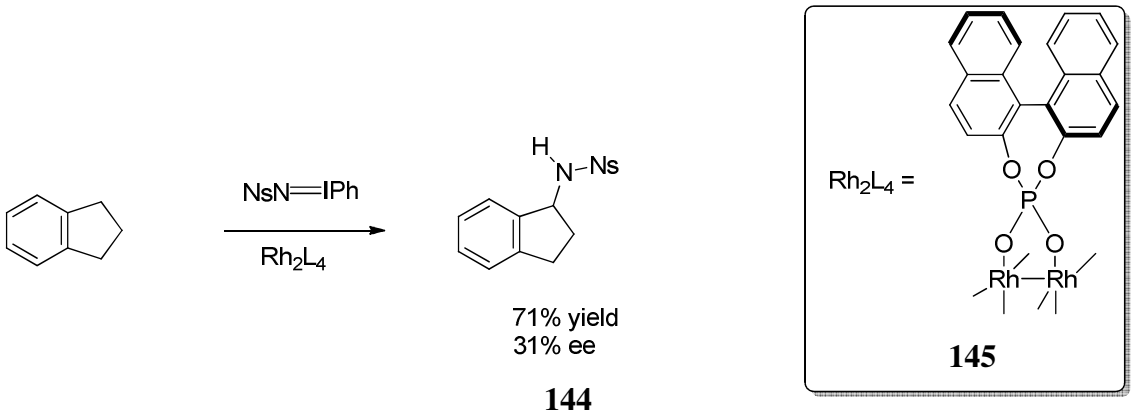


Scheme 1.38 (*$Rh_2(esp)_2$ reproduced from reference*[114])

1.4.7 Enantioselective intermolecular C–H amination reactions of α-sulfonyl nitrenes

Intermolecular C–H amination can be an effective transformation, especially at activated sites. This has been particularly explored using enantioselective catalysts.

The first report of an asymmetric intermolecular C–H amination was made by Müller and co-workers, achieving 31% ee in the synthesis of **144** when indan underwent amination in the presence of a chiral rhodium catalyst **145** (**Scheme 1.39**).[133]

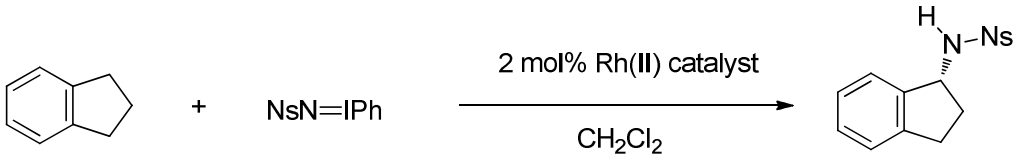


Scheme 1.39[133]

Hashimoto carried out a more extensive investigation into the chiral rhodium catalysed intermolecular C–H amination reactions of indane (**Table 1.19**).[134] The results of an initial catalyst screen [including Rh_2(*S*-PTTL)$_4$, Rh_2(*S*-PTA)$_4$, Rh_2(*S*-PTV)$_4$ *etc*] revealed that Rh_2(*S*-PTTL)$_4$ was the most promising catalyst, resulting in enantioselectivities of up to 28% ee (**Table 1.19**, entry 1). Alteration of Rh_2(*S*-PTTL)$_4$ was subsequently made by replacing the four hydrogen atoms on the phthalimido group with electron withdrawing

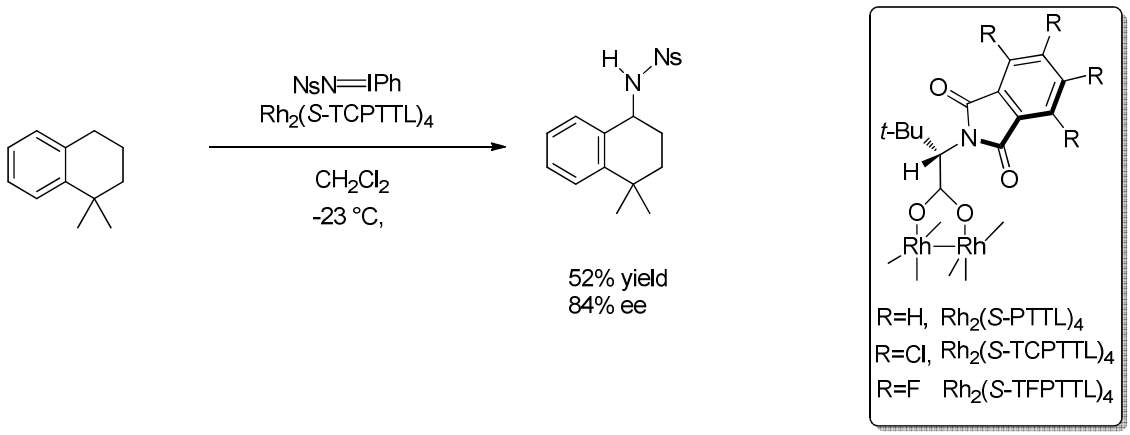
groups. Replacing hydrogen with fluorine [Rh_2(*S*-TFPTTL)$_4$] resulted in an increase in enantioselectivity from 28 to 54% ee (**Table 1.19**, entries 1 and 3), with a further increase to 66% ee being observed when hydrogen was replaced with chlorine [Rh_2(*S*-TCPTTL)$_4$] (**Table 1.19**, entry 4). In an effort to improve this result further reactions were conducted at lower temperatures; a reaction was carried out at –23 °C and –40 °C in the presence of Rh_2(*S*-TCPTTL)$_4$ catalyst (**Table 1.19**, entries 5 and 6). Both temperature decreases resulted in an increase in enantioselectivity, however, –23 °C was deemed to be the optimum reaction temperature resulting in a reasonable time, yield and enantioselectivity (**Table 1.19**, entry 5).

Table 1.19 *Amination of indane employing chiral rhodium catalysts*[134]



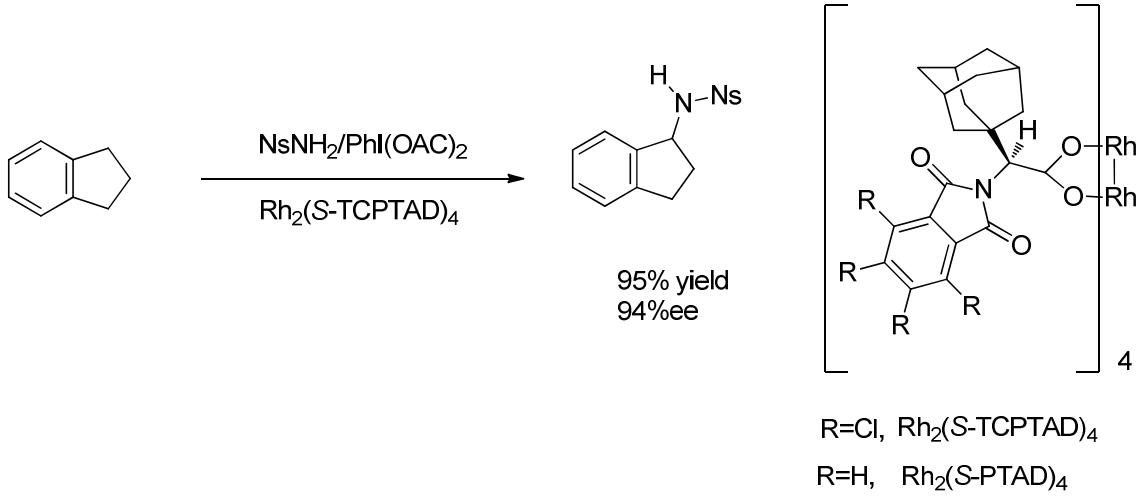
Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	Rh_2(*S*-PTTL)$_4$	0	0.5	79	28
2	Rh_2(*S*-PTTL)$_4$	–23	24	53	27
3	Rh_2(*S*-TFPTTL)$_4$	0	0.5	89	54
4	Rh_2(*S*-TCPTTL)$_4$	0	0.5	87	66
5	Rh_2(*S*-TCPTTL)$_4$	–23	6	82	70
6	Rh_2(*S*-TCPTTL)$_4$	–40	12	51	73

With the optimum catalyst conditions in hand, Hashimoto and co-workers applied the catalyst to a wider range of substrates, demonstrating that enantioselectivities of up to 84% ee could be attained using Rh_2(*S*-TCPTTL)$_4$ as a catalyst (**Scheme 1.40**).[134]



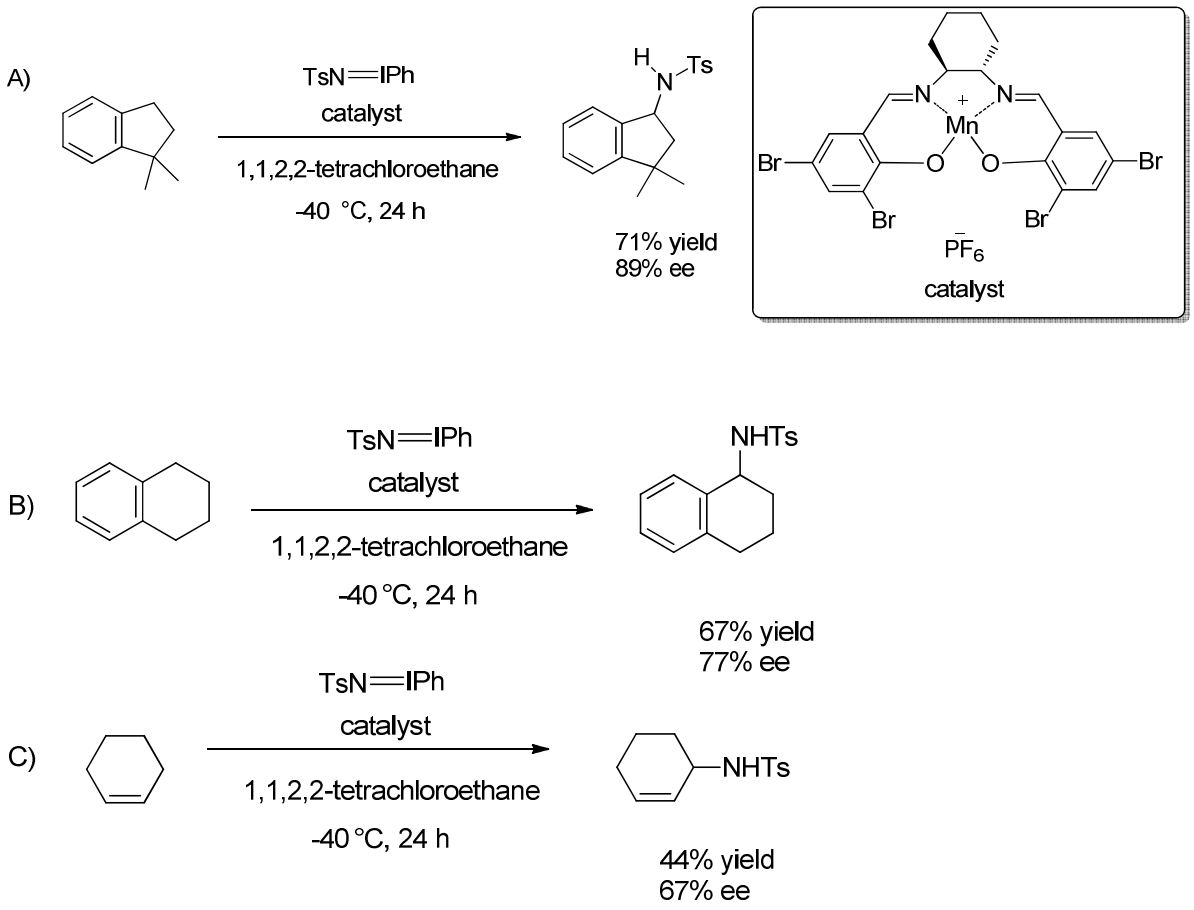
Scheme 1.40[134]

Building on this work, Davies further extended the catalyst scope. Davies and Reddy modified Rh_2(*S*-PTAD)$_4$ by replacing the four protons with chlorine atoms. An increase in enantioselectivity from 59% ee to 94% ee was observed when Rh_2(*S*-TCPTAD)$_4$ was used instead of Rh_2(*S*-PTAD)$_4$ (**Scheme 1.41**).[39]



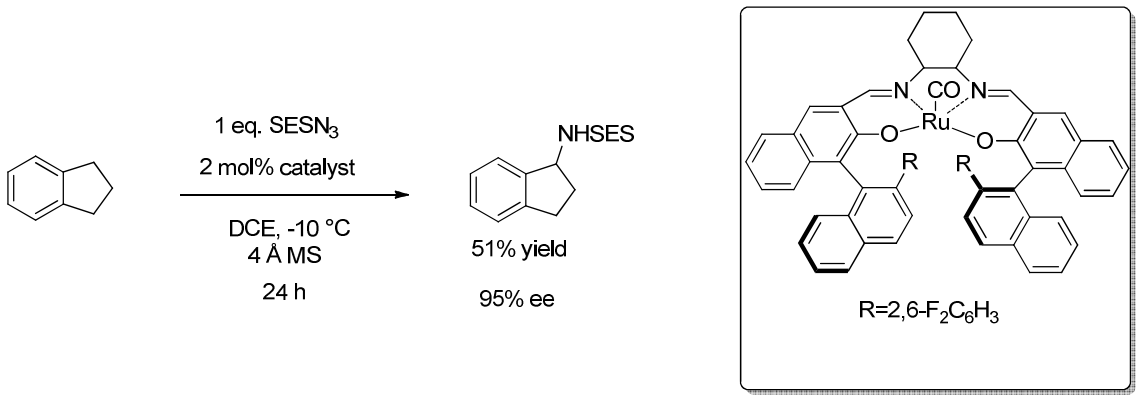
Scheme 1.41[39]

Enantioselectivities of up to 89% ee have been reported by Katsuki and Kohmura in the asymmetric intermolecular amidation reactions of 1,1-dimethyl indane, catalysed by (salen)manganese(III) complexes (**Scheme 1.42 A**)[122] It was found that including electron withdrawing groups, such as bromine, on the ligand had a positive effect on enantioselectivity.



Scheme 1.42[122]

Katsuki and co-workers demonstrated regio- and enantioselective intermolecular C–H amination, employing ruthenium(CO)-salen complexes as catalysts, achieving enantioselectivities of greater than 95% ee (**Scheme 1.43**).[135]

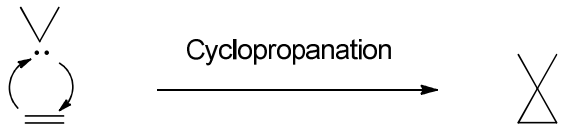


Scheme 1.43[135]

1.5 Cyclopropanation and Aziridination

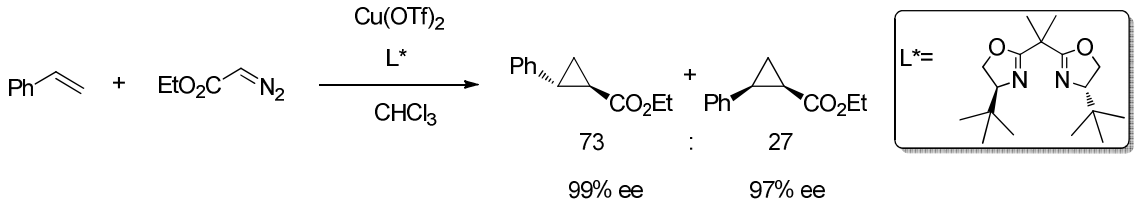
1.5.1 Inter- and intramolecular cyclopropanation reactions of α-diazocarbonyl compounds - Background

Transition metal catalysed cyclopropanation reactions of α-diazocarbonyl compounds are a very effective method for the synthesis of the cyclopropane moiety;[1,5,12–14,136,137] owing to the fact that both the inter- and intramolecular reaction can occur with excellent diastereo- and enantiocontrol. A number of transition metals have been reported to catalyse cyclopropanation reactions effectively; copper, rhodium, iridium, iron, cobalt, palladium and ruthenium can be counted in their number.[56,138–149] Intermolecular cyclopropanation reactions are believed to proceed *via* the concurrent formation of two new carbon carbon bonds to the "carbene" carbon by means of a concerted process (**Scheme 1.44**).[1] Generally the reaction is accepted to occur *via* a singlet carbene.



Scheme 1.44

A wide range of catalysts have been applied to intermolecular cyclopropanation producing cyclopropanes with excellent enantioselectivities, including complexes of rhodium, cobalt, ruthenium and iridium.[25,150–153] However, copper based catalysts have proved to be particularly useful for this transformation,[82,149,154–156] with enantioselectivities of up to 93% ee being achieved with copper-semicorrin catalysts[157] and up to 99% ee in the presence of copper-bisoxazoline catalysts (**Scheme 1.45**).[155]

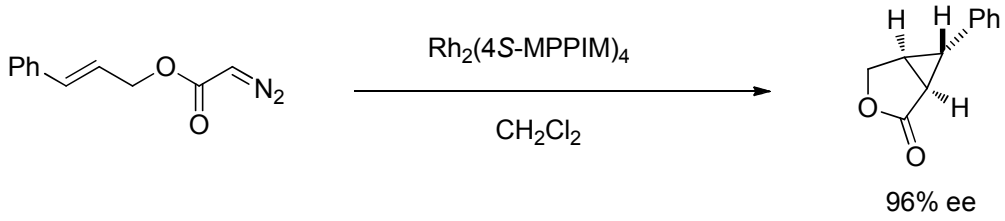


Scheme 1.45

As the transition state for the intermolecular and intramolecular cyclopropanation reaction are different, owing to additional constraints in the intramolecular version,

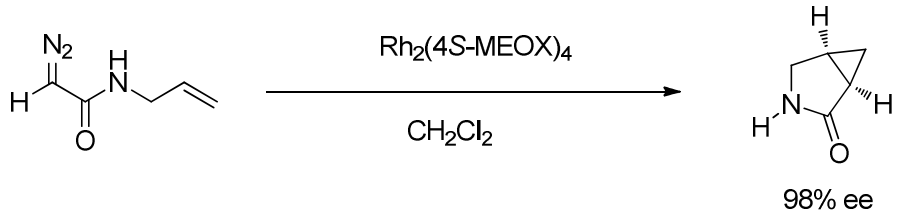
catalysts that give rise to excellent enantio- and diastereocontrol in the intermolecular reaction are not guaranteed to have the same effect in the intramolecular reaction.

The first report of an intramolecular cyclopropanation reaction was made in 1961 and since then a substantial number of reports have appeared in the literature, exploring a variety of different substrates and catalysts. Chiral rhodium carboxylates have emerged as a powerful catalyst for this transformation with enantioselectivities of greater than 95% ee being reported (**Scheme 1.46**).[68,158,159]



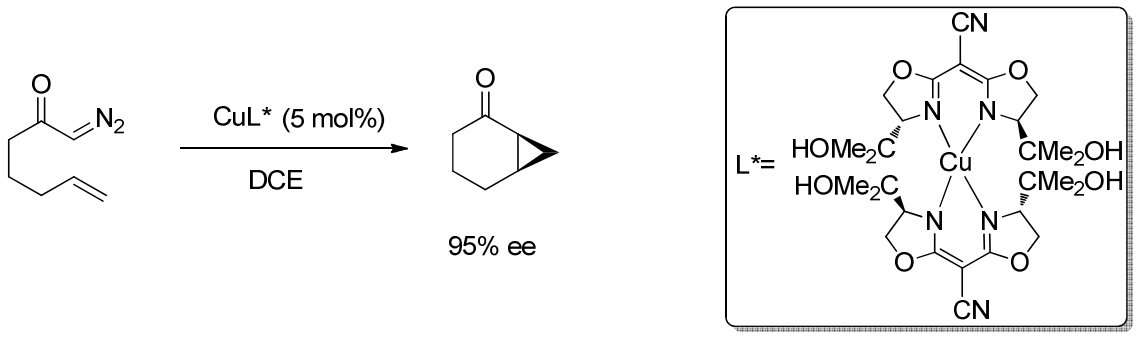
Scheme 1.46

Chiral rhodium carboxamidates[159–161] and chiral rhodium complexes that contain aryl *ortho*metalated aryl phosphine ligands have also been employed, giving rise to cyclopropanation products with enantioselectivities of greater than 90% ee. For example, the chiral rhodium carboxamidate catalyst $Rh_2(4S\text{-MEOX})_4$ has been employed in ɣ-lactam synthesis, with enantioselectivities of up to 98% ee being achieved (**Scheme 1.47**).[159]



Scheme 1.47

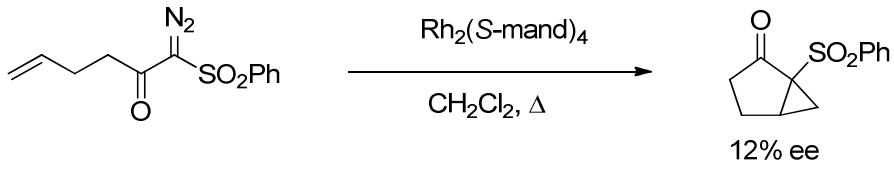
Copper catalysts have also been utilised effectively in the intramolecular cyclopropanation reactions of α-diazocarbonyl compounds, with enantioselectivities of up to 95% ee being obtained when a chiral copper-semicorrin species was employed as a catalyst for this transformation (**Scheme 1.48**).[162]



Scheme 1.48

1.5.2 Intramolecular cyclopropanation reactions of α-diazosulfones

Initial reports of the use of α-diazosulfones for the intramolecular C–H insertion reaction were made independently by Monteiro[75] and McKervey,[76] with the first enantioselective version of this report made by McKervey and co-workers, who achieved a 12% ee for the rhodium mandelate catalysed cyclopropanation reaction of α-diazosulfone **146** (**Scheme 1.49**).[75,76]

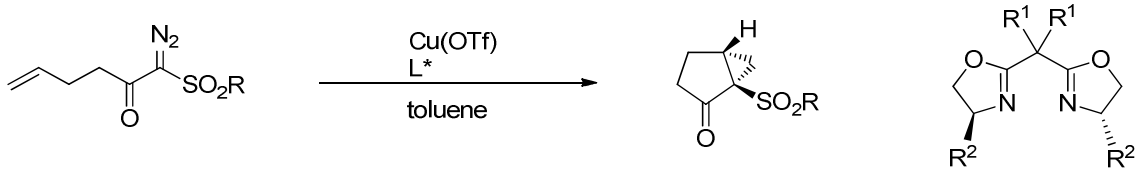


146 **146**

Scheme 1.49[76]

Nakada's team have conducted an extensive investigation into intramolecular cyclopropanation of α-diazo-β-keto sulfones employing copper-bisoxazoline catalysts, making significant progress in achieving high enantioselectivities for this transformation.[32] In the preliminary investigation, it was discovered that α-diazosulfone **147** bearing a bulky mesityl sulfone group gave rise to cyclopropanation products with higher enantiopurities (72–93% ee, **Table 1.20**, entries 4–6) than α-diazosulfone **146** containing the phenyl sulfone moiety (65–75% ee, **Table 1.20**, entries 1–3). A number of commercially available bisoxazoline ligands were examined, with ligand **148**, containing a benzyl substituent on the linker carbon, giving rise to the best result (93% ee, **Table 1.20**, entry 6)

Table 1.20 *Asymmetric copper catalysed cyclopropanation reactions of α-diazosulfones* **146** *and* **147**



146 R=Ph
147 R=Mes

149 R=Ph
151 R=Mes

150 R^1 =Me, R^2=*i*-Pr
152 R^1 =Me, R^2=Bn
148 R^1 =Bn, R^2=*i*-Pr

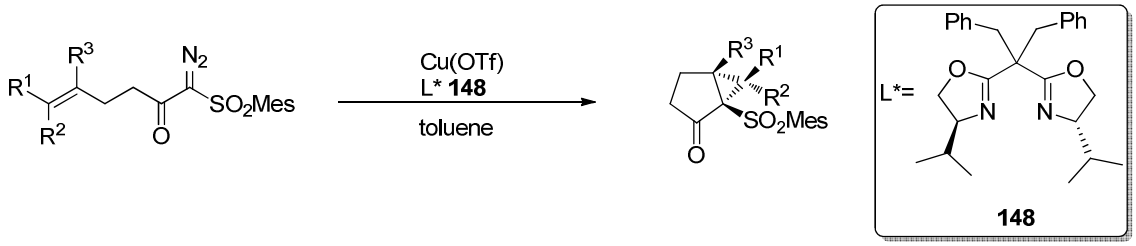
Entry	R	L*	Temperature	Time (h)	Yield (%)	ee (%)
1	Ph	**150**	rt	2	91	65 (1*R*)
2	Ph	**152**	rt	2	67	75 (1*R*)
3	Ph	**148**	rt	2	61	73 (1*R*)
4	Mes	**150**	50 °C	1.5	93	83 (1*R*)
5	Mes	**152**	rt, 50 °C[a]	2, 2[a]	78	72 (1*R*)
6	Mes	**148**	rt, 50 °C[a]	2, 2.5[a]	87	93 (1*R*)

a. The reaction temperature was raised from rt to 50 °C after 2 h, and remained at this temperature for an additional 2 h (entry 5) and 2.5 h (entry 6).

Further substrate modifications were explored; the substitution on the alkene bond was altered to investigate the impact that this would have on the enantiopurity of the cyclopropane products. While substitution on the terminal position on the alkene did not alter the enantioselectivity greatly (93% ee, **Table 1.20**, entry 6, *cf.* 92% ee **Table 1.21**, entry 3), substitution on the internal position of the alkene had a positive outcome, with

98% ee being the highest value attained on placing either a methyl or bromo substituent on the internal position of the double bond (**Table 1.21**, entries 1–2).

Table 1.21 *Asymmetric copper catalysed cyclopropanation reactions of α-diazosulfones* **153-156**

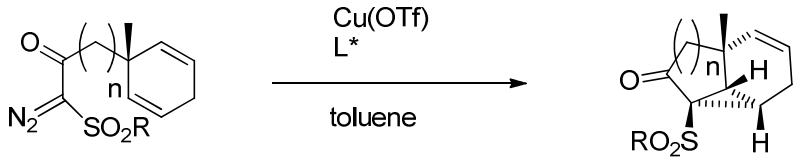


Entry	R^1	R^2	R^3	α-diazosulfone	cyclo-propane	Temp	Time (h)	Yield (%)	ee (%)
1	H	H	Me	**153**	**157**	50 °C	2	90	98 (1*R*)
2	H	H	Br	**154**	**158**	50 °C	2.5	63	98 (1*S*)
3	Me	Me	H	**155**	**159**	rt	5	84	92 (1*R*)
4	H	H	CH_2OTr	**156**	**160**	rt, 50 °C, 70 °C	3.5, 13, 7	98	91 (1*R*)

a. The reaction temperature was raised from rt to 50 °C after 3.5 h, it remained at this temperature for 13 h, and was then raised again to 70 °C where it remained for an addition 7 h.

The synthesis of tricyclic compounds was subsequently investigated (**Table 1.22**, entries 1-6). For each of the three cyclopropane products **161**, **162** and **163** presented on **Table 1.22**, excellent enantiocontrol was achieved in each case with either bisoxazoline ligand **150** or **148**. When n=1, ligand **148** resulted in the highest level of enantiocontrol (**Table 1.22**, entry 2), whereas when n=2, ligand **150** gave the best result (**Table 1.22**, entries 3 and 5), suggesting a specific substrate-sulfone ligand combination is required to achieve the best results.[32]

Table 1.22 *Asymmetric copper catalysed cyclopropanation reactions of α-diazosulfones* **164-166**

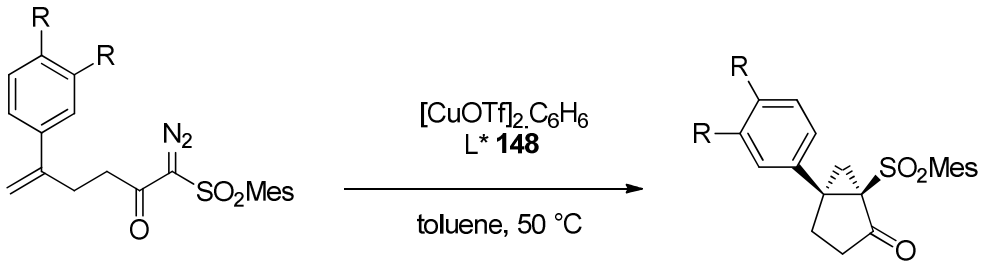


Entry	R	n	α-diazosulfone	cyclo-propane	L	Temp	Time (h)	Yield (%)	ee (%)
1	Mes	1	**164**	**161**	**150**	rt, 50 °C	2, 20	76	79
2	Mes	1	**164**	**161**	**148**	rt, 50 °C	1, 27	61	93
3	Ph	2	**165**	**162**	**150**	rt	3.5	78	92
4	Ph	2	**165**	**162**	**148**	rt, 50 °C	1, 2	37	90
5	Mes	2	**166**	**163**	**150**	rt	27	69	97
6	Mes	2	**166**	**163**	**148**	rt, 50 °C	1, 29	7	87

a. The reaction temperature was raised throughout the course of the reaction. The time that the reaction spent at each temperature is indicated in the above Table through the use of a comma.

An investigation was also carried out into the copper catalysed cyclopropanation reactions of 5-aryl-1-diazo-1-mesitylsulfonyl-5-hexen-2-ones. In this instance, the substituent on the 5-aryl group has a substantial impact on the enantiocontrol of the reaction; namely when the aryl ring is not substituted enantioselectivities of up to 96% ee are seen, however, when methoxy subtituents were employed no enantioinduction was observed (**Table 1.23**, entries 1–2).[163]

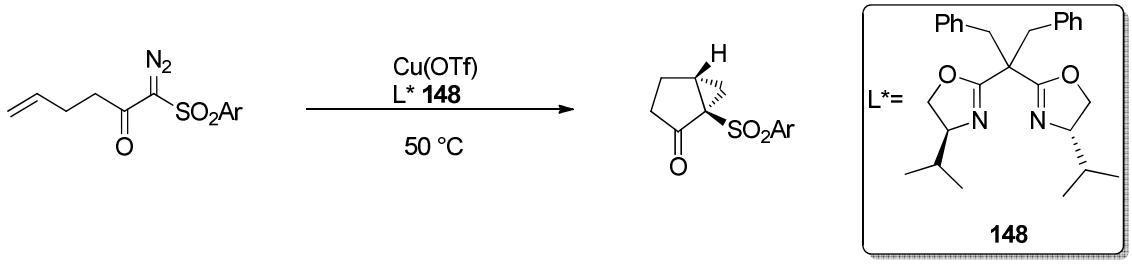
Table 1.23 *Asymmetric copper catalysed cyclopropanation reactions of α-diazosulfones* **167**, **168**

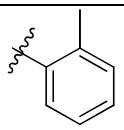
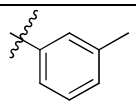
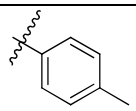
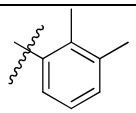
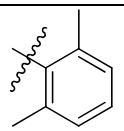
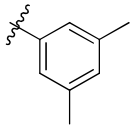


Entry	R	α-diazosulfone	cyclopropane	Yield (%)	ee (%)
1	H	**167**	**169**	95	96 (1*R*)
2	OMe	**168**	**170**	55	0

A subsequent study was carried out into the structure-enantioselectivity relationship of cyclopropanation reactions of α-diazosulfones bearing methyl substituted phenyl groups.[164] The outcome of this investigation is presented in **Table 1.24**. The position of the methyl group on the benzene ring has a substantial effect on the enantiopurity of the cyclopropanation products, with placement at the 2- position having a positive impact on the outcome of the enantioselectivities for this reaction (**Table 1.24**, entries 1, 4–5).

Table 1.24 *Asymmetric copper catalysed cyclopropanation reactions of α-diazosulfones* **171-176**

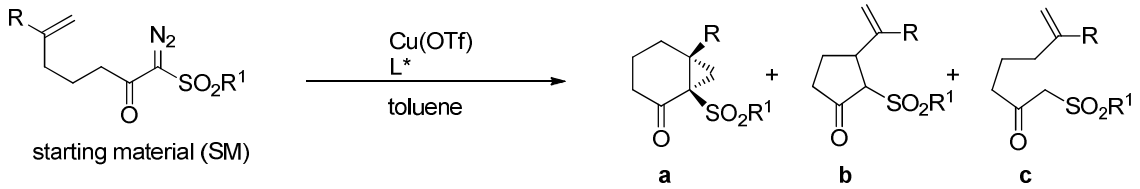


Entry	Ar	α-diazosulfone	cyclopropane	Yield (%)	ee (%)
1		**171**	**177**	98	86
2		**172**	**178**	97	77
3		**173**	**179**	95	69
4		**174**	**180**	82	91
5		**175**	**181**	82	91
6		**176**	**182**	91	62

Nakada and co-workers subsequently concentrated on substrates designed for six-membered ring formation.[165] Once again high enantioselecitvites were achieved for each of the cyclopropanation substrates listed in **Table 1.25** (89–98% ee); with ligand **148**

giving the best results, suggesting once again that a specific substrate-ligand interaction is at play when achieving high enantiomeric excess. While cyclopropanation was the major reaction pathway observed in all instances, there was evidence for two additional competing reaction pathways: C–H insertion and diazo reduction (**Table 1.25**). In every case, these products were isolated in minor amounts, however, their formation appears to be independent of the nature of the substrate or the ligand (**Table 1.25**).

Table 1.25 *Asymmetric copper catalysed cyclopropanation reactions of α-diazosulfones* **183-186**[165]

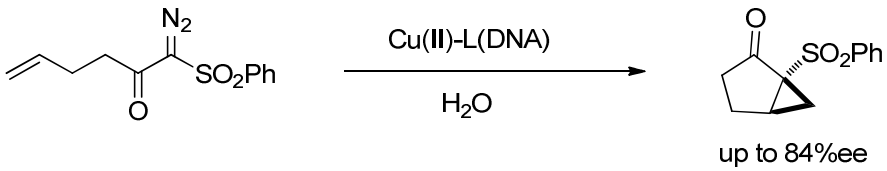


Entry	R	R^1	L^*	SM	Temp	Time (h)	Yield (%) a	ee (%) a	Yield (%) b and c (b : c)
1	H	Ph	**150**	**183**	rt	2	58	92 (1*R*)	19 (20 : 1)
2	H	Ph	**148**	**183**	rt	14	41	89 (1*R*)	14 (14 : 1)
3	Me	Ph	**148**	**184**	rt	2	62	93 (1*R*)	15 (18 : 1)
4	H	Mes	**148**	**185**	50 °C	16	31	98 (1*R*)	17 (4 : 1)
5	Me	Mes	**148**	**186**	50 °C	4	43	98 (1*R*)	15 (3 :1)

In conclusion, optimum enantioselectivities were generally achieved with the sterically demanding mesityl sulfone or 2-substituted phenyl sulfones while internal substitution on the alkene was also advantageous. In terms of ligands, the best result is achieved with **148** Excellent enantioselectivities are also achieved for six-membered ring formation, however, competition with C–H insertion is observed in this instance.

Nakada and Hirai also demonstrated the synthetic utility of the asymmetric copper catalysed intramolecular cyclopropanation reaction of α-diazosulfones, employing this transformation as a key step in the synthesis of a number of natural products, including (–)platencin.[166]

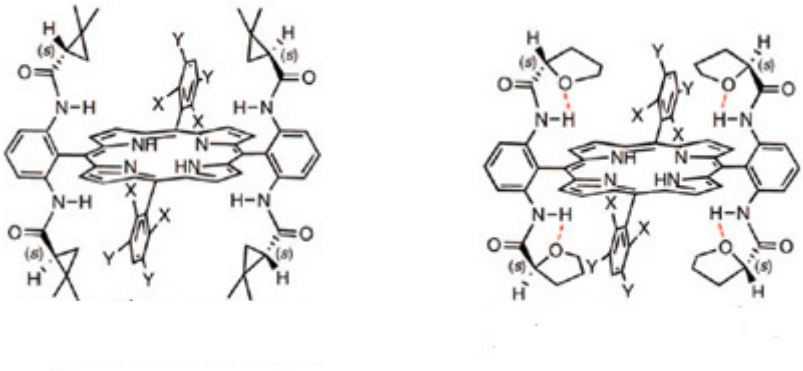
Interestingly, DNA-based organometallic catalysts have been utilised in the intramolecular cyclopropanation reaction of α-diazosulfone with enantioselectivities of up to 84% ee being achieved (**Scheme 1.50**).[167]



Scheme 1.50

1.5.3 Intermolecular cyclopropanation reactions of α-diazosulfones

While asymmetric intermolecular cyclopropanation reactions of alkenes employing diazo compounds is a well-established methodology, there is very little literature precedent for the use of α-diazosulfones as the carbene precursor.[22,168] An investigation into the cobalt catalysed cyclopropanation of styrene using 1-[(diazomethyl)sulfonyl]-4-methylbenzene **1**, employing a range of chiral porphyrin ligands (**Figure 1.7**) was carried out. These catalysts had been shown to be quite successful for cyclopropanation reactions employing diazoacetates.[169]

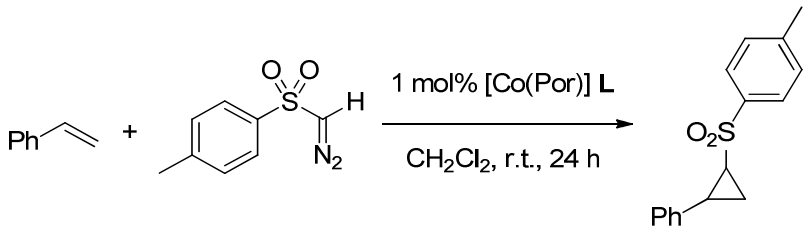


187 (3,5-Di^{t}Bu-ChenPhyrin) **188 (3,5-Di^{t}Bu-ZhuPhyrin)**
189 (2,6-DiMeO-ChenPhyrin) **190 (2,6-DiMeO-ZhuPhyrin)**

Figure 1.7 (*reproduced from reference*[22])

A range of chiral porphyrin ligands were investigated (**Table 1.26**, entries 1–4), all resulting in excellent diastereocontrol, with nearly exclusively *trans* products being formed (**Table 1.26**, entries 1–4). Ligand **190** resulted in the best enantiocontrol, resulting in the formation of cyclopropane **191**in 92% ee (**Table 1.26**, entry 4).

Table 1.26 *Cobalt catalysed intermolecular C–H insertion reactions of α-diazosulfone* **191**

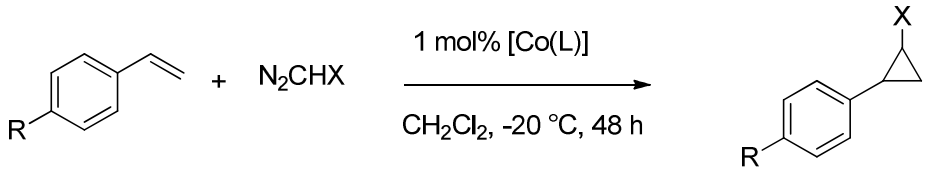


1 **191**

Entry	Ligand	Yield (%)	*trans* : *cis*	ee (%)
1	**187**	86	>99 : 1	14 (1*S*,2*R*)
2	**189**	78	>99 : 1	56 (1*S*,2*R*)
3	**188**	30	>99 : 1	54 (1*R*,2*S*)
4	**190**	99	>99 : 1	92 (1*R*,2*S*)

This catalyst system was further extended for reactions employing N_2CHMs and N_2CHNs as carbene sources (**Table 1.27**, entries 1–2) and for a variety of aromatic olefins bearing different substituents at the *para* position (**Table 1.27**, entries 3–5). In each instance, both high diastereoselectivities as well as high enantioselectivities were observed.

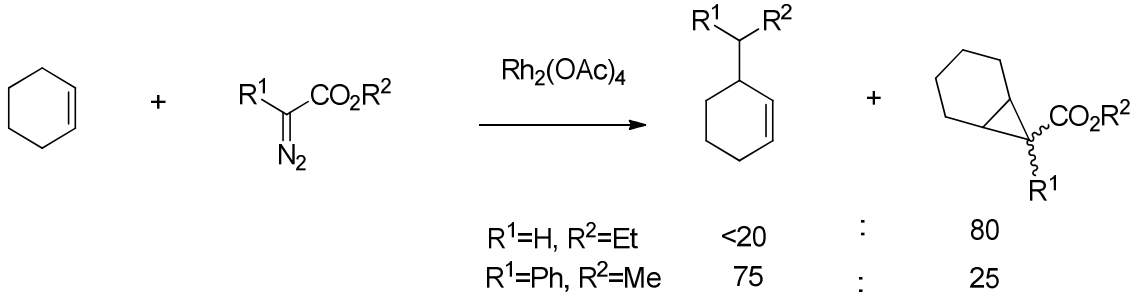
Table 1.27 *Cobalt catalysed intermolecular C–H insertion reactions of α-diazosulfones precursors*



Entry	R	L	X	Yield (%)	*trans* : *cis*	%ee
1	H	**190**	Ms	97	>99 : 1	96
2	H	**190**	Ns	99	>99 : 1	90
3	*t*-Bu	**190**	Ts	57	>99 : 1	94
4	OMe	**190**	Ts	72	>99 : 1	95
5	CF_3	**190**	Ts	88	>99 : 1	95

Note: Ms=4-methoxybenzenesulfonyl, Ns=4-nitrobenzenesulfonyl

Competition exists between cyclopropanation and C–H insertion reaction pathways where both are possible; substrate and catalyst structure ultimately dictate which is the predominant pathway. Interestingly, when two substituents are present on the α-diazocarbonyl compound, insertion is favoured significantly over cyclopropanation.[170]



Scheme 1.51

1.5.4 Nitrene-Aziridination

Significant progress has been made in aziridination reactions between nitrenes and alkenes since the pioneering report made by Kwart and Kahn in 1967, where an aziridination reaction between benzenesulfonyl azide and cyclohexene catalysed by copper-bronze was described.[108] A number of important contributions have been made to the field since then, for example Groves and Takahashi reported the aziridination of alkenes using a manganese-nitrene intermediate prepared *in situ* from a nitride complex,[171] and Mansuy and co-workers reported the Fe(III)- and Mn(III)-porphyrin catalysed aziridination of alkenes with [*N*- (*p*-toluenesulfony1)imino]phenyliodinane.[172–174] A wide variety of catalysts have been employed for this transformation, for example copper, rhodium, iron *etc*.

As is the case with the mechanism of the C–H amination of nitrenes the mechanism of aziridination is subject to speculation and debate; there are reports in the literature for a stepwise triplet mechanism or a concerted singlet pathway (**Figure 1.8**). The concerted singlet pathway is associated with retention of stereochemical integrity, whereas the triplet pathway is believed to be responsible for partial/complete loss of stereochemistry.[8]

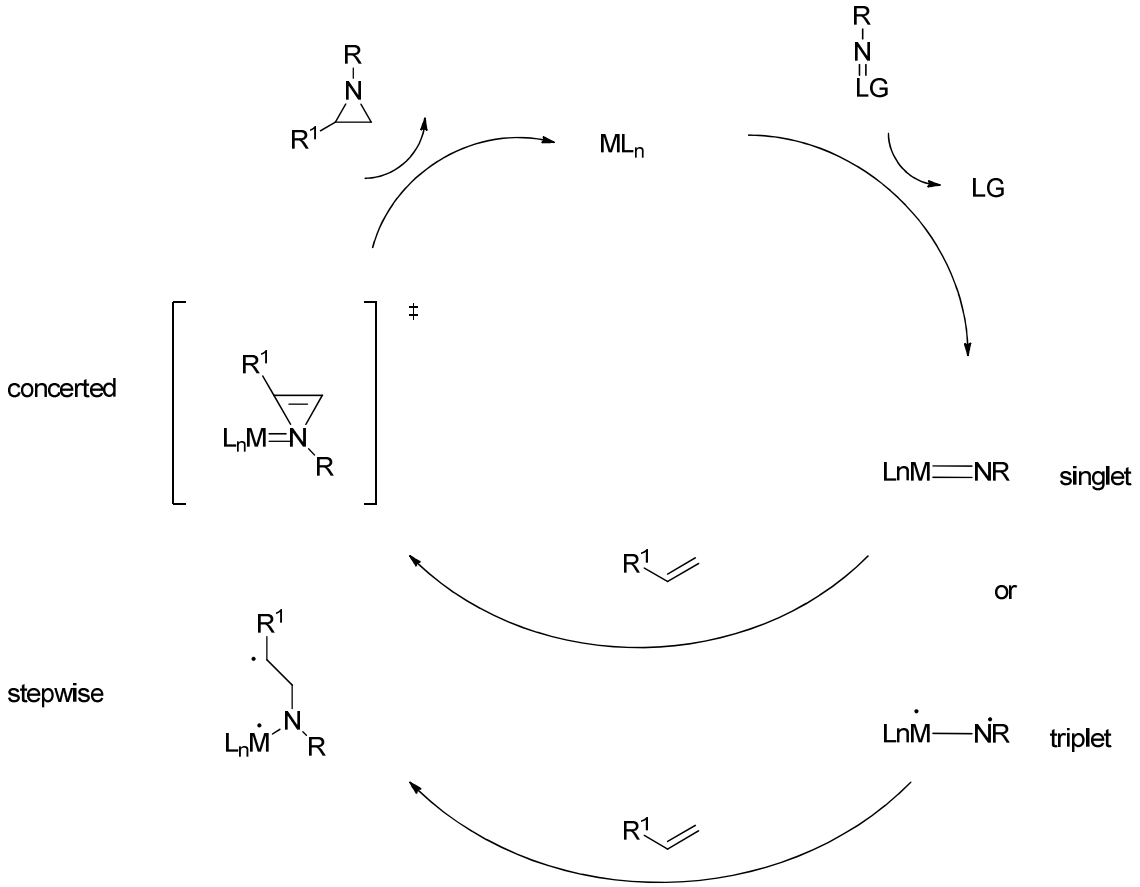
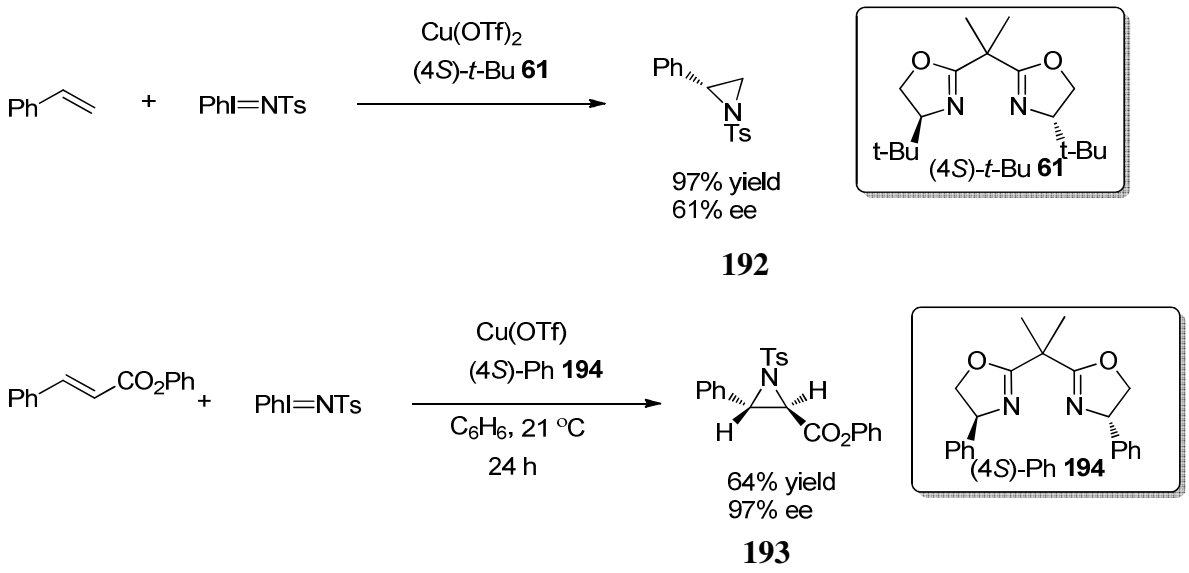


Figure 1.8[175]

However, in a recent publication into the mechanism of copper and silver catalysed alkene aziridination reactions, an alternative mechanism was proposed; one involving a concomitant involvement of a singlet and triplet nitrene.[175] It is reported in this paper that mechanistic differences exist between the two metals.

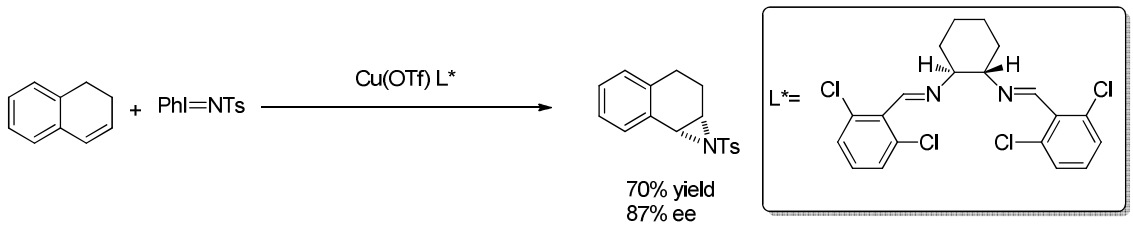
1.5.5 Enantioselective intermolecular aziridination

A significant breakthrough was made in 1991 by Evans and co-workers, who reported the first asymmetric copper catalysed intermolecular aziridination reaction, employing $Cu(OTf)_2$/(4*S*)-*t*-Bu **61** as a catalyst, attaining aziridine **192** in 61% ee,[155] after initially demonstrating that Cu(I) and Cu(II) salts were effective catalysts for this transformation.[176] Concurrently, Masamune and Lowenthal made a similar observation.[177] In a subsequent publication by Evans and co-workers, 97% ee was achieved in the synthesis of aziridine **193** when Cu(OTf)/(4*S*)-Ph **194** was employed.[178]



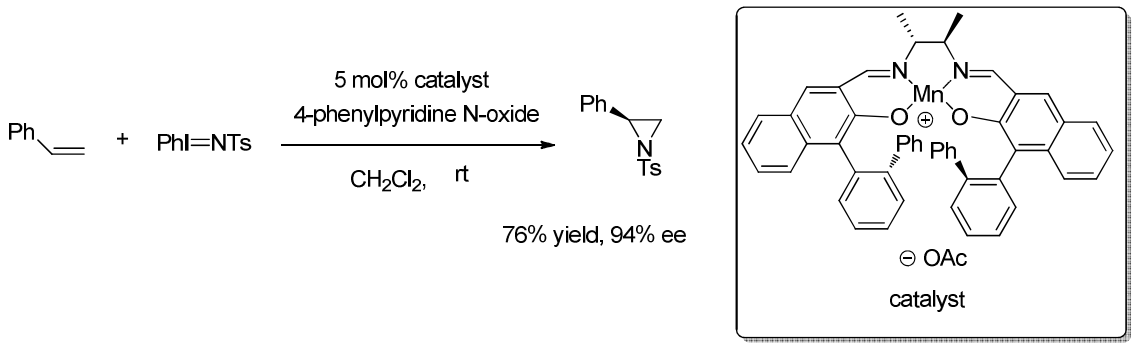
Scheme 1.52[155,178]

Jacobsen and co-workers reported enantioselectivities of up to 87% ee for intermolecular aziridination reactions employing chiral copper catalysts bearing benzylidene derivatives of 1,2- diaminocyclohexane, as depicted in **Scheme 1.53**.[179]



Scheme 1.53[179]

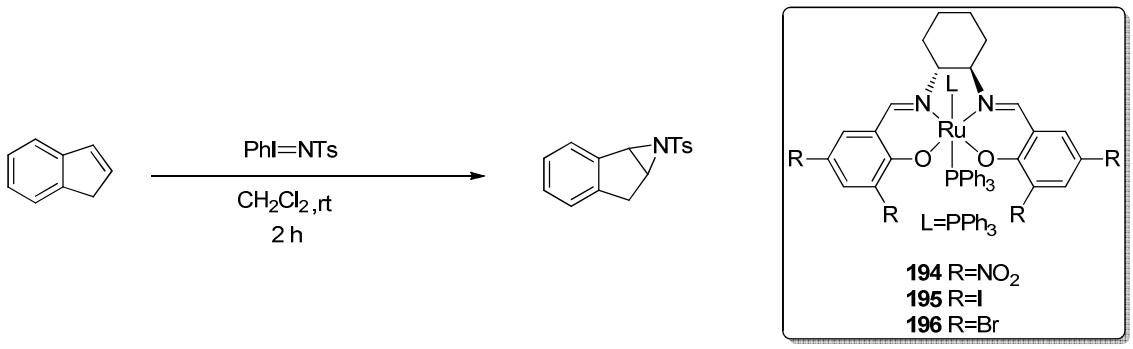
Katsuki and Nishikori reported achieving enantioselectivities of up to 94% ee for intermolecular aziridination of styrene, with modified (salen)manganese(III) complexes employed as catalysts.[180]



Scheme 1.54[180]

Che and co-workers demonstrated that aziridination of indene could be achieved using chiral ruthenium(II)-salen catalysts in values of up to 83% ee, with very strong sensitivity to variation in the ligand structure (**Table 1.28**).[181]

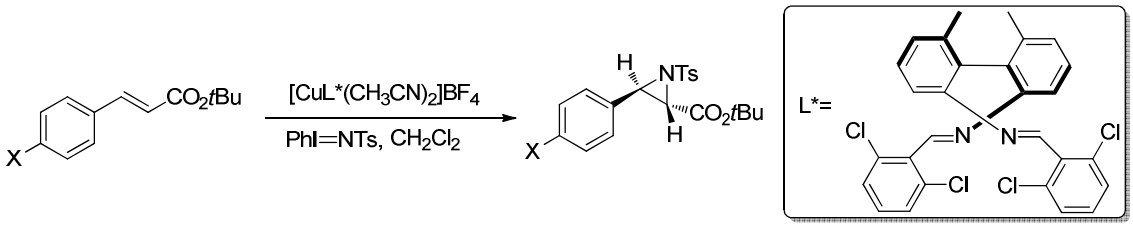
Table 1.28 *Ruthenium(II)-salen catalysed aziridination* [181]



Entry	R (Ligand)	Yield (%)	ee (%)
1	NO_2 **195**	68	83
2	I **196**	74	42
3	Br **197**	74	19

Alkene aziridiation has been achieved in up to 98% ee by Scott and co-workers, employing a copper-biaryldiimine complex (**Table 1.29**).[182,183]

Table 1.29 *Copper catalysed aziridination* [182]

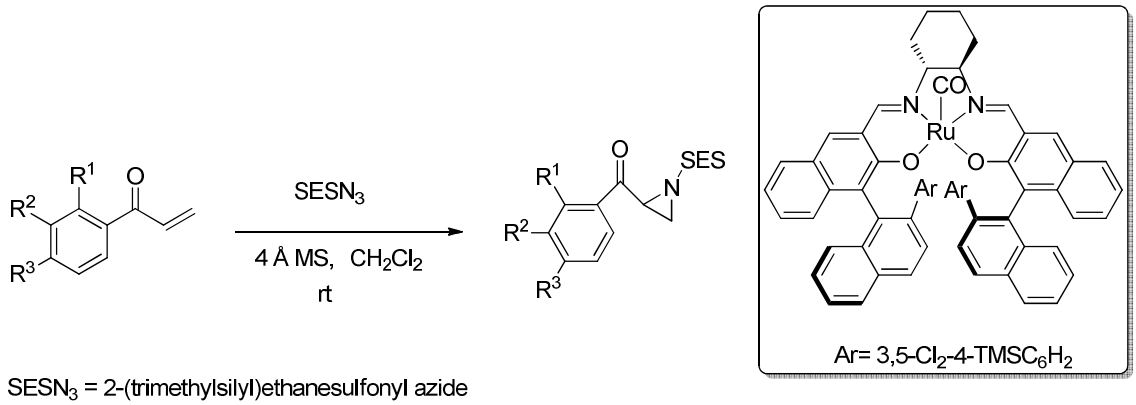


Entry	X	Yield (%)	ee (%)
1	H	77	89
2	OMe	67	93
3	Me	82	88
4	F	45	98
5	Cl	89	92
6	Br	59	98

In addition, Müller and co-workers achieved enantioselectivities for the aziridination of *cis*-β-methylstyrene of up to 73% ee with Pirrung's catalyst.[113]

Katsuki and co-workers examined the use of azides as nitrene precursors and employed ruthenium(CO)-salen complexes in the aziridination of both conjugated and unconjugated alkenes, achieving enanatioselectivities of greater than 99% ee **Table 1.30**[141,184–188] and **Table 1.31**.[187]

Table 1.30 *Asymmetric ruthenium(CO)-salen catalysed aziridination of conjugated terminal olefins, employing SESN$_3$* [185,186,188,189]

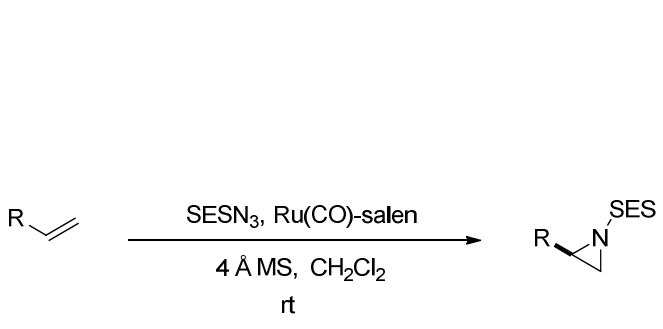


$SESN_3$ = 2-(trimethylsilyl)ethanesulfonyl azide

Entry	R^1	R^2	R^3	Yield (%)	ee (%)
1	H	H	H	99	>99
2	H	H	Cl	96	>99
3	H	Cl	H	96	>99
4	Cl	H	H	98	>99
5	H	H	OMe	92	>99
6	H	OMe	H	99	>99

The ruthenium complex shown in **Table 1.30**[187] that displayed excellent enantiocontrol for the aziridination of conjugated terminal olefins was not sufficiently active for the aziridination of less reactive non-conjugated terminal olefins. Therefore Katsuki and co-workers designed a more active catalyst that contained trifluoromethyl groups at the 3- and 5- positions instead of chlorine substituents. The rationale behind this design is that if the lone pair on the sulfonyl oxygen atom could interact with a vacant orbital then the reactivity of the nitrene intermediate would be enhanced, and it is established that the C–F bond has a low lying anti-bonding orbital.

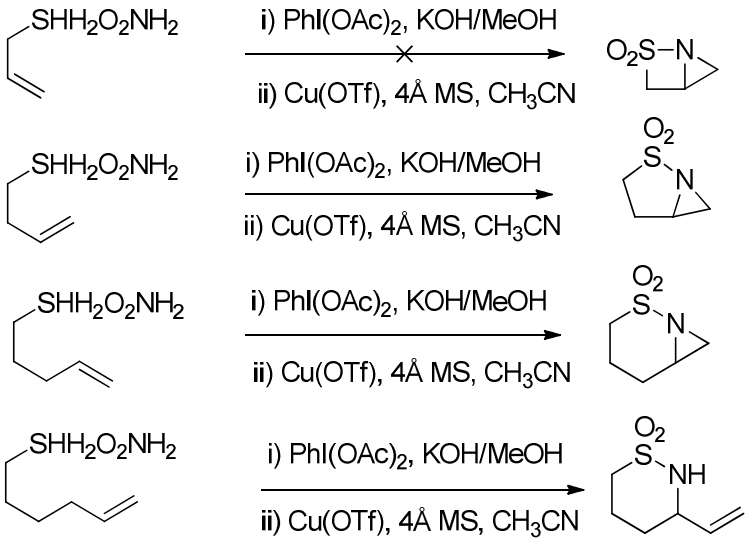
Table 1.31 *Asymmetric ruthenium(CO)-salen catalysed aziridination of non-conjugated terminal olefins, employing SESN$_3$* [187]



Entry	R	catalyst (mol%)	Yield (%)	ee (%)
1	Ph	0.5	99	90
2	*p*-ClC$_6$H$_4$	1	96	90
3	*n*-Bu	3	74	99

1.5.6 Enantioselective intramolecular aziridination reactions

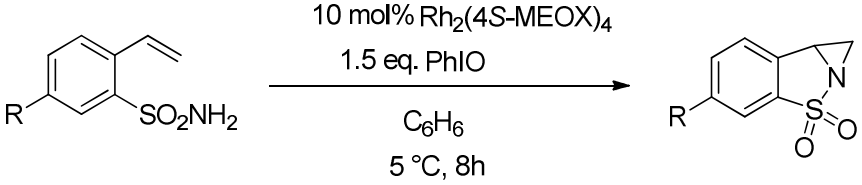
Intramolecular asymmetric transition metal catalysed aziridination reactions of α-sulfonyl nitrenes has been reported by several groups.[8,118,190,191] In one report Dodd and Dauban employed copper triflate to catalyse several aziridination reactions using α-sulfonyl nitrenes (**Scheme 1.55**).[118] While both five- and six-membered aziridination product were synthesised, not surprisingly the strained four membered ring did not form. Unexpectedly, C–H insertion rather than aziridination occurred in one instance.



Scheme 1.55

The synthesis of five-membered sulfone containing rings was achieved with enantioselectivities of up to 76% ee in the presence of $Rh_2(4S\text{-MEOX})_4$ (**Table 1.32**, entry 1). Changing the substituent at the *para* position on the benzene ring did not have a significant impact on the resulting enantiopurity of the reaction products (**Table 1.32**, entries 2 and 3).[192]

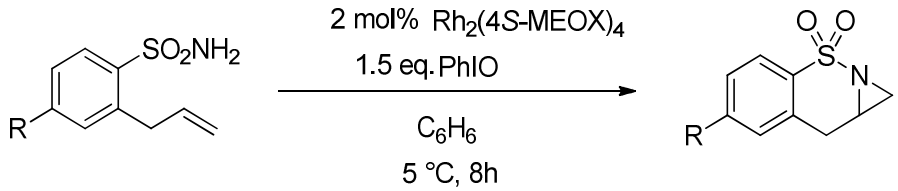
Table 1.32 *$Rh_2(4S\text{-MEOX})_4$ catalysed intramolecular aziridination of **44**, **198** and **199***



Entry	R	Starting material	Product	Yield (%)	ee (%)
1	H	**44**	**200**	90	76
2	Me	**198**	**201**	71	74
3	Br	**199**	**202**	74	75

This reaction can also be extended to the synthesis of six-membered heterocycles, however, the enantiopurities of the reaction products were moderately lower than those obtained for five-membered ring synthesis (57% ee *cf.* 76% ee, **Table 1.33**, entry 1 *cf.* **Table 1.32** entry 1). The highest enantioselectivity was achieved with the *p*-Cl substituent at 67% ee (**Table 1.33**, entry 3).

Table 1.33 *$Rh_2(4S\text{-MEOX})_4$ catalysed intramolecular aziridination of **203**, **204** and **205***

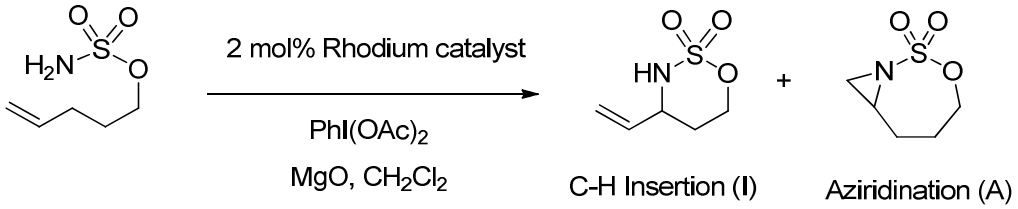


Entry	R	Starting Material	Product	Yield (%)	ee (%)
1	H	**203**	**206**	71	57
2	Me	**204**	**207**	73	55
3	Cl	**205**	**208**	68	67

Intramolecular cyclopropanation of α-diazosulfone substrates has been shown to be a key step in the synthesis of natural product (−)-agelastatin A by Du Bois and Wehn.[191]

Competition between C–H amination and aziridination pathways exists when both routes are feasible. Recently, a mechanistic investigation was carried out into the Rh(II) catalysed intramolecular C–H amination and aziridination of 4-pentenylsulfamate (**Table 1.34**),[127] and it was demonstrated that DFT calculations are largely in agreement with results obtained experimentally. As can clearly be seen in **Table 1.34**, the catalyst has a profound effect on the overall outcome of the reaction.

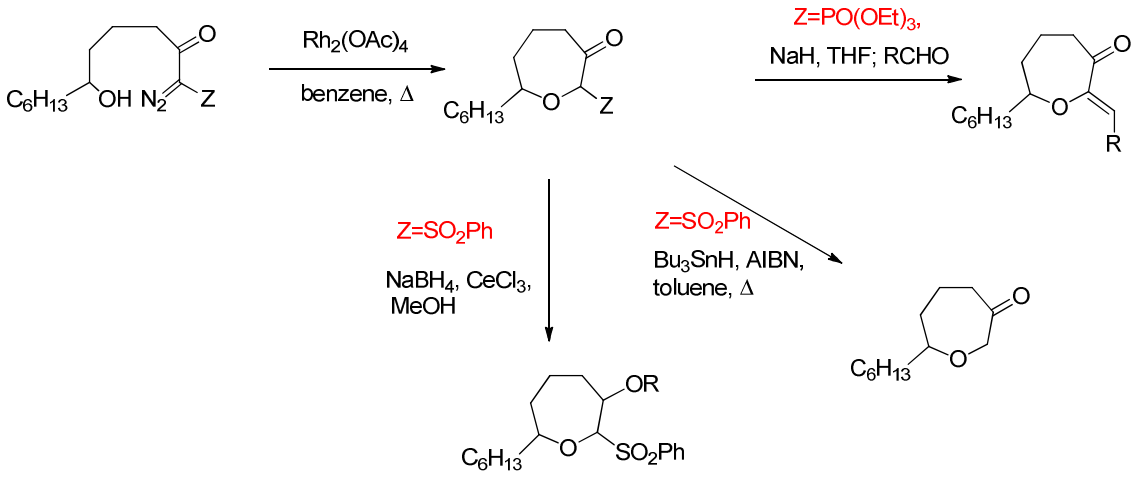
Table 1.34 *Rh(II) catalysed C–H amination and aziridination of 4-pentenylsulfamate*



Entry	Catalyst	I/A (Experimental)	I/A (Calculated)
1	$Rh_2(NHCOCF_3)_4$	1 : 4	1 : 11
2	$Rh_2(OAc)_4$	1 : 1	0.8 : 1
3	$Rh_2(NCH_3CHO)_4$	>20 : 1 [Rh_2(*S*-nap)$_4$]	>20 : 1

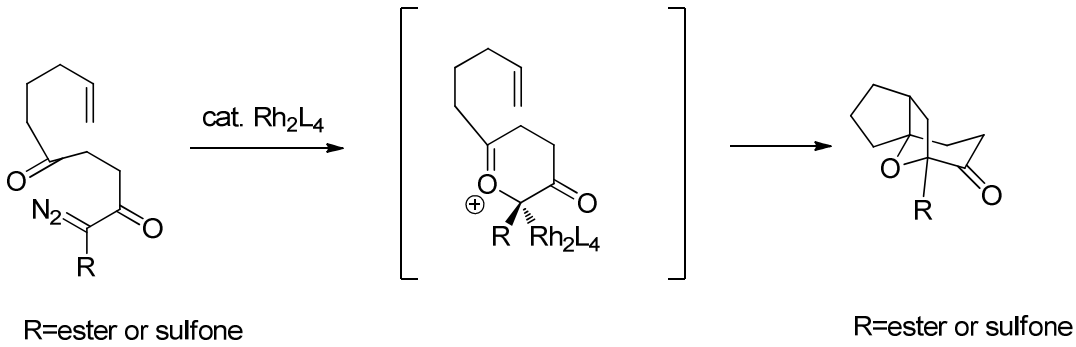
1.6 Miscellaneous reactions

While the reactivity of α-diazosulfones in C–H insertion and cyclopropantion reactions have been investigated extensively, there are other examples of the reactivity of these systems, in many cases displaying similar reactivity to the analogous α-diazocarbonyl compounds. Thus, Moody and co-workers demonstrated comparable intramolecular O–H insertion reactions with a series of α-diazo-β-keto esters, sulfones and phosphonates to form oxepanes as illustrated in **Scheme 1.56**, mediated by rhodium acetate. While the O–H insertion process proceeded very similarly for each substrate of the series, further elaboration of the sulfone or phosphonate moieties provides synthetic diversity.[193]



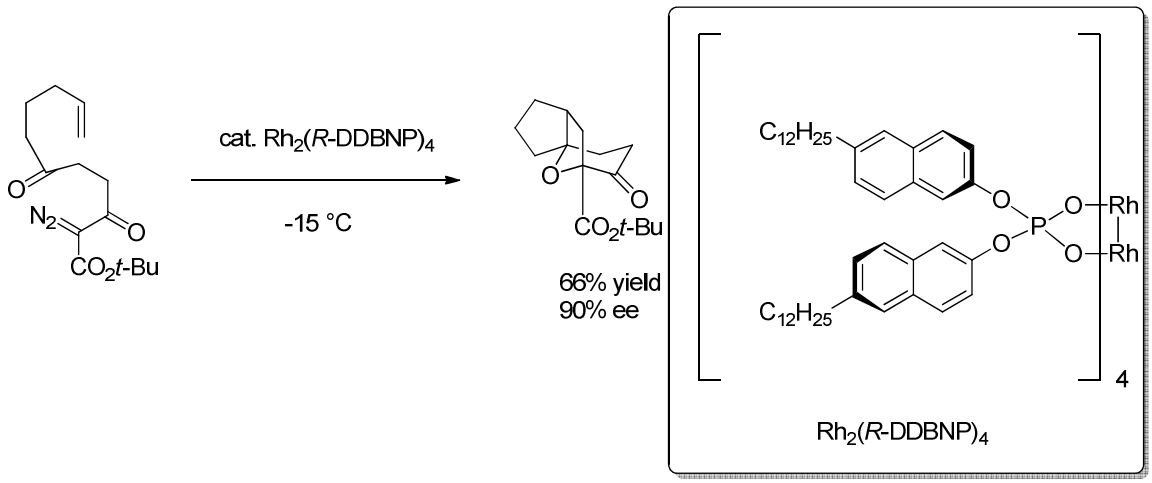
Scheme 1.56

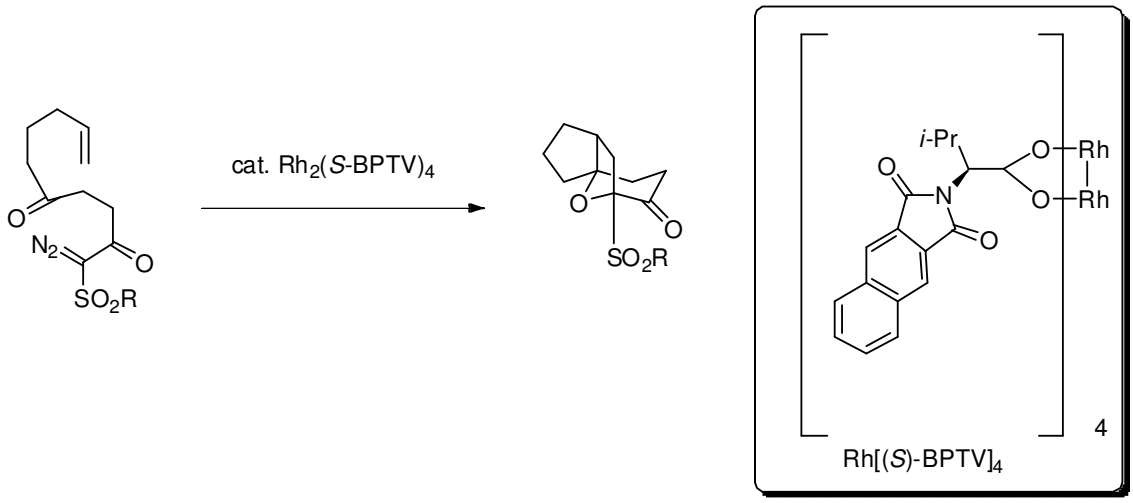
Hodgson and co-workers extended his study of enantioselective tandem carbonyl ylide formation/[3+2] cycloaddition, originally developed for α-diazo-β-keto-esters, to the analogous α-diazo-β-keto sulfones (**Scheme 1.57**).[194]



Scheme 1.57

While the enantioselectivity was somewhat less in the sulfone series (**Scheme 1.58**),[194,195] notably the outcome was sensitive to the nature of the sulfone, with better results for the phenyl sulfone than the methyl sulfone (**Scheme 1.58**).



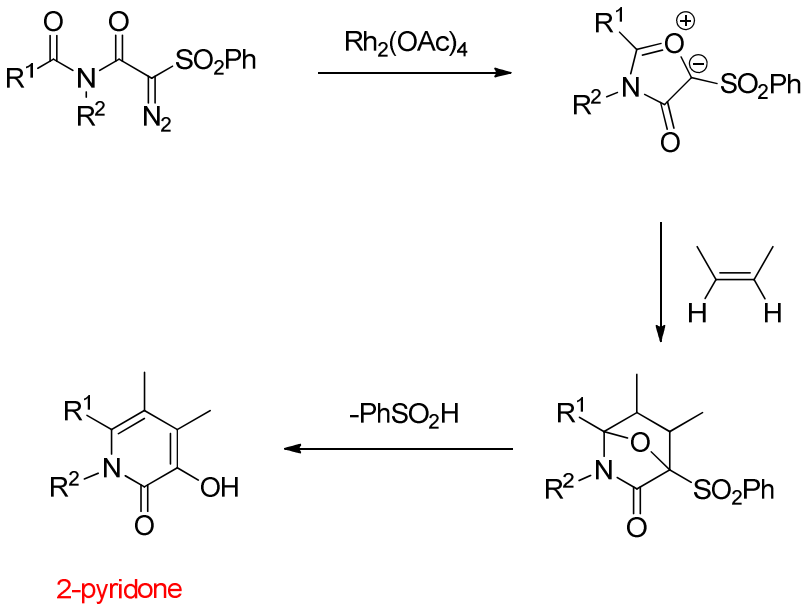


209 R=Ph
211 R=Me

210 R=Ph, er=71.5:28.5
212 R=Me, er=66.5:33.5

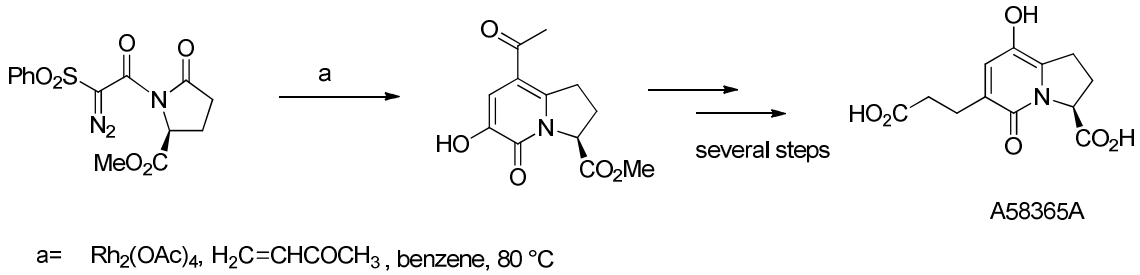
Scheme 1.58

Padwa and co-workers developed a new synthetic route to 2-pyridones through exposure of α-diazosulfones to rhodium acetate leading to the formation of an isomünchnone dipole which undergoes cycloaddition with a range of dipolarophiles leading to 2-pyridones, following loss of the sulfone moiety (**Scheme 1.59**).[196–198]



Scheme 1.59

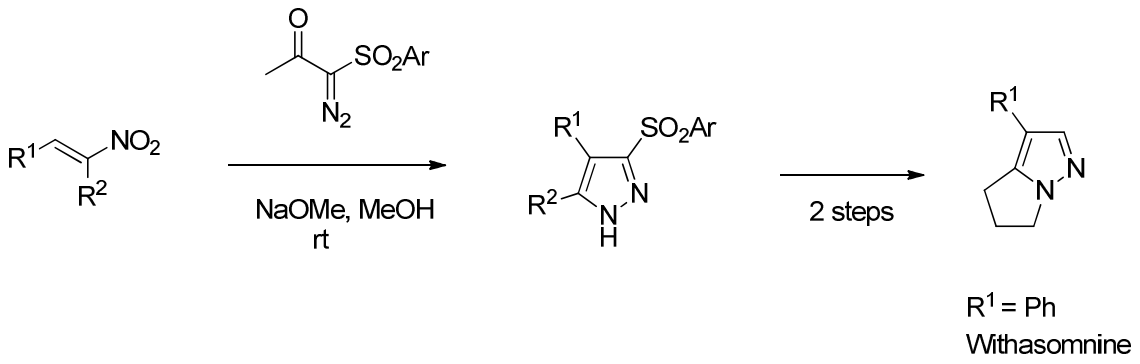
The power of this synthetic methodology has been demonstrated in the synthesis of the ACE inhibitor (–)-A58365A, as illustrated below in **Scheme 1.60**.[196] Gilbertson and co-workers have recently reported the application of this methodology to generate a pyridone library.[199]



a= $Rh_2(OAc)_4$, $H_2C{=}CHCOCH_3$, benzene, 80 °C

Scheme 1.60

As another illustration of the synthetic utility of α-diazosulfones, the synthesis of sulfonyl pyrazoles through base mediated reaction with nitroalkenes is an interesting example of reaction with retention of the diazo moiety (**Scheme 1.61**).[200]



Scheme 1.61

1.7 Conclusions

C–H insertion and amination reactions and cyclopropanation and aziridination based on sulfonyl carbenes and sulfonyl nitrenes are powerful synthetic transformations; particularly in the context of effective enantiocontrol as demonstrated in recent years through use of enantioselective catalysts. The presence of the sulfonyl substituent has a profound impact both on the ability to generate the reactive carbene/nitrene, and its stability and reactivity. In systems where both C–H insertion and cyclopropanation are feasible, the outcome is both catalyst and substrate dependant.

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Chapter 2
Introduction to Results and Discussion

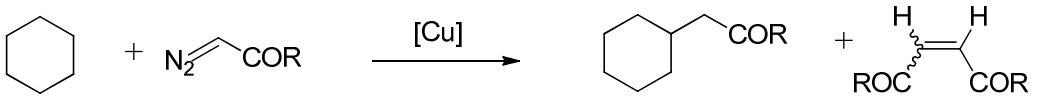
"If you can make one heap of all your winnings and risk it on one turn of pitch-and-toss,
And lose, and start again at your beginnings and never breathe a word about your loss……" Rudyard Kipling

2.1 Project Background

There are many synthetic strategies available for the formation of new carbon-carbon bonds in organic chemistry. Of these, transition metal catalysed C–H insertion reactions of α-diazocarbonyl compounds offer many advantages. Not only does this transformation allow the activation of a previously unactivated C–H bond, but it has also been shown to be an effective method for constructing both carbo- and heterocycles in a chemo-, regio-, diastereo- and enantioselective manner.[1–8]

Pioneering work in this area reported the use of copper based catalysts, however these reactions demonstrated poor selectivities and were deemed to be of little synthetic use.[8] Studies carried out by Scott and DeCisso on the intermolecular C–H insertion reactions of diazocarbonyls **1** and **2** with cyclohexane clearly demonstrated poor reaction efficiencies, with the insertion products **3** and **4** constituting the minor component of the reaction mixture and byproducts such as the dimers **5** and **6** making up the rest of the reaction products (**Table 2.1**).[9]

Table 2.1 *Results reported by Scott[9] for copper catalysed intermolecular C–H insertion reactions of α-diazocarbonyls with cyclohexane.*



1 R=OEt
2 R=Ph

3 R=OEt
4 R=Ph

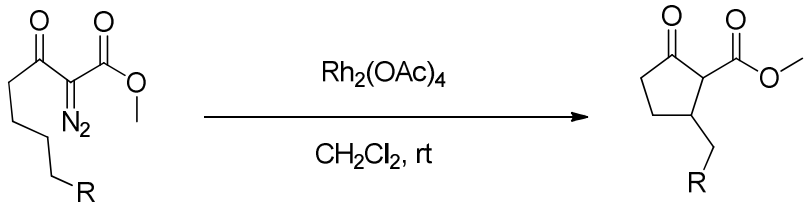
5 R=OEt
6 R=Ph

R	[Cu]	Products		
		Diazo	Insertion	Dimer
OEt	None	98	<1	0
	$CuSO_4$	0	24	40
	CuCl	0	15	61
Ph	None	92	0	0
	$CuSO_4$	0	17	9
	CuCl	0	9	29

However, with the introduction of rhodium acetate, Teyssie and co-workers demonstrated the synthetic potential of the transition metal catalysed C–H insertion reaction of α-

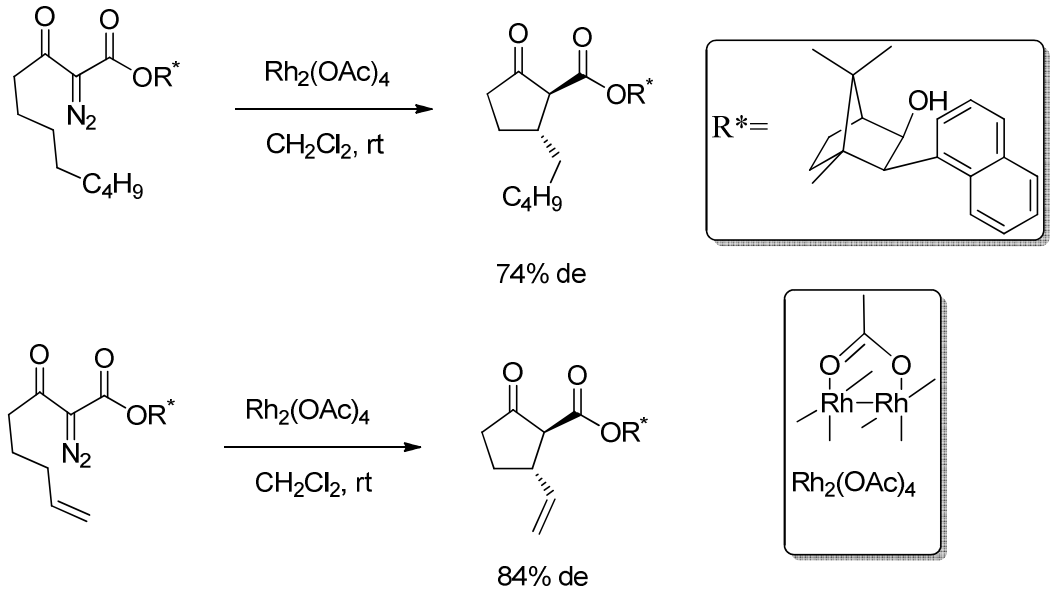
diazocarbonyl compounds, with the intermolecular C–H insertion reaction of ethyl diazoacetate into unsubstituted alkanes.[10]

A great deal of research was carried out into the intramolecular version of this reaction by Taber and co-workers, who discovered a number of important trends in the rhodium acetate catalysed intramolecular C–H insertion reactions of α-diazo-β-keto-esters. The main product of these reactions is generally a cyclopentanone ring, demonstrating that five-membered ring formation is preferred in the C–H insertion reactions of α-diazo-β-keto-esters with acylic freely rotating chains, showing excellent regiocontrol.[11] This observation was also made by Wenkert and co-workers.[12] In addition to this, it was also discovered that C–H insertion is favoured into a methine group over a methylene group which is preferred over insertion into a methyl group (**Scheme 2.1**).[11,13]



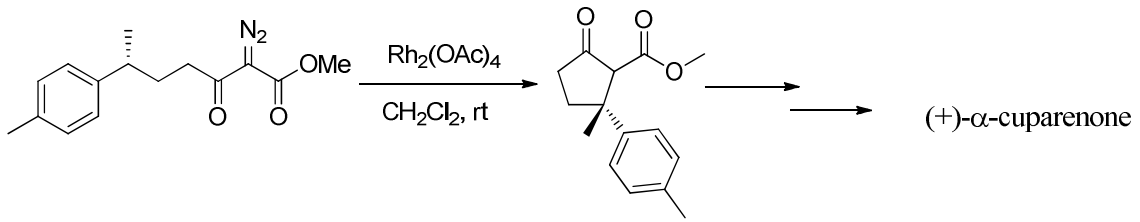
Scheme 2.1

Taber demonstrated excellent diastereocontrol in the C–H insertion process through the use of chiral auxiliaries as illustrated in **Scheme 2.2**.[14]



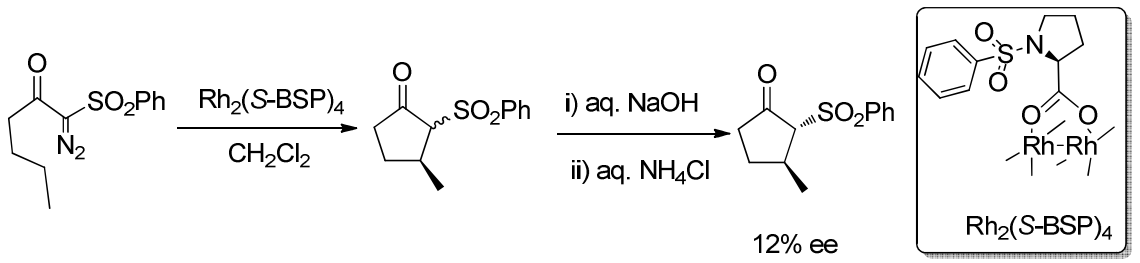
Scheme 2.2

Another important trend observed by the Taber group was that when C–H insertion occurs at a stereocentre, the reaction proceeds with retention of stereochemistry; a fact that was used in the synthesis of (+)-α-cuparenone[15] (**Scheme 2.3**).



Scheme 2.3

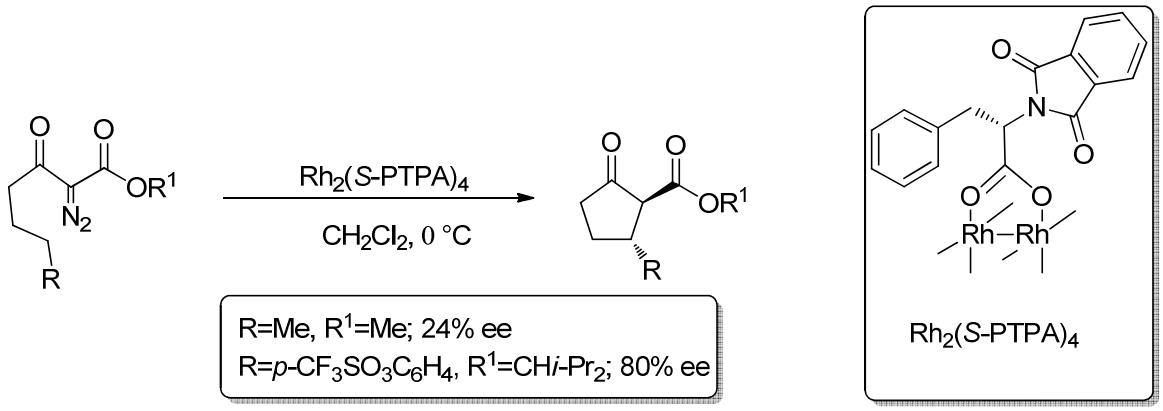
The first reported example of an asymmetric transition metal catalysed C–H insertion reaction was made by McKervey and and co-workers when they exposed α-diazo-β-keto sulfone **7** to Rh_2(*S*-BSP)$_4$ catalyst to yield 2-sulfonylcyclopentanone **8** in a 12% ee with a 90% yield[16] (**Scheme 2.4**).



7 **8**

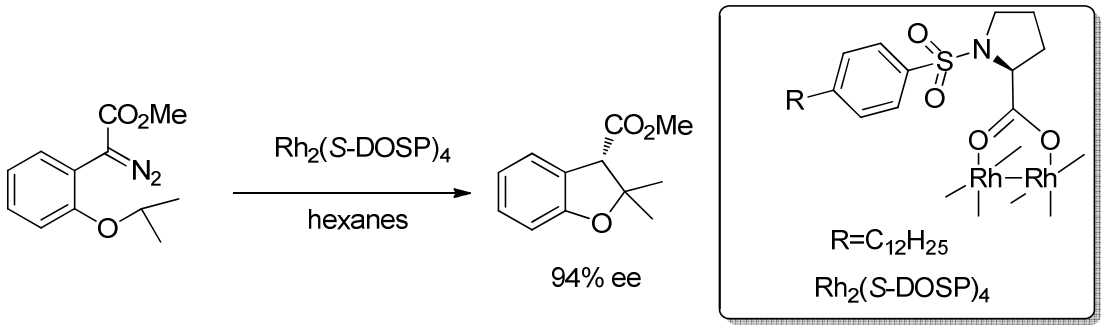
Scheme 2.4

Since this initial report, enormous efforts have been invested in the development of asymmetric rhodium catalysts for C–H insertion processes. Hashimoto and Ikegami focused on rhodium carboxylates derived from amino acids.[17–19] They achieved enantioselectivities of up to 80% ee with Rh_2(*S*-PTPA)$_4$. However, it was found that high levels of enantioselectivity obtained were substrate dependant, requiring bulky ester substituents (R^1=CH-*i*-Pr_2) to maintain high levels of enantiocontrol. The group adjacent to the insertion site also had an effect on the enantiopurity of the cyclopentanones, with electron withdrawing groups giving rise to the best enantioselectivities (R=*p*-$CF_3SO_3C_6H_4$) (**Scheme 2.5**).



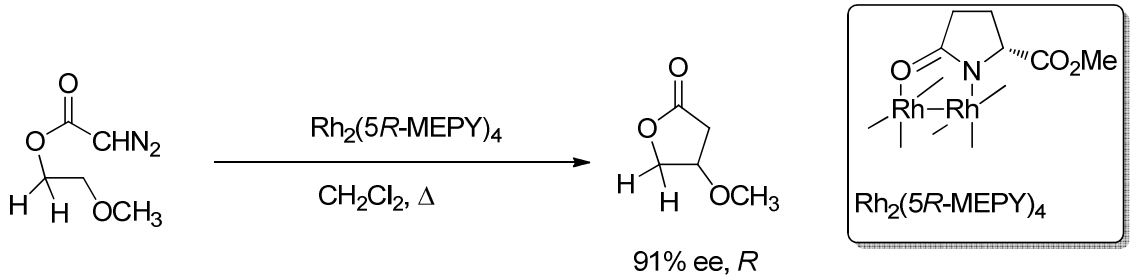
Scheme 2.5

At the same time Davies and co-workers modified the benzene sulfonyl prolinate catalyst reported by McKervey, by the addition of a dodecyl group at the *para* position of the benzene ring attached to the sulfonyl group [Rh_2(*S*-DOSP)$_4$]. Excellent enantioselectivities were achieved in the intramolecular C–H insertion of aryldiazoacetates with Rh_2(*S*-DOSP)$_4$ as illustrated in **Scheme 2.6**.[20]



Scheme 2.6

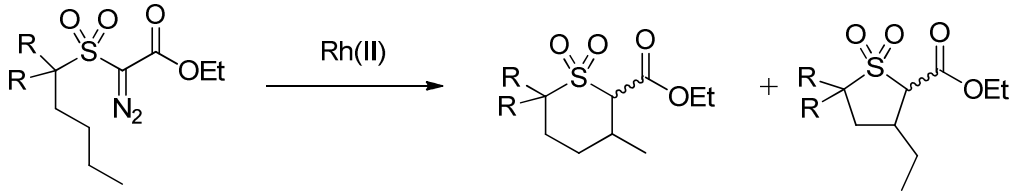
Doyle and coworkers have had tremendous success with rhodium carboxamidate catalysts [for *e.g.* Rh_2(5*R*-MEPY)$_4$] in C–H insertion reactions where the C–H bond is activated by a heteroatom (**Scheme 2.7**),[21] although these catalysts are in general insufficiently active to generate cyclopentanones.



Scheme 2.7

The Maguire team commenced an investigation into reactions of α-diazo-β-oxo sulfones where the sulfone and carbonyl groups were reversed; C–H insertion in this instance would potentially lead to cyclic sulfones. Early work in this research group was carried out by Kelleher,[22] O'Riordan[23] and Flynn[24] using rhodium based catalysts. While Kelleher only reported the five-membered sulfolane ring compounds, O'Riordan also saw evidence for six-membered ring thiopyran products. This was quite unusual as five-membered ring products usually predominate. Carrying on from this work, Flynn carried out an extensive study on the rhodium catalysed C–H insertion reactions of a range of α-diazo-β-oxo sulfones. Flynn discovered that a range of different isomers (*cis*/*trans* sulfolane, *cis*/*trans* thiopyran) resulted in differing amounts depending on the nature of the substrate and rhodium catalyst employed. The use of rhodium based catalysts gave rise to predominately *trans* thiopyrans and *trans* sulfolanes, a fact also reported by Novikov and co-workers.[25,26] Both Novikov[25] and Du Bois and co-workers [27] also examined the C–H insertion reactions of α-diazosulfonates which lead to δ-sultones. Novikov and co-workers carried out extensive research into the catalyst and substrate effects on the outcome of the C–H insertion reactions of α-diazo-β-oxo sulfones. For the C–H insertion reactions of α-diazo-β-oxo sulfone **9** when an electron deficient catalyst, such as rhodium perfluorobutyrate was used, the major product isolated from the reaction was sulfolane **10** (**Table 2.2**, entry 4). All other catalysts led predominately to thiopyran **11** (**Table 2.2**, entries 1–3). However, in the case of the α-diazo-β-oxo sulfone **12** the major product is sulfolane **13**, regardless of the catalyst. This demonstrates that the substrate also has an impact on product outcome. When the position α to the sulfone is substituted the major reaction product is sulfolane (**Table 2.2**, entries 5–6), and in the absence of this substitution the thiopyran predominates (**Table 2.2**, entries 1–3).[26]

Table 2.2 *Rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfones.*[26]



9 R=H
12 R=Me

11 R=H
14 R=Me

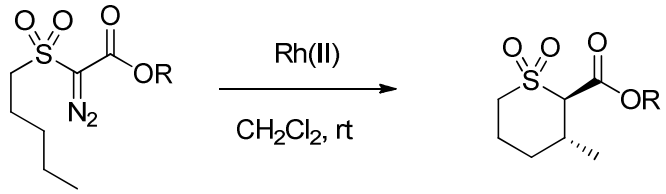
10 R=H
13 R=Me

Entry	R	Rh(II)[b]	Thiopyran (Yield %)[a]	Sulfolane (Yield %)[a]
1	H	$Rh_2(OAc)_4$	65	9
2	H	$Rh_2(esp)_4$	70	9
3	H	$Rh_2(cap)_4$	60	8
4	H	$Rh_2(pfb)_4$	27	49
5	Me	$Rh_2(OAc)_4$	5	75
6	Me	$Rh_2(pfb)_4$	-	64

a. Isolated yields.

Recently Novikov and co-workers explored the impact of chiral rhodium catalysts on the enantioselectivity of the C–H insertion reaction of α-diazo-β-oxo sulfones.[28] The results are summarised in **Table 2.3**. The catalysts giving the best enantioselectivity were Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTAD)$_4$, affording *trans* thiopyran **11** in 45% ee in both cases (**Table 2.3**, entries 2, 3). Lowering reaction temperature from room temperature to 0 °C gave rise to a moderate increase in enantioselectivity from 45 to 50% ee for thiopyran **11** in the presence of Rh_2(*S*-PTTL)$_4$ (**Table 2.3**, entry 2). In comparison to the moderate enantioselectivities achieved, high diastereocontrol was observed when a chiral menthyl ester was employed as a chiral auxiliary. When this compound underwent the reaction in the presence of Rh_2(*S*-PTTL)$_4$, 90% de was achieved (**Table 2.3**, entry 5).[28] However, when the opposite enantiomer of the chiral menthyl ester was used, the selectivity was reversed toward the other enantiomer, suggesting that the effect of the menthyl ester was more as a directing chiral auxiliary rather than acting as a bulky substituent (**Table 2.3**, entry 6).

Table 2.3 *Asymmetric rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfones.*[28]



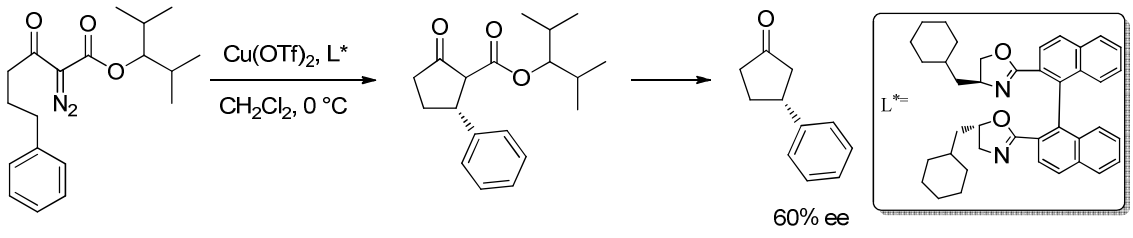
9 R=Et
15 R=(–)-Menthyl
17 R=(+)-Menthyl

11 R=Et
16 R=(–)-Menthyl
18 R=(+)-Menthyl

Entry	R	Rh(II)	Thiopyran (ee%)
1	Et	Rh_2(*S*-DOSP)$_4$	0
2[a]	Et	Rh_2(*S*-PTTL)$_4$	45
3	Et	Rh_2(*S*-PTAD)$_4$	45
4	Et	Rh_2(*S*-PTPA)$_4$	33
5[b]	(–)-Menthyl	Rh_2(*S*-PTTL)$_4$	90[b]
6	(+)-Menthyl	Rh_2(*S*-PTTL)$_4$	–40[b]

a. When this reaction was repeated at 0 °C, the enantioselectivity of thiopyran **11** increased to 50% ee.
b. The result reported for this entry is a diastereoselectivity.

While a great deal of advancement in the period since 1990 was made in the area of rhodium catalysed C–H insertion reactions, a number of reports have begun to emerge in recent years on the use of chiral copper catalysts for C–H insertion reactions of α-diazocarbonyl compounds, as summarised in a 2012 review.[4] Müller and Boléa reported achieving enantioselectivities of up to 60% ee in the synthesis of cyclopentanone **19** using chiral copper catalysis, as demonstrated in **Scheme 2.8**.[29,30] However, good enantioselectivities were only achieved with complex bisoxazoline ligands and very sterically demanding ester substituents. Reactions with simple esters and commercially available bisoxazoline ligands led only to very moderate enantioselectivities, in the region of 20–30% ee.

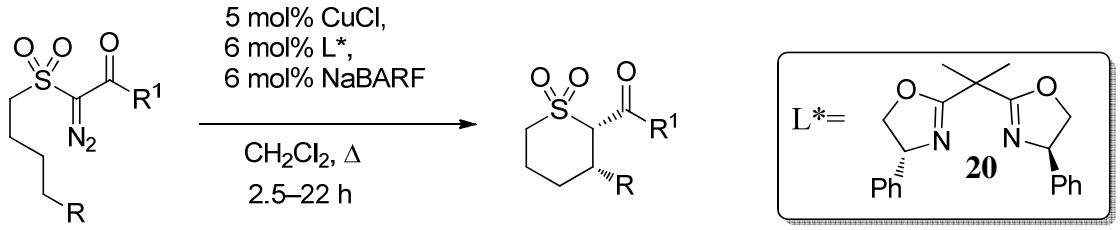


19

Scheme 2.8

A breakthrough in chiral copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones was made by Maguire and Flynn, when enantioselectivities of up to 98% ee were achieved in *cis* thiopyran synthesis with CuCl, a phenyl substituted bisoxazoline ligand [(4*R*)-Ph-**20**] and NaBARF as the catalyst system. This marks the highest reported enantioselectivity for a copper mediated C-H insertion to date. The results of this study are shown in **Table 2.4**.[31] The success of this catalyst was in part due to the presence of the additive NaBARF.[32,33] NaBARF had previously been reported to enhance reaction enantioselectivities in copper-bisoxazoline catalysed aromatic addition reactions,[34] as well as N–H[35] insertion and O–H[36,37] insertion reactions.

Table 2.4 *Enantioselective synthesis of* cis *thiopyrans via asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones.*[31]

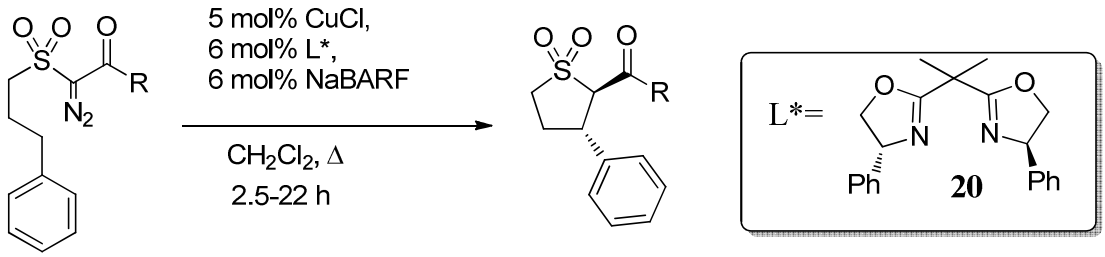


Entry	R	R^1	α-diazo-β-oxo sulfones	*cis* thiopyrans	Yield (%)[a]	ee (%)[b]
1	Ph	Me	**21**	**22a**	30	85
2	Ph	Ph	**23**	**24a**	49	97
3[c]	Ph	OMe	**25**	**26a**	47	98
4	Bn	OMe	**27**	**28a**	42	96
5	Et	OMe	**29**	**30a**	68	97
6	4-tolyl	OMe	**31**	**32a**	64	96
7	4-anisyl	OMe	**33**	**34a**	56	91
8[d]	4-nitrophenyl	OMe	**35**	**36a**	-	-
9	Oct	OBn	**37**	**38a**	66	90

a. Yield obtained after purification using column chromatography
b. Enantioselectivity measured using chiral HPLC
c. This reaction was repeated, with the exception that the catalyst was pre-formed before the addition of α-diazo-β-oxo sulfone **25** in dichloromethane; *cis* thiopyran **26a** was isolated in 98% ee and 21% yield.
d. Reaction complete within 2.5 h, but there was no evidence for C–H insertion products.

Enantioselectivities remained high for α-diazoesters (**Table 2.4**, entries 3–9) as well as α-diazoketones (**Table 2.4**, entries 1–2). Tolerance in enantioselectivity was also shown for a range of C–H insertion sites, with benzylic (**Table 2.4**, entries 1–3, 6–8) and non-benzylic insertion sites (**Table 2.4**, entries 4–5, 9) resulting in high enantiopurities.

Table 2.5 *Enantioselective synthesis of* trans *sulfolanes via asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones.*[31]

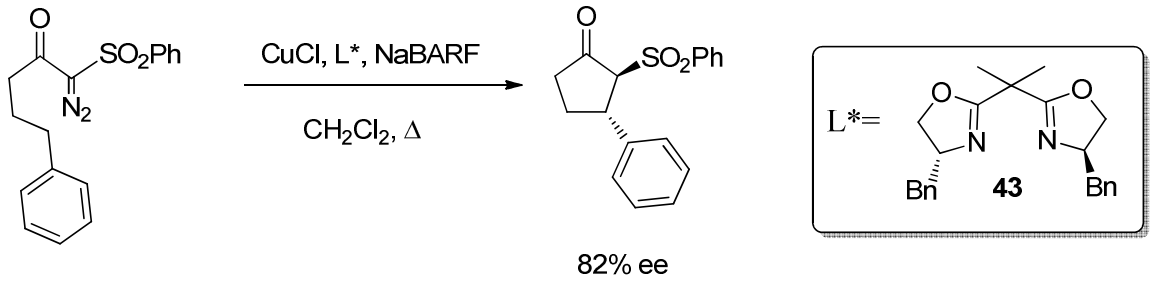


Entry	R	α-diazo-β-oxo sulfones	*trans* sulfolane	Yield (%)[a]	ee (%)[b]
1	OEt	**39**	**40b**	57	60
2	Me	**41**	**42b**	40	40

a. Yield obtained after purification using column chromatography.
b. Enantioselectivity measured using chiral HPLC.

In systems where C–H insertion to form thiopyrans is not possible, sulfolane formation results instead. Lower enantioselectivities, of 60% ee, were achieved for *trans* sulfolane synthesis using the CuCl-NaBARF-L* catalyst system (**Table 2.5**, entries 1, 2). Carrying on from these initial findings by Flynn, work in this project involved further investigation into the catalyst system (varying the copper source, ligand, and additive) as well as further extending the substrate scope. These aims will be elaborated in **Section 2.2**.

When CuCl-NaBARF-L* was applied to cyclopentanone synthesis, enantioselectivities of up to 82% ee were achieved when (4*R*)-Bn **43** (**Scheme 2.9**)[38–41] was used and up to 89% ee when (3*R*,8*S*)-Ind **44** was used,[32,33] further demonstrating the utility of the CuCl-NaBARF-L* system in enantioselective ring construction.



Scheme 2.9

2.2 Project Aims

Owing to the unprecedented success of the CuCl-NaBARF-(4*R*)-Ph **20** catalyst in the enantioselective synthesis of *cis* thiopyrans **22**, **24**, **26**, **28**, **30**, **32**, **34**, **36**, **38** further investigation into this process was warranted. The key objectives of this work were:

1) To design and synthesise a range of α-diazo-β-oxo sulfones to enable exploration of the impact of the substrate structure on the outcome of the C–H insertion process, in terms of efficiency, regioselectivity and enantioselectivity.
2) To examine the influence of each of the elements of the CuCl-NaBARF-L* catalyst system on the reaction outcome, in terms of efficiency, regioselectivity and enantioselectivity.
3) To explore the impact of variation of the linker chain on the enantioselective C–H insertion, as all of the previous studies had focused on freely rotating alkyl chains.
4) To explore reactions of α-diazoamide derivatives as an extension of earlier work with esters and ketones.
5) To investigate the insertion reactions of unsaturated α-diazo-β-oxo sulfones, where intramolecular cyclopropanation is a likely reaction pathway.

The results of this study are contained in five chapters as summarised below.

2.3 Summary

1) The synthesis of a series of known α-diazo-β-oxo sulfones **21**, **23**, **25**, **27**, **29**, **37**, **39** and **41** as well as a range of novel α-diazo-β-oxo sulfones **45**–**63** is discussed in Chapter 3, as summarised in **Figure 2.1**. The structures of these α-diazo-β-oxo sulfones were selected to enable detailed investigation of the influence of variation of the substrate structure on the subsequent C–H insertion reactions. Ketone and ester derivatives were explored as an extension of Flynn's work, while investigation of the α-diazoamides was undertaken for the first time during this work. The impact of moving from a freely rotating alkyl chain as a linker to the use of the more rigid aryl linker was a key part of this study. The unsaturated derivatives **59**–**61**, **63** were designed to enable investigation of competition between C–H insertion and cyclopropanation.

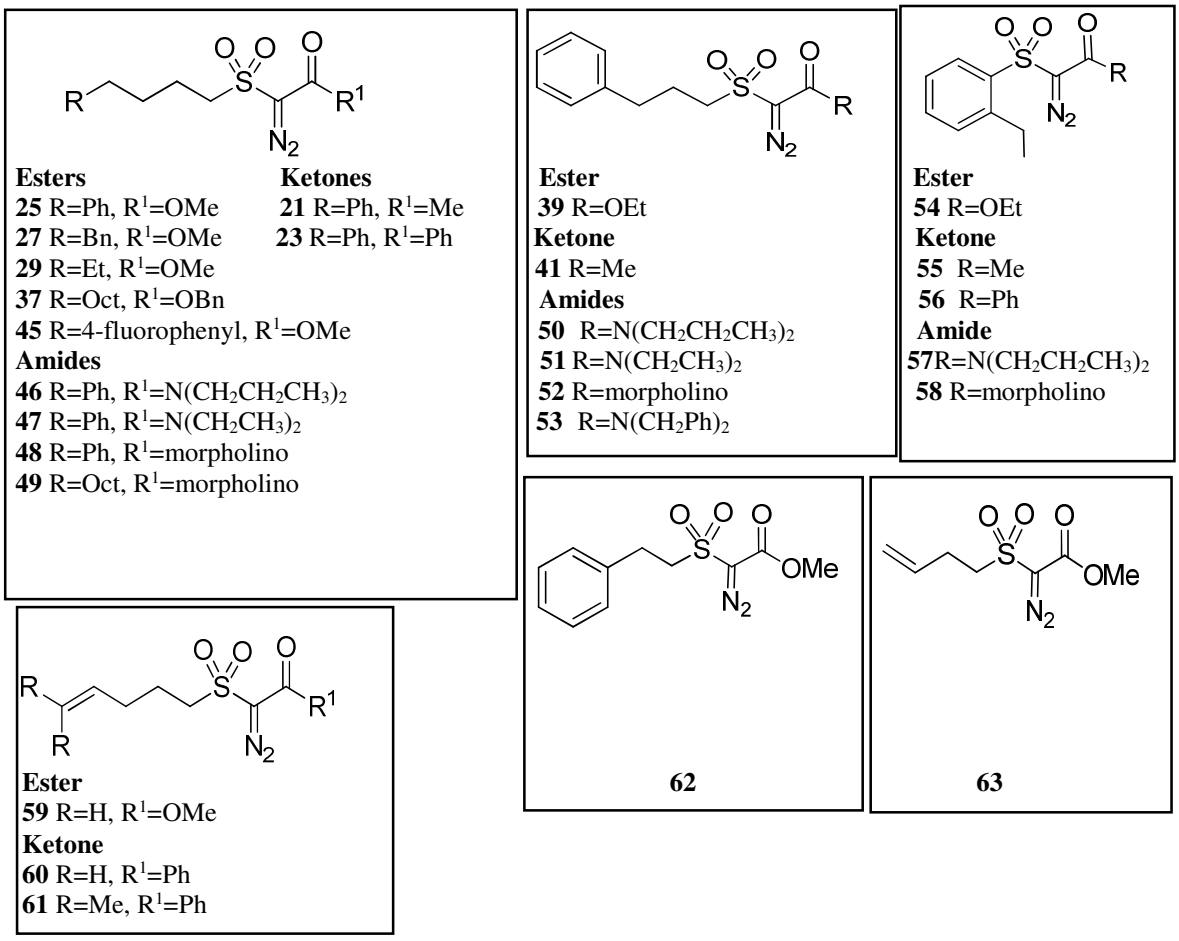
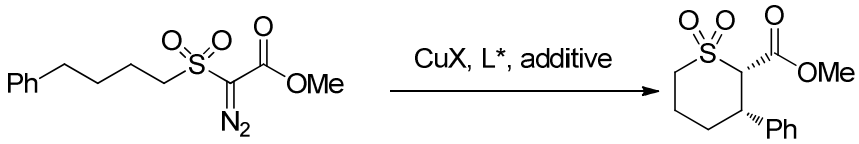


Figure 2.1

2) Chapter 4 focuses on a detailed investigation to explore the impact of each component of the catalyst system on the outcome of C–H insertion of α-diazo-β-oxo sulfones **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41**, **45** and **62**. The α-diazo-β-sulfonyl ester **25** was selected as the initial model as this substrate gave rise to the highest enantioselectivity (98% ee) in Flynn's original study. Impact of variation of the copper salt was examined through the use of $CuCl_2$ and $Cu(OTf)_2$. The effect of the additive, both the nature and the amount, was explored by using KBARF, KPF_6, $NaPF_6$, $LiPF_6$, $NaBF_4$, KBARF, $NaB(C_6H_5)_4$. The influence of the nature of the bisoxazoline ligand was explored using a range of commercially available ligands (**Scheme 2.10**).



25 **26a**

Scheme 2.10

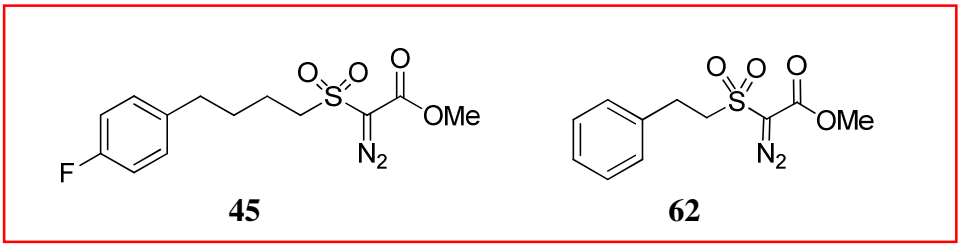
Building on this model study, a number of substrates **21**, **23**, **27**, **29**, **37**, **39** and **41** (**Figure 2.2**) which had been explored by Flynn, using only the phenyl substituted bisoxazoline ligand **20**, were subjected to a detailed study using a series of bisoxazoline ligands to determine the influence of the ligand structure on both the chemo- and stereoselectivity in the C–H insertion process.

Substrates **21** and **23** were chosen to explore the impact of having a ketone functional group at the α-diazocarbonyl site, substrates **27**, **29** and **37** were selected to investigate the ligand effect in insertion at non-benzylic C–H insertion sites and substrates **39** and **41** were included to investigate the ligand effect in sulfolane formation.

23 **21** Variation of α-diazo-carbonyl, to include α-diazoketone	**27** **29** **37** Variation of C–H insertion site; non-benzylic site of C–H insertion	**39** **41** Variation of length of alkyl chain, blocking thiopyran formation and directing insertion to afford sulfolanes.

Figure 2.2

In addition, two novel α-diazo-β-oxo sulfones **45** and **62** (**Figure 2.3**) were prepared for investigation in these ligand studies. Substrate **45** was selected to explore the electronic impact at the site of insertion, and substrate **62** was designed to explore reactivity when neither thiopyran nor sulfolane formation is possible.



45 **62**

Figure 2.3

3) Chapter 5 describes exploration of the impact of a rigid aryl linker, in place of the freely rotating alkyl chains, on copper mediated C–H insertion. Detailed investigation of catalyst effects in the C–H insertion reactions of the three novel α-diazo-β-oxo sulfones **54**–**56** (**Figure 2.4**) was undertaken, thereby enabling exploration of both α-diazoester **54** and α-diazoketone **55**–**56** derivatives. Chiral rhodium catalysts were explored, with substrate **54** to enable comparison with copper mediated transformation.

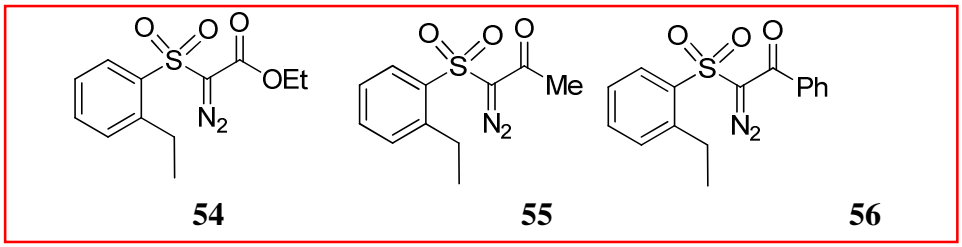
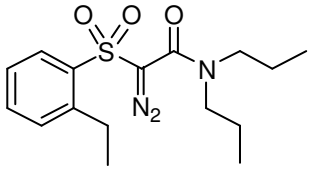


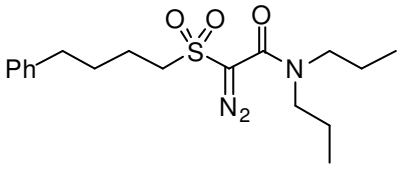
Figure 2.4

4) Further substrate modifications are discussed in Chapter 6. In this chapter we extend the discussion to include α-diazo-β-amido sulfones. A number of amide groups were chosen for investigation, namely *N*,*N*-dipropyl amide, *N*,*N*-diethyl amide, morpholino and *N*,*N*-dibenzyl amide. Ten novel α-diazo-β-amido sulfones **46**–**53**, **57**, **58** were prepared, as summarised in **Figure 2.5**.

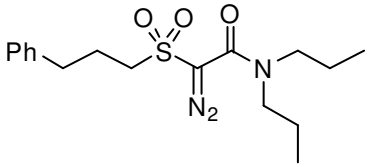
***N*,*N*-dipropyl amide substrates**



57

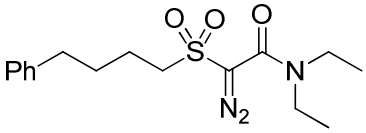


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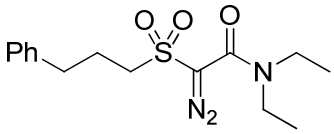


50

***N*,*N*-diethyl amide substrates**

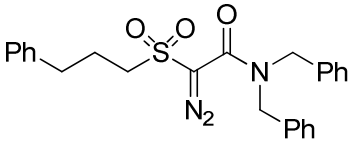


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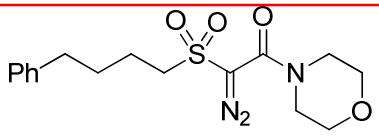
51

***N*,*N*-dibenzyl amide substrate**

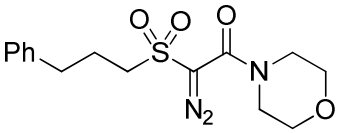


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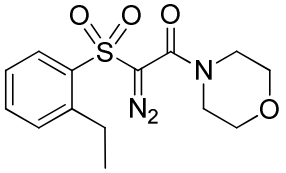
Morpholine amide substrates



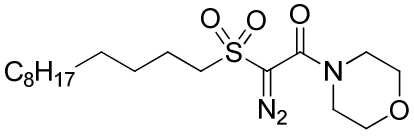
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52



58



49

Figure 2.5

A variety of sulfonyl groups was incorporated to enable investigation of the competition between C–H insertion into the sulfonyl chain to form thiopyrans or sulfolanes or into the amide moiety to form β- or ɣ- lactams (**Figure 2.6**). While this work predominately focused on the use of chiral copper catalysts, brief investigation of the use of enantioselective rhodium catalysts is also included.

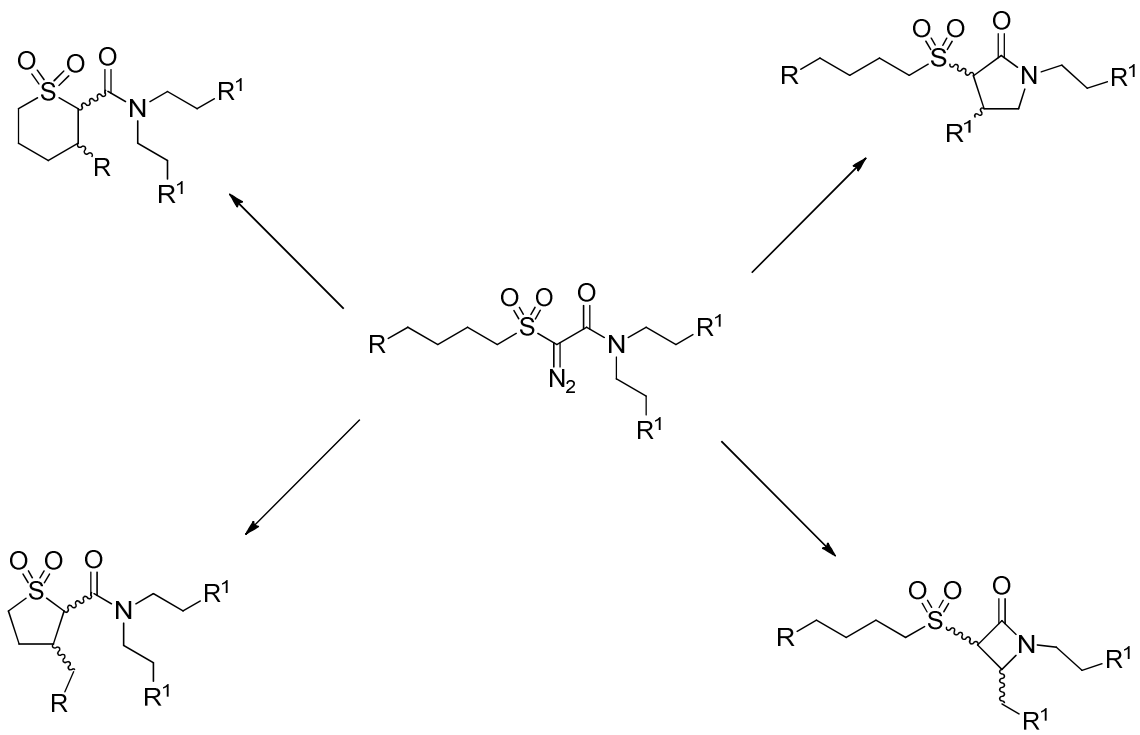


Figure 2.6

5) The final chapter (Chapter 7) focuses on the copper catalysed reactions of unsaturated α-diazo-β-oxo sulfones **59–61** and **63**. The presence of unsaturation leads to the possibility of cyclopropanation, as an alternative reaction pathway to C–H insertion. The substrates were designed to enable investigation of the impact of an ester or ketone substituent, in addition to the influence of substitution on the alkene (**Figure 2.7**). A brief study employing chiral rhodium catalysts is also presented in this chapter.

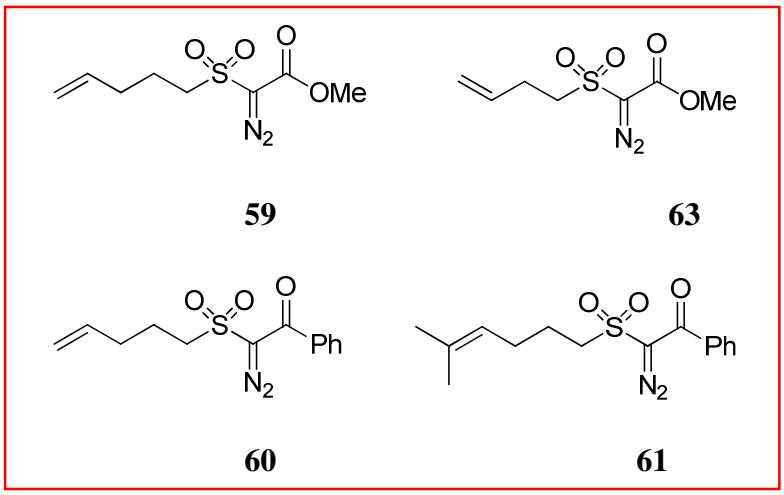


Figure 2.7

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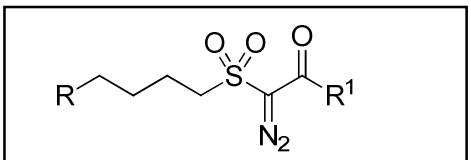
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Chapter Three
Synthesis of α-diazo-β-oxo sulfones

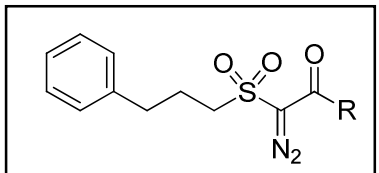
"If you can force your heart and nerve and sinew to serve your turn long after they are gone, and so hold on when there is nothing in you except the Will which says to them: 'Hold on!.....' Rudyard Kipling

3.1 Synthesis of α-Diazo-β-Oxo Sulfones

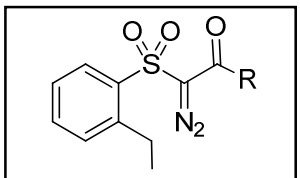
The initial aim of this project was to synthesise the following α-diazo-β-oxo sulfone **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41**, **45**–**63** substrates, selected for investigation as discussed in Chapters 4-7. Compounds **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41** were previously synthesised by Flynn,[1,2] while compounds **45**–**63** have not previously been reported (**Figure 3.1**).



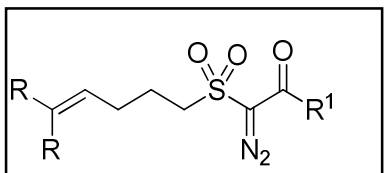
Esters **Ketones**
25 R=Ph, R^1=OMe **21** R=Ph, R^1=Me
27 R=Bn, R^1=OMe **23** R=Ph, R^1=Ph
29 R=Et, R^1=OMe
37 R=Oct, R^1=OBn
45 R=4-fluorophenyl, R^1=OMe
Amides
46 R=Ph, R^1=$N(CH_2CH_2CH_3)_2$
47 R=Ph, R^1=$N(CH_2CH_3)_2$
48 R=Ph, R^1=morpholino
49 R=Oct, R^1=morpholino



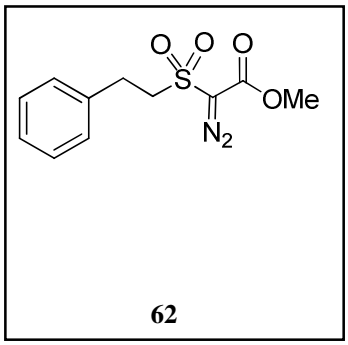
Ester
39 R=OEt
Ketone
41 R=Me
Amides
50 R=$N(CH_2CH_2CH_3)_2$
51 R=$N(CH_2CH_3)_2$
52 R=morpholino
53 R=$N(CH_2Ph)_2$



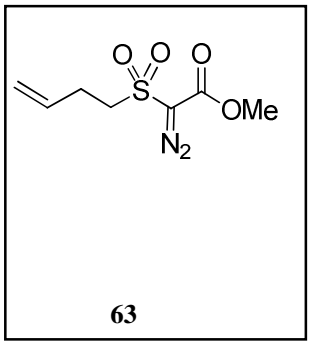
Ester
54 R=OEt
Ketone
55 R=Me
56 R=Ph
Amide
57 R=$N(CH_2CH_2CH_3)_2$
58 R=morpholino



Ester
59 R=H, R^1=OMe
Ketone
60 R=H, R^1=Ph
61 R=Me, R^1=Ph



62

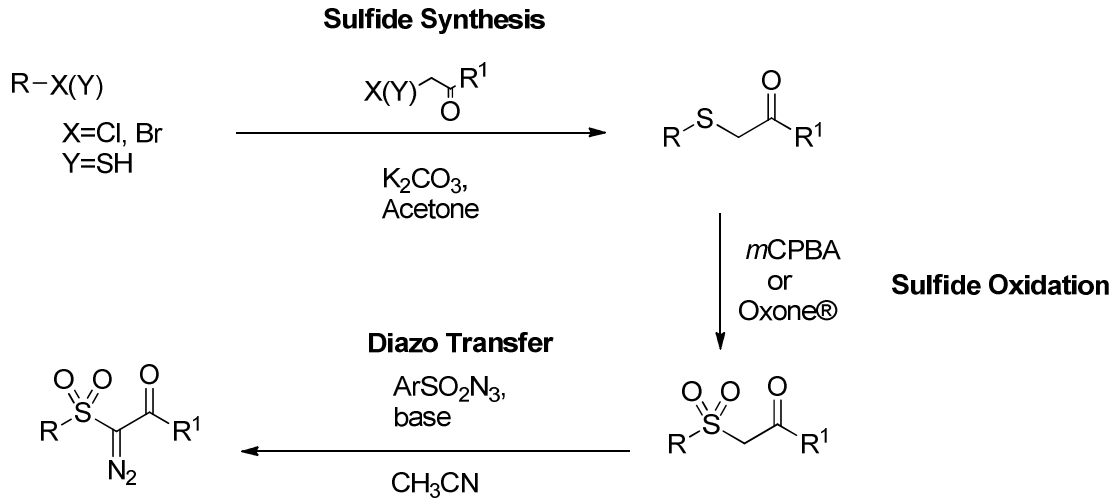


63

Figure 3.1

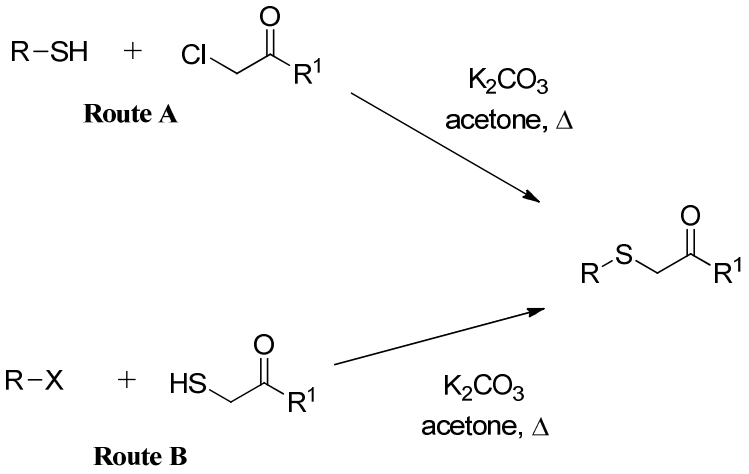
The general approach used for the synthesis of α-diazo-β-oxo sulfones **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41**, **45**–**63** is outlined in **Scheme 3.1.** The key stage in the synthesis of these α-diazo-β-oxo sulfones is the formation of a β-oxo-sulfide intermediate. Once a β-oxo-sulfide has been accessed, oxidation to the corresponding β-oxo-sulfone can be readily achieved, using either *m*CPBA or Oxone®. In general, the β-oxo-sulfides are carried through to the β-oxo-sulfones without purification and the sulfones are purified chromatographically prior to diazo transfer, to yield α-diazo-β-oxo sulfone substrates.

For the known α-diazo-β-oxo sulfone compounds **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41**, which had previously been synthesised by Flynn, the same synthetic approach was employed with just slight modifications in the synthesis of the precursors, as recommended by Flynn.



Scheme 3.1

The synthesis of the β-oxo-sulfide intermediates was accomplished in two ways, as outlined in **Scheme 3.2**. The first method involved a reaction between an alkyl thiol and an α-haloketone or α-haloester using potassium carbonate as a base (**Scheme 3.2**, **Route A**). The second method employed an α-thiocarbonyl compound reacting with an alkyl halide, again utilising potassium carbonate as a base (**Scheme 3.2**, **Route B**). The route used depended almost entirely on the commercial availability of the precursors.

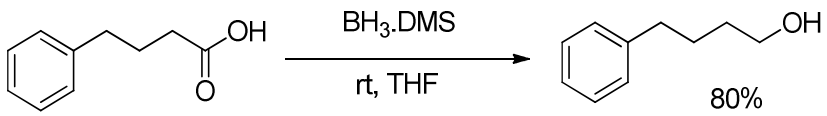


Scheme 3.2

3.2 Preparation of precursors to β-oxo-sulfide compounds

Prior to discussing the synthesis of the β-oxo-sulfide intermediates, the synthesis of all precursor compounds, required for both **Route A** and **Route B** is discussed. These precursor compounds include both alkyl halides and alkyl thiols. The synthesis of these compounds required between one and four synthetic steps.

3.2.1 Preparation of Precursor Alcohol



64

Scheme 3.3

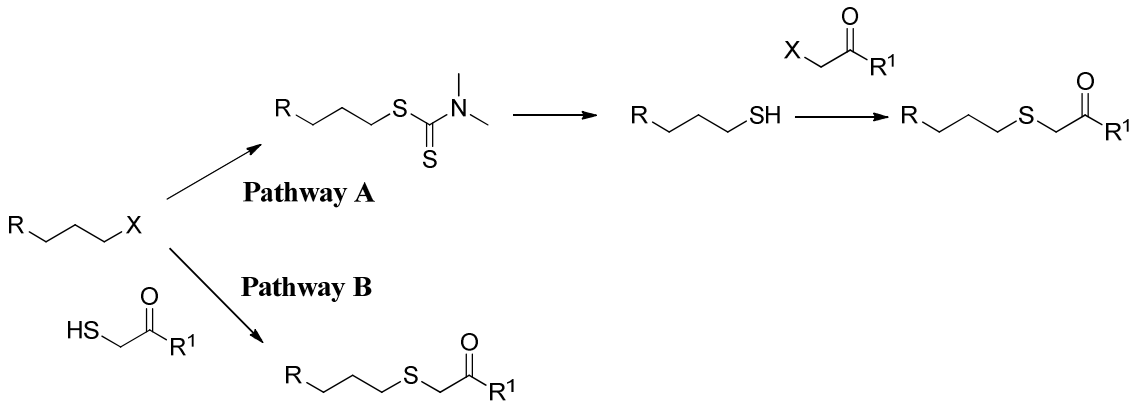
Reduction of 4-phenylbutyric acid to 4-phenylbutan-1-ol **64**[2,3] was carried out using borane dimethyl sulfide complex, at room temperature in dry THF over 1 h, according to a known procedure[4] for the preparation of a similar but not identical compound (**Scheme 3.3**). Primary alcohol **64** was obtained in 80% yield as a colourless oil in a high degree of purity, when the reaction was carried out on ~3g scale. During the course of this work, this reaction was repeated many times on scales of up to 20 g. In all cases, yields obtained were > 70% and the alcohol was always obtained in a sufficiently pure form to use without further purification thus accessing multigram quantities of **64** required for further synthetic steps was relatively straight forward. When this reaction was carried out on a scale of > 5 g, addition of the borane dimethyl sulfide complex to the solution of 4-phenylbutyric acid was carried out at 0 °C, due to the exothermic nature of this reaction.

3.2.2 Preparation of Alkyl Halides

The synthesis of alkyl halides were required for two transformations.

1) To be converted to a thiol *via* the synthesis of a dimethyldithiocarbamic acid derivative (**Scheme 3.4**, **Pathway A**).

2) To react as an electrophile with an α-thiocarbonyl compound, to synthesise a β-oxo-sulfide directly (**Scheme 3.4**, **Pathway B**).

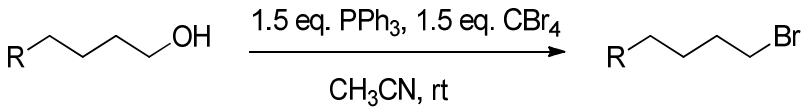


Scheme 3.4

A number of alkyl halide compounds **65**–**68** were synthesised during this project. Both alkyl bromides and alkyl iodides were synthesised utilising a range of methods.

3.2.2.1 Conversion of alcohols to bromides; the Appel reaction

Table 3.1 *Synthesis of alkyl bromides using the Appel reaction*



Entry	SM	R	Time (h)	Product	Yield (%)
1	**64**	Ph	3 h	**65**[2,5]	69[a]
2	**69**	Bn	2 h	**66**[6]	132[b]

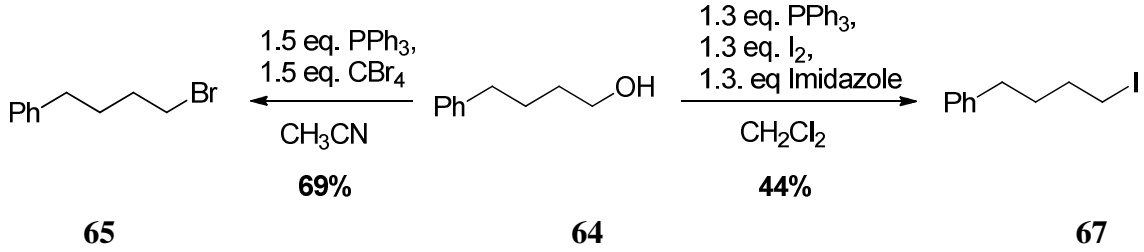
a. Purified material contains ~12% bromoform.
b. Purified material contains ~25% bromoform.

In this project two alcohols were converted to their corresponding bromides *via* the Appel reaction. While alcohol **64** was synthesised as described above, alcohol **69** was commercially available. The general reaction conditions used involved stirring an alcohol with triphenylphosphine and carbon tetrabromide in acetonitrile at room temperature, a procedure previously reported by Zou and co-workers,[4] however neither alkyl halide **65** or **66** were prepared in this publication. Flynn[2] prepared 4-phenyl-1-bromobutane **65** according to this procedure and Suzuki and co-workers [6] had also prepared 5-phenyl-1-bromopentane **66** according to this methodology.

There are two main byproducts formed during the Appel reaction: triphenylphosphine oxide and bromoform. Both alkyl bromides **65** and **66** were purified using column

chromatography. The relatively non-polar alkyl bromides were easily separated from the much more polar triphenylphosphine oxide, however, complete separation of the alkyl bromide compounds from bromoform was not as straightforward. In the case of alkyl halide **65**, which was obtained in 69% yield (**Table 3.1**, entry 1) ~12% bromoform remained; however, separation of alkyl halide **66** from bromoform proved to be more challenging, with relatively larger quantities of the impurity remaining in the purified product (**Table 3.1**, entry 2). Further purification was not attempted at this stage and impure alkyl halides **65** and **66** were carried forward to the next step. Both reactions were carried out on ~5–6 g scale and the alkyl bromides **65** and **66** were obtained in multi-gram quantities as colourless oils. While the alkyl bromides **65** and **66** were generally reacted within a few days of synthesis, they were relatively stable compounds which could be stored for a number of weeks without difficulty.

3.2.2.2 Conversion of alcohols to alkyl iodides



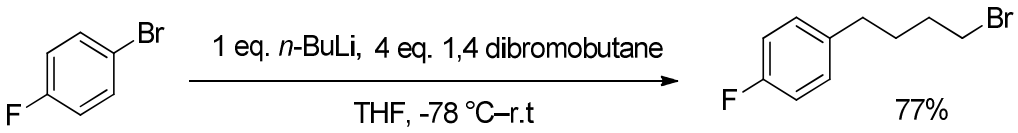
Scheme 3.5

While conversion of alcohol **64** to alkyl bromide **65** proved to be relatively successful, in terms of mass recovery and product purity (69%, **Table 3.1**, entry 1), the conversion of alcohol **64** to alkyl iodide **67**[7] was considered as an alternative. Preparation of alkyl iodide **67**[7] was made using a literature procedure[7] described for **67**, employing triphenylphosphine, iodine and imidazole (**Scheme 3.5**). Separation of alkyl iodide **67** from triphenylphosphine oxide was achieved using column chromatography. Alkyl iodide **67** was obtained as a colourless oil without noticeable impurities, in 44% yield, which is noticeably lower than the 69% achieved for alkyl bromide **65**. However it is worth mentioning that reaction to synthesise alkyl bromide **65** was carried out on ~5–6 g scale while synthesis of alkyl iodide **67** was carried out on ~20 g scale. Synthesis of alkyl halides **65** and **67** both have their advantages; alkyl iodide **67** can be obtained in a purer form than alkyl bromide **65**, leading to cleaner reactions in subsequent steps, however, alkyl iodide **67** is obtained in a much lower yield than alkyl bromide **65**. In addition, alkyl iodide **67** is less stable at room temperature than alkyl bromide **65** with noticeable

degradation within days of being synthesised, resulting in a colour change from clear to yellow to brown.

3.2.2.3 Synthesis of alkyl halides; lithium-halogen exchange

While 1-(4-bromobutyl)-4-fluorobenzene **68**[8] is a known compound, the reported synthesis involves several steps. During this work the synthesis of 1-(4-bromobutyl)-4-fluorobenzene **68**[8] was carried out *via* a lithium-halogen exchange using 1-bromo-4-fluorobenzene, *n*-butyl lithium and 1,4-dibromobutane in dry THF, according to a procedure reported by Flynn[2] for similar compounds (*p*-OMe, *p*-Me, *p*-NO_2 substitution) but not 1-(4-bromobutyl)-4-fluorobenzene **68**.[8] Excess 1,4-dibromobutane was removed by Kugelrohr distillation, to yield 1-(4-bromobutyl)-4-fluorobenzene **68** in 77% yield in multi-gram quantities which contained minor impurities. Further purification was not attempted at this stage.



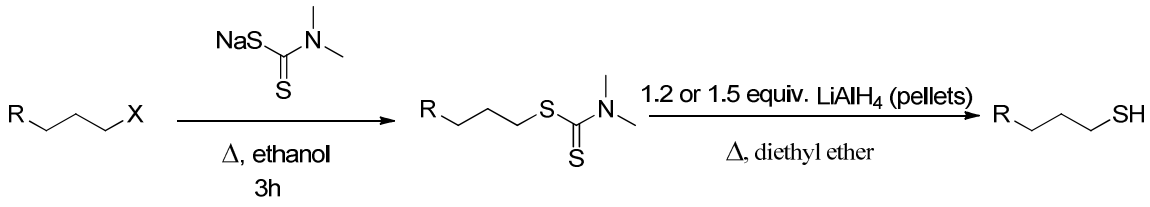
68

Scheme 3.6

Alkyl halides **65**–**68** were reacted directly with α-thiocarbonyl compounds to yield β-oxo sulfides, while alkyl halides **65** and **67** were used in the synthesis of thiol **70**.

3.2.3 Preparation of thiols using *N*,*N*-dimethyldithiocarbamic acid derivatives

Table 3.2 *Synthesis of* N,N-*dimethyldithiocarbamic acid derivatives and their corresponding thiols*



Entry	Alkyl Halide	R	X	*N*,*N*-dimethyldithiocarbamic acid derivatives	Yield (%)	Thiol	Time (h)	Yield[a] (%)
1	**71**	Ph	Cl	**72**[2]	58[a]	**73**[2,9]	3	99[c]

2	**67**	Bn	I	**74**[2]	82[b]	**70**[2,10]	2.5	83
3	**65**[d]	Bn	Br	**74**[2]	67[b]	**70**[2,10]	4	89

a. Not purified.
b. Purified using column chromatography on silica gel, not corrected for purity of alkyl bromide.
c. Contains ~10% unreacted starting material, *i.e*, *N*,*N*-dimethyldithiocarbamic acid derivatives.
d. Purified material contains ~12% bromoform.

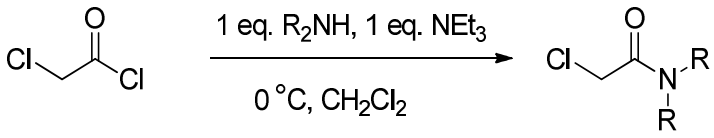
The alkyl halides **65**, **67**, **71** were readily converted to the analogous thiols **70** and **73** *via* initial formation of *N*,*N*-dimethyldithiocarbamic acid derivatives **74** and **72**, followed by lithium aluminium hydride reduction. Preparation of *N*,*N*-dimethyldithiocarbamic acid derivative **72** (**Table 3.2**, entry 1) was made using commercially available 1-chloro-3-phenylpropane and sodium dimethyldithiocarbamate under reflux in ethanol according to literature procedures.[2,11] This reaction was carried out on ~13 g scale and dimethyldithiocarbamic acid derivative **72** was isolated as colourless oil in 58% yield. Synthesis of dimethyldithiocarbamic acid derivative **74** (**Table 3.2**, entry 2) was carried out using the same method, with the exception that previously synthesised alkyl iodide **67** was used as the alkyl halide source. This reaction was carried out on ~3 g scale and after purification using column chromatography on silica gel, product **74** was obtained as a white solid in 82% yield in multi-gram quantities. Over the course of this work alkyl bromide **65** was also used as the alkyl halide source, with no noticeable differences in yield or product purity (**Table 3.2**, entries 2 and 3) when the purity of the starting alkyl bromide is taken into account.

Reduction of *N*,*N*-dimethyldithiocarbamic acid derivatives **72** and **74**, using a suspension of lithium aluminium hydride in refluxing diethyl ether, proved a very effective method for the synthesis of thiols **73** and **70** respectively. Flynn reported this protocol to be the best method for reducing *N*,*N*-dimethyldithiocarbamic acid derivatives; this was a modified procedure, adapted from Tsuboi and co-workers.[12] The suspension of lithium aluminium hydride in ether was freshly prepared before use, by refluxing a pellet of lithium aluminium hydride in diethyl ether for ~2 h prior to the addition of the *N*,*N*-dimethyldithiocarbamic acid derivative. Synthesis of thiol **73** was carried out on ~11 g scale (**Table 3.2**, entry 1) and was recovered as a colourless oil in 99% yield, however, this also contained ~10% unreacted starting material (*N*,*N*-dimethyldithiocarbamic acid derivitive **72**). Thiol **70** was isolated as a colourless oil in 83% yield (**Table 3.2**, entry 2) when this reaction was carried out on ~3 g scale, or 89% (**Table 3.2**, entry 3) when carried out on a ~5 g scale. Due to the malodorous nature of the two thiols, neither compound was purified and the scale of the reactions was kept below 11 g. Once prepared,

both thiols were reacted as soon as possible; neither was stored for a period of greater than three days prior to use. Storage at room temperature proved adequate; however, care was taken to ensure that the flask containing the thiol was thoroughly sealed, both to avoid contamination of surrounding areas with their odour and to prevent a significant loss in material due to evaporation of these relatively volatile compounds.

3.2.4 Preparation of α-chloroamides

Table 3.3 *Synthesis of α-chloroamide precursors*



Entry	R	Time (h)	α-chloroamide	Yield (%)
1	Bn	4.5	**75**[13]	73
2	Et	3.5	**76**[14]	83
3	Pr	3.5	**77**[15]	90
4	$(CH_2CH_2)_2O$	2.5	**78**[16]	39

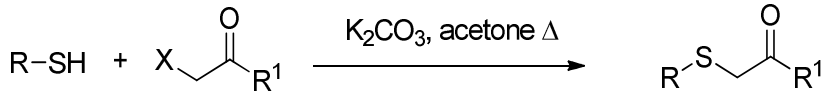
During the course of this work four α-chloroamides were synthesised, according to a general procedure described by Kissane *et al.*[17] for related compounds, but not these specific examples. All four compounds have been previously reported in the literature, following similar, but not identical, approaches. Reactions of α-chloroacetyl chloride with a series of secondary amines, in the presence of triethylamine, in dichloromethane led to α-chloro tertiary amides **75**–**78**, generally in good yields except for the morpholine derivative **78** (**Table 3.3**, entry 4). These reactions were generally conducted on a 10–15 g scale except for α-chloroamide **76**, which was carried out on ~3 g scale (**Table 3.2**, entry 2). Effective cooling was necessary due to the exothermic nature of these reactions. Each of the α-chloroamides **75**–**78** was sufficiently pure to use without further purification and all were obtained as coloured oils in multi-gram quantities. While the α-chloroamides were generally reacted with a thiol, to make β-amido-sulfides within a few days of synthesis, they have been successfully stored at room temperature for extended periods without noticeable degradation.

3.3 Preparation of β-oxo-sulfides

As was already discussed (**Section 3.1**), the synthesis of β-oxo-sulfides can be achieved using either **Route A** or **Route B**. Having successfully synthesised a number of alkyl halides, alkyl thiols and α-chloroacetamides, together with commercially available precursors, a range of β-oxo-sulfides was subsequently prepared. The reaction between a halide and thiol is an S_N2 type reaction, and requires the thiol to be converted to a thiolate anion using a base of appropriate strength. Reaction conditions had previously been optimised by Flynn, who reported that the use of potassium carbonate as base and acetone as solvent provided the best base/solvent combination for the synthesis of a range of β-oxo-sulfides. Therefore, these reaction conditions were used for the synthesis of β-oxo-sulfides prepared either *via* **Route A** or **Route B** with no further developmental work being carried out during this project. Suitable relative ratios of starting materials had also previously been optimised and were determined to be 1 : 1 : 1.1 equivalents of thiol : halide : base. Reaction scale varied from 1–10 g of thiol. In all cases, the reaction procedure remained the same and there were no observable differences in product yield or purity obtained. All sulfides were obtained in multigram quantities, were stored at room temperature and were used as quickly as possible (within one week of synthesis), without purification as a result of their odour.

3.3.1 Synthesis of β-oxo-sulfides: Route A

Table 3.4 *Synthesis of β-oxo-sulfides via Route A*



Entry	R	R^1	X	Time (h)	β-oxo-sulfide	Crude Yield (%)[a]
1	$Ph(CH_2)_3$	Me	Cl	19	**79**[2]	79
2	$Ph(CH_2)_4$	Me	Cl	18	**80**[2]	82
3	$Ph(CH_2)_4$	Ph	Br	19	**81**[2]	76
4	*n*-$C_{12}H_{25}$	OBn	Br	19	**82**[2]	Quantitative
5	2'-ethylphenyl	OEt	Br	19	**83**	97
6	2'-ethylphenyl	Ph	Br	21	**84**	99
7	2'-ethylphenyl	Me	Cl	20	**85**	68
8	$Ph(CH_2)_3$	$N(CH_2Ph)_2$	Cl	21	**86**	69
9	$Ph(CH_2)_3$	morpholino	Cl	18	**87**	93[b]
10	$Ph(CH_2)_4$	$N(CH_2CH_3)_2$	Cl	16	**88**	84
11	2'-ethylphenyl	morpholino	Cl	19	**89**	92
12	2'-ethylphenyl	$N(CH_2CH_2CH_3)_2$	Cl	21	**90**	95
13	*n*-$C_{12}H_{25}$	morpholino	Cl	18	**91**	78

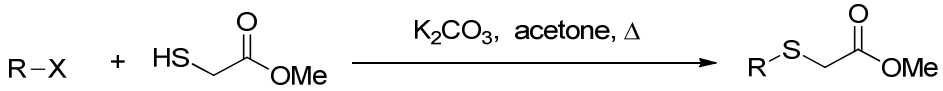
a. Reported yields are for crude material, which were sufficiently pure to use without purification.
b. ~60% pure with unidentified products.

Thirteen β-oxo-sulfides were synthesised *via* **Route A**. Seven of these compounds **82–85, 89–91** (**Table 3.4**, entries 4–7, 11–13) were prepared from commercially available thiols, while compounds **79–81** and **86–88** (**Table 3.4**, entries 1–3, 8–10) were prepared from thiols **70** and **73**, synthesised as part of this project (**Section 3.2.3**). In all cases, the α-haloketones (**Table 3.4**, entries 1–3, 6–7) and α-haloester (**Table 3.4**, entry 4) were purchased from a commercial source, while the α-chloroamides **75-78**, (**Table 3.4**, entry 8–13) were synthesised during the course of this work.

In general, yields and product purities obtained were highest with commercial precursors, with slightly lower yields and purities when thiols synthesised in this work were employed.

3.3.2 Synthesis of β-oxo-sulfides: Route B

Table 3.5 *Synthesis of β-oxo-sulfides via Route B*



Entry	R	X	Alkyl halide	Time (h)	Sulfide	Crude Yield (%)[a]
1	$Ph(CH_2)_4$	Br	**65**	21	**92**[2]	quantitative
2	$Ph(CH_2)_4$	I	**67**	21	**92**[2]	98
3	$Ph(CH_2)_5$	Br	**66**	18	**93**[2]	quantitative
4	$Ph(CH_2)_3$	Cl	**71**	17	**94**	91
5	Hex	Br	**95**	18	**96**[2]	100
6	$Ph(CH_2)_2$	Cl	**97**	21	**98**	100
7	$4\text{-}FC_6H_4(CH_2)_4$	Br	**68**	18	**99**	84
8	$H_2C{=}CH(CH_2)_2$	Br	**100**	21	**101**	89
9	$H_2C{=}CH(CH_2)_3$	Br	**102**	21	**103**	93

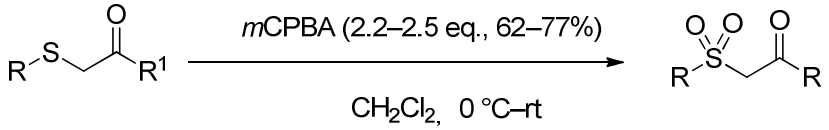
a. Reported yields are for crude material.

Compounds prepared *via* **Route B** involved the use of methyl thioglycolate as the reacting thiol with a range of alkyl halides, with potassium carbonate as base, in acetone. Some of the alkyl halides were commercially available (**Table 3.5**, entries 4–6, 8–9), while the remaining alkyl halides were synthesised during the course of this work (**Table 3.5**, entries 1–3, 7) (**Section 3.2.2**). All sulfides in **Table 3.5** were prepared in high yields, with sufficient purity for further use, and were used without further purification due to malodour. Compound **92** was synthesised using alkyl bromide **65** and alkyl iodide **67**, during the course of this work, with no noticeable difference in product yield or purity (**Table 3.5**, entries 1 and 2 respectively).

3.4 Synthesis of β-oxo-sulfones

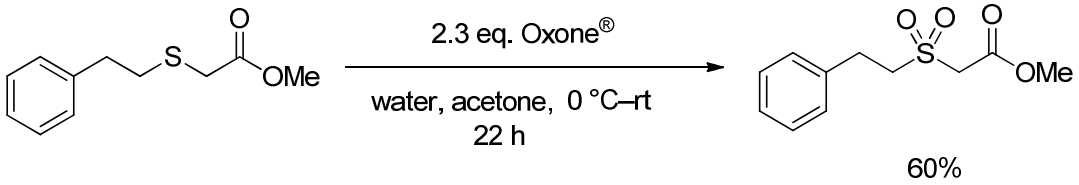
3.4.1 Synthesis of β-oxo-sulfones *via* oxidation of β-oxo-sulfides using *m*CPBA and Oxone®

Table 3.6 *Synthesis of β-oxo-sulfones from β-oxo-sulfides using mCPBA as oxidant*



Entry	R	R^1	β-oxo-sulfide	Time (h)	β-oxo-sulfone	Purified Yield (%)[a]
1	$Ph(CH_2)_3$	Me	**79**[2]	4	**104**[2]	55 (66[b])
2	$Ph(CH_2)_4$	Me	**80**[2]	4	**105**[2]	55 (79[b])
3	$Ph(CH_2)_4$	Ph	**81**[2]	20	**106**[2]	28 (68[b])
4	$Ph(CH_2)_4$	OMe	**92**[2]	3	**107**[2]	57
5	$Ph(CH_2)_5$	OMe	**93**[2]	4	**108**[2]	58
6	Hex	OMe	**96**[2]	25	**109**[2]	67
7	$Ph(CH_2)_3$	OMe	**94**	22	**110**	64
8	*n*-$C_{12}H_{25}$	OBn	**82**[2]	24	**111**[2]	86
9	4-$FC_6H_4(CH_2)_4$	OMe	**99**	5	**112**	42
10	2′-ethylphenyl	OEt	**83**	19	**113**	76
11	2′-ethylphenyl	Ph	**84**	17	**114**	53
12	2′-ethylphenyl	Me	**85**	22	**115**	75
13	2′-ethylphenyl	$N(CH_2CH_2CH_3)_2$	**90**	6	**116**	51[c]
14	2′-ethylphenyl	morpholino	**89**	7	**117**	72
15	$Ph(CH_2)_4$	$N(CH_2CH_3)_2$	**88**	6	**118**	51
16	$Ph(CH_2)_3$	morpholino	**87**	19	**119**	76
17	$Ph(CH_2)_3$	$N(CH_2Ph)_2$	**86**	25	**120**	65
18	*n*-$C_{12}H_{25}$	morpholino	**91**	7	**121**	60

a. Yields are reported for material after purification using column chromatography on silica gel.
b. Corrected for sulfoxide seen in ^{1}H NMR of the crude spectra.
c. After purification using column chromatography, followed by recrystallisation from IPA.



98 **122**

Scheme 3.7

Oxidation of β-oxo-sulfides to the corresponding β-oxo-sulfones **104–121** was achieved using 2.2–2.5 equivalents of *m*CPBA as oxidant (**Table 3.6**, entries 1–18). Each of the β-oxo-sulfides **79–94**, **96**, **99** was employed in further reactions without prior purification. In one instance, for compound **122** (**Scheme 3.7**), Oxone® was employed instead. A range of α-sulfonyl esters (**Table 3.6**, entries 4–10), α-sulfonyl ketones (**Table 3.6**, entries 1–3, 11–12) and α-sulfonyl amides (**Table 3.6**, entries 13–18) was synthesised during this project. While Flynn had described the synthesis of **104–109**, **111** (**Table 3.6**, entries 1–6, 8), β-oxo-sulfones **110**, **112–121** were prepared as novel compounds (**Table 3.6**, entries 7, 9–18, compound **122**, **Scheme 3.7**). The general procedure involved addition of *m*CPBA in dichloromethane, to the β-oxo-sulfides in dichloromethane at 0 °C. Reaction times varied from 3–25 h, as did the scale of the reaction (~1–20 g). Reactions were monitored using TLC analysis. In general sulfoxides were observed as the most polar compound, and appeared as a black spot on the baseline when stained with vanillin. The sulfone had the intermediate polarity and was generally seen to stain white in the presence of vanillin, with sulfides being the least polar and also staining white. In addition to TLC analysis, the use of ^{1}H NMR spectroscopy can be used to indicate if the transformation from β-oxo-sulfide to β-oxo-sulfone is complete. For each of the β-oxo-sulfones **104–112**, **118–121** (**Table 3.7**, entries 1–9, 15–18) a distinctive symmetrical multiplet is seen in the corresponding ^{1}H NMR spectra, in the region of 3.30–3.40 ppm for the CH_2 adjacent to the sulfone.

As the quality of commercial *m*CPBA varied significantly (between 62–77%) titration of *m*CPBA is recommended before use.[18] Once the reaction was complete, by TLC analysis, excess *m*CPBA was quenched with aqueous sodium metabisulfite solution. In earlier work, the use of "a" sodium metabisulfite "quench" was not implemented and separation of the β-oxo-sulfones from excess *m*CPBA proved to be difficult. While there is a possibility of decreased yields of the α-sulfonyl ketones due to adduct formation in the work up, during this work, no such issue was observed.

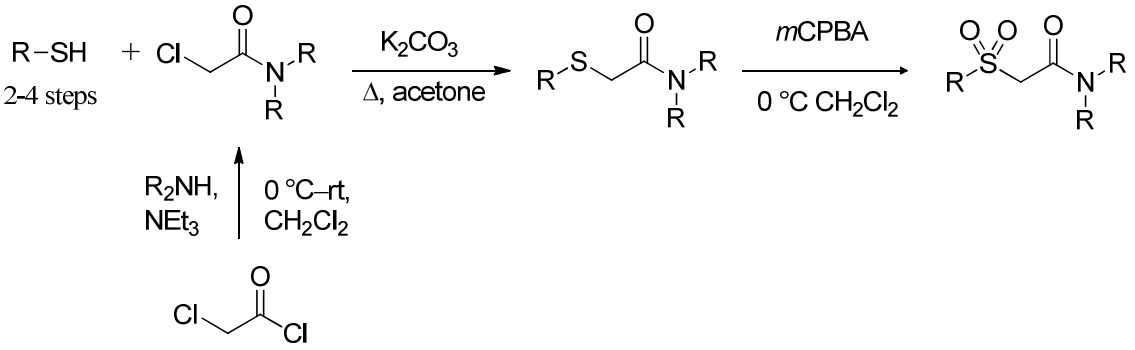
In general, use of *m*CPBA proved to be an effective method of oxidising β-oxo-sulfides to β-oxo-sulfones, with residual sulfoxide only seen in three cases **104–106**. These are once off experiments, conducted very early in this work and reduced yields may reflect the quality of the *m*CPBA rather than an issue with the oxidation. All β-oxo-sulfones were purified before use, and all were obtained in a high degree of purity as either

colourless/pale yellow oils or white solids, in multi-gram quantities, which were stored at room temperature for long periods of time without degradation.

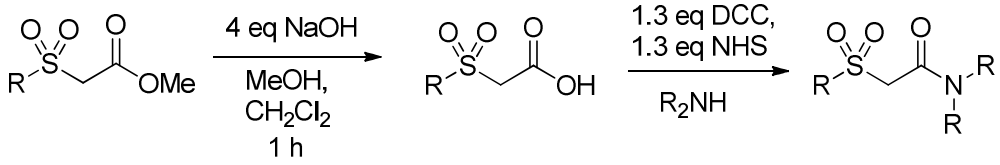
The yields reported (typically >50% as summarised in **Table 3.6**) reflect the fact that the sulfide precursors employed had not been purified in advance of oxidation rather than an inefficient transformation.

3.4.2 Alternative synthesis of β-amido-sulfones

The synthesis of α-sulfonyl amides can be achieved using **Route A**, where an alkyl thiol is reacted with an α-chloroamide in the presence of potassium carbonate, followed by *m*CPBA oxidation (**Scheme 3.8**) as summarised in **Tables 3.4** and **3.6**.
This linear approach is very time consuming, often requiring up to 5–7 steps in total (**Scheme 3.8**, **Pathway One**). Accordingly, an alternative divergent approach was explored (**Scheme 3.9**, **Pathway Two**), where 2-sulfonyl esters **107** and **110** were hydrolysed to the corresponding carboxylic acids **123** and **124**, followed by DCC coupling between an acid and a range of secondary amines in the presence of *N*-hydroxy succinimide (NHS). This route provided more ready access to a series of α-sulfonyl amides and is recommended for future work in this area.



Scheme 3.8 *Pathway One; β-amido-sulfone synthesis*



R=Ph$(CH_2)_4$ (**110**) R=Ph$(CH_2)_4$ (**124**), 89%
R=Ph$(CH_2)_3$ (**107**) R=Ph$(CH_2)_3$ (**123**), 76%

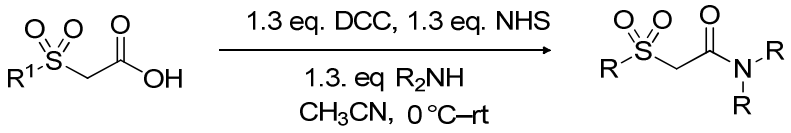
Scheme 3.9 *Pathway Two; β-amido-sulfone synthesis*

3.4.2.1 Synthesis of carboxylic acids; precursors for DCC reaction

Ester hydrolysis was conducted *via* addition of methanolic sodium hydroxide to a solution of the α-sulfonyl esters **110** and **107** in dichloromethane and methanol (**Section 3.4.2**, **Scheme 3.9**), following a literature procedure.[19] Both novel carboxylic acids were obtained as analytically pure white solids; no further purification was required. Both acids were also obtained in good yield (**Scheme 3.9**), in multi-gram quantities and could be stored at room temperature for periods of up to 6 months without loss of purity. Interestingly, a previous attempt to hydrolyse **110**, involving addition of aqueous NaOH to a solution of **110** in MeOH/THF at 50 °C for 5 hours, proved unsuccessful with neither starting material nor product material recovered.

3.4.2.2 Synthesis of β-amido-sulfones *via* DCC coupling reaction

Table 3.7 *Synthesis of β-amido-sulfones*



Entry	Carboxylic Acid	β-amido-sulfones	R^1	R	Time (h)	Yield[a] (%)
1	**123**	**125**	$Ph(CH_2)_3$	Et	24	50
2	**124**	**126**	$Ph(CH_2)_4$	Pr	48	56
3	**123**	**127**	$Ph(CH_2)_3$	Pr	23	53
4	**123**	**120**	$Ph(CH_2)_3$	Bn	48	49
5	**124**	**128**	$Ph(CH_2)_4$	$(CH_2CH_2)_2O$	48	49

a. Purified using column chromatography on silica gel.

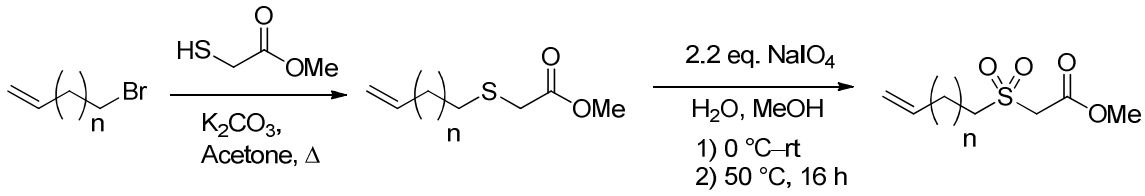
Five novel β-amido-sulfones were synthesised *via* a DCC coupling reaction between an acid and a secondary amine in the presence of NHS, in accordance with a published procedure.[20] Reaction times varied between 23–48 h. Each of the compounds **120**, **125-128** was obtained as either a colourless oil or a white solid after purification by column chromatography. Typically reactions were carried out between 2–4 g scale, and β-amido-sulfones **120**, **125**–**128** were obtained in multi-gram quantities and modest yields (**Table 3.7**, entries 1–5). For comparison purposes, β-amido-sulfone **120** was prepared using both **Pathway One** (**Table 3.6**, entry 17) in a 45% yield (65% oxidation, 69% sulfide) and *via* **Pathway Two** (**Table 3.7**, entry 4) in a 49% yield. Therefore, due to the overall yield and

number of steps, the DCC route proved much more amenable to provide access to muti-gram quantities of α-sulfonyl amides.

3.4.3 Synthesis of unsaturated β-oxo-sulfones

In order to investigate intramolecular cyclopropanation reactions, access to the novel unsaturated β-oxo-sulfones **129** and **130** was required. In total four such substrates **129-132** were synthesised. Two different methods were employed, based on the commercial availability of the precursors. Method One is outlined below; substrates **129** and **130** were synthesised *via* this method.

Table 3.8 *Synthesis of unsaturated β-oxo-sulfones (Method One)*



100, **102** **129**, **130**

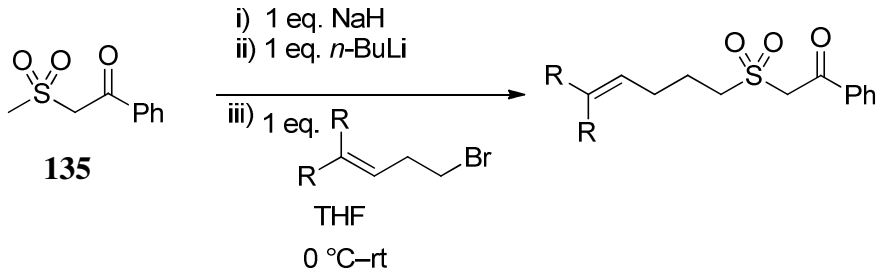
Entry	β-oxo sulfide	β-oxo sulfone	n	Time (h)	Yield[a] (%)
1	**102**	**129**	1	19	46 (70[b])
2	**100**	**130**	0	20	45 (90[b])

a. Yield refers to material purified by column chromatography.
b. Yield corrected for sulfoxide in crude material, as observed by ^{1}H NMR.

After the β-oxo-sulfides **102** and **100** were readily accessed in a single step, by alkylation of methyl thioglycolate (**Table 3.5**, entries **8** and **9**), oxidation to form the β-oxo-sulfones **129** and **130** was undertaken using $NaIO_4$ in aqueous methanol. Use of *m*CPBA was not attempted to avoid epoxide formation. The initial reaction of β-oxo-sulfide with $NaIO_4$ to form β-oxo-sulfoxide was quite exothermic and generally complete within three hours, however, the second oxidation to form β-oxo-sulfone was much slower. Considerable efforts were invested to optimise oxidation of **102**; little or no oxidation of the β-oxo-sulfoxide **133** was seen at room temperature. However, on heating to 50 °C for 16 h, a substantial portion of the β-oxo-sulfoxide **133** was oxidised to the β-oxo-sulfone **129**, though the reaction did not go to completion (**Table 3.8**, entry 1). Analysis of the ^{1}H NMR spectra of the crude product showed that the mixture contained 63% sulfone **129** and 37% sulfoxide **133** (**Table 3.8**, entry 1). Purification of multi-gram quantities of β-

oxo-sulfone **129** was easily carried out using column chromatography, due to the relatively large differences in polarity between the β-oxo-sulfoxide **133** and β-oxo-sulfone **129**. Approximately 3.5 g of β-oxo-sulfone **129** was isolated as a pure colourless oil. As this method proved adequate for the synthesis of the unsaturated β-oxo-sulfone **129**, with no evidence for epoxidation of the double bond, it was also used for the synthesis of β-oxo-sulfone **130**, (**Table 3.8**, entry 2). While ~1.6 g of β-oxo-sulfone **130** was isolated after purification, analysis of the ^{1}H NMR spectra of the crude reaction showed that it was composed of 50% β-oxo-sulfoxide **134**. As sufficient quantities of material were isolated in the case of both **129** and **130**, further optimisation of this process was not carried out at this stage.

Table 3.9 *Synthesis of β-oxo-sulfones using Method Two*



Entry	R	Time (h)	β-oxo-sulfone	Yield[a] (%)
1	H	20	**131**	40 (75%[b])
2	Me	19	**132**	22 (67%[c])

a. Yield refers to material purified by column chromatography.
b. Yield calculated accounting for unreacted starting material. ^{1}H NMR of crude product reveals that there is 47% starting sulfone **135** present.
c. Yield calculated accounting for unreacted starting material. ^{1}H NMR of crude product reveals that there is 67% starting sulfone **135** present.

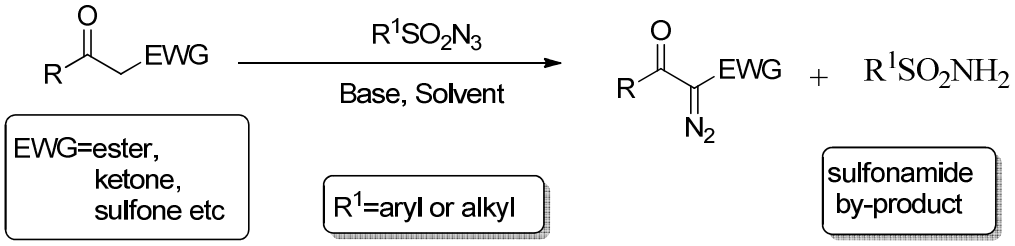
An alternative approach was explored for the synthesis of β-keto-sulfones **131** and **132**. Challenges associated with the efficiency of the periodate oxidation, coupled with the need to synthesise α-thio acetophenone, if Method One was pursued, were the key drivers in examining a different method. As generation of the dianion of commercially available 2-(methylsulfonyl)-1-phenylethanone was reported in the literature,[21] it was decided to explore its use here to synthesise β-oxo-sulfones **131** and **132** directly. In the literature report, the dianion of 2-(methylsulfonyl)-1-phenylethanone was reacted with 1-bromo-3-chloropropane to yield 2-(4-chlorobutyl)sulfonyl-1-phenylethanone in 79% yield.

As 2-(methylsulfonyl)-1-phenylethanone **135** was commercially available, selective α-alkylation was explored to yield the β-keto sulfones **131** and **132** directly. While the efficiencies of the alkylation reactions were relatively low, the desired β-keto sulfones were readily obtained in sufficient quantities for subsequent reaction in just a single step from commercial precursors.

Generation of the dianion of 2-(methylsulfonyl)-1-phenylethanone **135** was achieved using sequential addition of NaH and *n*-butyllithium. The order of addition of the bases, the temperature of the reaction mixture and the timing of addition are all important factors in the successful generation of the dianion and subsequent reaction with the alkyl halide. Low recovered yields for β-keto sulfones **131** and **132** were obtained, mainly due to the large amount of starting material present in the crude reaction mixtures in both cases (**Table 3.9**, entries 1 and 2).

3.5 Synthesis of α-diazo-β-oxo-sulfones

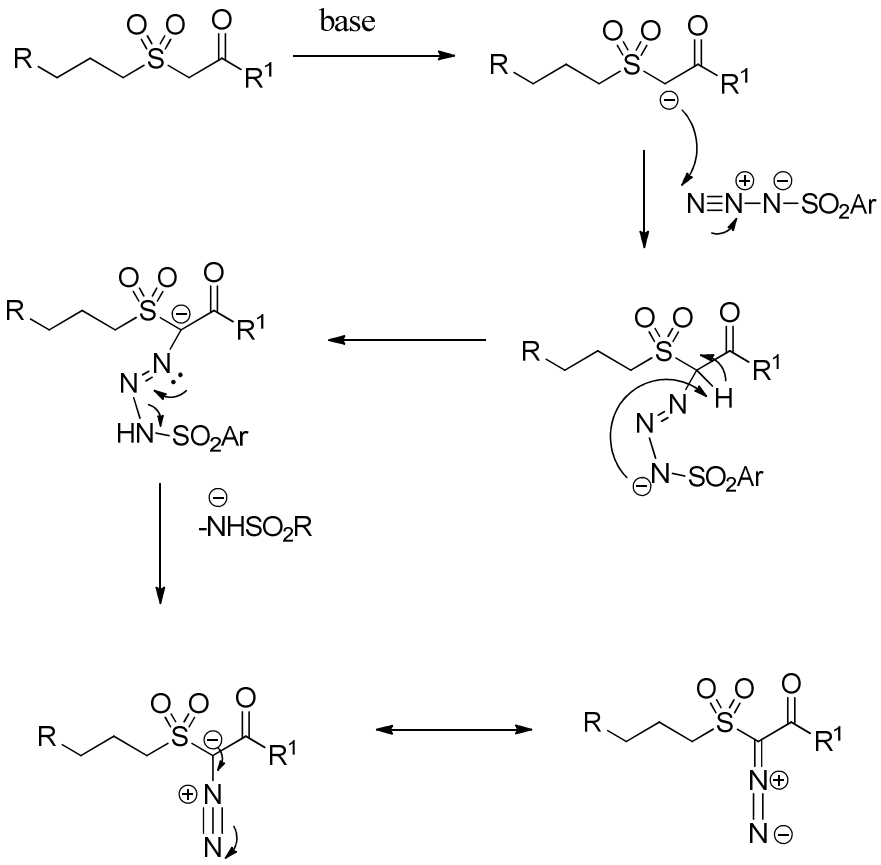
The synthesis α-diazocarbonyl compounds can be achieved using a variety of different methods.[22,23] One of the most popular routes to these compounds, developed by Regitz,[24] involves the transfer of a diazo moiety from a diazo transfer reagent to an active methylene compound. The methylene group is activated by the presence of two adjacent electron withdrawing groups as shown in **Scheme 3.10**. This method is generally used to synthesise β-keto esters, β-diketones, α-diazo-β-oxo sulfones *etc*.[23]



Scheme 3.10

In order for the diazo transfer reaction to take place, a base of appropriate strength is required to deprotonate the methylene group adjacent to the carbonyl group; bases commonly used include potassium carbonate, DBU, triethylamine and sodium hydride. There is a wide variety of diazo transfer reagents available, with different degrees of

reactivity and stability, *e.g.* mesyl azide,[25] *p*-toluenesulfonyl azide[26] and *p*-acetamidobenzenesulfonyl azide.[27,28] One of the most commonly used diazo transfer reagents is *p*-toluenesulfonyl azide, due to its generally good reactivity. However, the use of this reagent is less than ideal due to its low impact sensitivity and low initiation temperature.[29] Therefore, safer alternatives to this reagent are constantly being investigated. An additional consideration in choosing a diazo transfer reagent is the ability to separate the sulfonamide byproduct from the α-diazocarbonyl compound. The synthesis of α-diazocarbonyl compounds *via* diazo transfer is constantly being improved upon and further developed, as can been seen from a number of recent publications.[30–33] The mechanism for a diazo transfer reaction is outlined in **Scheme 3.11**.



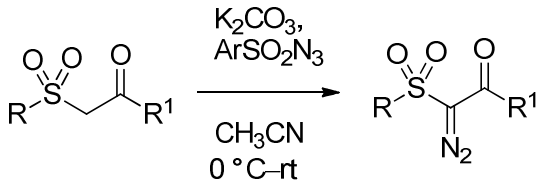
Scheme 3.11

3.5.1 Synthesis of α-diazo-β-keto-sulfones and α-diazo-β-ester-sulfones

The synthesis of known α-diazo-β-oxo sulfones **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41**[1,2] and novel α-diazo-β-oxo sulfones **45**, **54–56**, **59–63** was undertaken during this project using a variety of diazo transfer reagents, bases and temperatures. The reaction conditions for each of the compounds were not necessarily optimised. The work up that was employed on reaction completion depended on the initial reaction conditions. In all cases, reactions were monitored using TLC analysis. The disappearance of the methylene signal of the β-

oxo sulfone in the ^{1}H NMR was indicative of α-diazo-β-oxo sulfone formation. Infra-red analysis of these substrates was a crucial piece of evidence for α-diazocarbonyl formation with absorptions for the C=N_2 stretch seen in the region of ν_{max}/cm^{-1} 2103–2132 cm^{-1}. For safety purposes, reactions were conducted on scales of <3g.

Table 3.10 *Synthesis of α-diazo-β-keto-sulfone and α-diazo-β-ester-sulfone substrates*



Entry	R	R^1	β-oxo-sulfone	$ArSO_2N_3$	Time (h)	α-diazo-β-oxo-sulfone	Purified Yield (%)[a]
1	$Ph(CH_2)_3$	Me	**104** [2]	*p*-tosyl azide	3.5	**41**[1,2]	70
2	$Ph(CH_2)_4$	Me	**105**[2]	*p*-tosyl azide	2.5	**21**[1,2]	33
3	$Ph(CH_2)_4$	Ph	**106**[2]	*p*-tosyl azide	2.5	**23** [1,2]	31
4	$Ph(CH_2)_4$	OMe	**107**[2]	*p*-tosyl azide	3.5	**25**[1,2]	61
5	$Ph(CH_2)_4$	OMe	**107**[2]	*p*-ABSA	28	**25**[1,2]	58
6	$Ph(CH_2)_5$	OMe	**108**[2]	*p*-tosyl azide	3	**27**[1,2]	65
7	C_6H_{13}	OMe	**109**[2]	*p*-ABSA	18.5	**29** [1,2]	75
8	$Ph(CH_2)_3$	OEt		*p*-tosyl azide	3.5	**39**[1,2]	91
9	$C_{12}H_{25}$	OBn	**111**[2]	*p*-ABSA	18.5	**37**[1,2]	90
10	4-$FC_6H_4(CH_2)_4$[b]	OMe	**112**	*p*-tosyl azide	3.5	**45**	62
11	2-phenethyl[b]	OMe	**122**	*p*-ABSA[c]	6	**62**	53
12	2'-ethylphenyl[b]	OEt	**113**	*p*-ABSA	4	**54**	69
13	2'-ethylphenyl[b]	Ph	**114**	*p*-ABSA	5	**56**	81
14	2'-ethylphenyl[b]	Me	**115**	*p*-ABSA	4	**55**	71
15	H_2C=$CH(CH_2)_3$[b]	OMe	**130**	*p*-ABSA [d]	0.75	**63**	65
16	H_2C=$CH(CH_2)_4$[b]	OMe	**129**	*p*-ABSA[c,e]	0.17	**59**	60
17	H_2C=$CH(CH_2)_4$[b]	Ph	**131**	*p*-ABSA[e]	0.33	**60**	95
18	Me_2C=$CH(CH_2)_4$[b]	Ph	**132**	*p*-ABSA[e]	0.33	**61**	83

a. Yield refers to material purified by column chromatography.
b. Novel compounds prepared in this project.
c. DBU was employed as base instead of potassium carbonate.
d. Addition was carried out at room temperature and the reaction mixture was then heated to 40 °C
e. Reaction was carried out at room temperature.

Flynn prepared α-diazo-β-oxo sulfones **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41** using *p*-toluenesulfonyl azide and potassium carbonate in acetonitrile, from 0 °C to room temperature, according to a modified Regitz procedure developed by Koskinen and Muñoz.[34] The main advantage of using the Koskinen methodology is the ease with which

the sulfonamide byproduct is removed; concentration of the crude material followed by stirring in ether : hexane in 2:1 ratio renders the byproduct sulfonamide insoluble and thus it can be easily removed by filtration, reducing the amount present but not removing it completely. Flynn reports that purification using column chromatography is still necessary when this method is employed. Therefore, early work carried out in this project employed the same reaction conditions using ether in place of ether-hexane mixture. The synthesis of known α-diazo-β-oxo sulfones **21**, **23**, **25**, **27**, **39**, **41** as well as the novel α-diazo-β-oxo sulfone **45** were undertaken in this manner. Yields varied from low (<40%) for α-diazoketones **21** and **23** (**Table 3.10**, entries 2-3) to high (91%) for ethyl ester compound **39** (**Table 3.10**, entry 8). For the remaining compounds **25**, **27**, **41**, **45** yields were moderate (60–70%) (**Table 3.10**, entries 1, 4, 6, 10). These yields are consistent with previous reports and reflect the ease of chromatographic purification, rather than the efficiency of the diazo transfer. Despite the range of yields obtained, sufficient amounts of material were readily accessed for our purposes, so no attempt was made to further optimise these reactions.

Minor purification issues arose when separating α-diazo-β-oxo-sulfones **21**, **23**, **25**, **27**, **39**, **41**, **45** from *p*-toluenesulfonyl amide during column chromatography on silica gel. Occasionally fractions of material containing both the desired α-diazo-β-oxo-sulfone and the *p*-toluenesulfonyl amide byproduct were obtained. Therefore, due to issues with purification and safety considerations arising from the use of *p*-tosyl azide, *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) was investigated as an alternative diazo transfer reagent.[29] *p*-ABSA is not impact sensitive and has a relatively high initiation temperature, making it a much safer alternative to *p*-tosyl azide. In addition *p*-ABSA is a stable solid at room temperature, giving it greater ease of handling than *p*-tosyl azide which is a viscous oil that freezes on storage in a freezer. A simpler purification procedure was employed when *p*-ABSA was utilised, when compared to using *p*-tosyl azide. In the case of *p*-ABSA, the crude reaction mixture was adsorbed onto silica gel and purified immediately using column chromatography.

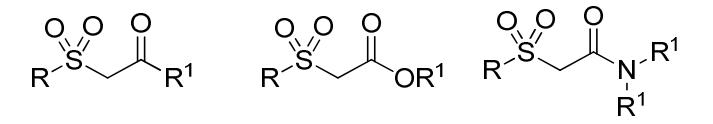
Initially the synthesis of methyl ester α-diazo-β-oxo-sulfone substrate **25** employing *p*-acetamidobenzenesulfonyl azide was explored. The sulfonamide byproduct in this case is much more polar than any of the α-diazo-β-oxo-sulfone substrates generated in this project, allowing efficient purification of the α-diazo-β-oxo-sulfone substrates. While the yields obtained for α-diazo-β-oxo-sulfone **25** were comparable using both diazo transfer

reagents *p*-ABSA and *p*-tosyl azide (58% and 65% respectively) (**Table 3.10**, entries 4 and 5), much longer reaction times were required for *p*-ABSA (28 h) than for *p*-tosyl azide (3.5 h). However, the advantages of ease of purification and safer handling of *p*-ABSA outweigh the disadvantage of the increased reaction time and therefore *p*-ABSA is recommended for future work in this area. It also needs to be highlighted that the work-up procedures for each of the two methods is different; when the method employing *p*-ABSA is used, the crude product is adsorbed on silica gel and purified using column chromatography, while the method employing *p*-tosyl azide is diluted with ether, filtered and concentrated prior to purification using chromatography.

The remaining α-diazo-β-oxo-sulfone substrates **29**, **37**, **54**–**56**, **59**–**63** listed in **Table 3.10** were synthesised using *p*-ABSA (**Table 3.10**, entries 7, 9, 11–18). Moderate to excellent yields were obtained in all cases (58–95%), and all compounds were obtained as yellow oils or solids. In certain cases minor modifications were made to the general procedure. In two instances, DBU was employed as a base instead of potassium carbonate (**Table 3.10**, entries 11 and 16), with no detectable difference in the outcome. Cooling to 0 °C of the reaction mixture prior to the addition of *p*-ABSA was not carried out for the synthesis of α-diazo-β-oxo sulfones **59-61** (**Table 3.10**, entries 15–18), instead the addition was carried out at room temperature, again without detectable impact. The synthesis of α-diazo-β-oxo sulfone **63** (**Table 3.10**, entry 15) proved more challenging than the synthesis of the other α-diazo-β-oxo sulfones listed on **Table 3.10**. It was found that the reaction does not proceed at room temperature, and after stirring at this temperature for 24 h, only starting material was recovered. However, on heating the reaction mixture to 40 °C, full conversion of β-oxo-sulfone **130** to the corresponding α-diazo-β-oxo sulfone **63** had taken place within 45 minutes. It was also discovered that α-diazo-β-oxo-sulfone **63** was unstable at room temperature, and had started to degrade to unidentified components, within 24 hours of storage at this temperature. Therefore, it was generally used within a few hours of being made. Other than compound **63**, the remaining α-diazo-β-oxo sulfone compounds listed on **Table 3.10** were stable on storage at room temperature and a ^{1}H NMR spectrum obtained of methyl ester α-diazo-β-oxo-sulfone substrate **25** following storage at room temperature for three years showed the compound still to be pure.

3.5.2 Synthesis of α-diazo-β-amido-sulfones

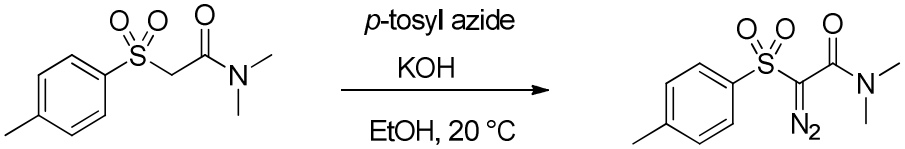
While diazo transfer has been successfully carried out to a methylene group adjacent to a sulfone and a ketone/ester, the same transformation to a methylene group next to a sulfone and an amide had not previously been attempted in this group. An initial consideration for the synthesis of α-diazo-β-amido sulfones is the acidity of the methylene CH_2 in the starting sulfone material; inspection of Evans' pKa table[39] reveals that the methylene CH_2 adjacent to an amide is less acidic than that next to an ester which is in turn less acidic than that next to a ketone (**Figure 3.2**) therefore making deprotonation of this site less favourable, making transformation to the corresponding diazo compound potentially more difficult.



decreasing acidity

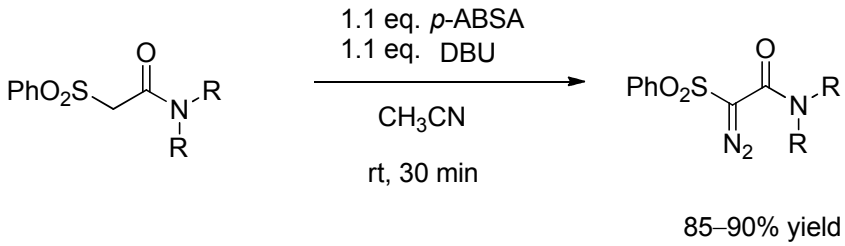
Figure 3.2

There are limited reports of such transformations in the literature.[23,35] Regitz and Maas highlighted a handful of examples from the 1970s where *p*-tosyl azide had been successfully utilized to carry out transformations of this type, one of which is highlighted in **Scheme 3.12**.[23]



Scheme 3.12

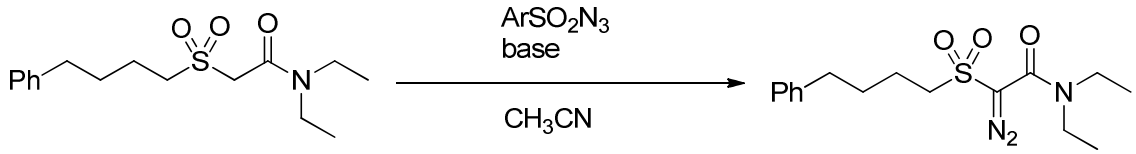
Recently, Jung and co-workers reported the use of *p*-ABSA as a diazo transfer reagent, in conjunction with DBU as a base, in the synthesis of α-diazo-α-(phenylsulfonyl)acetamides in excellent yields (85–90%) (**Scheme 3.13**).[35]



Scheme 3.13

Initially the same diazo transfer conditions were attempted to synthesise α-diazo-β-amido-sulfone **47** as had been successfully utilised to synthesis α-diazo-β-keto-sulfones and α-diazo-β-ester-sulfones. These conditions led to recovery of starting material (**Table 3.11**, entries 1 and 2).

Table 3.11 *Investigation into the synthesis of α-diazo-β-amido-sulfone* **47**



118 **47**

Entry	Base	$ArSO_2N_3$	Temperature	Time (h)	Yield (%)
1[a]	K_2CO_3	*p*-tosyl azide	0 °C–rt	24	SM
2[a]	K_2CO_3	*p*-ABSA	0 °C–rt	24	SM
3[a]	DBU	*p*-NBSA	0 °C–rt	24	SM
4[b]	DBU	*p*-NBSA	40 °C	0.58	51

a. Order of addition of reagents was as follows; diazo transfer reagent was added to a stirring solution of base and sulfone **118**.

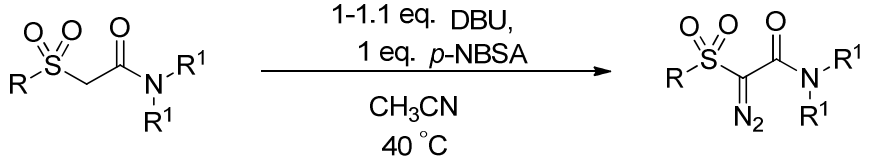
b. Order of addition of reagents was as follows; Base was added to a stirring solution of diazo transfer reagent and sulfone **118**.

The use of *p*-nitrobenzenesulfonyl azide (*p*-NBSA) and DBU were investigated, however, changing the base and diazo transfer reagent resulted in the recovery of starting material (**Table 3.11**, entry 3). At this point a number of modifications in reaction procedure were employed; the reaction temperature was raised to 40 °C and the order of addition of reagents was also changed. In this instance DBU in acetonitrile was added to sulfone **118** and *p*-NBSA in acetontrile. Changing the order of addition of reagents was also explored, as Jung had reported short reaction times and efficient reactions when DBU was added to a solution of α-(phenylsulfonyl)acetamide and *p*-ABSA, leading to the α-diazo-β-amido-sulfone.[35] Presumably, the different order of addition leads to a more efficient reaction as

the diazo transfer reagent is available for reaction as soon as the sulfonyl anion is generated. It is possible that prolonged contact of the sulfone starting material with base, in the presence of heat could cause degradation of the material. Applying these conditions caused the reaction to proceed within 1 h, with a reasonable yield of 51% (**Table 3.11**, entry 4). While this reaction worked well, it should be stated that care must be exerted when heating diazo transfer reagents, due to their heat sensitivity. The work-up procedure that was employed for this reaction was the same as was used for reactions employing *p*-ABSA; the crude reaction mixture was adsorbed onto silica gel and immediately purified using column chromatography.

Having established a suitable set of diazo transfer conditions for the synthesis of novel α-diazo-β-amido sulfone **47**, these conditions were subsequently applied to the synthesis of an additional nine novel α-diazo-β-amido sulfones **46**, **48**–**53**, **57**, **58**. The results of these reactions are presented in **Table 3.12**.

Table 3.12 *Synthesis of α-diazo-β-amido-sulfones*



Entry	R	R^1	β- sulfonyl amide	Time (h)	α-diazoacetamide	Purified Yield (%)[a]
1	$Ph(CH_2)_3$	Et	**125**	1.25	**51**	63
2	$Ph(CH_2)_3$	Pr	**127**	1.08	**50**	63
3	$Ph(CH_2)_3$	$(CH_2CH_2)_2O$	**119**	1.25	**52**	32
4	$Ph(CH_2)_3$	Bn	**120**	1	**53**	52
5	$Ph(CH_2)_4$	Et	**118**	0.58	**47**	51
6	$Ph(CH_2)_4$	Pr	**126**	1.08	**46**	61
7[b]	$Ph(CH_2)_4$	$(CH_2CH_2)_2O$	**128**	0.92	**48**	20
8	$C_{12}H_{25}$	$(CH_2CH_2)_2O$	**121**	1	**49**	63
9[b]	2'-ethylphenyl	Pr	**116**	1.25	**57**	59
10	2'-ethylphenyl	$(CH_2CH_2)_2O$	**117**	1.25	**58**	32

a. Yield refers to material purified by column chromatography.
b. Two equivalents of DBU were employed.

Each of the reactions presented in **Table 3.12**, was complete in less than 1.5 h; the reactions were monitored by TLC analysis, and once deemed complete were adsorbed onto silica gel before chromatographic purification. A good visual indication that the reaction has gone to completion was that the solution turns a bright yellow colour.

However, it has been seen throughout this work that prolonged contact with base/heat can cause this yellow colour to change to orange/brown. Generally, the yields suffer as a consequence of this prolonged contact. When such crude material is purified, very polar orange residues are often seen at the top of the column, which generally require methanol to be eluted off the column. The identity of this material is unknown. Separation of the sulfonamide byproduct, generated in the reaction, from the diazo compound occasionally proved difficult. In these instances, the purified reaction mixture of the sulfonamide and diazo compound was dissolved in dichloromethane and was washed with 1 M NaOH, which proved successful in removing the sulfonamide byproduct. None of the reactions reported in the experimental **Section 3.7** utilised this basic work up. Generally 1–1.1 equivalents of DBU were employed, however, two equivalents of base were used in two instances (**Table 3.12**, entries 7 and 9), in an attempt to see if stirring with an extra equivalent of base would remove the sulfonamide byproduct before purification. In both instances, the sulfonamide was not obtained after purification, suggesting that this method was successful. However, the yield of α-diazo-β-oxo sulfone **48** was uncharacteristically low (20%, **Table 3.12**, entry 7), which may be as a result of stirring with excess base. Each compound was purified using column chromatography immediately after reaction completion. While moderate yields of α-diazo-β-amido-sulfones (**Table 3.12**) were achieved in the majority of cases, (**Table 3.12**, entries 1–2, 4–6, 8–9), low yields were achieved for compounds **48**, **52**, **58** (**Table 3.12**, entries 3, 7 and 10). However, in all cases sufficient quantities of the key diazo derivative were obtained for catalyst studies and, therefore, no further optimisation was undertaken. Each compound was prepared as a yellow oil/solid and was stored for periods of up to three months without noticeable degradation.

3.5.2.1 Spectroscopic characteristics of α-diazo-β-oxo-amides

Infra-red characteristics

In line with most α-diazocarbonyl compounds, the carbonyl stretch in the IR spectra are characteristic of successful diazo transfer with carbonyl stretch shifting from ν_{max}/cm^{-1} 1639–1652 cm^{-1}, for the precursor sulfonyl amides, to ν_{max}/cm^{-1} 1624–1639 cm^{-1} for the analogous diazo derivatives. In addition, the characteristic diazo band at 2094–2110 cm^{-1} is seen.

^{1}H NMR characteristics

An interesting feature of the ^{1}H NMR spectra of α-sulfonyl amides is that the two CH_2 groups adjacent to the nitrogen appear as two separate 2H signals, while the corresponding signals in the ^{1}H NMR spectra of the α-diazo-β-amido sulfone appears as one 4H signal. This can be rationalised on the basis of some well-established facts. In the case of α-sulfonyl amides the lone pair of electrons present on the nitrogen atom is potentially delocalised into the carbonyl group as shown in **Figure 3.3**. However, in the case of α-diazo-β-amido sulfones, additional resonance forms can exist (**Figure 3.3**). The fact that the carbonyl group is in conjugation with the diazo functionality reduces its interaction with the lone pair of electrons on the nitrogen atom. The resulting greater conformational freedom of the amide on the α-diazo-β-amido sulfone accounts for this observation.

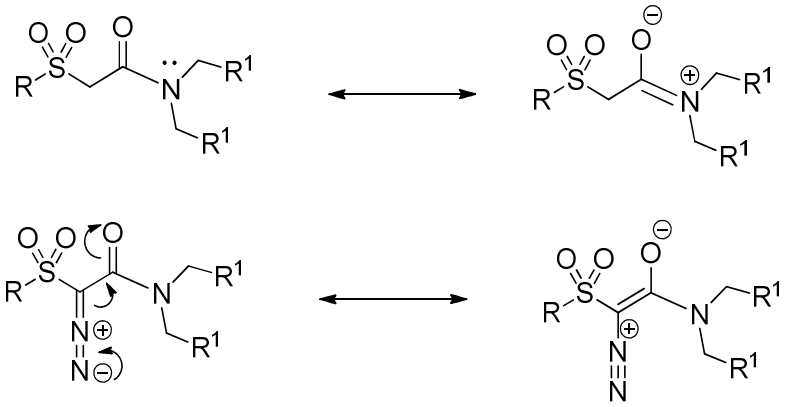


Figure 3.3

In the case of the *N*,*N*-diethyl and *N*,*N*-dipropyl α-diazo-β-amido sulfones and β-amido sulfone substrates this effect can be seen for the terminal CH_3 of the *N*,*N*-dialkyl group. In the case of the α-diazo-β-amido sulfone one six hydrogen triplet appears for the two CH_3 groups, however in the case of the β-amido sulfone, two separate three hydrogen triplets are seen. An example of a ^{1}H NMR of β-oxo sulfone **118** and α-diazo-β-oxo sulfone **47** are shown in **Figure 3.4**.

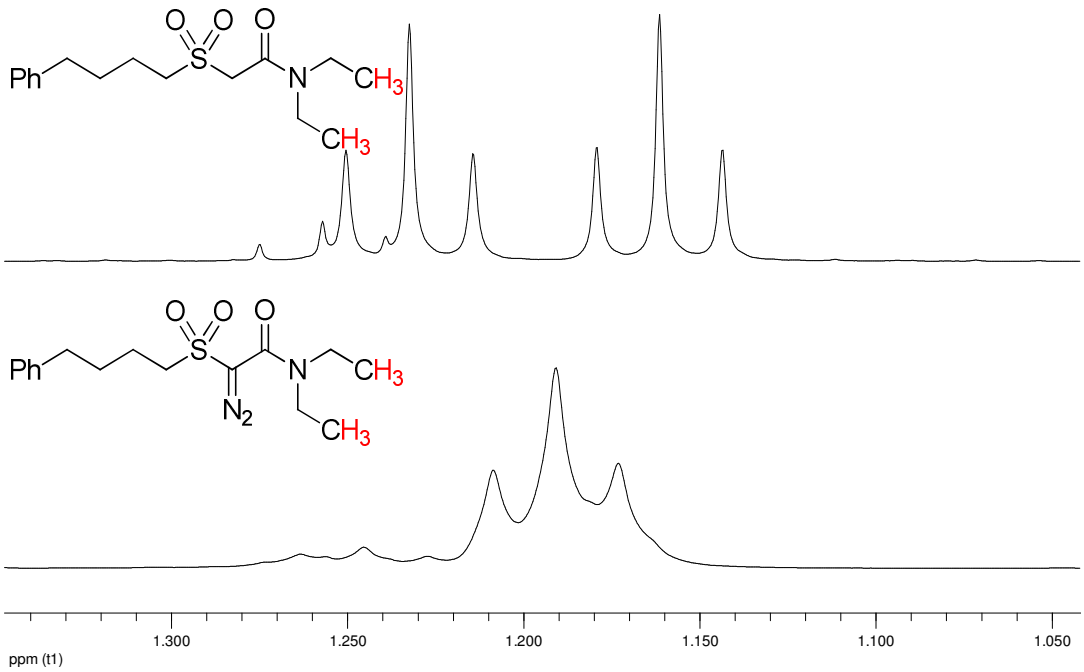


Figure 3.4

^{13}C characteristics

For a number of α-diazoamides **46**–**48**, **50**, **52** and precursor sulfonyl amide **121** the signal for the NCH_2 was noticeably broadened in the ^{13}C NMR spectra, presumably again associated with restricted rotation. This was not seen in all cases but is highlighted in the experimental where seen.

3.6 Conclusion

Thus, in this work twenty seven α-diazosulfones were prepared and characterised, ninteen of which were novel. Each of the novel β-oxo-sulfones and each of the novel α-diazo-β-oxo-sulfones were fully characterised using ^{1}H NMR, ^{13}C NMR, (HETCOR and COSY correlations where necessary), IR spectroscopy, high resolution mass spectrometry and elemental analysis where possible. Melting points were obtained for solid compounds.

3.7 Experimental

General Procedures

Solvents utilised in this work were distilled prior to use. The following methods were employed: ethyl acetate was distilled from potassium carbonate; tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl; hexane was distilled prior to use; ethanol was distilled from magnesium ethoxide; dichloromethane (DCM) was distilled from phosphorus pentoxide and was further distilled from calcium hydride for use in the cyclisation reactions reported in Chapters 6 and 7. Organic phases were dried using anhydrous magnesium sulfate. Unless specifically stated, all reactions reported in this thesis were carried out under an inert nitrogen atmosphere.

Infra-red (IR) spectra were recorded as potassium bromide (KBr) discs for solids or as thin films on sodium chloride plates for oils on a Perkin Elmer Paragon 1000 FT-IR spectrometer. In a few instances, IR spectra were recorded neat on a PerkinElmer Spectrum Two; operating in Universal Attenuated Total Reflectance (UATR) mode.
^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer. ^{1}H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer. ^{1}H (500 MHz) and ^{13}C (125.8 MHz) NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer. ^{1}H (600 MHz) and ^{13}C (150.9 MHz) NMR spectra were recorded on a Bruker Avance 600 NMR spectrometer. Unless otherwise stated, all spectra were recorded in deuterated chloroform $CDCl_3$ using tetramethylsilane (TMS) as an internal standard at room temperature (~20 °C). Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H spectra are labelled as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublet of doublets), td (triplet of doublets), ddt (doublet of doublet of triplets), dddd (doublet of doublet of doublet of doublets), m (multiplet) and sym m (symmetrical multiplet). Apparent multiplicity refers to a situation where two or more independent protons show similar coupling constants, resulting in a simpler splitting pattern than expected. ^{13}C NMR spectra were calibrated using the solvent signals, *i.e.* $CDCl_3$=δ_C 77.0 ppm and were assigned with the aid of DEPT experiments, unless otherwise stated. The use of two dimensional NMR experiments (HSQC, HMBC, HETCOR, COSY and NOESY) to aid assignments was made on a number of occasions in this project and it will

be indicated when they were used to aid in the assignment of a compound. For previously synthesised compounds, spectroscopic details were in agreement with reported values unless specifically stated otherwise. ^{1}H NMR spectra, IR spectra and melting point (m.p.) analysis were recorded for all previously prepared compounds, with ^{13}C NMR, LRMS and elemental and/or HRMS being additionally obtained for novel compounds.

Wet flash chromatography was carried either carried out manually or using an automated chromatography system. Automated chromatography was carried out using a Varian (971-FP) which is equipped with an automated fraction collector and UV detector. Chromatographic purification of compounds in Chapters 3 and 4 was carried out manually, while chromatographic purification of compounds in Chapters 5 and 7 was carried out using the Varian. In all cases Kieselgel gel 60, 0.040-0.063 mm (Merck) was used. Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualisation was accomplished using UV (254 nm) light detection, vanillin staining and potassium permanganate staining.

The enantiopurity of chiral compounds was measured using chiral stationary phase high performance liquid chromatography (HPLC), carried out on a Chiralpak® ASH and Chiralpak ® OJ-H purchased from Daicel Chemical Industries Limited. Additional chiral columns utilised for determination of the enantiopurity of samples included Lux™ Amylose-2, Lux™ Cellulose-2 or Lux™ Cellulose-4 purchased from Phenomenex. Full details of the column conditions and mobile phases can be found in Appendix II. The majority of HPLC analysis was performed on a Waters alliance 2690 separations module with a UV detector. In one case HPLC analysis was carried out on an Agilent Technologies 1120 LC fitted with a UV detector and a light scattering detector (Agilent Technologies 385-ELSD). The enantiopurity of one of the compounds was measured using chiral ^{1}H NMR experiments, employing [(+)-Eu(hfc)$_3$] as a chiral shift reagent. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^T$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}.

Elemental analysis was carried out by Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple

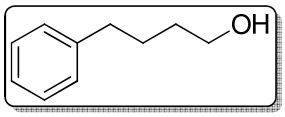
quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in electrospray ionization mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. Samples prepared for either LRMS or HRMS employed acetonitrile as solvent.

Single crystal X-ray analysis was conducted by Dr. S. E. Lawrence and Dr. A. S. Sinha, Department of Chemistry, National University of Ireland, Cork, using a Bruker APEX II DUO diffractometer, at temperature 100, using graphite monochromatic Mo Kα (λ = 0.7107 Å) radiation, fitted with an Oxford Cryosystems Cobra low-temperature device. Single crystal X-ray diffraction data was collected on a Bruker SMART X2S diffractometer. All calculations and refinement were made using the APEX software. The structures were solved using direct methods and refined on F^2 using SHELXL-97.[36] Analysis was undertaken with the SHELX suite of programs[36] and diagrams prepared with Mercury 3.0.[37] All non-hydrogen atoms were located and refined with anisotropic thermal parameters. Hydrogen atoms were included in calculated positions or were located and refined with isotropic thermal parameters.

Three diazo transfer reagents were used in this project to effect diazo transfer reaction to β-oxo sulofones to yield α-diazo-β-oxo sulfone compounds. The reagents *p*-tolunesulfonyl azide (*p*-tosyl azide),[26] *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[28] and *p*-nitrobenzenesulfonyl azide (*p*-NBSA) were synthesised from *p*-toluenesulfonyl chloride, *p*-acetamidobenzenesulfonyl chloride and *p*-nitrobenzenesulfonyl chloride respectively, using sodium azide, according to standard literature procedures. The synthesis of *p*-NBSA was carried out using the same method reported for *p*-ABSA, using *p*-nitrobenzenesulfonyl chloride as the sulfonyl chloride precursor.[40] Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) was prepared according to standard literature procedure.[38] The quality of *m*CPBA was determined using a titration, according to standard literature procedures.[18]

Preparation of precursor alcohols

4-Phenylbutan-1-ol[1,2] 64

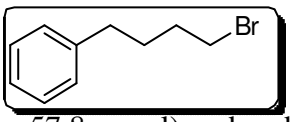


Borane-dimethylsulfide complex (1.80 g, 2.3 mL, 23.7 mmol) was added over 15 min to a solution of phenylbutyric acid (2.99 g, 18.2 mmol) in dry tetrahydrofuran (30 mL) and the mixture was stirred at room temperature for 2 h. Methanol (20 mL) was then added to destroy any remaining borane. The solvents were removed under reduced pressure and the crude residue was partitioned between dichloromethane (30 mL) and water (30 mL). The aqueous layer was extracted with dichloromethane (2 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield 4-phenylbutan-1-ol **64** (2.18 g, 80%) as a colourless oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1,2] ν_{max}/cm^{-1} (film): 3340 (OH), 2935, 2860 (CH), 1604 (C=C, Ar), 1496, 1454 (C=C, Ar), 1061, 1030 (C–O); δ_H ($CDCl_3$, 400 MHz): 1.30 (1H, br s, O*H*), 1.56–1.78 [4H, m, C(2)H_2 and C(3)H_2], 2.65 [2H, t, *J* 7.5, C(4)H_2], 3.66 [2H, t, *J* 6.3, C(1)H_2], 7.15–7.22 (3H, m, Ar*H*), 7.24–7.33 (2H, m, Ar*H*).

Preparation of arylalkyl halides

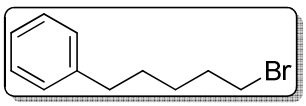
Preparation of arylalkyl bromides

4-Phenyl-1-bromobutane[1,3] 65



A solution of 4-phenylbutan-1-ol **64** (5.79 g, 38.5 mmol) in acetonitrile (150 mL) was treated with triphenylphosphine (15.16 g, 57.8 mmol) and carbon tetrabromide (19.17 g, 57.8 mmol) at room temperature. The resulting colourless solution was stirred at room temperature for 3 h. Sodium hydroxide (15%) was added to adjust the pH to *approx.* 9, at which point the solution turned pale green. Acetonitrile was removed under reduced pressure and diethyl ether (50 mL) was added. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Following purification of the crude product by chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, 4-phenyl-1-bromobutane **65** (5.69 g, 69%) was isolated as a colourless oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1,3] ν_{max}/cm^{-1} (film): 2938, 2857 (CH), 1603 1496, 1454 (C=C, Ar) 699; δ_H ($CDCl_3$, 400 MHz): 1.71–1.96 [4H, m, C(2)H_2 and C(3)H_2], 2.64 [2H, t, *J* 7.5, C(4)H_2], 3.41 [2H, t, *J* 6.7, C(1)H_2], 7.14–7.22 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*).

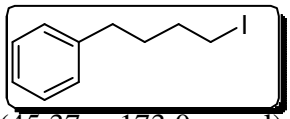
(5-Bromopentyl)benzene[4] 66



The title compound was prepared using the procedure described for 4-phenyl-1-bromobutane **65**, using 5-phenylpentan-1-ol (5.00 g, 30.0 mmol), triphenylphosphine (12.06 g, 46.0 mmol), carbon tetrabromide (15.14 g, 46.0 mmol) and acetonitrile (140 mL). The resulting solution was stirred at room temperature for 2 h. Following work up and purification by chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (5-bromopentyl)benzene **66** (8.99 g, 132%) was isolated as a colourless oil, which was used without further purification, despite the presence of bromoform. Spectroscopic characteristics are consistent with those previously reported;[4] ν_{max}/cm^{-1} (film): 2934, 2857 (CH), 1603, 1496, 1453 (C=C, Ar), 699; δ_H ($CDCl_3$, 400 MHz): 1.41–1.55 [2H, m, C(3)H_2], 1.57–1.69 [2H, m, C(2)H_2 or C(4)H_2], 1.79–1.93 [2H, m, C(2)H_2 or C(4)H_2], 2.54–2.66 [2H, m, C(5)H_2], 3.38 [2H, t, *J* 6.9, C(1)H_2], 7.11–7.12 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*).

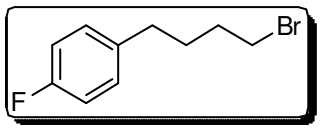
Preparation of arylalkyl iodides

(4-Iodobutyl)benzene[5] 67



A solution of 4-phenylbutan-1-ol **64** (20 g, 133.0 mmol) in dichloromethane (250 mL) was treated with triphenylphosphine (45.37 g, 173.0 mmol), imidazole (11.8 g, 173.0 mmol) and iodine (43.90 g, 173.0 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 30 min, then at room temperature for 18 h. The resulting orange solution was washed with sat. sodium metabisulfite solution (2 × 40 mL) and the layers separated. The organic layer was washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Following purification of the crude product by chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (4-iodobutyl)benzene **67** (15.35 g, 44%) was isolated as a colourless oil. Spectroscopic characteristics are consistent with those previously reported;[5] ν_{max} /cm^{-1} (film): 3026, 2934, 2856 (CH), 1603, 1496, 1454 (C=C, Ar), 1207, 600; δ_H ($CDCl_3$, 400 MHz): 1.71–1.96 [4H, m, C(2)H_2 and C(3)H_2], 2.64 [2H, t, *J* 7.5, C(4)H_2], 3.18 [2H, t, *J* 6.9, C(1)H_2], 7.14–7.22 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*).

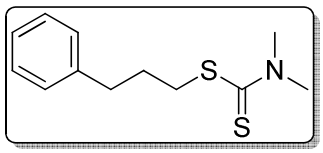
1-(4-Bromobutyl)-4-fluorobenzene[6] 68



A solution of 1-bromo-4-fluorobenzene (7.50 g, 4.7 mL, 42.6 mmol) in dry tetrahydrofuran (100 mL) was treated dropwise with *n*-butyllithium [2.5 M, in hexanes, 20.9 mL, 46.7 mmol], at −78 °C under an atmosphere of nitrogen over 30 min. After stirring for a further 30 min of stirring at −78 °C, the solution was treated with 1,4-dibromobutane (38.85 g, 21.5 mL, 170.4 mmol). The resulting solution was stirred overnight, while warming to room temperature. The resulting yellow solution was partitioned between water (150 mL) and diethyl ether (150 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Any remaining 1,4-dibromobutane was removed using Kugelröhr distillation to yield 1-(4-bromobutyl)-4-fluorobenzene **68** (7.62 g, 77%) as a pale yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[6] ν_{max}/cm^{-1} (film): 2939, 2860 (CH), 1601, 1510 (C=C, Ar), 1222; δ_H ($CDCl_3$, 300 MHz): 1.67–1.94 [4H, m, C(2)H_2 and C(3)H_2], 2.61 [2H, t, *J* 7.5, C(4)H_2], 3.38–3.45 [2H, m, C(1)H_2], 6.89–7.02 (2H, m, Ar*H*), 7.06–7.19 (2H, m, Ar*H*).

Preparation of dimethyldithiocarbamic acid derivatives

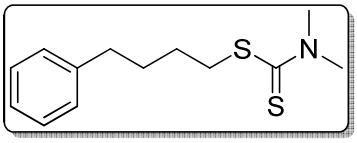
***N*,*N*-Dimethyldithiocarbamic acid 3-phenylpropyl ester[1] 72**



Sodium dimethyldithiocarbamate (40% w/v aqueous solution, 11.99 g, 30 mL, 83.8 mmol) was diluted with ethanol (60 mL) and treated with 1-chloro 3-phenylpropane (12.96 g, 12.0 mL, 83.8 mmol). The mixture was stirred while heating under reflux for 3 h. Ethanol was removed under reduced pressure and the residue was partitioned between dichloromethane (50 mL) and water (50 mL). The aqueous layer was extracted with dichloromethane (2 × 25 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give *N*,*N*-dimethyldithiocarbamic acid 3-phenylpropyl ester **72** (11.64 g, 58%) as a yellow oil. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2927, 2856 (CH), 1496, 1454 (C=C, Ar), 1374, 1253, 985, 700 (CS); δ_H ($CDCl_3$, 400 MHz): 1.96–2.10 [2H, m, C(2)H_2], 2.69–2.79 [2H, m, C(1)H_2 or C(3)H_2], 3.25–3.33

[2H, m, C(1)H_2 or C(3)H_2], 3.35 (3H, br s, NCH_3), 3.53 (3H, br s, NCH_3), 7.13–7.22 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*).

_N,N_-Dimethyldithiocarbamic acid 4-phenylbutyl ester[2] 74



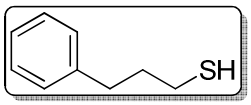
The title compound was prepared using the procedure for dimethyldithiocarbamic acid 3-phenylpropyl ester **72**, using sodium dimethyldithiocarbamate (40% w/v aqueous solution, 3.52 g, 8.8 mL, 24.6 mmol), 4-phenyl-1-iodobutane **67** (3.51 g, 13.5 mmol) and ethanol (25 mL), while heating under reflux for 3 h. Following work up and purification of the crude product by chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, *N*,*N*-dimethyldithiocarbamic acid 4-phenylbutyl ester **74** (2.79 g, 82%) was isolated as an off white solid. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2932, 2888 (CH), 1602, 1495 (C=C, Ar), 1370, 1251, 983, 740 (CS); δ_H ($CDCl_3$, 300 MHz): 1.71–1.82 [4H, m, C(2)H_2 and C(3)H_2], 2.57–2.72 [2H, m, C(4)H_2], 3.25–3.41 [5H, m, including C(1)H_2 and at 3.36 3H, br s, NCH_3], 3.55 (3H, br s, NCH_3), 7.13–7.22 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*).

Note; An excess of sodium dimethyldithiocarbamate was used in this experiment, in general equimolar quantities are sufficient.

Preparation of thiols

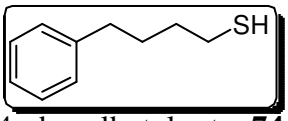
Thiols are extremely malodorous compounds and extreme care must be taken to ensure that these compounds are not removed from the fume cupboard without taking appropriate measures. All glassware, gloves, any equipment used in the preparation of thiols must be soaked in aqueous sodium hypochlorite bleach prior to washing. Therefore, all thiols prepared during the course of this work were used without any further purification. All solutions were concentrated using a rotary evaporator in a fume cupboard.

3-Phenylpropyl-1-thiol[1,7] 73



A solution of *N*,*N*-dimethyldithiocarbamic acid 3-phenylpropylester **72** (11.0 g, 46.0 mmol), in diethyl ether (50 ml), was added to a suspension of lithium aluminium hydride (2.11 g, 55.6 mmol) in diethyl ether (80 mL), under reflux and stirred at these conditions for 3 h and then at room temperature for a further 18 h. Aqueous HCl (2 M, 150 mL) was **carefully** added to the solution over 1 h. The mixture was stirred for a further 45 min, until no more evolution of hydrogen gas was observed. The mixture was then extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give 3-phenylpropyl-1-thiol **73** (6.92 g, 99%) as a malodorous colourless oil which was used without further purification. The reaction did not go to completion with *approx*. 10% starting material present by ^{1}H NMR analysis. Spectroscopic characteristics are consistent with those previously reported;[1,7] ν_{max}/cm^{-1} (film): 3027, 2933 (CH), 1604, 1497, 1454 (C=C, Ar), 744, 700 (SH); δ_H ($CDCl_3$, 400 MHz): 1.35 (1H, t, *J* 7.8, S*H*), 1.87–1.99 [2H, m, C(2)H_2], 2.53 [2H, apparent q, *J* 7.4, C(1)H_2], 2.67–2.74 [2H, m, C(3)H_2], 7.11–7.20 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*).

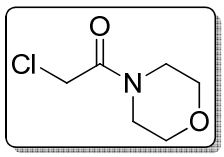
4-Phenylbutyl-1-thiol[1,8] 70



The title compound was prepared using the procedure for 3-phenylpropyl-1-thiol **73**, using *N*,*N*-dimethyldithiocarbamic acid 4-phenylbutyl ester **74** (2.0 g, 7.9 mmol) in diethyl ether (30 mL) and lithium aluminium hydride (0.45 g, 11.9 mmol) in diethyl ether (15 mL), heated while stirring under reflux for 2.5 h. Following the work up, 4-phenylbutyl-1-thiol **70** (1.10 g, 83%) was isolated as a malodorous colourless oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1,8] ν_{max}/cm^{-1} (film): 2933 (CH), 1640, 1604, 1496, 1453 (C=C, Ar), 699 (SH); δ_H ($CDCl_3$, 400 MHz): 1.33 (1H, t, *J* 7.8, S*H*), 1.56–1.81 [4H, m, C(2)H_2 and C(3)H_2], 2.46–2.68 [4H m, C(1)H_2 and C(4)H_2], 7.10–7.22 (3H, m, Ar*H*), 7.23–7.33 (2H, m, Ar*H*).

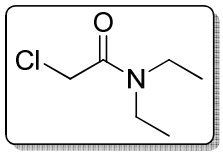
Preparation of α-chloroacetamides

2-Chloro-1-morpholinoethanone[9] 78



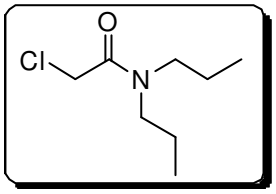
A solution of chloroacetyl chloride (10.0 g, 7.0 mL, 88.5 mmol) in dichloromethane (50 mL) was added to a solution of morpholine (7.35 g, 7.4 mL, 84.4 mmol) and triethylamine (8.93 g, 12.3 mL, 88.2 mmol) in dichloromethane (30 mL) over 30 min, at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for a further 2 h, while slowly warming to room temperature, at which point distilled water (70 mL) was added and the layers separated. The organic layer was washed with saturated sodium bicarbonate solution (3 × 40 mL) and hydrochloric acid (2 × 40 mL, 2 M), brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 2-chloro-1-morpholinoethanone **78** (6.30 g, 39%), which was isolated as an orange oil and was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[9] ν_{max}/cm^{-1} (film): 2968, 2923, 2860 (CH), 1651 (CO), 1440, 1270, 1234, 1115, 966 (C–O); δ_H ($CDCl_3$, 300 MHz): 3.40–3.52 (2H, m, morpholine CH_2), 3.58–3.61 (2H, m, morpholine CH_2), 3.65–3.71 (4H, m, morpholine CH_2), 4.08 (2H, s, ClCH_2CO).

2-Chloro-*N*,*N*-diethylacetamide[10] 76



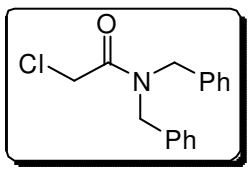
The title compound was prepared according to the method used for 2-chloro-1-morpholinoethanone **78**, using chloroacetyl chloride (2.0 g, 1.4 mL, 17.7 mmol), *N*,*N*-diethylamine (1.29 g, 1.83 mL, 17.7 mmol), triethylamine (1.79 g, 2.5 mL, 17.7 mmol) and dichloromethane (50 mL). Following the work up 2-chloro-*N*,*N*-diethylacetamide **76** (2.19 g, 83%) was isolated as an orange oil. Spectroscopic characteristics are consistent with those previously reported;[10] ν_{max}/cm^{-1} (film): 2978, 2937 (CH), 1651 (CO), 1464, 1434, 1256, 1172, 792; δ_H ($CDCl_3$, 300 MHz): 1.10 (3H, t, *J* 7.2, one of NCH_2CH_3), 1.20 (3H, t, *J* 7.2, one of NCH_2CH_3), 3.32–3.46 (4H, m, NCH_2CH_3), 4.07 (2H, s, ClCH_2CO).

2-Chloro-*N*,*N*-dipropylacetamide[11] 77



The title compound was prepared according to the method used for 2-chloro-1-morpholinoethanone **78**, using chloroacetyl chloride (15.0 g, 10.5 mL, 133 mmol), *N*,*N*-dipropylamine (13.43 g, 18.20 mL, 133 mmol), triethylamine (13.45 g, 18.5 mL, 133 mmol) and dichloromethane (300 mL). Following the work up, 2-chloro-*N*,*N*-dipropylacetamide **77** (21.3 g, 90%) was isolated as an orange oil. Spectroscopic characteristics are consistent with those previously reported;[11] ν_{max}/cm^{-1} (film): 2967, 2936, 2877 (CH), 1652 (CO), 1457, 1430, 1124, 794 (C-O); δ_H ($CDCl_3$, 300 MHz): 0.90 (3H, t, *J* 7.4, one of $NCH_2CH_2CH_3$), 0.95 (3H, t, *J* 7.4, one of $NCH_2CH_2CH_3$), 1.53–1.72 (4H, sym m, $NCH_2CH_2CH_3$), 3.22–3.41 (4H, sym m, $NCH_2CH_2CH_3$), 4.07 (2H, s, $ClCH_2CO$).

***N*,*N*-Dibenzyl-2-chloroacetamide[12] 75**

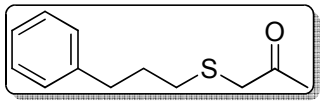


The title compound was prepared according to the method used for 2-chloro-1-morpholinoethanone **78**, using chloroacetyl chloride (10.0 g, 7.0 mL, 88.5 mmol), *N*,*N*-dibenzylamine (17.46 g, 17.0 mL, 88.5 mmol), triethylamine (8.93 g, 12.2 mL, 88.5 mmol) and dichloromethane (300 mL). Following the work up, *N*,*N*-dibenzyl-2-chloroacetamide **75** (17.6 g, 73%) was isolated as an orange oil. Spectroscopic characteristics are consistent with those previously reported;[12] ν_{max}/cm^{-1} (film): 3064, 3031 (CH), 1658 (CO), 1426, 1212, 699 (C-O); δ_H ($CDCl_3$, 300 MHz): 4.23 (2H, s, $ClCH_2CO$), 4.48 (2H, s, one of NCH_2Ph), 4.63 (2H, s, one of NCH_2Ph), 7.09–7.41 (10H, ArH).

General Procedure A for sulfide synthesis[1]

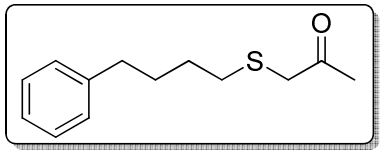
Potassium carbonate was added as a solid to a solution of thiol in acetone, while stirring at room temperature. The reaction mixture was then stirred at room temperature for 15 min. The chloro-, bromo- or iodo compound was added over two minutes, dropwise, neat to the reaction mixture. The reaction mixture was then stirred while heating under reflux for 18-20 h. The solution was cooled and filtered, to remove any insoluble salts, and concentrated under reduced pressure to give the crude sulfide. Due to their malodorous nature, sulfides were used without further purification, and as a result novel sulfides were not fully characterised. However, full characterisation of the corresponding sulfones was carried out.

1-(3-Phenylpropylthio)propan-2-one[1] 79



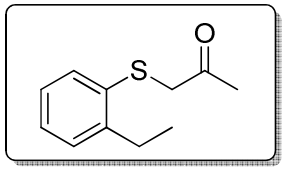
The title compound was prepared using general procedure **A**, using potassium carbonate (0.91 g, 6.6 mmol), 3-phenylpropyl-1-thiol **73** (1.00 g, 6.60 mmol) and chloroacetone (0.64 g, 0.55 mL, 6.90 mmol) in acetone (20 mL) stirred under reflux for 19 h. Following the work up, 1-(3-phenylpropylthio)propan-2-one **79** (1.1 g, 79%) was isolated as an odorous brown oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 1708 (CO), 746, 701 (CS); δ_H ($CDCl_3$, 400 MHz): 1.82–1.95 [2H, m, C(2′)H_2], 2.28 (3H, s, COCH_3), 2.45–2.53 [2H, m, C(1′)H_2 or C(3')H_2], 2.65–2.73 [2H, m, C(1′)H_2 or C(3′)H_2], 3.21 (2H, s, SCH_2CO), 7.12–7.22 (3H, m, Ar*H*), 7.23–7.43 (2H, m, Ar*H*).

1-(4-Phenylbutylthio)propan-2-one[1] 80



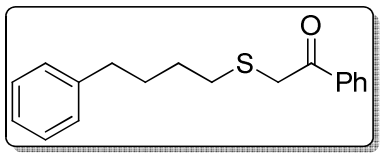
The title compound was prepared using general procedure **A**, using potassium carbonate (1.00 g, 7.3 mmol), 4-phenylbutyl-1-thiol **70** (1.1 g, 6.6 mmol) and chloroacetone (0.61 g, 0.52 mL, 6.6 mmol) in acetone (300 mL) stirred under reflux for 18 h. Following the work up, 1-(4-phenylbutylthio)propan-2-one **80** (1.20 g, 82 %) was isolated as an odorous brown oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 1705 (CO), 1604 (C=C, Ar), 700 (CS); δ_H ($CDCl_3$, 300 MHz): 1.51–1.79 [4H, m, C(2′)H_2 and C(3′)H_2], 2.27 (3H, s, COCH_3), 2.45–2.55 [2H, m, C(1′)H_2 or C(4′)H_2], 2.56–2.67 [2H, m, C(1′)H_2 or C(4′)H_2], 3.18 (2H, s, SCH_2CO), 7.10–7.23 (3H, m, Ar*H*), 7.24–7.34 (2H, m, Ar*H*).

1-[(2-Ethylphenyl)thio]propan-2-one 85



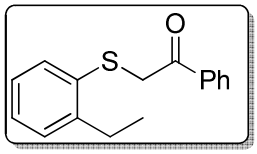
The title compound was prepared using general procedure **A**, using potassium carbonate (8.81 g, 63.7 mmol), 2-ethylbenzenethiol (8.00 g, 7.8 mL, 57.9 mmol) and chloroacetone (5.36 g, 4.6 mL, 57.9 mmol) in acetone (175 mL) stirred under reflux for 20 h. Following the work, up 1-[(2-ethylphenyl)thio]propan-2-one **85** (7.61 g, 68%) was isolated as a yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2967, 2932 (CH), 1712 (CO), 1470, 1443, (C=C, Ar), 1356, 1231, 1149, 751 (CS); δ_H ($CDCl_3$, 300 MHz): 1.24 (3H, t, *J* 7.5, $ArCH_2CH_3$), 2.27 (3H, s, COCH_3), 2.80 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.66 (2H, s, $SCH_2CO_2CH_3$), 7.12–7.22 (3H, m Ar*H*), 7.23–7.28 (1H, m Ar*H*).

2-(4-Phenylbutylthio)-1-phenylethanone[1] 81



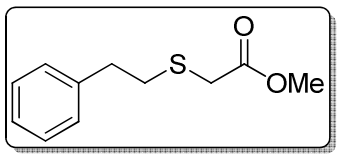
The title compound was prepared using general procedure **A**, using potassium carbonate (0.91 g, 6.6 mmol), 4-phenylbutyl-1-thiol **70** (1.10 g, 6.6 mmol) and bromoacetophenone (1.2 g, 6.00 mmol) in acetone (30 mL) stirred under reflux for 19 h. Following the work up, 2-(4-phenylbutylthio)-1-phenylethanone **81** (1.31 g, 76%) was isolated as an odorous yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2933 (CH), 1674 (CO), 1598, 1449 (C=C, Ar), 1277, 748, 700 (CS); δ_H ($CDCl_3$, 300 MHz): 1.52–1.79 [4H, m, C(2′)H_2 and C(3′)H_2], 2.47–2.71 [4H, m, C(1′)H_2 and C(4′)H_2], 3.75 (2H, s, SCH_2CO), 7.07–7.12 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*), 7.40–7.51 (2H, m, Ar*H*), 7.52–7.61 (1H, m, Ar*H*), 7.91–8.01 (2H, m, Ar*H*).

2-[(2-Ethylphenyl)thio]-1-phenylethanone 84



The title compound was prepared using general procedure **A**, using potassium carbonate (6.59 g, 47.7 mmol), 2-ethylbenzenethiol (6.00 g, 5.85 mL, 43.4 mmol) and 2-bromo-1-phenylethanone (8.60 g, 43.4 mmol) in acetone (180 mL) stirred under reflux for 21 h. Following the work up, 2-[(2-ethylphenyl)thio]-1-phenylethanone **84** (11.12 g, 99%) was isolated as an orange oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2967 (CH), 1693 (CO), 1466, 1450 (C=C, Ar), 751 (CS); δ_H ($CDCl_3$, 400 MHz): 1.18 (3H, t, *J* 7.5, ArCH$_2$CH_3), 2.76 (2H, q, *J* 7.5, ArCH_2CH$_3$), 4.24 (2H, s, SCH_2CO), 7.11–7.21 (3H, m, Ar*H*), 7.35–7.40 (1H, m, Ar*H*), 7.41–7.49 (2H, m, Ar*H*), 7.53–7.61 (1H, m, Ar*H*), 7.90–7.97 (2H, m, Ar*H*).

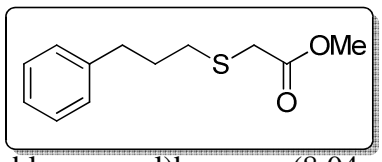
Methyl 2-(phenethylthio)acetate 98



The title compound was prepared using general procedure **A**, using potassium carbonate (5.41g, 39.1 mmol), methyl thioglycolate (3.77 g, 3.23 mL, 35.5 mmol) and (2-chloroethyl)benzene (5.00 g, 4.7 mL, 35.5 mmol) in acetone (180 mL) stirred under reflux for 21 h. Following the work up, methyl 2-(phenethylthio)acetate **98** (7.92 g, 100%, including ~15% methyl thioglycolate by ^{1}H NMR) was isolated as a yellow oil which was used without further purification; ν_{max}/cm^{-1} (film): 3028, 2952 (CH), 1730 (CO),

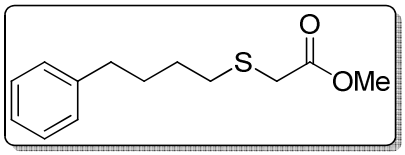
1604, 1498, 1436, 1455 (C=C, Ar), 1280, 1129 (CO_2Me), 699 (CS); δ_H ($CDCl_3$, 400 MHz): 2.90 [4H, s, C(2′)H_2 and C(1′)H_2], 3.22 (2H, s, SO_2CH_2CO), 3.72 (3H, s, $COOCH_3$), 7.16–7.24 (3H, m, Ar*H*), 7.25–7.33 (2H, m, Ar*H*).

Methyl 2-[(3-phenylpropyl)thio]acetate 94



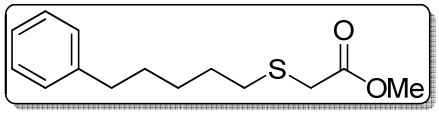
The title compound was prepared using general procedure **A**, using potassium carbonate (7.91 g, 57.0 mmol), methyl thioglycolate (5.50 g, 4.6 mL, 51.8 mmol), (3-chloropropyl)benzene (8.04 g, 7.4 mL, 51.9 mmol) in acetone (30 mL) stirred under reflux for 17 h. Following the work up, methyl 2-[(3-phenylpropyl)thio]acetate **94** (10.6 g, 91%) was isolated as a yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 3026, 2950, 2856 (CH), 1736 (CO), 1497, 1453 1436, 1279, 1128, 1008, 746, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 1.86–1.96 [2H, m, C(2′)H_2], 2.59–2.65 [2H, m, C(3′)H_2], 2.66–2.73 [2H, m, C(1′)H_2], 3.20 (2H, s, SCH_2CO), 3.69 (3H, s, $COOCH_3$), 7.13–7.20 (3H, m, Ar*H*), 7.23–7.30 (2H, m, Ar*H*).

Methyl 2-(4-phenylbutylthio)acetate[1] 92



The title compound was prepared using general procedure **A**, using potassium carbonate (3.92 g, 28.4 mmol), methyl thioglycolate (2.74 g, 2.3 mL, 25.8 mmol) and (4-bromobutyl)benzene **65** (5.74 g, 25.8 mmol) in acetone (100 mL) stirred under reflux for 21 h. Following the work up, methyl 2-(4-phenylbutylthio)acetate **92** (6.8 g, quantitative) was isolated as an odorous yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2934 (CH), 1738 (CO), 1436 (C=C, Ar), 1279, 1136 (C–O), 700 (CS); δ_H ($CDCl_3$, 400 MHz): 1.58–1.81 [4H, m, C(2′)H_2 and C(3′)H_2], 2.58–2.69 [4H, m, C(1′)H_2 and C(4′)H_2], 3.20 (2H, s, SCH_2CO), 3.72 (3H, s, $COOCH_3$), 7.10–7.21 (3H, m, Ar*H*), 7.30–7.32 (2H, m, Ar*H*).

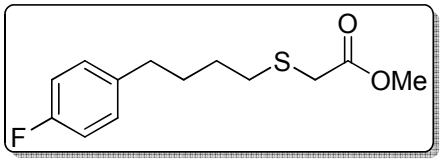
Methyl 2-(5-phenylpentylthio)acetate[1] 93



The title compound was prepared using general procedure **A**, using potassium carbonate (4.55 g, 33 mmol), methyl thioglycolate (3.21 g, 2.7 mL, 30 mmol) and (5-bromopentyl)benzene **66** (6.80 g, 30 mmol) in acetone (120 mL) stirred under reflux for 18 h. Following the work up, methyl 2-(5-phenylpentylthio)acetate **93**

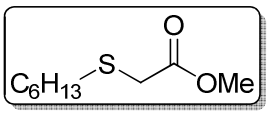
(8.59 g, quantitative) was isolated as an odorous yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2935 (CH), 1737 (CO), 1436 (C=C, Ar), 1279, 1150 (C–O), 700 (CS); δ_H ($CDCl_3$, 400 MHz): 1.37–1.53 [2H, m, C(3′)H_2], 1.56–1.71 [4H, m, C(2′)H_2 and C(4′)H_2], 2.56–2.67 [4H, m, C(1′)H_2 and C(5′)H_2], 3.21 (2H, s, SCH_2CO), 3.73 (3H, s, COOCH_3), 7.11–7.23 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*).

Methyl 2-{[4-(4-fluorophenyl)butyl]thio}acetate 99



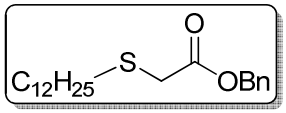
The title compound was prepared using general procedure **A**, using potassium carbonate (3.60 g, 26.0 mmol), methyl thioglycolate (3.50 g, 2.9 mL, 32.9 mmol) and 1-(4-bromobutyl)-4-fluorobenzene **68** (7.61 g, 32.9 mmol) in acetone (300 mL) stirred under reflux for 18 h. Following the work up, methyl 2-{[4-(4-fluorophenyl)butyl]thio}acetate **99** (7.12 g, 84 %) was isolated as an odorous yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2934 (CH), 1738 (CO), 1601 (C=C, Ar), 1510 (C=C, Ar), 1280, 1221, 1158 (C–O), 825, 701 (CS); δ_H ($CDCl_3$, 300 MHz): 1.55–1.79 [4H, m, C(2′)H_2 and C(3′)H_2], 2.56–2.72 [4H, m, C(1′)H_2 and C(4′)H_2], 3.20 (2H, s, SCH_2CO), 3.72 (3H, s, COOCH_3), 6.90–7.02 (2H, m, Ar*H*), 7.05–7.17 (2H, m, Ar*H*).

Methyl 2-(hexylthio)acetate[1] 96



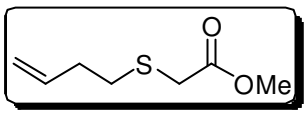
The title compound was prepared using general procedure **A**, using potassium carbonate (14.51 g, 105.0 mmol), methyl thioglycolate (10.16 g, 8.6 mL, 95.0 mmol) and 1-bromohexane (15.62 g, 13.3 mL, 95.0 mmol) in acetone (200 mL) stirred under reflux for 18 h. Following the work up, methyl 2-(hexylthio)acetate **96** (18.21 g, 100%) was isolated as an odorous clear oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2929 (CH), 1739 (CO), 1278, 1135 (C–O); δ_H ($CDCl_3$, 400 MHz): 0.89 [3H, t, *J* 6.8, C(6′)H_3], 1.23–1.45 [6H, m, C(5′)H_2, C(4′)H_2, C(3′)H_2], 1.53–1.69 [2H, m, C(2′)H_2], 2.59–2.68 [2H, m, C(1′)H_2], 3.22 (2H, s, SCH_2CO), 3.74 (3H, s, COOCH_3).

Benzyl 2-(dodecylthio)acetate[1] 82



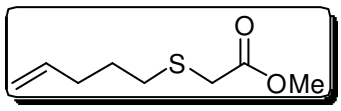
The title compound was prepared using general procedure **A**, using potassium carbonate (6.61 g, 47.9 mmol), dodecanethiol (8.79 g, 10.4 mL, 43.5 mmol) and benzyl bromoacetate (9.96 g, 6.9 mL, 43.5 mmol) in acetone (220 mL) stirred under reflux for 19 h. Following the work up, benzyl 2-(dodecylthio)acetate **82** (18.51 g, quantitative %) was isolated as a pale yellow oil, which was used without further purification. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 2924, 2853 (CH) 1736 (CO), 1458 (C=C, Ar),1274, 1129 (C-O), 750, 696 (CS); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 6.9, C(12′)H_3], 1.15–1.40 [18H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2], 1.50–1.63 [2H, m, C(2′)H_2], 2.55–2.67 [2H, m, C(1′)H_2], 3.25 (2H, s, SCH_2CO), 5.17 (2H, s, CO_2CH_2Ph), 7.25–7.46 (5H, m, Ar*H*).

Methyl 2-(but-3-en-1-ylthio)acetate 101



The title compound was prepared using general procedure **A**, using potassium carbonate (5.63 g, 40.7 mmol), 4-bromobut-1-ene (5.0 g, 37.0 mmol) and methyl thioglycolate (3.93 g, 3.3 mL, 37.0 mmol) in acetone (100 mL) stirred under reflux for 21 h. Following the work up, methyl 2-(but-3-en-1-ylthio)acetate **101** (5.28 g, 89%) was isolated as an odorous pale yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2953, 2925 (CH), 1739 (CO), 1641 (C=C, Ar), 1437, 1281, 1134, 1009, 918 (CS); δ_H ($CDCl_3$, 400 MHz): 2.36 [2H, apparent q, *J* 7.0, C(2′)H_2], 2.71 [2H, t, *J* 7.40, C(1′)H_2], 3.24 (2H, s, SCH_2CO), 3.74 (3H, s, COOCH_3), 4.98–5.16 [2H, m, C(4′)H_2], 5.75–5.88 [1H, m, C(3′)H_2].

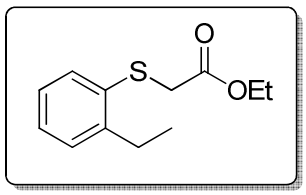
Methyl 2-(pent-4-en-1-ylthio)acetate 103



The title compound was prepared using general procedure **A**, using potassium carbonate (4.07 g, 29.5 mmol), 5-bromopent-1-ene (4.0 g, 26.8 mmol) and methyl thioglycolate (2.81 g, 2.4 mL, 26.5 mmol) in acetone (80 mL) stirred under reflux for 21 h. Following the work up, methyl 2-(pent-4-en-1-ylthio)acetate **103** (4.32 g, 93%) was isolated as an odorous pale yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2952, 2932 (CH), 1738 (CO), 1641 (C=C, Ar), 1437, 1279, 1134, 1010, 914 (CS); δ_H ($CDCl_3$, 400 MHz): 1.65–1.76 [2H, m, either C(2′)H_2 or C(3′)H_2], 2.09–2.22 [2H, m, either C(2′)H_2 or C(3′)H_2],

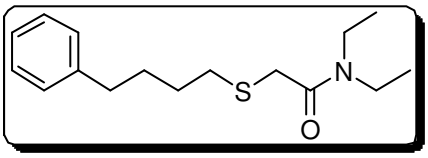
2.60–2.69 [2H, m, C(1′)H_2], 3.23 (2H, s, SCH_2CO), 3.74 (3H, s, COOCH_3), 4.93–5.09 [2H, m, C(5′)H_2], 5.72–5.85 [1H, m, C(4′)H].

Ethyl 2-[(2-ethylphenyl)thio]acetate 83



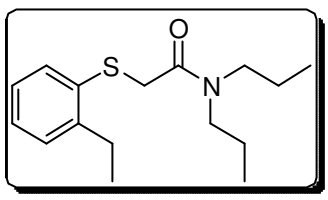
The title compound was prepared using general procedure **A**, using potassium carbonate (6.73 g, 48.7 mmol), 2-ethylbenzenethiol (6.00 g, 5.86 mL, 43.4 mmol) and ethyl 2-bromoacetate (7.30 g, 4.85 mL, 43.7 mmol) in acetone (200 mL) stirred under reflux for 19 h. Following the work up, ethyl 2-[(2-ethylphenyl)thio]acetate **83** (9.50 g, 97%) was isolated as a clear oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2967 (CH), 1735 (CO), 1470 (C=C, Ar), 1268, 1129, 1029 (C–O), 750 (CS); δ_H ($CDCl_3$, 400 MHz): 1.17–1.28 (6H, two overlapping t, appears as m, ArCH$_2$CH_3 and OCH$_2$CH_3), 2.82 (2H, q, *J* 7.6, ArCH_2CH$_3$), 3.61 (2H, s, SCH_2CO$_2$Et), 4.15 (2H, q, *J* 7.2, OCH_2CH$_3$), 7.13–7.22 (3H, m, ArH), 7.37–7.40 (1H, m, ArH).

***N*,*N*-Diethyl-2-[(4-phenylbutyl)thio]acetamide 88**



The title compound was prepared using general procedure **A**, using potassium carbonate (1.01 g, 7.30 mmol), 4-phenylbutyl-1-thiol **70** (1.10 g, 6.62 mmol), 2-chloro-*N*,*N*-diethylacetamide **76** (0.93 g, 6.62 mmol) in acetone (30 mL) stirred under reflux for 16 h. Following the work up, *N*,*N*-diethyl-2-[(4-phenylbutyl)thio]acetamide **88** (1.55 g, 84%) was isolated as a yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2973 2932 (CH), 1640 (CO), 1454, 1431, 1282, 1110, 700 (CS); δ_H ($CDCl_3$, 400 MHz): 1.06 (3H, t, *J* 7.2, one of NCH$_2$CH_3), 1.15 (3H, t, *J* 7.2, one of NCH$_2$CH_3), 1.50–1.85 [4H, m, C(2′)H_2 and C(3′)H_2], 2.53–2.78 [4H, m, C(1′)H_2 and C(4′)H_2], 3.23 (2H, s, SCH_2CO), 3.31–3.48 (4H, sym m, 2 × NCH_2CH$_3$), 7.09–7.22 (3H, m, ArH), 7.23–7.35 (2H, m, ArH).

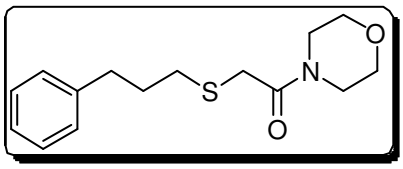
2-[(2-Ethylphenyl)thio]-*N*,*N*-dipropylacetamide 90



The title compound was prepared using general procedure **A**, using potassium carbonate (5.37 g, 39.0 mmol), 2-ethylbenzenethiol (5.0 g, 4.9 mL, 36.0 mmol) and 2-chloro-*N*,*N*-dipropylacetamide **77** (6.39 g, 36.0 mmol) in acetone (120 mL) stirred under reflux for 21 h. Following the work up, 2-[(2-ethylphenyl)thio]-*N*,*N*-dipropylacetamide **90** (9.51 g, 95 %) was isolated as a light brown oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2964, 2932, 2873 (CH), 1642 (CO),

1466, 1102, 749 (C-O); δ_H ($CDCl_3$, 400 MHz): 0.84–0.96 (6H, two overlapping 3H t, 2 × $NCH_2CH_2CH_3$), 1.23 (3H, t, *J* 7.5, $ArCH_2CH_3$), 1.49–1.70 (4H, sym m, 2 × $NCH_2CH_2CH_3$), 2.82 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.17–3.25 (2H, sym m, one of $NCH_2CH_2CH_3$), 3.26–3.33 (2H, sym m, one of $NCH_2CH_2CH_3$), 3.71 (2H, s, SCH_2CO), 7.12–7.23 (3H, m, Ar*H*), 7.41–7.45 (1H, m, Ar*H*).

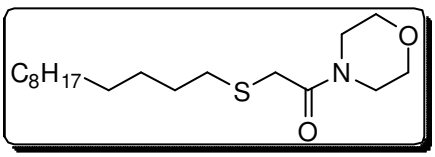
1-Morpholino-2-[(3-phenylpropyl)thio]ethanone 87



The title compound was prepared using general procedure **A**, using potassium carbonate (1.63 g, 11.8 mmol), 3-phenylpropyl-1-thiol **73** (1.65 g, 10.8 mmol) and 2-chloro-1-morpholinoethanone **78** (1.77 g, 10.8 mmol) in acetone (40 mL) stirred under reflux for 18 h. Following the work up, 1-morpholino-2-[(3-phenylpropyl)thio]ethanone **87** (2.81 g, 93%) was isolated as an odorous brown oil, (~60% pure, by ^{1}H NMR contains unidentified material) which was used without further purification; δ_H ($CDCl_3$, 400 MHz): 1.90–2.14 [2H, m, C(2′)H_2], 2.64–2.85 [4H, m, C(1′)H_2 and C(3′)H_2], 3.25–3.80 [10H, m, 8H morpholine CH_2 and SCH_2CO), 7.13–7.24 (3H, m, Ar*H*), 7.25–7.34 (2H, m, Ar*H*).

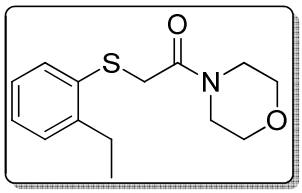
(Note: IR was not measured due to the malodorous nature of compound)

2-(Dodecylthio)-1-morpholinoethanone 91



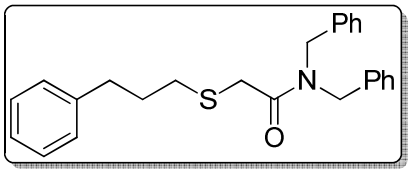
The title compound was prepared using general procedure **A**, using potassium carbonate (3.76 g, 27.2 mmol), dodecane-1-thiol (7.02 g, 8.3 mL, 34.7 mmol) and 2-chloro-1-morpholinoethanone **78** (5.0 g, 30.6 mmol) in acetone (100 mL) stirred under reflux for 18 h. Following the work up, 2-(dodecylthio)-1-morpholinoethanone **91** (7.92 g, 78%) was isolated as a yellow oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2919 (CH), 1649 (CO), 1459, 1274, 1117, 1040, 965, 850, 722 (CS); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 6.8, C(12′)H_3], 1.17–1.32 [16H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2], 1.34–1.44 [2H, m, C(3′)H_2], 1.56–1.67 [2H, m, C(2′)H_2], 2.58–2.68 [2H, m, C(1′)H_2], 3.29 (2H, s, CH_2, SCH_2CO), 3.46–3.55 (2H, m, morpholine CH_2), 3.57–3.63 (2H, m, morpholine CH_2), 3.65–3.76 (4H, m, morpholine CH_2).

2-[(2-Ethylphenyl)thio]-1-morpholinoethanone 89



The title compound was prepared using general procedure **A**, using potassium carbonate (2.61 g, 18.9 mmol), 2-ethylbenzenethiol (2.37 g, 2.3 mL, 17.2 mmol) and 2-chloro-1-morpholinoethanone **78** (2.80 g, 17.2 mmol) in acetone (50 mL) stirred under reflux for 19 h. Following the work up, 2-[(2-ethylphenyl)thio]-1-morpholinoethanone **89** (4.21 g, 92%) was isolated as a brown oil, which was used without further purification; ν_{max}/cm^{-1} (film): 2965, 2927 2858 (CH), 1644 (CO) 1436, 1274, 1256, 1115, 1038, 752 (CS); δ_H ($CDCl_3$, 400 MHz): 1.24 (3H, t, *J* 7.5, $ArCH_2CH_3$), 2.81 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.43–3.51 (2H, m, morpholine CH_2), 3.58–3.68 (6H, m, morpholine CH_2), 3.69 (2H, s, SCH_2CO), 7.14–7.24 (3H, m, Ar*H*), 7.43–7.48 (1H, m, Ar*H*).

***N*,*N*-Dibenzyl-2-[(3-phenylpropyl)thio]acetamide 86**



The title compound was prepared using general procedure **A**, using potassium carbonate (2.18 g, 15.8 mmol), 3-phenylpropyl-1-thiol **73** (2.20 g, 14.4 mmol) and *N*,*N*-dibenzyl-2-chloroacetamide **75** (3.94 g, 14.4 mmol) in acetone (40 mL) stirred under reflux for 21 h. Following the work up, *N*,*N*-dibenzyl-2-[(3-phenylpropyl)thio]acetamide **86** (3.85 g, 69%) was isolated as an odorous brown oil, which was used without further purification; ν_{max}/cm^{-1} (film): 3063, 3028, 2930 (CH), 1645 (CO), 1496, 1452, 1362, 1253, 1079, 745, 700 (CS); δ_H ($CDCl_3$, 400 MHz): 1.84–2.09 [2H, m, C(2′)H_2], 2.67–2.77 [4H, m, C(1′)H_2 and C(3′)H_2], 3.35 (2H, s, SCH_2CO), 4.54 (2H, s, one of $NCH_2C_6H_5$), 4.60 (2H, s, one of $NCH_2C_6H_5$), 7.09–7.44 (15H, m, Ar*H*).

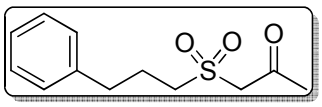
General Procedure (B) for Oxidation of Sulfides to Sulfones

A solution of *m*CPBA in dichloromethane was added dropwise to a solution of sulfide in dichloromethane over *approx* 30 min at 0 ºC under an atmosphere of nitrogen. The resulting solution was stirred for between 3−18 h, while warming to room temperature. Reaction monitoring was carried out using TLC analysis. The crude mixture was washed with saturated aqueous sodium metabisulfite solution (× 2), saturated aqueous sodium bicarbonate (× 4) and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the crude sulfone. In certain cases, washings with aqueous sodium metabisulfite solution were not carried out as indicated where relevant. The crude sulfone was further purified using column chromatography on silica gel, with hexane: ethyl acetate as the solvent system.

Approximately 10 mL of saturated aqueous sodium metabisulfite solution was used for every 10 mmol excess of *m*CPBA. Washings with aqueous sodium bicarbonate solution were carried out until no more effervescence was observed.

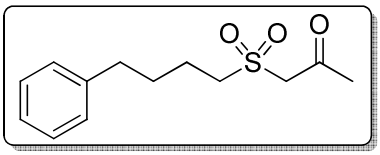
The purity of commercially available *m*CPBA varied throughout the course of this work. In certain cases *m*CPBA was used without prior titration, and its purity was assumed to be 77%, as states on the bottle. In other cases, titration was carried out prior to use and the purity was determined to be less than 62% and 66 %. Excess *m*CPBA was used in all cases. Between 2.1 eq. and 2.5 eq. were used. In general, 2.1 or 2.2 eq. was used in earlier work, with 2.5 eq. being used in later work as it was found that higher product yields were obtained with 2.5 eq. However in cases where 2.2 or 2.1 eq. was found to be adequate, no changes were made to this in later work.

1-(Phenylpropylsulfonyl)propan-2-one[1] 104



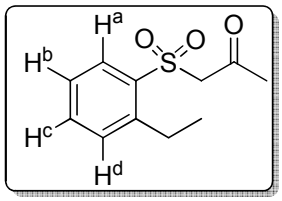
The title compound was prepared using general procedure **B**, using 1-(phenylpropylthio)propan-2-one **79** (1.10 g, 5.3 mmol) and *m*CPBA (77% w/w, 2.5 g, 11.0 mmol) in dichloromethane (50 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 3 h. Following the work up the ^{1}H NMR of the crude product indicated 83% sulfone and 17% sulfoxide formation. Following purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90) as eluent, 1-(phenylpropylsulfonyl)propan-2-one **104** [0.7 g, 55% and 66% corrected for sulfoxide (sulfoxide was observed in the ^{1}H NMR of the crude product, but was not isolated after purification)] was isolated as a pale yellow oil. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 1719 (CO), 1320, 1116 (SO_2); δ_H ($CDCl_3$, 400 MHz): 2.10–2.22 [2H, m, C(2′)H_2], 2.39 (3H, s, COCH_3), 2.77 [2H, t, *J* 7.5, C(3′)H_2], 3.05–3.13 [2H, m, C(1′)H_2], 4.00 (2H, s, SO_2CH_2CO), 7.12–7.35 (5H, m, Ar*H*).

1-(4-Phenylbutylsulfonyl)propan-2-one[1] 105



The title compound was prepared using general procedure **B**, using 1-(4-phenylbutylthio)propan-2-one **80** (1.1 g, 5.0 mmol) and *m*CPBA (77% w/w, 2.9 g, 13.0 mmol) in dichloromethane (50 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 3 h. Following the work up the ^{1}H NMR of the crude product indicated 70% sulfone and 30% sulfoxide formation. Following purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, 1-(4-phenylbutylsulfonyl)propan-2-one **105** [0.71 g, 55% and 79% corrected for sulfoxide (sulfoxide was observed in the ^{1}H NMR of the crude product, but was not isolated after purification)] was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1] mp 49–50 °C (Lit; mp 51–52 °C);[1] ν_{max}/cm^{-1} (KBr): 1728 (CO), 1297, 1077 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.69–1.96 [4H, m, C(2′)H_2 and C(3′)H_2], 2.42 (3H, s, COCH_3), 2.67 [2H, t, *J* 7.3, C(4′)H_2], 3.08–3.18 [2H, m, C(1′)H_2], 3.99 (2H, s, SO_2CH_2CO), 7.11–7.24 (3H, m, Ar*H*), 7.25–7.34 (2H, m, Ar*H*).

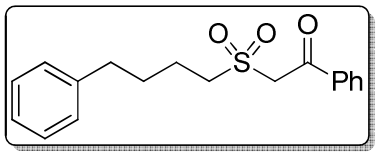
1-[(2-Ethylphenyl)sulfonyl]propan-2-one 115



The title compound was prepared using general procedure **B**, using 1-[(2-ethylphenyl)thio]propan-2-one **85** (4.5 g, 23.2 mmol) and *m*CPBA (66% w/w, 13.1 g, 50.9 mmol) in dichloromethane (220 mL), stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 21 h. Following the work up, and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, 1-[(2-ethylphenyl)sulfonyl]propan-2-one **115** (3.93 g, 75%) was isolated as a clear oil; ν_{max}/cm^{-1} (film): 2928 (CH), 1717 (CO), 1311, 1150 (SO_2), 746 (CS); δ_H ($CDCl_3$, 300 MHz): 1.34 (3H, t, *J* 7.5, $ArCH_2CH_3$), 2.40 (3H, s, $COCH_3$), 3.06 (2H, q, *J* 7.5, $ArCH_2CH_3$), 4.18 (2H, s, $SO_2CH_2CO_2CH_3$), 7.32–7.46 (2H, overlapping dd and ddd, appears as m, ArH^d and ArH^b), 7.60 (1H, ddd, *J* 1.3, 7.6, 7.6, ArH^c), 7.95 (1H, dd, *J* 1.2, 8.0, ArH^a); δ_C ($CDCl_3$, 75.5 MHz) 15.9 (CH_3, $ArCH_2CH_3$), 26.1 (CH_2, $ArCH_2CH_3$), 31.6 (CH_3, $COCH_3$), 67.9 (CH_2, SO_2CH_2CO), 126.6 (CH, aromatic CH^b), 130.2 (CH, aromatic CH^a), 131.2 (CH, aromatic CH^d), 134.5 (CH, aromatic CH^c), 136.5 (C, aromatic *C*), 144.5 (C, aromatic *C*), 195.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_3S$ $[M+H]^+$, 227.0742. Found 227.0723.

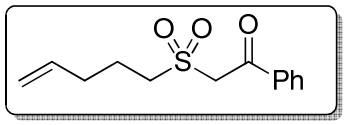
NMR assignment was aided using COSY and HETCOR experiments

2-(4-Phenylbutylsulfonyl)-1-phenylethanone[1] 106



The title compound was prepared using general procedure **B**, using 2-(4-phenylbutylthio)-1-phenylethanone **81** (1.3 g, 4.5 mmol) and *m*CPBA (77% w/w, 2.5 g, 11.3 mmol) in dichloromethane (80 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 19 h. Following the work up the ^1H NMR of the crude product indicated 43% sulfone and 57% sulfoxide formation. Following purification by column chromatography on silica gel using ethyl acetate-hexane (10:90–20:80–30:70) as eluent, 2-(4-phenylbutylsulfonyl)-1-phenylethanone **106** [0.41 g, 28% and 68% corrected for sulfoxide (sulfoxide was observed in the ^1H NMR of the crude product, but was not isolated after purification)] was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1] mp 80–81 ºC (Lit; mp 92–93 °C);[1] ν_{max}/cm^{-1} (KBr): 1686 (CO) 1336, 1300, 1131 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.74–1.98 [4H, m, C(2′)H_2 and C(3′)H_2], 2.68 [2H, t, *J* 7.4, C(4′)H_2], 3.24–3.35 [2H, m, C(1′)H_2], 4.55 (2H, s, SO_2CH_2CO), 7.15–7.23 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*), 7.49–7.57 (2H, m, Ar*H*), 7.62–7.71 (1H, m, Ar*H*), 7.97–8.03 (2H, m, Ar*H*).

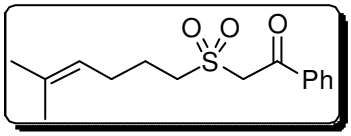
2-(Pent-4-en-1-ylsulfonyl)-1-phenylethanone 131



A solution of 2-(methylsulfonyl)-1-phenylethanone (2.0 g, 10.1 mmol) in dry THF (25 mL) was added to sodium hydride [0.40 g, 0.24 g calculated, 60% w/w (suspension in mineral oil), 10.1 mmol] at 0 °C under an atmosphere of nitrogen. The resulting solution was stirred at 0 °C for 30 min at which point *n*-butyllithium [2.2M (in hexanes), 4.0 mL, 10.1 mmol] was added slowly over 20 min, taking care to maintain the temperature at 0 °C. After an additional 10 min of stirring at 0 °C, 4-bromobut-1-ene (1.36 g, 10.1mmol) was added neat, and the resulting solution was stirred for 3 h, while returning to room temperature. The reaction mixture was acidified with hydrochloric acid (2 M, aqueous solution, 10 mL) and extracted with ether (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Following the work up, the analysis of the ^{1}H NMR spectrum of the crude product indicated that the reaction contained 53% sulfone and 47% starting material. [Relative amounts calculated from the ^{1}H NMR spectra of the crude product using SO_2CH_2CO signal; δ_H=4.57 (2H, s, SO_2CH_2CO), for sulfone product **131** and δ_H=4.61 (2H, s, SO_2CH_2CO), for starting material sulfone **135**. An additional peak is observed for starting material sulfone **135**; δ_H =3.16 (3H, s, SO_2CH_3). Following purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, 2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **131** (1.02 g, 40%) was isolated as a white solid. mp 65–66 ºC, ν_{max} /cm^{-1} (KBr): 3053, 2961, 2920 (CH), 1688 (CO), 1642, 1599 (C=C, Ar), 1451, 1334, 1322, 1257, 1213, 1134, 1121 (SO_2), 995, 913, 895, 755, 689 (CS); δ_H ($CDCl_3$, 600 MHz): 1.96–2.05 [2H, m, C(2′)H_2], 2.19–2.29 [2H, m, C(3′)H_2], 3.22–3.31 [2H, m, C(1′)H_2], 4.57 (2H, s, SO_2CH_2CO), 5.02–5.17 [2H, m, C(5′)H_2], 5.72–5.83 [1H, sym m, C(4′)*H*], 7.53 (2H, t, *J* 7.7, ArH_{meta}), 7.66 (1H, t, *J* 7.4, ArH_{para}), 8.00 (2H, d, *J* 8.0, ArH_{ortho}); δ_C ($CDCl_3$, 150.9 MHz): 21.0 [CH_2, *C*(2′)H_2], 32.1 [CH_2, *C*(3′)H_2], 53.0 [CH_2, *C*(1′)H_2], 59.6 (CH_2, SO_2CH_2CO), 116.7 [CH_2, *C*(5′)H_2], 129.0 (2 × CH, aromatic *C*H$_{meta}$), 129.3 (2 × CH, aromatic *C*H$_{ortho}$), 134.7 (CH, aromatic *C*H$_{para}$), 135.7 (C, aromatic, *C*), 136.2 [CH, *C*(4′)H], 189.3 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{17}O_3S$ $[M+H]^+$, 253.0898. Found 253.0893. m/z (ESI+): 253.3 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

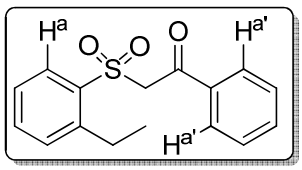
2-[(5-Methylhex-4-en-1-yl)sulfonyl]-1-phenylethanone 132



The title compound was prepared using the procedure described for 2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **131**, using 2-(methylsulfonyl)-1-phenylethanone (1.69 g, 8.5 mmol), THF (20 mL), sodium hydride [0.34 g, 0.20 g calculated, 60% w/w (suspension in mineral oil), 0.20 g, 8.5 mmol], *n*-butyllithium [2.2 M (solution in hexanes), 3.4 mL, 8.5 mmol] and 5-bromo-2-methylpent-2-ene (1.4 mL, 8.5 mmol). Following the work up the analysis of the ^{1}H NMR of the crude product indicated that the reaction contained 33% sulfone and 67% starting material. [Relative amounts calculated from the ^{1}H NMR spectra of the crude product using SO_2CH_2CO signal; δ_H=4.55 (2H, s, SO_2CH_2CO), for sulfone product **132** and δ_H=4.61 (2H, s, SO_2CH_2CO), for starting material sulfone **135**. An additional peak is observed for starting material sulfone **135**; δ_H=3.16 (3H, s, SO_2CH_3). Following purification using column chromatography on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, 2-[(5-methylhex-4-en-1-yl)sulfonyl]-1-phenylethanone **132** (0.52 g, 22%) was isolated as a white crystalline solid; mp 59–60 ºC, ν_{max}/cm^{-1} (KBr): 3060, 2998, 2959, 2918, 2874 (CH), 1687 (CO), 1600 (C=C), 1450, 1333, 1321, 1289, 1213, 1132, 1120 (SO_2), 995, 896, 753, 690 (CS); δ_H ($CDCl_3$, 600 MHz): 1.61 [3H, s, C(6′)H_3 or CH_3], 1.71 [3H, s, C(6′)H_3 or CH_3], 1.90–1.96 [2H, m, C(2′)H_2], 2.13–2.19 [2H, m, C(3′)H_2], 3.20–3.37 [2H, m, C(1′)H_2], 4.55 (2H, s, SO_2CH_2CO), 5.09 [1H, t, *J* 7.1, C(4′)*H*], 7.53 (2H, t, *J* 7.8, ArH_{meta}), 7.66 (1H, t, *J* 7.4, ArH_{para}), 8.02 (2H, d, *J* 7.8, ArH_{ortho}); δ_C ($CDCl_3$, 150.9 MHz): 17.8 [CH_3, *C*(6′)H_3 or *C*H_3], 22.1 [CH_2, *C*(2′)H_2], 25.7 [CH_3, *C*(6′)H_3 or *C*H_3], 26.5 [CH_2, *C*(3′)H_2], 53.2 [CH_2, *C*(1′)H_2], 59.5 (CH_2, SO_2CH_2CO), 122.0 [CH, *C*(4′)H], 129.0 (2 × CH, aromatic *C*H_{ortho}), 129.3 (2 × CH, aromatic *C*H_{meta}), 134.0 [C, aromatic, *C* or *C*(5′)], 134.6 [CH, aromatic, *C*H_{para}], 135.7 [C, aromatic, *C* or *C*(5′)], 189.3 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{21}O_3S$ $[M+H]^+$, 281.1211. Found 281.1209. m/z (ESI+): 281.3 $[M+H]^+$.

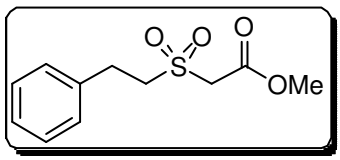
Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-(2-Ethylphenylsulfonyl)-1-phenylethanone 114



The title compound was prepared according to general procedure **B** using 2-[(2-ethylphenyl)thio]-1-phenylethanone **84** (8.00 g, 31.2 mmol) and *m*CPBA (66% w/w, 23.34 g, 89.3 mmol) in dichloromethane (250 mL), stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 16 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60–60:40–80:20) as eluent, 2-(2-ethylphenylsulfonyl)-1-phenylethanone **114** (4.80 g, 53%) was isolated as a white solid. An analytical sample was obtained, by recrystallision from *iso* propyl alcohol, for CHN and melting point analysis; mp 78–79 ºC (Found: C, 66.64; H, 5.47; $C_{16}H_{16}O_3S$ requires C, 66.64; H, 5.59%); ν_{max}/cm^{-1} (KBr): 2983 (CH), 1675 (CO), 1316, 1214, 1154 (SO_2); δ_H ($CDCl_3$, 400 MHz): 1.32 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.07 (2H, q, *J* 7.5, $ArCH_2CH_3$), 4.76 (2H, s, SO_2CH_2CO), 7.27–7.35 (1H, m, Ar*H*), 7.38–7.43 (1H, m, Ar*H*), 7.44–7.52 (2H, m, Ar*H*), 7.53–7.65 (2H, m, Ar*H*), 7.88 (1H, dd, *J* 1.3, 8.0, ArH^a), 7.93 (2H, ddd, *J* 1.6, 1.6, 8.5, $ArH^{a'}$); δ_C ($CDCl_3$, 75.5 MHz): 15.9 (CH_3, $ArCH_2CH_3$), 26.2 (CH_2, $ArCH_2CH_3$), 63.7 (CH_2, SO_2CH_2CO), 126.4, 128.8, 129.4, 130.7, 131.1, 134.3 (6 signals seen for 7 aromatic *C*H carbons), 134.4 (C, aromatic *C*), 135.9 (C, aromatic *C*), 136.6 (C, aromatic *C*), 187.9 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{17}O_3S$ $[M+H]^+$, 289.0898. Found 289.0895. m/z (ESI+): 289.1 $[M+H]^+$.

Methyl 2-(phenylethylsulfonyl)acetate 122

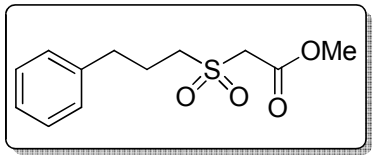


A solution of Oxone® (50.5 g, 82.1 mmol) in distilled water (430 mL) was added dropwise over 1 h to a solution of methyl 2-(phenylethylthio)acetate **98** (7.5 g, 35.7 mmol) in acetone (100 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 21 h. The reaction mixture was concentrated under reduced pressure. The crude sulfone was then dissolved in dichloromethane (80 mL) and washed with distilled water (2 × 50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield the crude sulfone. Purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, yielded methyl 2-(phenylethylsulfonyl)acetate **122** (5.23 g, 60%) as a colourless oil, which later solidified to yield a low melting white solid; ν_{max}/cm^{-1} (film): 1744 (CO), 1319, 1116 (SO_2); δ_H ($CDCl_3$, 400 MHz): 3.10–3.24 [2H, m, C(1′)H_2 or C(2′)H_2], 3.49–3.60 [2H, m, C(2′)H_2 or C(1′)H_2], 3.80 (3H, s, $COOCH_3$), 3.88 (2H, s,

SO_2CH_2CO), 7.19–7.40 (5H, m, Ar*H*); δ_C ($CDCl_3$, 100.6 MHz): 28.2 [CH_2, *C*(1′)H_2 or *C*(2′)H_2], 53.3 (CH_3, $COOCH_3$), 54.8 [CH_2, *C*(1′)H_2 or *C*(2′)H_2], 57.5 (CH_2, SO_2CH_2CO), 127.2 (CH, aromatic *C*H), 128.6 (CH, 2 × aromatic *C*H), 129.0 (CH, 2 × aromatic *C*H), 137.1 (C, aromatic *C*), 163.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_4S$ $[M+H]^+$, 243.0681. Found 243.0691. m/z (ESI+): 243.29 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HETCOR and COSY.

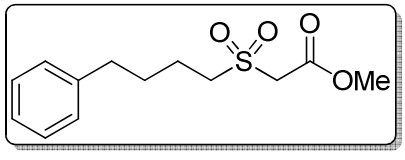
Methyl 2-[(3-phenylpropyl)sulfonyl]acetate 110



The title compound was prepared using general procedure **B**, using methyl 2-[(3-phenylpropyl)thio]acetate **94** (20.0 g, 89.2 mmol) and *m*CPBA (66% w/w, 52.8 g, 202 mmol) in dichloromethane (400 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 21 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–60:40) as eluent, methyl 2-[(3-phenylpropyl)sulfonyl]acetate **110** (14.6 g, 64%) was isolated as a clear oil; ν_{max}/cm^{-1} (film): 3028, 3005, 2954 (CH), 1744 (CO), 1455, 1438, 1323, 1218, 1143, 1116 (SO_2) 752, 702 (CS); δ_H ($CDCl_3$, 600 MHz): 2.16–2.26 [2H, m, C(2′)H_2], 2.80 [2H, t, *J* 7.4, C(3′)H_2], 3.21–3.27 [2H, m, C(1′)H_2], 3.79 (3H, s, $COOCH_3$), 3.94 (2H, s, SO_2CH_2CO), 7.19 (2H, d, *J* 7.4, ArH_{ortho}), 7.23 (1H, t, *J* 7.4, ArH_{para}), 7.31 (2H, t, *J* 7.5, ArH_{meta}); δ_C ($CDCl_3$, 150.9 MHz): 23.4 [CH_2, *C*(2′)H_2], 34.1 [CH_2, *C*(3′)H_2], 52.7 [CH_2, *C*(1′)H_2], 53.3 (CH_3, $COOCH_3$), 57.3 (CH_2, SO_2CH_2CO), 126.6 (CH, aromatic CH_{para}) 128.4 (2 × CH, aromatic CH_{ortho}), 128.7 (2 × CH, aromatic CH_{meta}), 139.7 (C, aromatic *C*), 163.5 (C, *C*O); (HRMS) (ESI+): Exact mass calculated for $C_{12}H_{17}O_4S$ $[M+H]^+$, 257.0848. Found 257.0844. m/z (ESI-): 255.3 $(M-H)^-$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

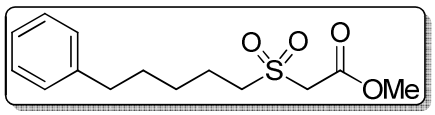
Methyl 2-(4-phenylbutylsulfonyl)acetate[1] 107



The title compound was prepared using general procedure **B**, (washings using saturated aqueous sodium metabisulfite solution were not carried out here) using methyl 2-(4-phenylbutylthio)acetate **92** (5.71 g, 23.0 mmol) and *m*CPBA (77% w/w,

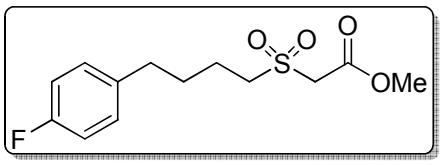
10.19 g, 45.5 mmol) in dichloromethane (180 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 2 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, methyl 2-(4-phenylbutylsulfonyl)acetate **107** (3.60 g, 57%) was isolated as a clear oil. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 1742 (CO), 1322, 1108 (SO_2); δ_H ($CDCl_3$, 400 MHz): 1.74–1.97 [4H, m, C(2′)H_2 and C(3′)H_2], 2.67 [2H, t, *J* 7.4, C(4′)H_2], 3.22–3.32 [2H, m, C(1′)H_2], 3.81 (3H, s, COOCH_3), 3.93 (2H, s, SO_2CH_2CO), 7.13–7.24 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*).

Methyl 2-(5-phenylpentylsulfonyl)acetate[1] 108



The title compound was prepared using general procedure **B**, (washings using saturated aqueous sodium metabisulfite solution were not carried out here) using methyl 2-(5-phenylpentylthio)acetate **93** (8.68 g, 34.3 mmol) and *m*CPBA (62%, 20.0 g, 72.2 mmol) in dichloromethane (220 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 3 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, methyl 2-(5-phenylpentylsulfonyl)acetate **108** (5.70 g, 58%) was isolated as a clear oil. Spectroscopic characteristics are consistent with those previously reported;[1] ν_{max}/cm^{-1} (film): 1743 (CO), 1324, 1106 (SO_2); δ_H ($CDCl_3$, 400 MHz): 1.42–1.56 [2H, m, C(3′)H_2], 1.61–1.75 [2H, m, C(4′)H_2], 1.83–1.95 [2H, m, C(2′)H_2], 2.63 [2H, t, *J* 7.6, C(5′)H_2], 3.19–3.28 [2H, m, C(1′)H_2], 3.81 (3H, s, COOCH_3), 3.95 (2H, s, SO_2CH_2CO), 7.12–7.22 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*).

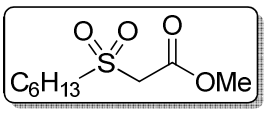
Methyl 2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate 112



The title compound was prepared using general procedure **B**, using methyl 2-{[4-(4-fluorophenyl)butyl]thio}acetate **99** (7.04 g, 27.3 mmol) and *m*CPBA (77% w/w, 11.85 g, 52.8 mmol) in dichloromethane (300 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 4 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–50:50–80:20) as eluent, methyl 2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate **112** (3.32 g, 42%) was isolated as a clear oil which later crystallised to yield a white solid. A sample was recrystallised from *iso*propyl

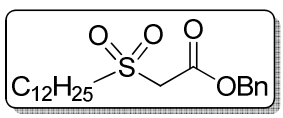
alcohol, for CHN and melting point analysis; mp 42–43 ºC; (Found: C, 53.85; H, 6.26; $C_{13}H_{17}FO_4S$ requires C, 54.15; H, 5.94 %); ν_{max}/cm^{-1} (KBr): 1746 (CO), 1510, 1277, 1217, 1141 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.68–1.97 [4H, m, C(2′)H_2 and C(3′)H_2], 2.65 [2H, t, *J* 7.4, C(4′)H_2], 3.23–3.34 [2H, m, C(1′)H_2], 3.82 (3H, s, COOCH_3), 3.95 (2H, s, SO_2CH_2CO), 6.92–7.03 (2H, m, Ar*H*), 7.06–7.18 (2H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 21.4, 30.2 [2 × CH_2, *C*(2′)H_2 and *C*(3′)H_2], 34.5 [CH_2, *C*(4′)H_2], 53.2 [CH_2, *C*(1′)H_2], 53.4 (CH_3, O*C*H_3), 57.3 (CH_2, SO_2CH_2CO), 115.0 (2 × ArCH, d, $^2J_{CF}$ 21.1, *C*(3)H, *C*(5)H], 129.7 [2 × ArCH, d, $^3J_{CF}$ 7.7, *C*(2)H, *C*(6)H], 136.67 [C, d, $^4J_{CF}$ 3.0, *C*(1)], 161.3 [C, $^1J_{CF}$ 243.5, *C*(4)], 163.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{18}FO_4S$ $[M+H]^+$, 289.0914. Found 289.0910. m/z (ESI+): 289.1 $[M+H]^+$.

Methyl 2-(hexylsulfonyl)acetate[1] 109



The title compound was prepared using general procedure **B** using methyl 2-(hexylthio)acetate **96** (18.0 g, 94.5 mmol) and *m*CPBA (77% w/w, 46.6 g, 208 mmol) in dichloromethane (650 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 24 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, methyl 2-(hexylsulfonyl)acetate **109** (14.1 g, 67%) was isolated as a low melting point white solid. Spectroscopic characteristics are consistent with those previously reported;[1] mp 30–31 ºC; ν_{max}/cm^{-1} (KBr): 1758, 1746 (CO), 1318, 1281, 1149, 1111 (SO_2); δ_H ($CDCl_3$, 400 MHz): 0.90 [3H, t, *J* 7.0, C(6′)H_3], 1.28–1.53 [6H, m, C(5′)H_2, C(4′)H_2, C(3′)H_2], 1.80–1.93 [2H, m, C(2′)H_2], 3.20–3.30 [2H, m, C(1′)H_2], 3.83 (3H, s, COOCH_3), 3.96 (2H, s, SO_2CH_2CO).

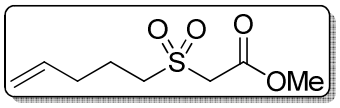
Benzyl 2-(dodecylsulfonyl)acetate[1] 111



The title compound was prepared using general procedure **B**, using benzyl 2-(dodecylthio)acetate **82** (18.0 g, 51.3 mmol) and *m*CPBA (77%, 35.4 g, 158 mmol) in dichloromethane (600 mL) stirred at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 23 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, benzyl 2-(dodecylsulfonyl)acetate **111** (12.5 g, 86%) was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported; mp 63–64 ºC (Lit. mp 62–64 °C)[1]; ν_{max}/cm^{-1} (KBr): 1734 (CO), 1327, 1161 (SO_2); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 6.8, C(12′)H_3],

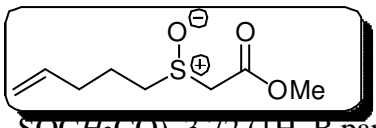
1.18–1.46 [18H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2], 1.77–1.88 [2H, m, C(2′)H_2], 3.14–3.23 [2H, m, C(1′)H_2], 3.98 (2H, s, SCH_2CO), 5.24 (2H, s, CO_2CH_2Ph), 7.37 (5H, br s, Ar*H*).

Methyl 2-(pent-4-en-1-ylsulfonyl)acetate 129



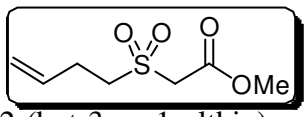
A solution of sodium (meta)periodate (≥ 99.8% ACS reagent) (17.9 g, 83.6 mmol) in distilled water (150 mL) was added to a solution of methyl 2-(pent-4-en-1-ylthio)acetate **103** (7.50 g, 36.0 mmol) in methanol (150 ml) over 30 min at 0 °C, under an atmosphere of nitrogen. The resulting solution slowly returned to room temperature over 3 h. TLC analysis of the crude reaction mixture indicated that the reaction had not gone to completion (only the intermediate sulfoxide was present). The reaction mixture was then warmed to 50 °C and was stirred for 16 h at this temperature. After the reaction mixture had cooled to room temperature, it was partitioned with brine (100 mL) and dichloromethane (100 mL). The aqueous layer was washed with dichloromethane (4 × 50 mL), the combined organic layers were washed with brine (50 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Following the work up, analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated 63% sulfone and 37% sulfoxide formation. [Relative amounts were calculated from the ^{1}H NMR spectra of the crude product using OMe signal; δ_H=3.82 (3H, s, COOCH_3) for sulfone **129** and δ_H=3.79 (3H, s, COOCH_3) for sulfoxide **133**] The crude reaction mixture was purified by column chromatography, on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–30:70–40:60) as eluent, methyl 2-(pent-4-en-1-ylsulfonyl)acetate **129** (3.45g, 46%, 70% corrected for sulfoxide, using the ^{1}H NMR spectra of the crude product mixture) was isolated as a colourless oil; (Found: C, 46.05; H, 6.65, S, 15.89, $C_8H_{14}O_4S$ requires C, 46.58; H, 6.84, S, 15.55%); ν_{max}/cm^{-1} (film): 3003, 2980, 2955 (CH), 1745 (CO), 1642 (C=C, Ar), 1439, 1323, 1141, 1112 (SO_2), 917 (CS); δ_H ($CDCl_3$, 600 MHz): 1.94–2.05 [2H, m, C(2′)H_2], 2.21–2.28 [2H, m, C(3′)H_2], 3.23–3.29 [2H, m, C(1′)H_2], 3.82 (3H, s, COOCH_3), 3.98 (2H, s, SO_2CH_2CO), 5.05–5.14 [2H, m, C(5′)H_2], 5.72–5.82 [1H, m, C(4′)*H*]; δ_C ($CDCl_3$, 150.9 MHz): 21.0 [CH_2, *C*(2′)H_2], 32.1 [CH_2, *C*(3′)H_2], 52.8 [CH_2, *C*(1′)H_2], 53.4 (CH_3, COO*C*H_3), 57.3 (CH_2, SO_2*C*H_2CO), 116.8 [CH_2, *C*(5′)H_2], 136.1 [CH, *C*(4′)H], 163.6 (C, *C*O); Exact mass calculated for $C_8H_{15}O_4S$ [M+H$^+$, 207.0691. Found 207.0682. m/z (ESI+): 207.4 [M+H]$^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.



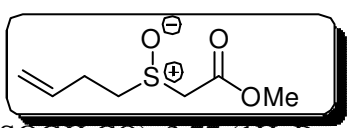
Characteristic signals were seen for the sulfoxide **133**; δ_H ($CDCl_3$, 400 MHz): 3.67 (1H, A part of ABq, *J* 13.7, one of $SOCH_2CO$), 3.72 (1H, B part of ABq, *J* 13.7, one of $SOCH_2CO$), 3.79 (3H, s, $COOCH_3$).

Methyl 2-(but-3-en-1-ylsulfonyl)acetate 130



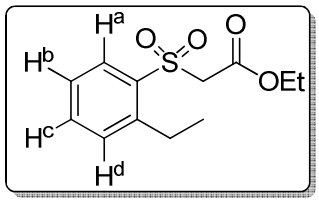
The title compound was prepared using the procedure described for methyl 2-(pent-4-en-1-ylsulfonyl)acetate **129**, using methyl 2-(but-3-en-1-ylthio)acetate (3.0 g, 18.7 mmol) **101**, methanol (75 mL), sodium (meta)periodate ($\geq$99.8% ACS reagent) (9.21 g, 43.0 mmol) and distilled water (75 mL). Addition of the sodium metaperiodate solution to the solution of sulfide **101** was carried out at 0 °C, under an atmosphere of nitrogen. The resulting solution slowly returned to room temperature over 3 h, at which point it was warmed to 50 °C and was stirred for 17 h at this temperature. Following the work up the analysis of the ^{1}H NMR spectrum of the crude product indicated 50% sulfone and 50% sulfoxide formation. [Relative amounts were calculated from the ^{1}H NMR spectra of the crude product using the OMe signal; δ_H=3.83 (3H, s, $COOCH_3$) for sulfone **130** and δ_H=3.80 (3H, s, $COOCH_3$) for sulfoxide **134**.] Following purification using column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60) as eluent, methyl 2-(but-3-en-1-ylsulfonyl)acetate **130** (1.62 g, 45%, 90% corrected for sulfoxide, using the ^{1}H NMR spectra of the crude product mixture) was isolated as a colourless oil; ν_{max}/cm^{-1} (film): 3005, 2955 (CH), 1744 (CO), 1643 (C=C, Ar), 1438, 1401, 1321, 1219, 1140, 1112, 1002 (SO_2), 915, 823 (CS); δ_H ($CDCl_3$, 600 MHz): 2.60–2.68 [2H, sym m, C(2′)H_2], 3.32–3.40 [2H, m, C(1′)H_2], 3.83 (3H, s, $COOCH_3$), 4.00 (2H, s, SO_2CH_2CO), 5.12–5.25 [2H, m, C(4′)H_2], 5.79–5.89 [1H, m, C(3′)*H*]; δ_C ($CDCl_3$, 150.9 MHz) 26.2 [CH_2, *C*(2′)H_2], 52.6 [CH_2, *C*(1′)H_2], 53.4 (CH_3, $COOCH_3$), 57.5 (CH_2, SO_2CH_2CO), 117.9 [CH_2, *C*(4′)H_2], 133.5 [CH, *C*(3′)H], 163.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_7H_{13}O_4S$ $[M+H]^+$ 193.0535. Found 193.0527. m/z (ESI+): 193.4 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.



Characteristic signals were seen for the sulfoxide **134**; δ_H ($CDCl_3$, 400 MHz) 3.70 (1H, A part of ABq, *J* 13.7, one of $SOCH_2CO$), 3.77 (1H, B part of ABq, *J* 13.7, one of $SOCH_2CO$), 3.80 (3H, s, $COOCH_3$).

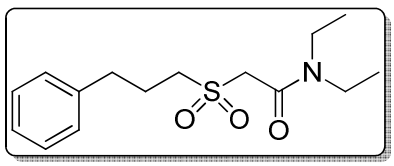
Ethyl 2-(2-ethylphenylsulfonyl)acetate 113



The title compound was prepared using general procedure **B**, using ethyl 2-[(2-ethylphenyl)thio]acetate **83** (10.00 g, 45 mmol) and *m*CPBA (77% w/w, 22.2 g, 99 mmol) in dichloromethane (250 mL), at 0 ºC for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 18 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, ethyl 2-(2-ethylphenylsulfonyl)acetate **113** (8.82 g, 76%) was isolated as a clear oil; (Found: C, 56.17; H, 6.39, $C_{12}H_{16}O_4S$ requires C, 56.23; H, 6.29%); ν_{max}/cm^{-1} (film): 2982 (CH), 1743 (CO), 1323, 1155 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.14 (3H, t, *J* 7.1, OCH_2CH_3), 1.34 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.07 (2H, q, *J* 7.5, $ArCH_2CH_3$), 4.09 (2H, q, *J* 7.1, OCH_2CH_3), 4.15 (2H, s, $SO_2CH_2CO_2Et$), 7.32–7.48 (2H, overlapping dd and ddd, appears as m, ArH^d and ArH^b), 7.57 (1H, ddd, *J* 7.5, 7.5, 1.4, ArH^c), 7.97 (1H, dd, *J* 8.0, 1.3, ArH^a); δ_C ($CDCl_3$, 75.5 MHz): 13.7 (CH_3, OCH_2CH_3), 15.8 (CH_3, $ArCH_2CH_3$), 26.0 (CH_2, $ArCH_2CH_3$), 61.1 (CH_2, SO_2CH_2CO), 62.2 (CH_2, OCH_2CH_3), 126.3 (CH, aromatic CH^b), 130.6 (CH, aromatic CH^a), 131.0 (CH, aromatic CH^d), 134.6 (CH, aromatic CH^c), 136.2 (C, aromatic *C*), 144.5 (C, aromatic *C*), 162.1 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{17}O_4S$ $[M+H]^+$ 257.0845. Found 257.0848. m/z (ESI+:) 257.2 $[M+H]^+$.

NMR assignment was aided using COSY and HETCOR experiments.

***N*,*N*-Diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide 125**

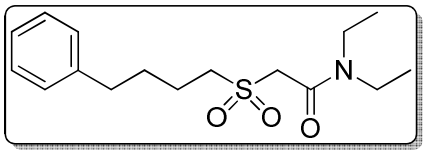


A solution of *N*,*N*-dicyclohexylcarbodiimide (DCC) (1.87 g, 9.08 mmol) in acetonitrile (20 mL) was added dropwise to a solution of 2-[(3-phenylpropyl)sulfonyl]acetic acid **123** (2.20 g, 9.08 mmol), diethylamine (0.66 g, 0.94 mL, 9.08 mmol) and *N*-hydroxysuccinimide (1.05 g, 9.08 mmol) in acetonitrile (40 mL) over *approx* 10 min at 0 ºC under an atmosphere of nitrogen. The resulting solution was stirred for 24 h, while warming to room temperature. The resulting solution was filtered to remove any insoluble byproducts and concentrated under reduced pressure to give the crude sulfone. Following purification, using column chromatography on silica gel with ethyl acetate-hexane (10:90–20:80–40:60–60:40) as eluent, *N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **125** (1.36 g, 50%) was isolated as a colourless oil; ν_{max}/cm^{-1} (film): 2977, 2937 (CH), 1641 (CO), 1455, 1318,

1149, 1128, 1114 (SO_2), 752, 702 (CS); δ_H ($CDCl_3$, 600 MHz): 1.15 (3H, t, *J* 7.2, one of NCH_2CH_3), 1.22 (3H, t, *J* 7.2, one of NCH_2CH_3), 2.16–2.27 [2H, m, C(2′)H_2], 2.78 [2H, t, *J* 7.6, C(3′)H_2], 3.27–3.34 [2H, m, C(1′)H_2], 3.37–3.51 (4H × 2, overlapping q appears as sym m, 2 × NCH_2CH_3), 3.97 (2H, s, SO_2CH_2CO), 7.16–7.23 (3H, m, Ar*H*), 7.26–7.34 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz); 12.8 (CH_3, one of NCH_2CH_3), 14.3 (CH_3, one of NCH_2CH_3), 23.6 [CH_2, *C*(2′)H_2], 34.2 [CH_2, *C*(3′)H_2], 41.1 (CH_2, one of NCH_2CH_3), 43.3 (CH_2, one of NCH_2CH_3), 52.9 [CH_2, *C*(1′)H_2], 56.0 (CH_2, SO_2CH_2CO), 126.4 (CH, aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 128.6 (CH, 2 × aromatic *C*H), 140.0 (C, aromatic *C*), 161.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{24}NO_3S$ $[M+H]^+$, 298.1477. Found 298.1470. m/z (ESI+): 298.30 $[M+H]^+$.

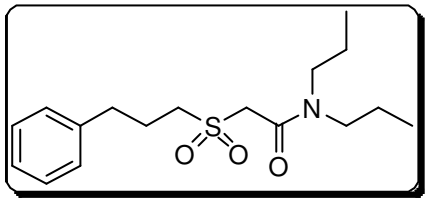
Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

_N_,_N_-Diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide 118



The title compound was prepared using general procedure **B**, using *N*,*N*-diethyl-2-[(4-phenylbutyl)thio]acetamide **88** (6.40 g, 22.9 mmol) and *m*CPBA (66% w/w, 14.5 g, 57.3 mmol) in dichloromethane (250 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 5 h. Following the work up and purification by column chromatography, on silica gel with ethyl acetate-hexane (10:90–20:80–50:50–80:20) as eluent, *N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide **118** (3.61 g, 51%) was isolated as a colourless oil; ν_{max}/cm^{-1} (film): 2934 (CH), 1639 (CO), 1452, 1317, 1148 (SO_2), 751 (CS); δ_H ($CDCl_3$, 300 MHz): 1.16 (3H, t, *J* 7.2, one of NCH_2CH_3), 1.23 (3H, t, *J* 7.2, one of NCH_2CH_3), 1.72–1.84 [2H, m, C(2′)H_2 or C(3′)H_2], 1.86–1.99 [2H, m, C(2′)H_2 or C(3′)H_2], 2.61–2.72 [2H, m, C(4′)H_2], 3.29–3.36 [2H, m, C(1′)H_2], 3.37–3.51 (4H, sym m, 2 × NCH_2CH_3), 3.98 (2H, s, SO_2CH_2CO), 7.12–7.22 (3H, m, Ar*H*), 7.23–7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 12.8 (CH_3, one of NCH_2CH_3), 14.4 (CH_3, one of NCH_2CH_3), 21.6 [CH_2, *C*(2′)H_2 or *C*(3′)H_2], 30.1 [CH_2, *C*(2′)H_2 or *C*(3′)H_2], 35.4 [CH_2, *C*(4′)H_2], 41.2 [CH_2, one of NCH_2CH_3], 43.4 [CH_2, one of NCH_2CH_3], 53.4 [CH_2, *C*(1′)H_2], 56.0 (CH_2, SO_2CH_2CO), 126.0 (CH, aromatic *C*H), 128.3 (CH, 2 × aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 141.4 (C, aromatic *C*), 161.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{26}NO_3S$ $[M+H]^+$, 312.1633. Found 312.1628. m/z (ESI+): 623.3 $[2M+H]^+$, m/z (ESI-): 310.4 $[M-H]^-$.

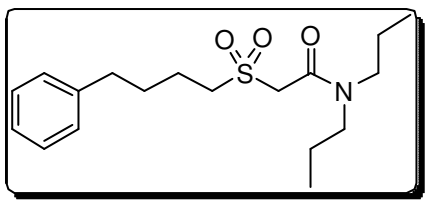
2-[(3-Phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide 127



The title compound was prepared according to the procedure described for *N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **125**, using DCC (1.87 g, 9.08 mmol), 2-[(3-phenylpropyl)sulfonyl]acetic acid **123** (2.20 g, 9.08 mmol), dipropylamine (0.93 g, 1.26 mL, 9.2 mmol) and *N*-hydroxysuccinimide (1.05 g, 9.10 mmol) in acetonitrile (65 mL) stirred at 0 ºC and slowly allowed to warm to room temperature while stirring for 23 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60–50:50–60:40–80:20) as eluent, 2-[(3-phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide **127** (1.56 g, 53%) was isolated as a colourless oil; ν_{max}/cm^{-1} (film): 2965, 2936, 2876 (CH), 1641 (CO), 1455, 1319, 1149, 1115 (SO_2), 749, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 0.91 (3H, t, *J* 7.4, one of $NCH_2CH_2CH_3$), 0.93 (3H, t, *J* 7.4, one of $NCH_2CH_2CH_3$), 1.52–1.69 (4H, sym m, 2 × $NCH_2CH_2CH_3$), 2.16–2.25 [2H, m, C(2′)H_2], 2.78 [2H, t, *J* 7.6, C(3′)H_2], 3.27–3.39 [6H, m, 2 × $NCH_2CH_2CH_3$ and C(1′)H_2], 3.99 (2H, s, SO_2CH_2CO), 7.16–7.23 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 11.2 (CH_3, one of $NCH_2CH_2CH_3$), 11.3 (CH_3, one of $NCH_2CH_2CH_3$), 20.8 (CH_2, one of $NCH_2CH_2CH_3$), 22.4 (CH_2, one of $NCH_2CH_2CH_3$), 23.6 [CH_2, *C*(2′)H_2], 34.3 [CH_2, *C*(3′)H_2], 48.4, 50.7, 52.9 (3 × CH_2, 2 × $NCH_2CH_2CH_3$ and *C*(1′)H_2], 56.1 (CH_2, SO_2CH_2CO), 126.4 (CH, aromatic *C*H) 128.5 (2 × CH, aromatic *C*H), 128.6 (2 × CH, aromatic *C*H), 140.1 (C, aromatic *C*), 161.9 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{17}H_{28}NO_3S$ $[M+H]^+$, 326.1790. Found 326.1788. m/z (ESI+): 326.30 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-[(4-Phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide 126

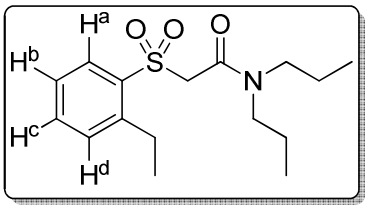


The title compound was prepared according to the procedure described for *N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **125**, using DCC (2.66 g, 12.9 mmol), 2-[(4-phenylbutyl)sulfonyl]acetic acid **124** (3.0 g, 11.7 mmol), dipropylamine (1.31 g, 1.77 mL, 12.9 mmol), and *N*-hydroxysuccinimide (1.48 g, 12.9 mmol) in acetonitrile (80 mL) stirred at 0 ºC and slowly allowed to warm to room temperature while stirring for 48 h.

Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60–50:50–80:20) as eluent, 2-[(4-phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide **126** (2.23 g, 56%) was isolated as a colourless oil; ν_{max}/cm^{-1} (film): 2964, 2937 (CH), 1641 (CO), 1455, 1319, 1149 (SO_2), 701 (CS); δ_H ($CDCl_3$, 400 MHz): 0.91 (3H, t, *J* 7.3, one of $NCH_2CH_2CH_3$), 0.94 (3H, t, *J* 7.3, one of $NCH_2CH_2CH_3$), 1.53–1.69 (4H, m, 2 × $NCH_2CH_2CH_3$), 1.73–1.84 [2H, m, C(3')H_2], 1.87–1.97 [2H, m, C(2′)H_2], 2.62–2.70 [2H, m, C(4′)H_2], 3.26–3.41 [6H, m, 2 × $NCH_2CH_2CH_3$ and C(1′)H_2], 3.98 (2H, s, SO_2CH_2CO), 7.13–7.21 (3H, m, Ar*H*), 7.23–7.33 (2H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 11.2 (CH_3, one of $NCH_2CH_2CH_3$), 11.3 (CH_3, one of $NCH_2CH_2CH_3$), 20.8 (CH_2, one of $NCH_2CH_2CH_3$), 21.7 [CH_2, *C*(2′)H_2], 22.4 (CH_2, one of $NCH_2CH_2CH_3$), 30.1 [CH_2, *C*(3′)H_2], 35.4 [CH_2, *C*(4′)H_2], 48.4, 50.7, 53.4 (3 × CH_2, 2 × $NCH_2CH_2CH_3$ and *C*(1′)H_2], 56.0 (CH_2, SO_2CH_2CO), 126.0 (CH, aromatic *C*H), 128.3 (2 × CH, aromatic *C*H), 128.4 (2 × CH, aromatic *C*H), 141.4 (C, aromatic *C*), 161.9 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{18}H_{30}NO_3S$ $[M+H]^+$, 340.1946. Found 340.1932. m/z (ESI+): 340.3 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HETCOR and COSY.

2-[(2-Ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide 116

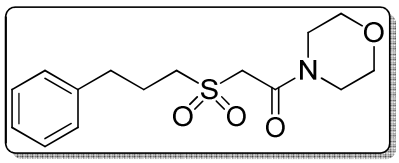


The title compound was prepared using general procedure **B**, using 2-[(2-ethylphenyl)thio]-*N*,*N*-dipropylacetamide **90** (8.0 g, 28.6 mmol) and *m*CPBA (66% w/w, 18.69 g, 71.5 mmol) in dichloromethane (300 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 5 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–50:50–60:40) as eluent, and further purification by recrystalisation from *iso*-propyl alcohol afforded 2-[(2-ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide **116** (4.54 g, 51%), which was isolated as a crystalline white solid; mp 105–106 ºC; ν_{max}/cm^{-1} (KBr): 2976, 2963, 2936 (CH), 1647 (CO), 1469, 1458, 1313, 1150 (SO_2), 808, 772 (CS); δ_H ($CDCl_3$, 600 MHz): 0.86 (3H, t, *J* 7.4, one of $NCH_2CH_2CH_3$), 0.94 (3H, t, *J* 7.4 one of $NCH_2CH_2CH_3$), 1.35 (3H, t, *J* 7.5, $ArCH_2CH_3$), 1.45–1.54 (2H, m, one of $NCH_2CH_2CH_3$), 1.58–1.66 (2H, m, one of $NCH_2CH_2CH_3$), 3.09 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.19–3.26 (2H, m, one of $NCH_2CH_2CH_3$), 3.37–3.46 (2H, m, one of $NCH_2CH_2CH_3$), 4.25 (2H, s, SO_2CH_2CO), 7.35 (1H, dd appears as t, *J* 7.7, ArH^b), 7.41 (1H, d, *J* 7.7, ArH^d), 7.58 (1H, dd appears as t, *J* 7.5, ArH^c), 7.95 (1H, d, *J* 8.0, ArH^a); δ_C

($CDCl_3$,150.9 MHz): 11.2 (CH_3, one of $NCH_2CH_2\mathit{C}H_3$), 11.3 (CH_3, one of $NCH_2CH_2\mathit{C}H_3$), 15.8 (CH_3, $ArCH_2\mathit{C}H_3$), 20.6 (CH_2, one of $NCH_2\mathit{C}H_2CH_3$), 22.2 (CH_2, one of $NCH_2\mathit{C}H_2CH_3$), 26.2 (CH_2, $Ar\mathit{C}H_2CH_3$), 48.1 (CH_2, one of $N\mathit{C}H_2CH_2CH_3$), 50.6 (CH_2, one of $N\mathit{C}H_2C\mathit{H}_2CH_3$), 60.0 ($CH_2$, $SO_2\mathit{C}H_2CO$), 126.2 (CH, aromatic $\mathit{C}H^b$), 130.5 (CH, aromatic $\mathit{C}H^a$), 130.9 (CH, aromatic $\mathit{C}H^d$), 134.2 (CH, aromatic $\mathit{C}H^c$), 136.6 (C, aromatic *C*), 144.7 (C, aromatic *C*), 160.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{26}NO_3S$ $[M+H]^+$, 312.1633. Found 312.1623. m/z (ESI+): 312.30 $[M+H]^+$, 623.3 $[2M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

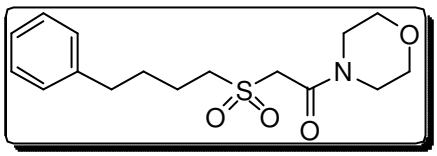
1-Morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone 119



The title compound was prepared using general procedure **B**, using 1-morpholino-2-[(3-phenylpropyl)thio]ethanone **87** (2.50 g, 8.94 mmol) and *m*CPBA (66% w/w, 5.85 g, 22.4 mmol) in dichloromethane (80 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 18 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–50:50–80:20) as eluent, 1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **119** (2.13 g, 76%) was isolated as a white crystalline solid; mp 125–127 ºC; (Found: C, 57.69; H, 6.86, N 4.42, $C_{15}H_{21}NO_4S$ requires C, 57.86; H, 6.80, N 4.50%); ν_{max}/cm^{-1} (neat, ATR): 2968, 2853 (CH), 1639, 1615 (CO), 1461, 1313, 1163, 1130, 1114 (SO_2), 751, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 2.17–2.29 [2H, m, C(2′)H_2], 2.79 [2H, t, *J* 7.6, C(3′)H_2], 3.18–3.27 [2H, m, C(1′)H_2], 3.56–3.64 [2H, sym m, morpholine CH_2], 3.65–3.72 (4H, sym m, morpholine CH_2), 3.73–3.78 [2H, sym m, morpholine CH_2], 4.04 (2H, s, $SO_2C\mathit{H}_2CO$), 7.16–7.25 (3H, m, Ar*H*), 7.27–7.34 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 23.5 [CH_2, *C*(2′)H_2], 34.1 [CH_2, *C*(3′)H_2], 42.7 [CH_2, morpholine N*C*H_2], 47.6 [CH_2, morpholine N*C*H_2], 52.8 [CH_2, *C*(1′)H_2], 55.9 (CH_2, $SO_2\mathit{C}H_2CO$), 66.4 (CH_2, morpholine O*C*H_2), 66.5 (CH_2, morpholine O*C*H_2), 126.5 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.6 (CH, 2 × aromatic *C*H), 139.8 (C, aromatic *C*), 160.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{22}NO_4S$ $[M+H]^+$, 312.1270. Found 312.1270. m/z (ESI+): 312.30 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

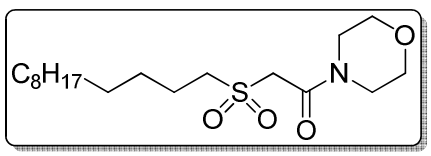
1-Morpholino-2-[(4-phenylbutyl)sulfonyl]ethanone 128



The title compound was prepared according to the procedure described for *N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **125**, using DCC (2.66 g, 12.9 mmol), 2-[(4-phenylbutyl)sulfonyl]acetic acid **124** (3.0 g, 11.7 mmol), morpholine (1.12 g, 1.12 mL, 12.9 mmol) and *N*-hydroxysuccinimide (1.468 g, 12.9 mmol) in acetonitrile (70 mL) stirred at 0 ºC and slowly allowed to warm to room temperature while stirring for 48 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60–50:50–80:20) as eluent, 1-morpholino-2-[(4-phenylbutyl)sulfonyl]ethanone **128** (1.85 g, 49%) was isolated as a white crystalline solid; mp 84–88 ºC (Found: C, 58.95; H, 7.11, N 4.05, $C_{16}H_{23}NO_4S$ requires C, 59.05; H, 7.12, N 4.30%); ν_{max}/cm^{-1} (neat, ATR): 1648, 1636 (CO), 1437, 1273, 1131, 1115 1033 (SO_2) 750 (CS); δ_H ($CDCl_3$, 600 MHz): 1.75–1.83 [2H, m, C(3′)H_2], 1.86–1.96 [2H, m, C(2′)H_2], 2.64–2.70 [2H, m, C(4′)H_2], 3.23–3.28 [2H, m, C(1′)H_2], 3.58–3.64 (2H, m, morpholine CH_2), 3.65–3.72 (4H, m, morpholine CH_2), 3.74–3.78 (2H, m, morpholine CH_2), 4.05 (2H, s, SO_2CH_2CO), 7.14–7.22 (3H, m, Ar*H*), 7.25–7.31 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 21.5 [CH_2, *C*(2′)H_2], 30.0 [CH_2, *C*(3′)H_2], 35.3 [CH_2, *C*(4′)H_2], 42.7 (CH_2, morpholine N*C*H_2), 47.6 (CH_2, morpholine N*C*H_2), 53.4 [CH_2, *C*(1′)H_2], 55.8 (CH_2, SO_2CH_2CO), 66.4 (CH_2, morpholine O*C*H_2), 66.5 (CH_2, morpholine O*C*H_2), 126.0 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 141.2 (C, aromatic *C*), 160.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{22}N_3O_4S$ $[M+H]^+$, 352.1331. Found 352.1321. m/z (ESI+): 352.2 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-(Dodecylsulfonyl)-1-morpholinoethanone 121

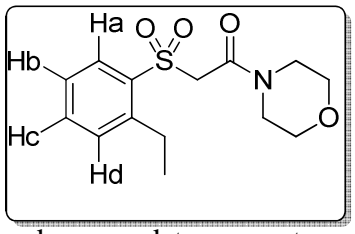


The title compound was prepared using general procedure **B**, using 2-(dodecylthio)-1-morpholinoethanone **91** (8.0 g, 24.3 mmol) and *m*CPBA (77% w/w, 13.60 g, 60.1 mmol) in dichloromethane (250 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 6 h. Following the work up and purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90–20:80–40:60–50:50–60:40–80:20) as eluent, 2-(dodecylsulfonyl)-1-morpholinoethanone

121 (5.26 g, 60%) was isolated as a crystalline white solid; mp 88–89 ºC (Found: C, 59.73; H, 9.51, N 3.80, S 8.67, $C_{18}H_{35}NO_4S$ requires C, 59.80; H, 9.76, N 3.87, S 8.87%); ν_{max}/cm^{-1} (KBr): 2957, 2921, 2850 (CH), 1647 (CO), 1474, 1445, 1272, 1116, 1041 (SO_2), 722 (CS); δ_H ($CDCl_3$, 600 MHz): 0.88 [3H, t, *J* 6.9, C(12′)H_3], 1.19–1.39 [16H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2], 1.40–1.49 [2H, m, C(3′)H_2], 1.83–1.92 [2H, m, C(2′)H_2], 3.20–3.25 [2H, m, C(1′)H_2], 3.60–3.65 (2H, m, morpholine CH_2), 3.66–3.74 (4H, m, morpholine CH_2), 3.75–3.79 (2H, m, morpholine CH_2), 4.05 (2H, s, SO_2CH_2CO); δ_C ($CDCl_3$, 150.9 MHz): 14.3 [CH_3, *C*(12′)H_3], 21.8, 22.7, 28.3, 29.1, 29.3, 29.4, 29.5, 29.6 (2 signals overlapping), 31.9 [10 × CH_2, *C*(11′)H_2, *C*(10′)H_2, *C*(9′)H_2, *C*(8′)H_2, *C*(7′)H_2, *C*(6′)H_2, *C*(5′)H_2, *C*(4′)H_2, *C*(3′)H_2, *C*(2′)H_2,], 42.7 (CH_2, br, morpholine N*C*H_2), 47.6 (CH_2, br, morpholine N*C*H_2), 53.6 [CH_2, *C*(1')H_2], 55.8 (CH_2, SO_2CH_2CO), 66.5 (CH_2, morpholine O*C*H_2), 66.6 (CH_2, morpholine O*C*H_2), 160.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{18}H_{36}NO_4S$ $[M+H]^+$, 362.2365. Found 362.2374. m/z (ESI+): 362.2 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-[(2-Ethylphenyl)sulfonyl]-1-morpholinoethanone 117

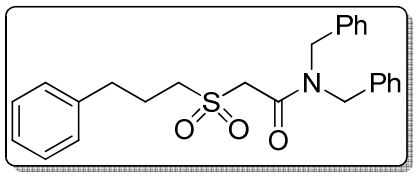


The title compound was prepared using general procedure **B**, using 2-[(2-ethylphenyl)thio]-1-morpholinoethanone **89** (4.0 g, 15.0 mmol) and *m*CPBA (77% w/w, 8.41 g, 37.5 mmol) in dichloromethane (150 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 6 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–50:50–80:20–90:10) as eluent, 2-[(2-ethylphenyl)sulfonyl]-1-morpholinoethanone **117** (3.23 g, 72%) was isolated a crystalline white solid; mp 109–111 ºC (Found: C, 56.76; H, 6.52, N 4.81, S 10.43, $C_{14}H_{19}NO_4S$ requires C, 56.55; H, 6.44, N 4.71, S 10.78%); ν_{max}/cm^{-1} (KBr): 3005, 2954, 2850 (CH), 1645 (CO), 1464, 1439, 1313, 1276, 1258, 1230, 1161, 1116, 1035 (SO_2), 815, 776, 751 (CS); δ_H ($CDCl_3$, 400 MHz): 1.35 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.10 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.56–3.62 [2H, sym m, morpholine CH_2], 3.64–3.71 [4H, sym m, morpholine CH_2], 3.76–3.82 [2H, sym m, morpholine CH_2], 4.27 (2H, s, SO_2CH_2CO), 7.34–7.41 (1H, ddd appears as m ArH^b), 7.41–7.46 (1H, dd appears as m, ArH^d), 7.60 (1H, ddd, *J* 7.6, 7.6, 1.4, ArH^c), 7.97 (1H, dd, *J* 8.0, 1.3, ArH^a); δ_C ($CDCl_3$, 75.5 MHz): 15.9 (CH_3, $ArCH_2CH_3$), 26.2 (CH_2,

Ar*C*$H_2$$CH_3$), 42.7 ($CH_2$, morpholine N*C*$H_2$), 47.6 ($CH_2$, morpholine N*C*$H_2$), 59.9 ($CH_2$, SO_2*C*H_2CO), 66.6 (CH_2, morpholine O*C*H_2), 66.7 (CH_2, morpholine O*C*H_2), 126.5 (CH, aromatic *C*H[b]), 130.3 (CH, aromatic *C*H[a]), 131.1 (CH, aromatic *C*H[d]), 134.5 (CH, aromatic *C*H[c]), 136.5 (C, aromatic *C*), 144.9 (C, aromatic *C*), 159.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{14}H_{20}NO_4S$ $[M+H]^+$, 298.1113. Found 298.1118. m/z (ESI+): 298.2 $[M+H]^+$.

***N*,*N*-Dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide 120**

Method (I) *via* oxidation



The title compound was prepared by using general procedure **B** using *N*,*N*-dibenzyl-2-[(3-phenylpropyl)thio]acetamide **86** (3.62 g, 9.30 mmol) and *m*CPBA (66% w/w, 6.08 g, 23.2 mmol) in dichloromethane (100 mL), stirred at 0 ºC for 1 h and warmed to room temperature while stirring for 24 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–50:50–80:20) as eluent, *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120** (2.56 g, 65%) was isolated as a white crystalline solid; mp 81–82 ºC ν_{max}/cm^{-1} (KBr): 3031, 2946, 2956, 2914 (CH), 1652 (CO), 1497, 1420, 1320, 1283, 1221, 1129 (SO_2), 752, 699 (CS); δ_H ($CDCl_3$, 400 MHz): 2.19–2.31 [2H, m, C(2′)*H*$_2$], 2.80 [2H, t, *J* 7.6, C(3′)*H*$_2$], 3.31–3.39 [2H, m, C(1′)*H*$_2$] 4.05 (2H, s, SO_2C*H*$_2$CO), 4.66 (2H, s, one of NC*H*$_2$C$_6$H$_5$), 4.68 (2H, s, one of NC*H*$_2$C$_6$H$_5$), 7.11–7.16 (2H, m, Ar*H*), 7.17–7.41 (13H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 23.6 [CH_2, *C*(2′)H_2], 34.2 [CH_2, *C*(3′)H_2], 49.4 (CH_2, one of N*C*H_2Ar), 51.2 (CH_2, one of N*C*H_2Ar), 53.0 [CH_2, *C*(1′)H_2], 56.3 (CH_2, SO_2*C*H_2CO), 126.2 (2 × CH, aromatic *C*H), 126.5 (CH, aromatic *C*H), 127.6 (3 × CH, aromatic *C*H), 128.1 (CH, aromatic *C*H), 128.5 (2 × CH, aromatic *C*H), 128.6 (2 × CH, aromatic *C*H), 128.8 (2 × CH, aromatic *C*H), 129.2 (2 × CH, aromatic *C*H), 135.3 (C, aromatic *C*), 135.9 (C, aromatic *C*), 139.9 (C, aromatic *C*), 163.2 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{25}H_{28}NO_3S$ $[M+H]^+$, 422.1790. Found 422.1786. m/z (ESI+): 422.30 $[M+H]^+$.

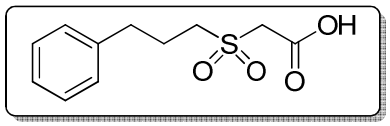
Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

Method (II) *via* coupling

The title compound was prepared according to the procedure described for *N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **125**, using DCC (2.44 g, 11.8 mmol), 2-[(3-phenylpropyl)sulfonyl]acetic acid **123** (2.20 g, 9.08 mmol), dibenzylamine (2.33 g, 2.23 mL, 11.8 mmol), and *N*-hydroxysuccinimide (1.35 g, 11.8 mmol) in acetonitrile (70 mL) stirred at 0 ºC and slowly allowed to warm to room temperature while stirring for 48 h. Following the work up and purification by column chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80–40:60–50:50) as eluent, *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120** (1.86 g, 49%) was isolated as a crystalline white solid. Spectral characteristics are identical to those reported above.

Synthesis of Carboxylic Acids

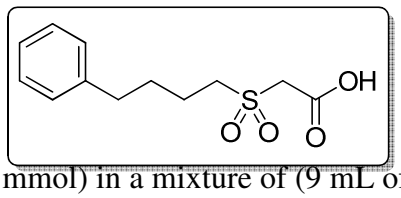
2-[(3-Phenylpropyl)sulfonyl]acetic acid 123



A solution of sodium hydroxide (6.24 g, 156 mmol) in (52 mL methanol) was added to a solution of methyl 2-[(3-phenylpropyl)sulfonyl]acetate **110** (10.00 g, 39.0 mmol) in (18 mL of dichloromethane) and (2 mL of methanol). The reaction mixture was stirred for 1h at room temperature, after which time TLC analysis deemed the reaction complete. The crude reaction mixture was concentrated under reduced pressure, whereupon ether (50 mL) was added and the resulting mixture was extracted with distilled water (50 mL). Hydrochloric acid (2 M, aqueous solution, 20 mL) was added to the aqueous layer which was then extracted with ether (2 × 50 mL), the ether layers were than combined and washed with brine (40 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 2-[(3-phenylpropyl)sulfonyl]acetic acid **123** as a white solid (7.17 g, 76%); mp 95–97 °C, (Found: C, 54.40; H, 5.75, $C_{11}H_{14}O_4S$ requires C, 54.53; H, 5.82,%); ν_{max}/cm^{-1} (KBr): 3014 (OH), 2953 (CH) 1703 (CO), 1427, 1317, 1291, 1263, 1147, 1120 (SO_2), 910, 748, 695 (CS); δ_H ($CDCl_3$, 600 MHz): 2.13–2.26 [2H, sym m, C(2')H_2], 2.79 [2H, t, *J* 7.5, C(3')H_2], 3.20–3.31 [2H, m, C(1')H_2], 3.99 (2H, s, SO_2CH_2CO), 6.08 (1H, br s, O*H*), 7.19 (2H, d, *J* 7.6, ArH_{ortho}), 7.23 (1H, t, *J* 7.3, ArH_{para}), 7.31 (2H, t, *J* 7.5, ArH_{meta}); δ_C ($CDCl_3$, 150.9 MHz): 23.4 [CH_2, *C*(2′)H_2], 34.1 [CH_2, *C*(3′)H_2], 52.9 [CH_2, *C*(1′)H_2], 57.2 (CH_2, br, SO_2CH_2CO), 126.6 (CH, aromatic *C*H_{para}) 128.4 (2 × CH, aromatic *C*H_{ortho}), 128.7 (2 x CH, aromatic *C*H_{meta}), 139.6 (C, aromatic *C*), 166.2 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{15}O_4S$ $[M+H]^+$, 243.0691. Found 243.0695. m/z (ESI-): 241.3 $[M-H]^-$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-[(4-Phenylbutyl)sulfonyl]acetic acid 124



A solution of sodium hydroxide (2.95 g, 74.0 mmol) in (25 mL methanol) was added to a solution of methyl 2-[(4-phenylbutyl)sulfonyl]acetate **107** (5.00 g, 18.5 mmol) in a mixture of (9 mL of dichloromethane) and (1 mL of methanol). The reaction mixture was stirred for 1 h at room temperature, after which time TLC analysis deemed the reaction complete. The crude reaction mixture was concentrated under reduced pressure, whereupon ether (30 mL) was added and the resulting mixture was then extracted with distilled water (30 mL). Hydrochloric acid (2 M, aqueous solution, 10 mL) was added to the aqueous layer which was then extracted with ether (2 × 30 mL), the ether layers were than combined and washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 2-[(4-phenylbutyl)sulfonyl]acetic acid **124** as a white solid (4.22 g, 89%); mp 82–83 °C, ν_{max}/cm^{-1} (KBr): 3063, 3028, 3005 (OH), 2938, 2855 (CH), 1717 (CO), 1458, 1423, 1330, 1297, 1284, 1273, 1226, 1129 (SO_2), 911, 761, 744, 699, 609 (CS); δ_H ($CDCl_3$, 400 MHz): 1.75–1.86 [2H, m, C(3′)H_2], 1.87–1.96 [2H, m, C(2′)H_2], 2.68 [2H, t, *J* 7.4, C(4′)H_2], 3.23–3.32 [2H, sym m, C(1′)H_2], 3.98 (2H, s, SO_2CH_2CO), 5.92 (1H, br s, O*H*), 7.12–7.23 (3H, m, Ar*H*), 7.24–7.36 (2H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 21.4, 30.0 [2 × CH_2, *C*(2′)H_2 and *C*(3′)H_2], 35.2 [CH_2, *C*(4′)H_2], 53.6 [CH_2, *C*(1′)H_2], 57.2 (CH_2, br, SO_2CH_2CO), 126.2 (CH, aromatic *C*H) 128.4 (2 × CH, aromatic *C*H), 128.5 (2 × CH, aromatic *C*H), 141.1 (C, aromatic *C*), 166.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{15}O_4S$ $[M-H]^+$, 255.0691. Found 255.0682. m/z (ESI-): 255.3 $[M-H]^-$.

Assignments were made with the aid of 2D experiments, which included HETCOR and COSY.

General Procedures for preparation of α-diazo-β-oxo sulfones

Procedure A

Potassium carbonate (ACS reagent, ≥99.0%) was added to a stirring solution of sulfone in acetonitrile at room temperature, stirring was continued for 10 min and then the reaction mixture was cooled to 0 ºC. A solution of 4-toluenesulfonyl azide in acetonitrile was added dropwise over 10 min under an atmosphere of nitrogen. Stirring was continued for a further 30 min at 0º C, then the mixture was removed from the ice bath and stirring was continued for 2–17 h at room temperature. Diethyl ether was then added to the crude reaction mixture. The volume of diethyl ether added was approximately half the total volume of acetonitrile used. Following filtration and concentration under reduced pressure the crude product was isolated. The crude α-diazo-β-oxo sulfone was further purified using column chromatography on silica gel, with hexane: ethyl acetate as the solvent system.

Procedure B

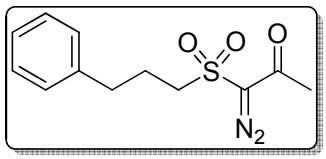
Potassium carbonate (ACS reagent, ≥99.0%) was added to a stirring solution of sulfone in acetonitrile at room temperature. Stirring was continued for 10 min and then the reaction mixture was cooled to 0 ºC. A solution of 4-acetamidobenzenesulfonyl azide in acetonitrile was added dropwise over 10 min under an atmosphere of nitrogen. Stirring was continued for a further 30 min at 0 ºC, then the mixture was removed from the ice bath and stirring was continued for 2–17 h at room temperature. On reaction completion (as indicated by TLC analysis), the contents of the reaction flask were poured (adsorbed) onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified using column chromatography with hexane: ethyl acetate as the solvent system.

Procedure C

4-Nitrobenzenesulfonyl azide was added neat to a solution of sulfone in acetonitrile, while stirring at room temperature. The reaction mixture was heated to 30 ºC. A solution of 1,8-diazabicycloundec-7-ene in acetonitrile was added dropwise over 15 min under an atmosphere of nitrogen. After the addition was complete, the reaction mixture was heated to 40 ºC, and stirring was continued at 40 ºC, until reaction completion (as indicated by TLC analysis. The total time for reaction completion never exceeded 1 h, and prolonged heating at temperatures of 40 ºC is not recommended due to the heat sensitive nature of diazo-transfer reagents.) Upon reaction completion, the contents of the reaction flask

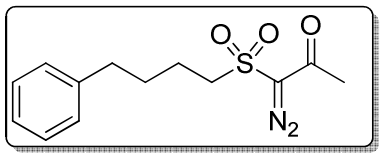
were poured (adsorbed) onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified using column chromatography with hexane: ethyl acetate as the solvent system.

1-(Phenylpropylsulfonyl)-1-diazopropan-2-one[1,13] 41



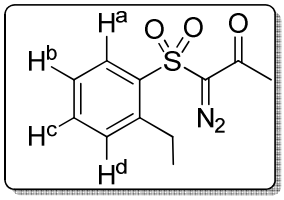
The title compound was prepared using general procedure **A** using potassium carbonate (0.25 g, 1.83 mmol), 1-(phenylpropylsulfonyl)propan-2-one **104** (0.4 g, 1.67 mmol) in acetonitrile (40 mL) and 4-toluenesulfonyl azide (0.33 g, 1.67 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 ºC for 30 min followed by 3 h at room temperature. Following the work up and purification of the crude product, by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent, 1-(phenylpropylsulfonyl)-1-diazopropan-2-one **41** (0.31 g, 70%) was isolated as a yellow oil. Spectroscopic characteristics are consistent with those previously reported; [1,13] ν_{max}/cm^{-1} (film): 2134 (C=N_2), 1665 (CO), 1325, 1269, 1142 (SO_2); δ_H ($CDCl_3$, 300 MHz): 2.07–2.23 [2H, m, C(2′)H_2], 2.31 (3H, s, COCH_3), 2.78 [2H, t, *J* 7.4, C(3′)H_2], 3.23–3.41 [2H, m, C(1′)H_2], 7.09–7.37 (5H, m, Ar*H*).

1-(4-Phenylbutylsulfonyl)-1-diazopropan-2-one[1,13] 21



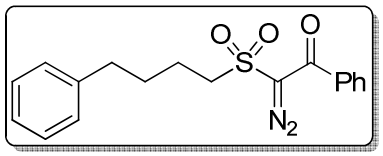
The title compound was prepared using general procedure **A** using potassium carbonate (0.41 g, 3.0 mmol), 1-(4-phenylbutylsulfonyl)propan-2-one **105** (0.7 g, 2.7 mmol) in acetonitrile (40 mL) and 4-toluenesulfonyl azide (0.53 g, 2.7 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 ºC for 30 min followed by 2 h at room temperature. Following the work up and purification of the crude product, by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent, 1-(4-phenylbutylsulfonyl)-1-diazopropan-2-one **21** (0.25 g, 33%) was isolated as a yellow solid. Spectroscopic characteristics are consistent with those previously reported;[1,13] ν_{max}/cm^{-1} (KBr): 2126 (C=N_2), 1655 (CO), 1324, 1286, 1140 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.72–1.93 [4H, m, C(2′)H_2 and C(3′)H_2], 2.36 (3H, s, COCH_3), 2.67 [2H, t, *J* 7.1, C(4′)H_2], 3.28–3.41 [2H, m, C(1′)H_2], 7.12–7.35 (5H, m, Ar*H*).

1-Diazo-1-[(2-ethylphenyl)sulfony]propane 55



The title compound was prepared using general procedure **B**, using K_2CO_3 (2.07g, 15.0 mmol), 1-[(2-ethylphenyl)sulfonyl]propan-2-one **115** (3.20 g, 14.1 mmol) and 4-acetamidobenzenesulfonyl azide (3.38 g, 14.1 mmol) dissolved in acetonitrile (40 mL) stirred at 0 °C for 1 h and then for 3 h while warming slowly to room temperature. The reaction mixture was adsorbed onto silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (40:80) as eluent, 1-diazo-1-[(2-ethylphenyl)sulfonyl]propan-2-one **55** (2.52 g, 71%) was isolated as a yellow oil; (Found: C, 52.43; H 4.97; N, 10.70; $C_{11}H_{12}N_2O_3S$ requires; C, 52.37; H, 4.79; N, 11.0; %); ν_{max}/cm^{-1} (film): 2974, 2938, 2878 (CH), 2115 (C=N_2), 1668 (CO), 1364, 1332, 1256, 1155 (SO_2), 764, 696 (CS); δ_H ($CDCl_3$, 300 MHz): 1.31 (3H, t, *J* 7.5, $ArCH_2CH_3$), 2.19 (3H, s, $COCH_3$), 2.98 (1H, q, *J* 7.5, $ArCH_2CH_3$), 7.36–7.49 (2H, overlapping dd and ddd, appears as m, ArH^d and ArH^b), 7.57 (1H, ddd, *J* 7.6, 7.5, 1.3 ArH^c), 8.10 (1H, dd, *J* 8.0, 1.2 ArH^a); δ_C ($CDCl_3$, 75.5 MHz): 15.0 (CH_3, $ArCH_2CH_3$), 25.7 (CH_2, $ArCH_2CH_3$), 27.0 (CH_3, CH_3), 126.5 (CH, aromatic CH^b), 130.1 (CH, aromatic CH^a), 131.2 (CH, aromatic CH^d), 134.3 (CH, aromatic CH^c), 139.3 (C, aromatic *C*), 143.6 (C, aromatic *C*), 186.1 (C, *C*O) (Diazo carbon not seen); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}N_2O_3S$ $[M+H]^+$, 253.0647; Found 253.0643. m/z (ESI+): 253.3 $[M+H]^+$.

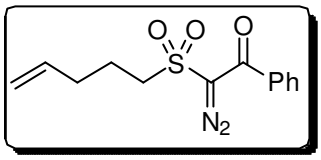
2-(4-Phenylbutylsulfonyl)-2-diazo-1-phenylethanone[1,13] 23



The title compound was prepared using general procedure **A**, using potassium carbonate (0.13 g, 1.0 mmol), 2-(4-phenylbutylsulfonyl)-1-phenylethanone **106** (0.3 g, 0.95 mmol) in acetonitrile (15 mL) and 4-toluenesulfonyl azide (0.19 g, 0.95 mmol) in acetonitrile (5 mL). The mixture was stirred at 0 ºC for 30 min followed by 2 h at room temperature. Following the work up and purification of the crude product, by chromatography on silica gel using ethyl acetate-hexane (10:90) as eluent, methyl 2-(4-phenylbutylsulfonyl)-2-diazo-1-phenylethanone **23** (0.1 g, 31%) was isolated as a pale yellow solid; mp 95–96 °C (Lit. mp 97–99 °C);[1] Spectroscopic characteristics are consistent with those previously reported;[1,13] ν_{max}/cm^{-1} (KBr): 2115 (C=N_2), 1649 (CO), 1331, 1283, 1225, 1138 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.70–1.97 [4H, m, C(2′)H_2 and

C(3′)H_2], 2.67 [2H, t, *J* 7.1, C(4′)H_2], 3.48–3.63 [2H, m, C(1′)H_2], 7.10–7.32 (5H, m, Ar*H*), 7.43–7.55 (2H, m, Ar*H*), 7.56–7.69 (3H, m, Ar*H*).

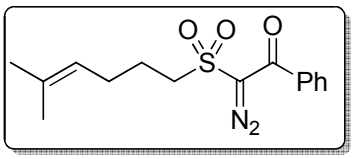
2-Diazo-2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone 60



The title compound was prepared using general procedure **B**, (without cooling to 0 ºC) using potassium carbonate (0.46 g, 3.4 mmol), 2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **131** (0.68 g, 2.57 mmol) in acetonitrile (25 mL) and 4-acetamidobenzenesulfonyl azide (0.62 g, 2.57 mmol) in acetonitrile (10 mL) stirred at room temperature for 20 min, whereupon TLC analysis deemed the reaction complete. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using gradient ethyl acetate-hexane (10:90–20:80–30:70) as eluent to afford 2-diazo-2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **60** (0.68 g, 95%) as a yellow solid; mp 93–94 ºC, ν_{max}/cm^{-1} (KBr): 2955, 2921, 2898, 2434 (CH), 2125 (C=N_2), 1651 (CO), 1599, 1579 (C=C, Ar), 1449, 1331, 1283, 1283, 1222, 1142, 1110 (SO_2), 924, 854, 770, 784, 708, 673 (CS); δ_H ($CDCl_3$, 600 MHz): 1.93–2.00 [2H, m, C(2′)H_2], 2.23 [2H, apparent q, *J* 7.1, C(3′)H_2], 3.51–3.58 [2H, m, C(1′)H_2], 5.04–5.11 [2H, m, C(5′)H_2], 5.69–5.87 [1H, sym m, C(4′)*H*], 7.51 (2H, t, *J* 7.8, ArH_{meta}), 7.61 (1H, t, *J* 7.5, ArH_{para}), 7.68 (2H, d, *J* 7.2, ArH_{ortho}); δ_C ($CDCl_3$, 150.9 MHz): 21.8 [CH_2, *C*(2′)H_2], 31.8 [CH_2, *C*(3′)H_2], 56.1 [CH_2, *C*(1′)H_2], 80.3 (C, *C*=N_2), 116.8 [CH_2, *C*(5′)H_2], 127.4 (2 × CH, aromatic, *C*H_{ortho}), 129.1 (2 × CH, aromatic *C*H_{meta}), 133.4 (CH, aromatic *C*H_{para}), 135.6 (C, aromatic, *C*), 136.0 [CH, *C*(4′)H], 183.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{15}N_2O_3S$ $[M+H]^+$ 279.0803. Found 279.0801. m/z (ESI+): 279.3 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-Diazo-2-[(5-methylhex-4-en-1-yl)sulfonyl]-1-phenylethanone 61

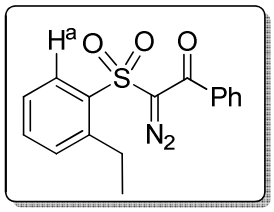


The title compound was prepared using general procedure **B** (without cooling to 0 ºC), using potassium carbonate (0.22 g, 1.56 mmol), 2-[(5-methylhex-4-en-1-yl)sulfonyl]-1-phenylethanone **132** (0.40 g, 1.4 mmol) in acetonitrile (20 mL) and 4-acetamidobenzenesulfonyl azide (0.34 g, 1.4 mmol) in acetonitrile (15 mL) stirred at room temperature for 20 min, whereupon TLC analysis deemed the reaction complete. The reaction mixture was subsequently adsorbed onto silica gel and purified by

chromatography, on silica gel using gradient ethyl acetate-hexane (10:90–20:80–30:70) as eluent to afford 2-diazo-2-[(5-methylhex-4-en-1-yl)sulfonyl]-1-phenylethanone **61** (0.36 g, 83%) as a yellow solid; mp 58–59 ºC, ν_{max}/cm^{-1} (KBr): 2958, 2932, 2917, 2878 (CH), 2112 (C=N_2), 1646 (CO), 1599, 1580 (C=C), 1462, 1446, 1409, 1337, 1317, 1286, 1226, 1184, 1141, 1129, 1110 (SO_2), 721, 699 (CS); δ_H ($CDCl_3$, 600 MHz): 1.61 [3H, s, C(6′)H_3 or CH_3], 1.70 [3H, s, C(6′)H_3 or CH_3], 1.85–1.92 [2H, m, C(2′)H_2], 2.16 [2H, apparent q, *J* 7.2, C(3′)H_2], 3.49–3.55 [2H, m, C(1′)H_2], 5.04–5.08 [1H, m, C(4′)*H*], 7.51 (2H, t, *J* 7.7, ArH_{meta}), 7.62 (1H, t, *J* 7.5, ArH_{para}), 7.68 (2H, d, *J* 7.7, ArH_{ortho}); δ_C ($CDCl_3$, 150.9 MHz): 17.8 [CH_3, *C*(6′)H_3 or *C*H_3], 22.9 [CH_2, *C*(2′)H_2], 25.7 [CH_3, *C*(6′)H_3 or *C*H_3], 26.3 [CH_2, *C*(3′)H_2], 56.2 [CH_2, *C*(1′)H_2], 80.2 (C, *C*=N_2), 121.8 [CH, *C*(4′)H], 127.4 (2 × CH, aromatic *C*H_{ortho}), 129.1 (2 × CH, aromatic *C*H_{meta}), 133.4 (CH, aromatic, *C*H_{para}), 134.2 [C, aromatic, *C* or *C*(5′)], 135.7 [C, aromatic, *C* or *C*(5′)], 183.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{19}N_2O_3S$ $[M+H]^+$, 307.1116. Found 307.1112. m/z (ESI+): 307.3 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

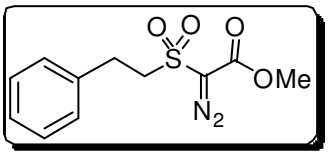
2-Diazo-2-[2-(ethylphenyl)sulfonyl]-1-phenylethanone 56



The title compound was prepared using the general procedure **B**, using potassium carbonate (1.38 g, 10 mmol), 2-(2-ethylphenylsulfonyl)-1-phenylethanone **114** (3.0 g, 9.1 mmol) in acetonitrile (50 mL) and 4-acetamidobenzenesulfonyl azide (2.2 g, 9.1 mmol) in acetonitrile (25 mL) stirred at 0 °C for 1 h and then removed from the ice bath and stirred at room temperature for 4 h. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (20:80–30:70) as eluent to afford 2-diazo-2-[2-(ethylphenyl)sulfonyl]-1-phenylethanone **56** (2.32 g, 81%) as a yellow crystalline solid: An analytical sample was obtained, by recrystallision from *iso* propyl alcohol, for CHN and melting point analysis; mp 104–105 °C (Found: C, 61.05; H, 4.55; N 8.92, $C_{16}H_{14}N_2O_3S$ requires C, 61.13; H, 4.49; N 8.91%); ν_{max}/cm^{-1} (KBr): 2967 (CH), 2117 (C=N_2), 1659 (CO), 1332, 1279, 1153 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.32 (3H, t, *J* 7.5, ArCH_2CH_3), 3.02 (2H, quartet, *J* 7.5, ArCH_2CH_3), 7.28–7.46 (4H, m, Ar*H*), 7.47–7.61 (4H, m, Ar*H*), 8.08 (1H, dd, *J* 1.3, 8.0, ArH^a); δ_C ($CDCl_3$, 75.5 MHz): 15.2 (CH_3, ArCH_2CH_3), 25.8 (CH_2, CH_2CH_3), 126.3 (CH, aromatic *C*H), 127.4 (CH, aromatic *C*H × 2), 128.8 (CH, aromatic *C*H × 2), 130.7 (CH, aromatic *C*H), 131.6 (CH, aromatic *C*H), 132.9 (CH, aromatic *C*H), 134.2 (CH, aromatic

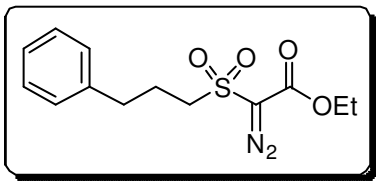
*C*H), 135.9 (C, aromatic *C*), 138.8 (C, aromatic *C*), 143.5 (C, aromatic *C*), 182.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{15}N_2O_3S$ $[M+H]^+$, 315.0803. Found 315.0799. m/z (ESI+): 315.1 $[M+H]^+$.

Methyl 2-diazo-2-(phenethylsulfonyl)acetate 62



The title compound was prepared using general procedure **B**, using DBU (0.69 g, 0.67 mL, 4.5 mmol), methyl 2-(phenethylsulfonyl)acetate **122** (1.0 g, 4.1 mmol) and 4-acetamidobenzenesulfonyl azide (0.99 g, 4.1 mmol) dissolved in acetonitrile (30 mL) stirred at 0 °C for 1 h and then for 5 h while warming slowly to room temperature. The reaction mixture was subsequently quenched with silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (40:80) as eluent to afford methyl 2-diazo-2-(phenethylsulfonyl)acetate **62** (0.62 g, 53%) as a yellow oily solid; (Found: C, 49.40; H 4.64; N, 10.30; S 12.30; $C_{11}H_{12}N_2O_4S$ requires; C, 49.24; H 4.51; N, 10.44; S 11.95 %); ν_{max}/cm^{-1} (KBr): 2960, 2925 (CH), 2136 (C=N_2), 1718 (CO), 1401, 1325, 1302, 1128, 1192 (SO_2), 751, 738, 713, 701 (CS); δ_H ($CDCl_3$, 400 MHz): 3.08–3.24 [2H, m, C(1′)H_2 or C(2′)H_2], 3.65–3.74 [2H, m, C(1′)H_2 or C(2′)H_2], 3.78 (3H, s, COOCH_3), 7.15–7.20 (2H, m, Ar*H*), 7.21–7.27 (1H, m, Ar*H*), 7.29–7.34 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 29.1 [CH_2, *C*(1′)H_2 or *C*(2′)H_2], 53.0 (CH_3, COO*C*H_3) 57.1 [CH_2, *C*(1′)H_2 or *C*(2′)H_2], 127.2 (CH, aromatic *C*H), 128.2 (CH, 2 × aromatic *C*H), 128.9 (CH, 2 × aromatic *C*H), 136.7 (C, aromatic *C*), 160.3 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}N_2O_4S$ $[M+H]^+$, 269.0596; Found 269.0588. m/z (ESI+): 269.29 $[M+H]^+$.

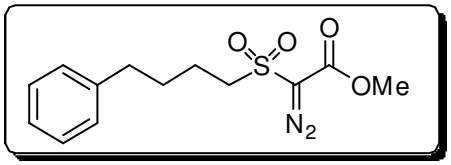
Ethyl-2-diazo-2-(3-phenylpropylsulfonyl)acetate[1,13] 39



The title compound was prepared using general procedure **A,** using potassium carbonate (0.57 g, 4.1 mmol), ethyl 2-[(3-phenylpropyl)sulfonyl]acetate[14] **136** (1.06 g, 3.7 mmol) in acetonitrile (50 mL) and 4-toluenesulfonyl azide (0.74 g, 3.7 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 ºC for 30 min followed by 3 h at room temperature. Following work up and purification of the crude product by chromatography on silica gel using ethyl acetate-hexane (10:90) as eluent to afford ethyl-2-diazo-2-(3-phenylpropylsulfonyl)acetate[1,13] **39** (1.0 g, 91%) as a yellow oil. Spectroscopic characteristics are consistent with those previously reported; ν_{max}/cm^{-1} (film): 2129 (C=N_2), 1711 (CO), 1335, 1291, 1148 (SO_2);

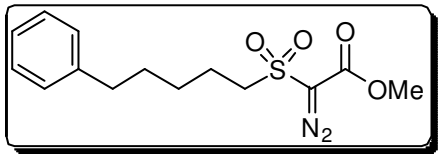
δ_H ($CDCl_3$, 300 MHz): 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 2.09–2.25 (2H, m, C(2′)H_2), 2.78 [2H, t, *J* 7.4, C(3′)H_2], 3.30–3.43 [2H, m, C(1′)H_2], 4.29 (2H, q, *J* 7.1 OCH_2CH_3), 7.12–7.36 (5H, m, Ar*H*).

Methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate[1,13] 25



The title compound was prepared using general procedure **A**, using potassium carbonate (1.32 g, 9.6 mmol), methyl 2-(4-phenylbutylsulfonyl)acetate **107** (2.4 g, 8.8 mmol) in acetonitrile (50 mL) and 4-toluenesulfonyl azide (1.75 g, 8.8 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 ºC for 30 min followed by 3 h at room temperature. Following work up and purification of the crude product by chromatography on silica gel using ethyl acetate-hexane (20:80) as eluent, methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **25** (1.60 g, 61%) was isolated as a yellow oil. Spectroscopic characteristics are consistent with those previously reported;[1,13] ν_{max}/cm^{-1} (film): 2131 (C=N_2), 1718 (CO), 1338, 1224, 1148 (SO_2); δ_H ($CDCl_3$, 400 MHz): 1.73–1.92 [4H, m, C(2′)H_2 and C(3′)H_2], 2.66 [2H, t, *J* 7.3, C(4′)H_2], 3.43–3.46 [2H, m, C(1′)H_2], 3.86 (3H, s, $COOCH_3$), 7.12–7.26 (3H, m, Ar*H*), 7.24–7.36 (2H, m, Ar*H*).

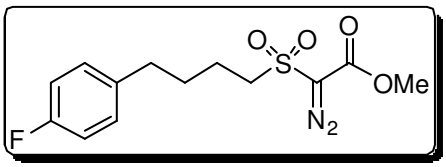
Methyl 2-diazo-2-(5-phenylpentylsulfonyl)acetate[1,13] 27



The title compound was prepared using general procedure **A** using potassium carbonate (0.38 g, 2.75 mmol), methyl 2-(5-phenylpentylsulfonyl)acetate **108** (0.7 g, 2.5 mmol) in acetonitrile (15 mL) and 4-toluenesulfonyl azide (0.5 g, 2.5 mmol) in acetonitrile (5 mL). The mixture was stirred at 0 ºC for 30 min followed by 2.5 h at room temperature. Following work up and purification of the crude product by chromatography, on silica gel using ethyl acetate-hexane (20:80) as eluent, methyl 2-diazo-2-(5-phenylpentylsulfonyl)acetate[1,13] **27** (0.5 g, 65%) was isolated as a yellow oil. Spectroscopic characteristics are consistent with those previously reported; ν_{max}/cm^{-1} (film): 2130 (C=N_2), 1716 (CO), 1337, 1298, 1147 (SO_2); δ_H ($CDCl_3$, 400 MHz): 1.43–1.53, 1.62–1.73 [2 × 2H, m, C(3')H_2 and C(4')H_2], 1.79–1.91 [2H, m, C(2′)H_2], 2.63 [2H, t, *J* 7.6, C(5′)H_2], 3.23–3.41 [2H, m, C(1′)H_2], 3.86 (3H, s, $COOCH_3$), 7.12–7.23 (3H, m, Ar*H*), 7.24–7.32 (2H, m, Ar*H*).

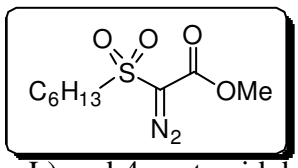
Methyl 2-diazo-2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate 45

Procedure A



Potassium carbonate (1.18 g, 8.6 mmol) was added to a stirring solution of methyl 2-(4-fluorophenylbutyl)sulfonylacetate **112** (2.25 g, 7.8 mmol) in acetonitrile (40 mL) at room temperature. Stirring was continued for 10 min and then the reaction mixture was cooled to 0 ºC. A solution of 4-tosyl azide (1.54 g, 7.8 mmol) in acetonitrile (10 mL) was added dropwise over 10 min under an atmosphere of nitrogen, stirred at 0 °C for 0.5 h and then removed from the ice bath and stirred at room temperature for 3 h. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica using ethyl acetate-hexane (20:80) as eluent, methyl 2-diazo-2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate **45** (1.04 g, 42%) was isolated as a yellow oil. In addition another fraction was recovered (0.52 g, 21%) that contained *approx*. 7% of an aromatic impurity. Therefore the overall yield is estimated to be 62%, by ^{1}H NMR analysis; ν_{max}/cm^{-1} (film): 2132 (C=N$_2$), 1718 (CO), 1510, 1336, 1299, 1222, 1145 (SO$_2$); δ_H (CDCl$_3$, 300 MHz): 1.67–1.94 [4H, m, C(2′)*H*$_2$, C(3′)*H*$_2$], 2.63 [2H, t, *J* 7.3, C(4′)*H*$_2$], 3.35–3.43 [2H, m, C(1′)*H*$_2$], 3.86 (3H, s, OC*H*$_3$), 6.92–7.03 (2H, m, Ar*H*), 7.06–7.16 (2H, m, Ar*H*); δ_C (CDCl$_3$, 75.5 MHz): 22.0, 29.8 [2 × CH$_2$, *C*(2′)H$_2$, *C*(3′)H$_2$], 34.4 [CH$_2$, *C*(4′)H$_2$], 53.2 (CH$_3$, O*C*H$_3$), 56.4 [CH$_2$, *C*(1′)H$_2$], 72.9 (C, *C*=N$_2$), 115.2 [2 × ArCH, d, $^2J_{CF}$ 21.1, *C*(3)H, *C*(5)H], 129.7 [2 × ArCH, d, $^3J_{CF}$ 7.7, *C*(2)H, *C*(6)H], 136.7 [C, d, $^4J_{CF}$ 3.2, *C*(1)], 160.5 (C, *C*O), 161.4 [C, $^1J_{CF}$ 243.8, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_{13}H_{16}FN_2O_4S$ $[M+H]^+$, 315.0815. Found 315.0828. m/z (ESI+): 315.1 $[M+H]^+$.

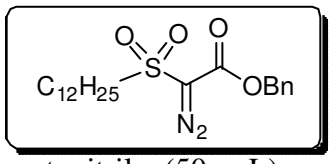
Methyl 2-diazo-2-(hexylsulfonyl)acetate[1,13] 29



The title compound was prepared using genera, l procedure **B**, using potassium carbonate (1.77 g, 12.8 mmol), methyl 2-(hexylsulfonyl)acetate **109** (2.20 g, 9.9 mmol) in acetonitrile (50 mL) and 4-acetamidobenzenesulfonyl azide (2.37 g, 9.9 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 ºC for 30 min followed by 18 h at room temperature. Following work up and purification of the crude product by chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, methyl 2-diazo-2-(hexylsulfonyl)acetate **29** (1.85 g, 75%) was isolated as a yellow oil. Spectroscopic characteristics are consistent with those previously reported;[1,13] ν_{max}/cm^{-1} (film): 2128

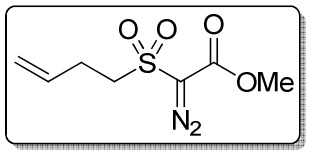
(C=N_2), 1719 (CO), 1336, 1297, 1145 (SO_2); δ_H ($CDCl_3$, 400 MHz): 0.90 (3H, t, *J* 7.0, C(6′)H_2), 1.24–1.52 [6H, m, C(5′)H_2, C(4′)H_2, C(3′)H_2], 1.74–1.90 [2H, m, C(2′)H_2], 3.33–3.43 [2H, m, C(1′)H_2], 3.88 (3H, s, COOCH_3).

Benzyl 2-diazo-2-(dodecylsulfonyl)acetate[1,13] 37



The title compound was prepared using general procedure **B**, using potassium carbonate (1.03 g, 7.5 mmol), benzyl 2-(dodecylsulfonyl)acetate **111** (2.20 g, 5.8 mmol) in acetonitrile (50 mL) and 4-acetamidobenzenesulfonyl azide (1.38 g, 5.8 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 ºC for 30 min followed by 18 h at room temperature. Following the work up and purification of the crude product by chromatography, on silica gel using ethyl acetate-hexane (10:90–20:80) as eluent, benzyl 2-diazo-2-(dodecylsulfonyl)acetate **37** (2.10 g, 90%) was isolated as a yellow solid. Spectroscopic characteristics are consistent with those previously reported;[1,13] mp 48–49 °C (Lit., 48–50 °C[1,13]); ν_{max}/cm^{-1} (KBr): 2129 (C=N_2), 1727 (CO), 1339, 1297, 1219, 1144 (SO_2); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 6.9, C(12′)H_3], 1.19–1.44 [18H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2], 1.73–1.85 [2H, m, C(2′)H_2], 3.30–3.39 [2H, m, C(1′)H_2], 5.29 (2H, s, CO_2CH_2Ph), 7.37 (5H, br s, Ar*H*).

Methyl 2-(but-3-en-1-ylsulfonyl)-2-diazoacetate 63



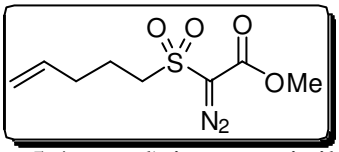
The title compound was prepared using general procedure **B** (without cooling to 0 ºC but instead heating to 40 ºC following addition), using potassium carbonate (0.39 g, 2.9 mmol), methyl 2-(but-3-en-1-ylsulfonyl)acetate **130** (0.50 g, 2.6 mmol) in acetonitrile (20 mL) and 4-acetamidobenzenesulfonyl azide (0.62 g, 2.6 mmol) in acetonitrile (10 mL) stirred at 40 °C for 45 min, whereupon TLC analysis deemed the reaction complete. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using gradient ethyl acetate-hexane (10:90–20:80) as eluent, methyl 2-(but-3-en-1-ylsulfonyl)-2-diazoacetate **63** (0.37 g, 65%) was isolated as a pale yellow oil; ν_{max}/cm^{-1} (film): 2959, 2359 (CH), 2131 (C=N_2), 1715 (CO), 1645 (C=C, Ar), 1436, 1338, 1297, 1222, 1144, 1085 (SO_2), 742 (CS); δ_H ($CDCl_3$, 600 MHz): 2.55–2.64 [2H, sym m, C(2′)H_2], 3.45–3.53 [2H, m, C(1′)H_2], 3.88 (3H, s, COOCH_3), 5.10–5.23 [2H, sym m, C(4′)H_2], 5.73–5.84 [1H, sym m, C(3′)*H*]; δ_C ($CDCl_3$, 150.9 MHz) 27.2 [CH_2, *C*(2′)H_2], 53.1 (CH_3, COOCH_3), 55.8 [CH_2, *C*(1′)H_2], 73.3 (C, *C*=N_2), 117.6 [CH_2,

C(4′)H_2], 133.3 [CH, *C*(3′)H], 160.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_7H_{11}N_2O_4S$ $[M+H]^+$, 219.0440. Found 219.0442.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

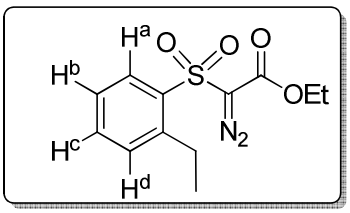
Note: This compound was relatively unstable to storage overnight at room temperature, and was generally used in subsequent reactions within a few hours of synthesis.

Methyl 2-diazo-2-(pent-4-en-1-ylsulfonyl)acetate 59



The title compound was prepared using general procedure **B** (without cooling to 0 ºC), using DBU (0.91 g, 0.89 mL, 5.96 mmol), methyl 2-(pent-4-en-1-ylsulfonyl)acetate **129** (1.05 g, 5.4 mmol) in acetonitrile (40 mL) and 4-acetamidobenzenesulfonyl azide (1.31 g, 5.4 mmol) in acetonitrile (15 mL) stirred at room temperature for 10 min, whereupon TLC analysis deemed the reaction complete. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using gradient ethyl acetate-hexane (10:90–20:80) as eluent to afford methyl 2-diazo-2-(pent-4-en-1-ylsulfonyl)acetate **59** (0.75 g, 60%) as a pale yellow oil; ν_{max}/cm^{-1} (neat, ATR): 2957 (CH), 2126 (C=N_2), 1713 (CO), 1642 (C=C, Ar), 1437, 1332, 1293, 1219, 1143, 1082 (SO_2), 740 (CS); δ_H ($CDCl_3$, 300 MHz): 1.87–2.02 [2H, m, C(2′)H_2], 2.22 [2H, apparent q, *J* 7.1, C(3′)H_2], 3.33–3.45 [2H, m, C(1′)H_2], 3.88 (3H, s, COOCH_3), 5.03–5.14 [2H, m, C(4′)H_2], 5.67–5.84 [1H, m, C(5′)H_2]; δ_C ($CDCl_3$, 75.5 MHz): 21.8 [CH_2, *C*(2′)H_2], 31.8 [CH_2, *C*(3′)H_2], 53.1 (CH_3, COO*C*H_3) 55.9 [CH_2, *C*(1′)H_2], 73.0 (C, *C*=N_2), 116.8 [CH_2, *C*(5′)H_2], 136.0 [CH, *C*(4′)H], 160.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_8H_{13}N_2O_4S$ $[M+H]^+$, 233.0596. Found 233.0594. m/z (ESI+): 233.3 $[M+H]^+$.

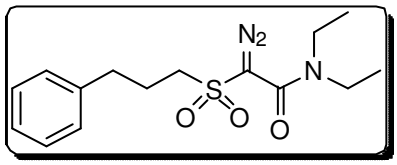
Ethyl-2-diazo-2-[(ethylphenyl)sulfonyl]acetate 54



The title compound was prepared using general procedure **B**, using potassium carbonate (0.57 g, 4.13 mmol), ethyl 2-(2-ethylphenylsulfonyl)acetate **113** (1.07 g, 3.8 mmol) in acetonitrile (40 mL) and 4-acetamidobenzenesulfonyl azide (0.90 g, 3.8 mmol) in acetonitrile (10 mL) stirred at 0 °C for 1 h and then removed from the ice bath and stirred at room temperature for 3 h. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (20:80) as eluent to afford ethyl-2-diazo-2-

[(ethylphenyl)sulfonyl]acetate **54** (0.73 g, 69%) as a yellow oil. (Found: C, 51.05; H, 5.15; N 9.64, $C_{12}H_{14}N_2O_4S$ requires C, 51.05; H, 5.00; N 9.92%); ν_{max}/cm^{-1} (film): 2982 (CH), 2126 (C=N_2), 1719 (CO), 1337, 1292, 1159 (SO_2); δ_H ($CDCl_3$, 300 MHz): 1.17 (3H, t, *J* 7.1, OCH_2CH_3), 1.31 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.00 (2H, quartet, *J* 7.5, $ArCH_2CH_3$), 4.16 (2H, quartet, *J* 7.1, OCH_2CH_3), 7.32–7.48 (2H, overlapping dd and ddd, appears as m, Ar*H*^{d} and Ar*H*^{b}), 7.57 (1H, ddd, *J* 1.4, 5.9, 7.6, Ar*H*^{c}), 8.10 (1H, dd, *J* 1.3, 8.0, Ar*H*^{a}); δ_C ($CDCl_3$, 75.5 MHz): 14.0 (CH_3, OCH_2CH_3), 15.2 (CH_3, $ArCH_2CH_3$), 25.8 (CH_2, $ArCH_2CH_3$), 62.3 (CH_2, OCH_2CH_3), 126.2 (CH, aromatic *C*H^b), 130.8 (CH, aromatic *C*H^a), 131.4 (CH, aromatic *C*H^d), 134.1 (CH, aromatic *C*H^c), 138.9 (C, aromatic *C*), 143.6 (C, aromatic *C*), 159.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{14}N_2O_4S$ $[M+H]^+$, 283.0761. Found 283.0753. m/z (ESI+): 283.1 $[M+H]^+$.

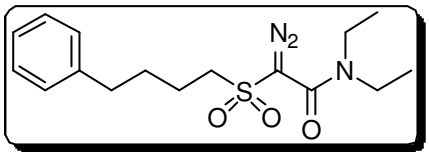
2-Diazo-*N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide 51



A solution of 1,8-diazabicycloundec-7-ene (DBU) (0.56 g, 0.55 mL, 3.66 mmol) in acetonitrile (10 mL) was added to a stirring solution of *N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **125** (1.09 g, 3.66 mmol) and 4-nitrobenzenesulfonyl azide (0.84 g, 3.66 mmol) in acetonitrile (30 mL) at 30 ºC, in accordance with procedure **C**. The mixture was heated to 40 ºC and stirred at 40 ºC for 1 h. On reaction completion, by TLC analysis, the reaction mixture was cooled to room temperature at which point the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a silica gel column and was purified using chromatography using ethyl acetate-hexane (20:80–30:70) as eluent to give 2-diazo-*N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **51** (0.75 g, 63%) as a yellow oil; $\nu_{max}cm^{-1}$ (film): 2980, 2938 (CH), 2096 (C=N_2), 1634 (CO), 1455, 1423, 1329, 1166, 1141 (SO_2), 751, 702 (CS); δ_H ($CDCl_3$, 600 MHz): 1.19 (6H, t, *J* 7.1, 2 × NCH_2CH_3), 2.12–2.25 [2H, m, C(2')H_2], 2.78 [2H, t, *J* 7.6, C(3′)H_2], 3.37 [4H, q, *J* 7.1, 2 × NCH_2CH_3], 3.56–3.36 [2H, sym m, C(1′)H_2], 7.15-7.25 (3H, m, Ar*H*), 7.27–7.33 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 13.1 (CH_3, 2 × NCH_2CH_3), 24.5 [CH_2, *C*(2′)H_2], 34.1 [CH_2, *C*(3′)H_2], 41.9 [CH_2, 2 × NCH_2CH_3], 56.9 [CH_2, *C*(1′)H_2], 68.9 (C, *C*=N_2), 126.5 (CH, aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 128.7 (CH, 2 × aromatic *C*H), 140.0 (C, aromatic *C*), 158.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{22}N_3O_3S$ $[M+H]^+$, 324.1382. Found 324.1378. m/z (ESI+): 324.2 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

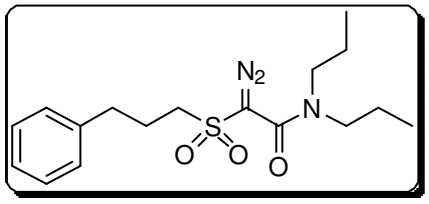
2-Diazo-*N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide 47



The title compound was prepared using general procedure **C**, using DBU (0.31 g, 0.30 mL, 2.04 mmol), *N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide **118** (0.58 g, 1.86 mmol) in acetonitrile (25 mL) and 4-nitrobenzenesulfonyl azide (0.42 g, 1.86 mmol) in acetonitrile (15 mL). The mixture was stirred at 40 ºC for 20 min then cooled. On reaction completion by TLC analysis, the reaction mixture was cooled to room temperature, at which point the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a silica gel column and was purified using chromatography using ethyl acetate-hexane (20:80–30:70) as eluent to afford 2-diazo-*N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide **47** (0.32 g, 51%) as a yellow solid; (Found: C, 56.67; H, 6.86; N 12.39, $C_{16}H_{23}N_3O_3S$ requires C, 56.95; H, 6.87; N 12.45%); ν_{max}/cm^{-1} (film): 2986, 2946 (CH), 2098 (C=N_2), 1638 (CO), 1423, 1325, 1140 (SO_2), 701 (CS); δ_H ($CDCl_3$, 600 MHz): 1.19 (6H, t, *J* 7.1, 2 × NCH_2CH_3), 1.70–1.96 [4H, m, C(2′)H_2 and C(3′)H_2], 2.66 [2H, t, *J* 7.4, C(4′)H_2], 3.37 [4H, q, *J* 7.1, 2 × NCH_2CH_3], 3.57–3.65 [2H, m, C(1′)H_2], 7.11–7.22 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 13.1 (CH_3, 2 × NCH_2CH_3), 22.4 [CH_2, *C*(2′)H_2], 29.8 [CH_2, *C*(3′)H_2], 35.3 [CH_2, *C*(4′)H_2], 41.8 [CH_2, br, 2 × NCH_2CH_3], 57.3 [CH_2, *C*(1′)H_2], 68.7 (C, *C*=N_2), 126.0 (CH, aromatic *C*H), 128.3 (CH, 2 × aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 141.3 (C, aromatic *C*), 158.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{24}N_3O_3S$ $[M+H]^+$, 338.1538. Found 338.1553. m/z (ESI+): 338.2 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-Diazo-2-[(3-phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide 50

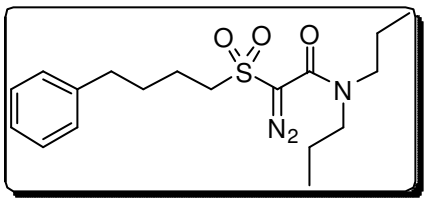


The title compound was prepared using general procedure **C**, using DBU (0.47 g, 0.46 mL, 3.07 g, mmol) in acetonitrile (12 mL) and 2-[(3-phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide **127** (1.0 g, 3.07 mmol) and 4-nitrobenzenesulfonyl azide (0.70 g, 3.07 mmol) in acetonitrile

(30 mL). The mixture was stirred at 40 ºC for 50 min, cooled, and the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. Following purification of the crude product by chromatography, on silica gel using ethyl acetate-hexane (20:80–30:70) as eluent, 2-diazo-2-[(3-phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide **50** (0.68 g, 63%) was isolated as a yellow oil; (Found: C, 57.82; H, 7.22, N, 11.50, $C_{17}H_{25}N_3O_3S$ requires C, 58.09; H, 7.17, N, 11.96%); ν_{max}/cm^{-1} (film): 2966, 2877 (CH), 2094 (C=N_2), 1632 (CO), 1497, 1419, 1329, 1234, 1141 (SO_2), 751, 702 (CS); δ_H ($CDCl_3$, 600 MHz): 0.91 (6H, t, *J* 7.4, 2 × $NCH_2CH_2CH_3$), 1.52–1.67 (4H, sym m, 2 × $NCH_2CH_2CH_3$), 2.13–2.24 [2H, m, C(2′)H_2], 2.78 [2H, t, *J* 7.6, C(3′)H_2], 3.21–3.29 [4H, m, 2 × $NCH_2CH_2CH_3$], 3.54–3.63 [2H, m, C(1′)H_2], 7.14–7.24 (3H, m, Ar*H*), 7.26–7.34 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 11.2 (CH_3, 2 × $NCH_2CH_2CH_3$), 21.3 (CH_2, br, 2 × $NCH_2CH_2CH_3$), 22.5 [CH_2, *C*(2′)H_2], 34.1 [CH_2, *C*(3′)H_2], 49.4 (CH_2, br, 2 × $NCH_2CH_2CH_3$), 56.9 [CH_2, *C*(1′)H_2], 68.9 (C, *C*=N_2), 126.5 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.6 (CH, 2 × aromatic *C*H), 140.0 (C, aromatic *C*), 158.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{17}H_{26}N_3O_3S$ $[M+H]^+$, 352.1695. Found 352.1684. m/z (ESI+): 352.3 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-Diazo-2-[(4-phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide 46

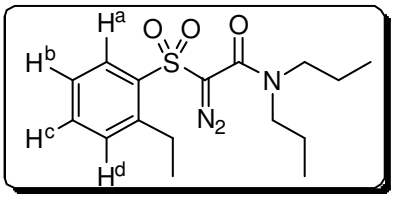


The title compound was prepared using general procedure **C**, using 1,8-diazabicycloundec-7-ene (0.89 g, 0.88 mL, 5.89 mmol) in acetonitrile (10 mL) and 2-[(4-phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide **126** (2.0 g, 5.89 mmol) and 4-nitrobenzenesulfonyl azide (1.34 g, 5.89 mmol) in acetonitrile (30 mL). The mixture was stirred at 40 ºC for 50 min, then cooled and the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of a silica gel and was purified by chromatography, using ethyl acetate-hexane (5:95–10:90–20:80–30:70) as eluent to afford 2-diazo-2-[(4-phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide **46** (1.31 g, 61%) as a yellow oil; ν_{max}/cm^{-1} (film): 2966, 2936 (CH), 2095 (C=N_2), 1636 (CO), 1420, 1331, 1141 (SO_2), 749, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 0.92 (6H, t, *J* 7.4, 2 × $NCH_2CH_2CH_3$), 1.55–1.64 (4H, m, 2 × $NCH_2CH_2CH_3$), 1.74–1.81 [2H, m, C(3′)H_2], 1.85–1.91 [2H, m, C(2′)H_2], 2.66 [2H, t, *J* 7.6, C(4′)H_2], 3.22–3.27 (4H, m, 2 × $NCH_2CH_2CH_3$), 3.58–3.63 [2H, m, C(1′)H_2], 7.14–7.21 (3H, m, Ar*H*), 7.25–7.30 (2H, m,

Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 11.2 (CH_3, 2 × $NCH_2CH_2CH_3$), 21.3 (CH_2, br, 2 × $NCH_2CH_2CH_3$), 22.4 [CH_2, $C(2')H_2$], 29.8 [CH_2, $C(3')H_2$], 35.3 [CH_2, $C(4')H_2$], 49.4 (CH_2, br, 2 × $NCH_2CH_2CH_3$), 57.3 [CH_2, $C(1')H_2$], 68.8 (C, C=N_2), 126.0 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 141.3 (C, aromatic *C*), 158.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{18}H_{28}N_3O_3S$ $[M+H]^+$, 366.1851. Found 366.1853. m/z (ESI+): 338.3 $[(M-N_2)+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

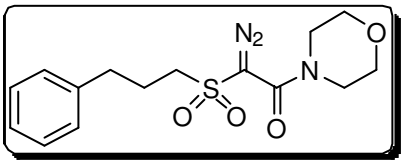
2-Diazo-2-[(2-ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide 57



The title compound was prepared using general procedure **C**, using 1,8-diazabicycloundec-7-ene (0.67 g, 0.65 mL, 4.40 mmol) in acetonitrile (10 mL) and 2-[(2-ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide **116** (0.70 g, 2.20 mmol) and 4-nitrobenzenesulfonyl azide (0.51 g, 2.20 mmol) in acetonitrile (20 mL). The mixture was stirred at 40 ºC for 1 h then cooled and the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified by chromatography using ethyl acetate-hexane (20:80–30:70) as eluent, to afford 2-diazo-2-[(2-ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide **57** (0.45 g, 59%) as a yellow oil; ν_{max}/cm^{-1} (film): 2967, 2936, 2877 (CH), 2089 (C=N_2), 1638 (CO), 1420, 1329, 1153 (SO_2), 687 (CS); δ_H ($CDCl_3$, 600 MHz): 0.85 (6H, t, *J* 7.4, 2 × $NCH_2CH_2CH_3$), 1.31 (3H, t, *J* 7.5, $ArCH_2CH_3$), 1.48–1.56 (4H, m, 2 × $NCH_2CH_2CH_3$) 2.99 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.21–3.27 (4H, m, 2 × $NCH_2CH_2CH_3$), 7.37 (1H, dd appears as t, *J* 7.7, ArH^b), 7.41 (1H, d, *J* 7.7, ArH^d), 7.55 (1H, dd appears as t, *J* 7.5 ArH^c), 8.08 (1H, d, *J* 8.0, ArH^a); δ_C ($CDCl_3$, 150.9 MHz): 11.1 (CH_3, 2 × $NCH_2CH_2CH_3$), 15.1 (CH_3, $ArCH_2CH_3$), 21.2 (CH_2, 2 × $NCH_2CH_2CH_3$), 25.9 (CH_2, $ArCH_2CH_3$), 49.2 (4H, m, 2 × $NCH_2CH_2CH_3$), 73.0 (C, C=N_2), 126.3 (CH, aromatic *C*H^b), 130.7 (2 × CH, aromatic *C*H^a and aromatic *C*H^d), 133.7 (CH, aromatic *C*H^c), 139.9 (C, aromatic *C*), 143.3 (C, aromatic *C*), 158.3 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{24}N_3O_3S$ $[M+H]^+$, 338.1538. Found 338.1551. m/z (ESI+): 338.3 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

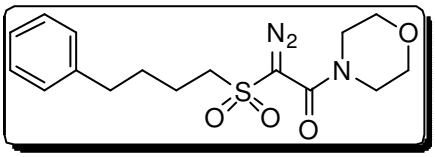
Diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone 52



The title compound was prepared using general procedure **C**, using DBU (0.24 g, 0.23 mL, 1.55 mmol) in acetonitrile (5 mL) and 1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **119** (0.44 g, 1.41 mmol) and 4-nitrobenzenesulfonyl azide (0.32 g, 1.41 mmol) in acetonitrile (20 mL). The mixture was stirred at 40 ºC for 1 h, then cooled and the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified by chromatography using ethyl acetate-hexane (20:80–30:70–60:40) as eluent 2-diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52** (0.17 g, 32%) was isolated as a yellow solid; mp 110–111 ºC (Found: C, 53.41; H, 5.79, N 12.27, $C_{15}H_{19}N_3O_4S$ requires C, 53.40; H, 5.68, N, 12.45%); ν_{max}/cm^{-1} (KBr): 2858 (CH), 2110 (C=N_2), 1636 (CO), 1440, 1427, 1322, 1286, 1227, 1140, 1112 (SO_2), 857, 774, 751, 706 (CS); δ_H ($CDCl_3$, 600 MHz): 2.14–2.22 [2H, m, C(2′)H_2], 2.78 [2H, t, *J* 7.6, C(3′)H_2], 3.47–3.58 [6H, m, C(1′)H_2 and morpholine CH_2], 3.63–3.73 [4H, m, morpholine CH_2], 7.16–7.20 (2H, m, Ar*H*), 7.21–7.25 (1H, m, Ar*H*), 7.28–7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 24.4 [CH_2, *C*(2′)H_2], 33.9 [CH_2, *C*(3′)H_2], 45.6 (CH_2, br, morpholine N*C*H_2), 56.9 [CH_2, *C*(1′)H_2], 66.4 (CH_2, morpholine O*C*H_2), 69.6 (C, *C*=N_2), 126.5 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.7 (CH, 2 × aromatic *C*H), 139.8 (C, aromatic *C*), 158.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{20}N_3O_4S$ $[M+H]^+$, 338.1175. Found 338.1177. m/z (ESI+): 338.30 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HSQC and COSY.

2-Diazo-1-morpholino-2-[(4-phenylbutyl)sulfony])ethanone 48

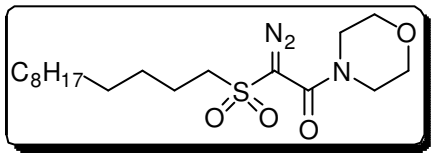


The title compound was prepared using general procedure **C**, using DBU (1.03 g, 1.01 mL, 6.76 mmol) in acetonitrile (15 mL), 1-morpholino-2-[(4-phenylbutyl)sulfonyl]ethanone **128** (1.1 g, 3.38 mmol) and 4-nitrobenzenesulfonyl azide (0.77 g, 3.38 mmol) in acetonitrile (25 mL). The mixture was stirred at 40 ºC for 40 min then cooled and the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified by chromatography using ethyl acetate-hexane (20:80–30:70) as eluent to afford 2-diazo-1-morpholino-2-[(4-phenylbutyl)sulfony])ethanone **48** (0.24 g, 20%) as a yellow solid; mp 114–115 ºC

ν_{max}/cm^{-1} (KBr): 2925, 2858 (CH), 2107 (C=N_2), 1627 (CO), 1436, 1317, 1290, 1142, 1110 (SO_2) 711, 698 (CS); δ_H ($CDCl_3$, 600 MHz): 1.74–1.83 [2H, m, C(3′)H_2], 1.85–1.93 [2H, m, C(2′)H_2], 2.66 [2H, t, *J* 7.6, C(4′)H_2], 3.50–3.58 [6H, m, C(1′)H_2 and morpholine CH_2], 3.69–3.72 [4H, m, morpholine CH_2], 7.14–7.22 (3H, m, Ar*H*), 7.25–7.31 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 22.4 [CH_2, *C*(2′)H_2], 29.8 [CH_2, *C*(3′)H_2], 35.3 [CH_2, *C*(4′)H_2], 45.6 [CH_2, br morpholine N*C*H_2], 57.5 [CH_2, *C*(1′)H_2], 66.4 [CH_2, morpholine O*C*H_2], 69.4 (C, *C*=N_2), 126.1 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 141.2 (C, aromatic *C*), 158.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{22}N_3O_4S$ $[M+H]^+$, 352.1331. Found 352.1321. m/z (ESI+): 352.2 $[M+H]^+$.

Assignments carried out with the aid of 2D experiments which included COSY and HSQC.

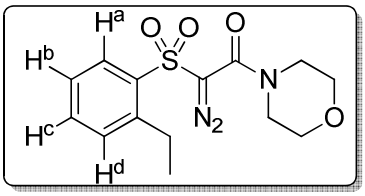
2-Diazo-2-(dodecylsulfonyl)-1-morpholinoethanone 49



The title compound was prepared using general procedure **C**, using 1,8-diazabicycloundec-7-ene (0.63 g, 0.62 mL, 4.15 mmol), 2-(dodecylsulfonyl)-1-morpholinoethanone **121** (1.5 g, 4.15 mmol) in acetonitrile (40 mL) and 4-nitrobenzenesulfonyl azide (0.95 g, 4.15 mmol) in acetonitrile (10 mL). The mixture was stirred at 40 ºC for 45 min, then cooled and the contents of the reaction flask were poured onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified using chromatography using ethyl acetate-hexane (20:80–30:70) as eluent to afford 2-diazo-2-(dodecylsulfonyl)-1-morpholinoethanone **49** (1.02 g, 63%) as a yellow solid; (Found: C, 56.10; H, 8.73, N 10.63, S 8.02, $C_{18}H_{33}N_3O_4S$ requires C, 55.79; H, 8.58, N 10.84, S 8.27%); mp 76–77 ºC; ν_{max}/cm^{-1} (KBr): 2921, 2851 (CH), 2115 (C=N_2), 1624 (CO), 1437, 1329, 1279, 1124 (SO_2), 776, 717 (CS); δ_H ($CDCl_3$, 300 MHz): 0.88 [3H, t, *J* 6.7, C(12′)H_3], 1.19–1.39 [16H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2], 1.40–1.51 [2H, m, C(3′)H_2], 1.76–1.95 [2H, m, C(2′)H_2], 3.43–3.59 [6H, m, C(1′)H_2 and morpholine CH_2], 3.68–3.76 [4H, sym m, morpholine CH_2]; δ_C ($CDCl_3$, 75.5 MHz): 14.1 [CH_3, *C*(12′)H_3], 22.7, 22.8, 28.1, 29.0, 29.2, 29.3, 29.5, 29.6 (2 signals overlapping), 31.9 [10 × CH_2, *C*(11′)H_2, *C*(10′)H_2, *C*(9′)H_2, *C*(8′)H_2, *C*(7′)H_2, *C*(6′)H_2, *C*(5′)H_2, *C*(4′)H_2, *C*(3′)H_2, *C*(2′)H_2], 45.7 (CH_2, morpholine N*C*H_2), 57.7 [CH_2, *C*(1′)H_2], 66.4 (CH_2, morpholine O*C*H_2), 69.5 (C, *C*=N_2), 158.8 (C, *C*O); HRMS (ESI+): Exact mass

calculated for $C_{18}H_{34}N_3O_4S$ $[M+H]^+$, 388.2270. Found 388.2259. m/z (ESI+): 388.4 $[M+H]^+$.

2-Diazo-2-[(2-ethylphenyl)sulfonyl]-1-morpholinoethanone 58

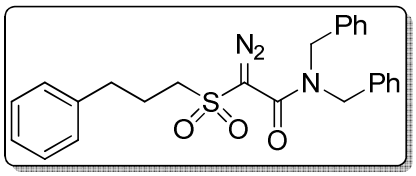


The title compound was prepared using general procedure **C**, using DBU (0.64 g, 0.63 mL, 4.20 mmol) in acetonitrile (10 mL) and 2-[(2-ethylphenyl)sulfonyl]-1-morpholinoethanone **117** (1.25 g, 4.20 mmol) and 4-nitrobenzenesulfonyl azide (0.96 g, 4.20 mmol) in acetonitrile (20 mL). The mixture was stirred at 40 ºC for 1 h, then cooled and the contents of the reaction flask were adsorbed onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified by chromatography using ethyl acetate-hexane (20:80–30:70–40:60) as eluent to give 2-diazo-2-[(2-ethylphenyl)sulfonyl]-1-morpholinoethanone **58** (0.43 g, 32%) as a yellow solid; mp 53–54 ºC; ν_{max}/cm^{-1} (KBr): 2967, 2923, 2859 (CH), 2108 (C=N_2), 1645 (CO), 1423, 1323, 1148, 1117 (SO_2), 716 (CS); δ_H ($CDCl_3$, 600 MHz): 1.32 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.00 (2H, q, *J* 7.5, $ArCH_2CH_3$), 3.49–3.54 [4H, sym m, morpholine CH_2], 3.65–3.71 [4H, sym m, morpholine CH_2], 7.38 (1H, dd appears as t, *J* 7.7, ArH^b), 7.43 (1H, d, *J* 7.7, ArH^d), 7.56 (1H, dd appears as t, *J* 7.4 ArH^c), 8.04 (1H, d, *J* 7.9, ArH^a); δ_C ($CDCl_3$, 150.9 MHz): 15.2 (CH_3, $ArCH_2CH_3$), 25.8 (CH_2, $ArCH_2CH_3$), 46.1 (CH_2, morpholine NCH_2), 66.5 (CH_2, morpholine OCH_2), 74.2 (C, *C*=N_2), 126.3 (CH, aromatic CH^b), 130.2 (CH, aromatic CH^a), 131.0 (CH, aromatic CH^d), 134.1 (CH, aromatic CH^c), 139.4 (C, aromatic *C*), 143.6 (C, aromatic *C*), 158.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{14}H_{18}N_3O_4S$ $[M+H]^+$, 324.1018. Found 324.1013. m/z (ESI+): 324.10 $[M+H]^+$.

Note: A ^1H NMR spectrum of **58** run on the 400 MHz spectrometer resulted in different splitting patterns to the spectrum run on the 600 MHz spectrometer. The different values are listed as follows; δ_H ($CDCl_3$, 400 MHz): 7.34–7.40 (1H, ddd appears as m, ArH^d), 7.41–7.46 (1H, dd appears as m, ArH^d) 7.57 (1H, ddd, *J* 7.6, 7.6, 1.4, ArH^c), 8.04 (1H, dd, *J* 8.0, 1.3 ArH^a).

Assignments were made with the aid of a 2D experiment (COSY).

***N*,*N*-Dibenzyl-2-diazo-2-[(3-phenylpropyl)sulfonyl]acetamide 53**



The title compound was prepared using general procedure **C**, using 1,8-diazabicycloundec-7-ene (0.69 g, 0.68 mL, 4.5 mmol), *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120** (1.75 g, 4.1 mmol) in acetonitrile (15 mL) and 4-nitrobenzenesulfonyl azide (0.90 g, 4.1 mmol) in acetonitrile (30 mL). The mixture was stirred at 40 ºC for 45 min, then cooled and the contents of the reaction flask were poured onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified by chromatography using ethyl acetate-hexane (20:80–30:70–60:40) as eluent to afford *N*,*N*-dibenzyl-2-diazo-2-[(3-phenylpropyl)sulfonyl]acetamide **53** (0.95 g, 52%) as a yellow solid; mp 96–97 ºC (Found: C, 66.80; H, 5.65; N 9.38, $C_{25}H_{25}N_3O_3S$ requires C, 67.09; H, 5.63; N 9.39%); ν_{max}/cm^{-1} (KBr): 3026, 2926 (CH), 2097 (C=N_2), 1638 (CO), 1458, 1436, 1421, 1329, 1139 (SO_2), 752, 699 (CS); δ_H ($CDCl_3$, 300 MHz): 2.13–2.28 [2H, m, C(2′)H_2], 2.80 [2H, t, *J* 7.6, C(3′)H_2], 3.57–3.68 [2H, m, C(1′)H_2], 4.52 (4H, s, 2 × NCH_2Ph), 7.11–7.43 (15H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 24.4 [CH_2, *C*(2′)H_2], 34.1 [CH_2, *C*(3′)H_2], 50.1 (CH_2, 2 × N*C*H_2Ph), 56.9 [CH_2, *C*(1′)H_2], 69.5 (C, *C*=N_2), 126.5 (CH, aromatic *C*H), 127.4 (CH, 3 × aromatic *C*H), 128.1 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 128.7 (CH, 2 × aromatic *C*H), 129.0 (CH, 5 × aromatic *C*H), 135.0 (C, 2 × aromatic *C*), 139.9 (C, aromatic *C*), 160.0 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{25}H_{26}N_3O_3S$ $[M+H]^+$, 448.1695. Found 448.1716. m/z (ESI+): 448.2 $[M+H]^+$.

Assignments were made with the aid of 2D experiments, which included HETCOR and COSY.

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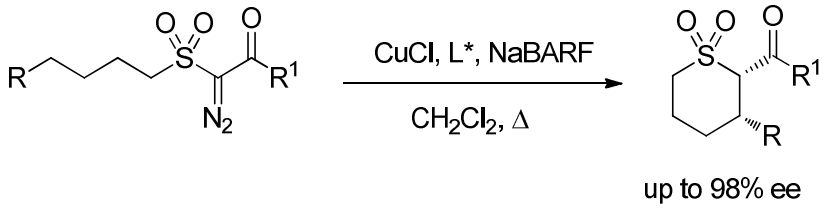
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Chapter Four
C–H insertion reactions of α-diazo-β-oxo sulfones

"If you can keep your head when all about you Are losing theirs and blaming it on you, If you can trust yourself when all men doubt you, But make allowance for their doubting too……" Rudyard Kipling

4.1 General experimental aspects of C–H insertion reactions



Scheme 4.1

As has been outlined in **Chapter 2**, the primary objective of this project was to further examine the role of the various catalytic components in the C–H insertion reactions of α-diazo-β-oxo-sulfones **21**, **23**, **25**, **27**, **29**, **37**, **39**, **41**. Based on results previously obtained by Flynn[1,2] α-diazo-β-oxo sulfone **25** was selected for initial investigation, due to the observed outstanding reaction efficiency, regioselectivity and enantioselectivity in the original study. The first aim was to explore the impact of variation of the bisoxazoline ligand (**Figure 4.1**), the copper salt, for example CuCl, $CuCl_2$ and $Cu(OTf)_2$, and the additive, for example NaBARF, KBARF, $NaPF_6$, KPF_6, $LiPF_6$, $NaBF_4$, on the reaction outcome.

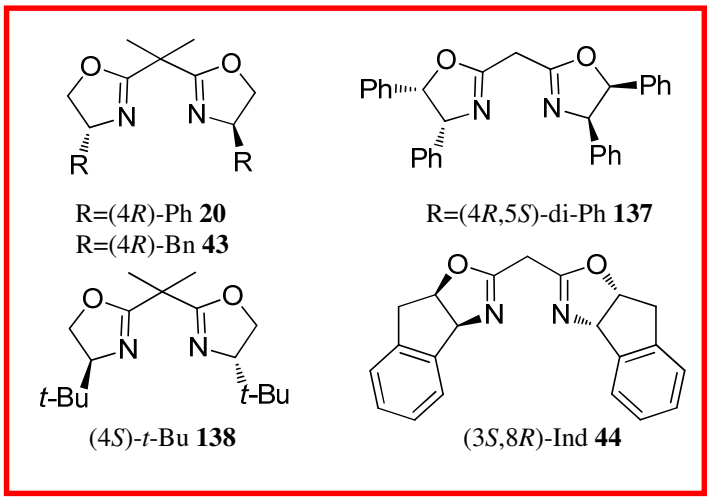


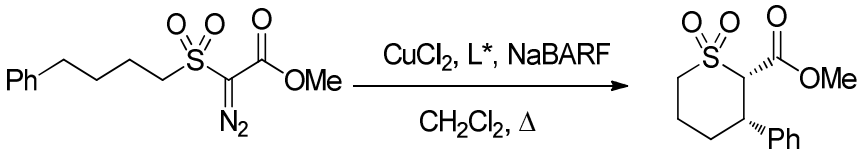
Figure 4.1

Before discussing the outcome of the catalyst screens, consideration of the general experimental approach and analytical techniques employed to provide comparative data across the study was undertaken. In any catalyst screen it is essential to hold the majority of variables constant to ensure that the reaction outcome is genuinely reflective of the impact of catalyst variation. Catalyst screens were conducted typically with 50–100 mg of the starting α-diazo-β-oxo sulfones. All copper catalysed reactions were conducted using a copper source (5 mol%), bisoxazoline ligand (6 mol%) (**Figure 4.1**) and an

additive NaBARF (6 mol%), unless otherwise stated. To begin with the three catalytic components were added to the reaction flask, followed by dichloromethane. A solution of the α-diazo-β-oxo sulfone in dichloromethane was added to the mixture at room temperature. The resulting reaction mixture was heated to reflux and the progress of reaction was monitored using IR spectroscopy for ~6 h, until the disappearance of the diazo stretch at ~2100 cm^{-1}; if reactions were not complete within ~6 h they were heated under reflux overnight. The crude product was recovered by evaporation followed by chromatographic purification.

4.1.1 Impact of catalyst pre-forming

One of the critical elements is whether the catalyst required pre-formation for optimum enantioselectivity. A study had been previously carried out by Flynn on pre-forming the catalyst prior to addition of the α-diazo-β-oxo-sulfone **25** and in general, for this series, there was no advantage evident in stirring the catalyst solution prior to addition of the α-diazo-β-oxo-sulfone substrate with (4*R*)-Ph ligand **20** since both sets of conditions afforded the product in 98% ee (**Scheme 4.2**). In fact Flynn reported a decrease in yield from 47% to 21% when the catalyst was pre-formed,[1,2] however, it is worth mentioning that yields were not optimised in Flynn's study (**Table 2.4**, entry 3). This is in direct contrast to the cyclopentanone series[3] and aromatic addition reactions,[4] where pre-formation of the catalyst is essential to achieving high enantioselectivity. Pre-forming copper catalysts has additional precedent in the literature, being previously reported for X–H insertion reactions.[5,6] The majority of the experiments reported in this section were carried out without pre-forming the catalyst to enable direct comparison with Flynn's work.



L*	Pre-forming catalyst (%ee)	Direct Addition (%ee)
R=(4*R*)-Ph **20**[*]	98	98
R=(4*R*)-Bn **43**	69	70
R=(3*S*,8*R*)-Ind **44**	77	66

[*]CuCl was used as the copper source instead of $CuCl_2$

Scheme 4.2

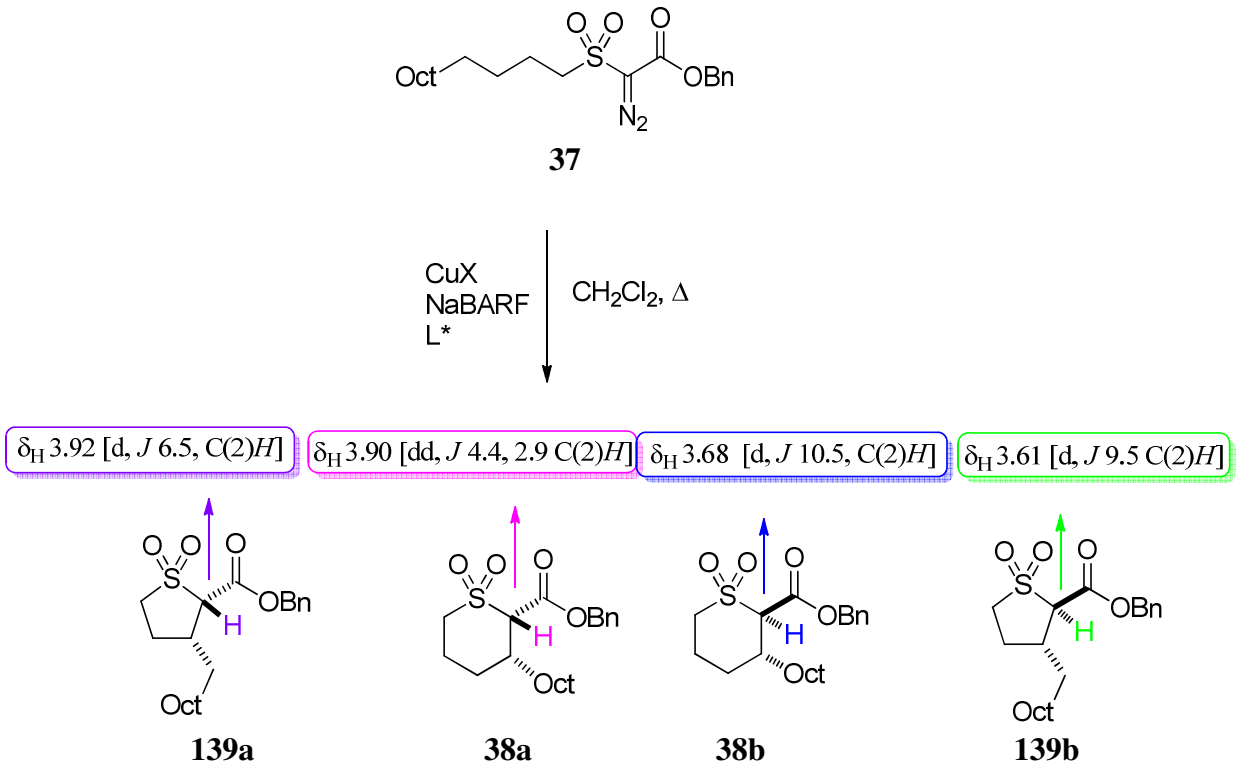
Recently, in this research group, Buckley[7] carried out a similar set of experiments for the synthesis of *cis* thiopyran **26a** using $CuCl_2$/NaBARF with (4*R*)-Bn **43** and (3*S*,8*R*)-Ind **44** ligands. In the presence of (4*R*)-Bn ligand **43**, once again no benefit was seen for catalyst pre-formation, however, in the presence of (3*S*,8*R*)-Ind ligand **44** an increase in enantioselectivity from 66 to 77% ee was observed when the catalyst was pre-formed (**Scheme 4.2**). In retrospect, there may be an impact through pre-generation of the catalyst which Flynn had not detected due to the high levels of enantiocontrol achieved, and for future studies evaluation of the impact of pre-forming the catalyst is warranted. In subsequent chapters, where novel α-diazocarbonyl compounds are employed, studies on pre-forming the catalyst are carried out and this method is used where necessary.

4.1.2 Analysis of crude reaction material

In each of the substrates studied in this work there are a number of possible C–H insertion reaction products, *i.e.*, *cis* thiopyran, *trans* thiopyran, *cis* sulfolane and *trans* sulfolane, in addition to a range of byproducts formed through other reaction pathways including O–H insertion, Cl abstraction, hydride abstraction, *etc*. Careful chromatography enables isolation of pure components of the reaction mixture, although it is not always possible to fully separate the components given the complexity of the product mixtures.

It is essential at the outset to identify characteristic signals for each of the products to enable estimation of the products present in the crude product mixtures, by ^{1}H NMR. Ideally, pure samples of each component would be isolated and characterised as single compounds; however, in some cases pure samples could not be isolated and in these instances signals were assigned in the crude spectra based on analogy to other components.

Flynn previously demonstrated that it is possible to achieve either partial or full separation of isomers. Taking the copper-mediated reaction of **37** as an example (**Scheme 4.3**), pure components of three of the four C–H insertion products (*cis* thiopyran **38a**, *trans* thiopyran **38b** and *trans* sulfolane **139b**) were isolated by careful chromatography and could be characterised as pure compounds.[1,2] Assignment of the *cis* sulfolane isomer **139a** is tentative, as a pure sample of this was not obtained after purification. The most characteristic signals which can be employed to enable quantisation in the crude reaction mixtures are highlighted [C(2)*H*] in **Scheme 4.3**.



Scheme 4.3

The ^{1}H NMR spectrum of *cis* thiopyran **38a** shows a characteristic doublet of doublets at 3.90 ppm for C(2)*H*, which arises from coupling with both the C(3)*H* proton and one of C(6)H_2 protons is due to long range W coupling.[1,2] The signal in the ^{1}H NMR spectrum for the C(2)*H* proton of *trans* thiopyran **38b** is a doublet at 3.68 ppm, while the signal for the C(2)*H* proton of *trans* sulfolane **139b** is a doublet at 3.61 ppm. A doublet at 3.92 ppm is tentatively assigned to the *cis* sulfolane **139a** isomer.

As illustrated, integration of these signals in the crude product mixture provides a method to estimate the relative amounts of each C–H insertion product (**Figure 4.2**).

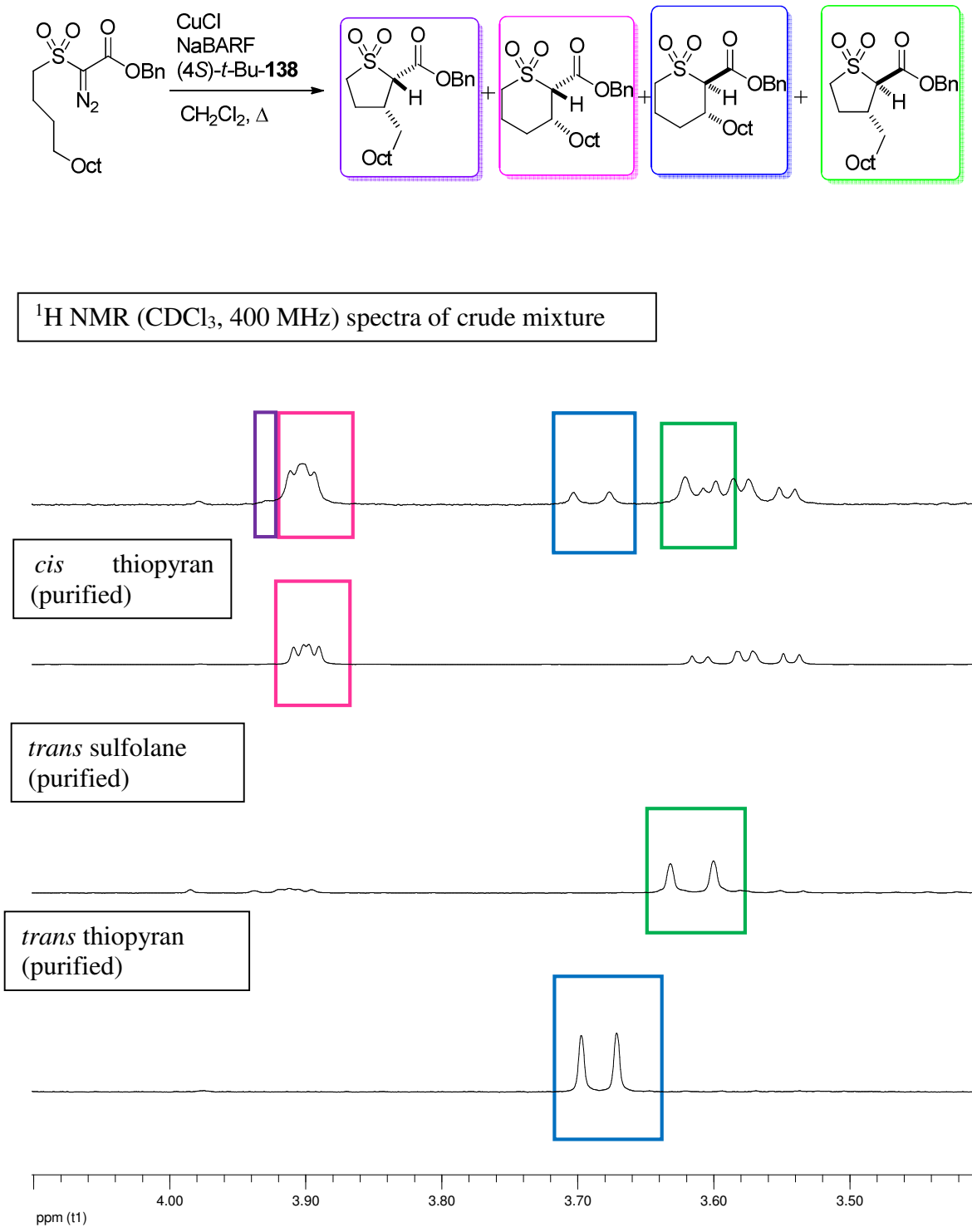


Figure 4.2 *Partial ^{1}H NMR spectra of crude product mixture and purified compounds (**Table 4.6**, entry 2) in $CDCl_3$, 400 MHz*

In general, in the majority of crude product mixtures, signals can be detected for three of the four isomers, while in some instances the *cis* sulfolane has been tentatively assigned. While C(2)*H* is the most commonly used for quantisation, in certain cases, the signal was

not clearly resolved and other signals (such as methoxy protons) were used instead (**Figure 4.3**).

In analysing the ^{1}H NMR spectra of crude products, a number of factors are studied; firstly, the proportion of the crude material which is due to C–H insertion (relative to the total including byproducts) which reflects the overall efficiency of C–H insertion relative to other pathways. Secondly, the relative amounts of each of the C–H insertion products are determined. Thirdly, the identity and amounts of competing reaction pathways are examined. The ^{1}H NMR spectra of the crude reaction mixtures for cyclisations of compounds **21**, **23**, **25**, **27**, **29**, **37**, **45** are illustrated in **Figure 4.3**, for reaction using CuCl-NaBARF-(4*R*,5*S*)-di-Ph **137** catalyst system.

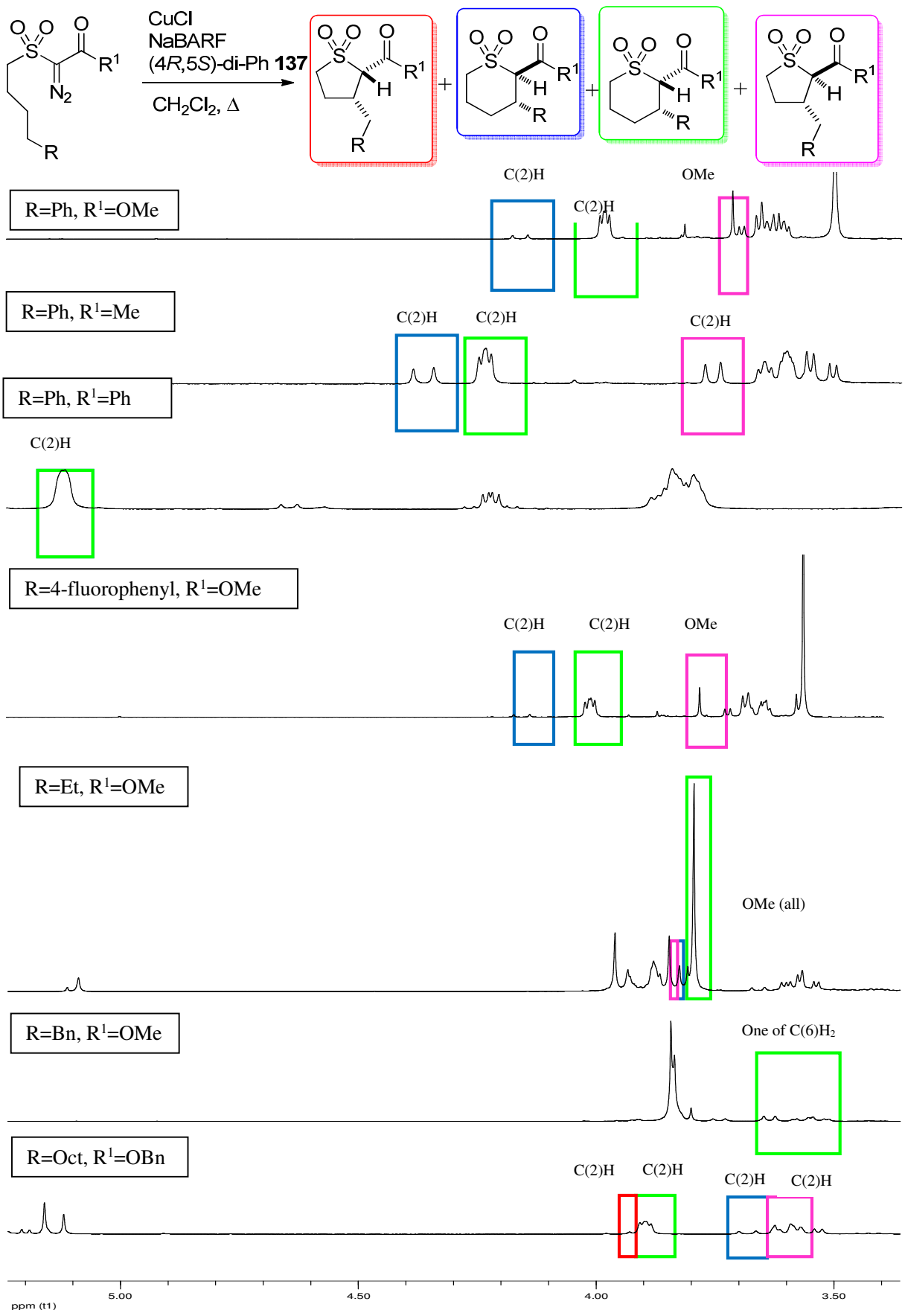


Figure 4.3 *^{1}H NMR spectra of crude product mixtures (400 MHz)*

4.1.3 Alternative Reaction Pathways to C–H insertion: Byproduct formation

Examination of the ^{1}H NMR spectra of the crude products from copper-catalysed reactions of the α-diazosulfonyl derivatives proves very useful in identifying and quantifying the major reaction pathways, usually C–H insertion, and in addition identifying the side products formed through competing reaction pathways, although in many cases pure samples of these have not been isolated for full characterisation. Among the side products observed are products of hydride abstraction, diazo reduction and X–H insertion/chlorine abstraction (as shown in **Figure 4.4**).[8] The hydride abstraction products are usually readily identified through the appearance of alkene protons. The reduction products are readily identified as they are the precursors to the α-diazo-β-oxo sulfone synthesis; the reappearance of the methylene singlets is particularly characteristic.

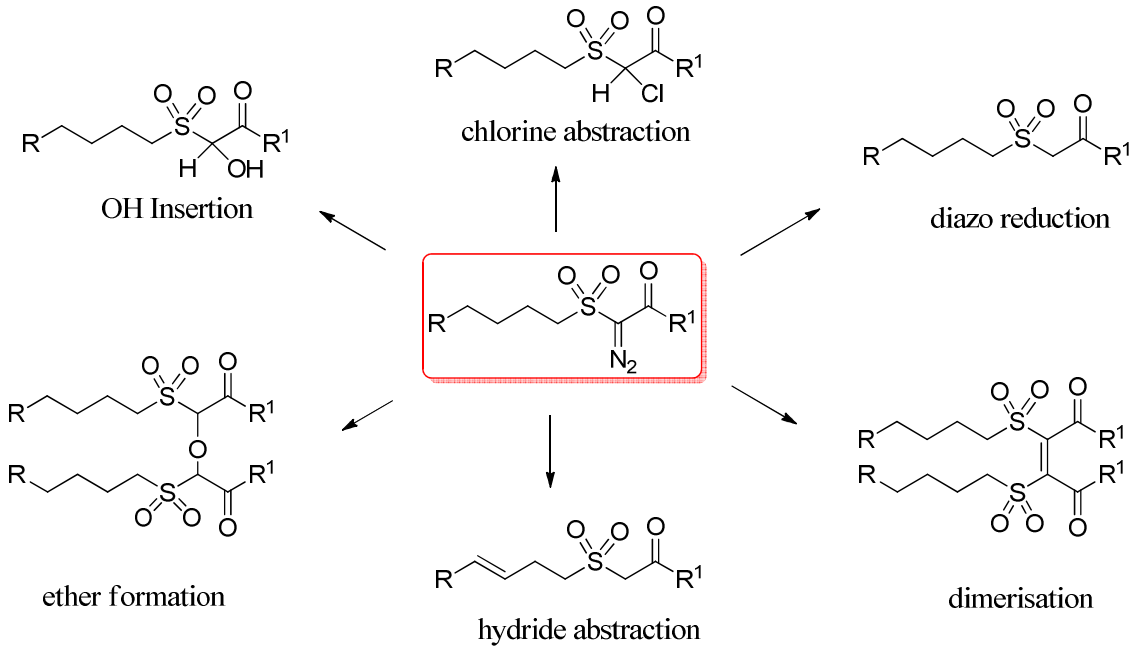
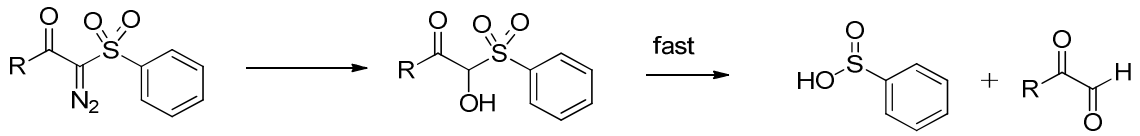


Figure 4.4

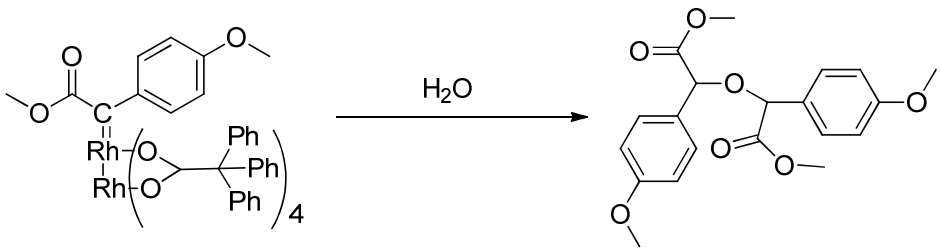
In the crude spectra, characteristic singlets are frequently seen in the region of δ_H 5.0–5.5 ppm. At the outset it was thought that these signals corresponded to insertion into water to generate the α-hydroxy sulfone **140** (**Figure 4.6**). However, exhaustive attempts to isolate and characterise the α-hydroxy sulfone derived from **25** proved unsuccessful. Similarly, in previous work in our lab, Slattery attempted isolation of an α-hydroxy sulfone without success,[3] and also a literature search has revealed that this moiety has not been reported. This led us to the conclusion that the α-hydroxyl sulfone may not be stable, which is supported by a recent report that describes a transient α-hydroxy sulfone, formed

by O–H insertion, which quickly degrades to an oxo-aldehyde and phenyl sulfinic acid (**Scheme 4.4**).[9]



Scheme 4.4[9]

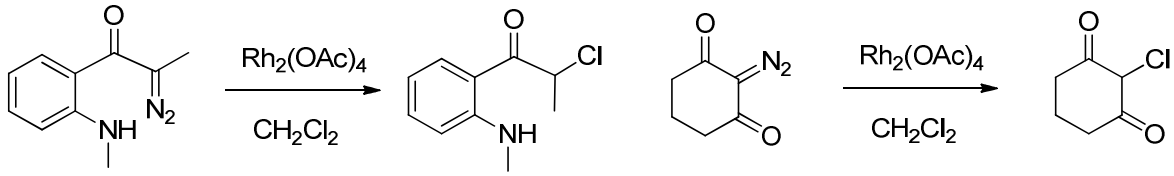
The next structure we envisaged to explain the singlets between δ_H 5.0–5.5 ppm was the ether derivative **141** (**Figure 4.6**). Even if the α-hydroxy sulfones are unstable, it could be envisaged that insertion into water to form a complexed hydroxy sulfone could be rapidly followed by a second O–H insertion, to lead to the ether. Recently, Davies and co-workers reported that when carbene complex **142** is reacted with water, symmetrical ether **143** is isolated.[10] However, in this project, all attempts to identify the ether by mass spectrometry proved unsuccessful.



142 **143**

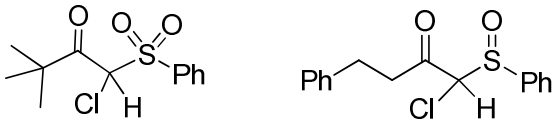
Scheme 4.5[10]

The next structure considered was an α-chlorosulfone **144** formed by chlorine abstraction from dichloromethane, as a "last resort" reaction pathway (**Figure 4.6**). Products formed *via* chlorine abstraction from dichloromethane have previously been reported in the literature by both Mountjoy[11] and Pirrung and co-workers,[12] when α-diazoketones were exposed to rhodium catalysts (**Scheme 4.6**).



Scheme 4.6[11,12]

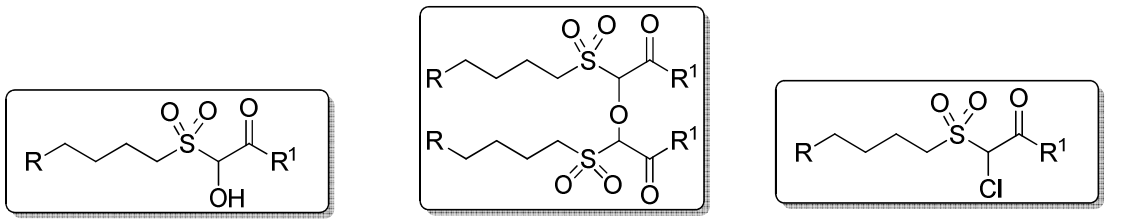
^{1}H NMR data for α-chlorosulfones includes singlets in the region of δ_H ~5.0–5.6 ppm (examples shown in **Figure 4.5**), values similar to those seen throughout this project.[13–15]



δ_H 5.63 (s) **δ_H 5.03 (s)**

Figure 4.5

In addition, in this research group, Ring[16] recently obtained a crystal structure for an α-chloro-sulfonamide, during her work on the asymmetric copper catalysed C–H insertion reactions of α-diazoacetamides, thus, providing concrete evidence that such products can be formed and are stable to purification by column chromatography. The realisation that chlorine abstraction is a significant pathway arose very late in this research. In future work, mass spectrometry analysis of the crude products may prove helpful in definitively identifying the chlorine abstraction products, due to the characteristic isotopic pattern associated with the presence of chlorine. Throughout this thesis, as the structure has not been definitively confirmed, a generic structure for X–H insertion is employed.



OH insertion product **symmetrical ether** **chlorine abstraction product**

140 **141** **144**

Figure 4.6

4.1.4 Chiral HPLC analysis

One of the key objectives of the catalyst screens is to explore the impact of ligand variation on the enantiopurity of the resulting C–H insertion products. Chiral HPLC analysis was employed throughout this work to determine the enantiopurity of the major reaction products, namely the *cis* thiopyran and the *trans* sulfolane. Full details of the HPLC conditions employed are included in **Appendix I**. Flynn had already developed chiral HPLC conditions to enable determination of enantiopurity for *cis* thiopyrans **22**,

24, **26**, **28**, **30**, **38** (**a**) and sulfolanes **40**, **42** (**b**). However, development of conditions for the novel compounds **145** and **146** in this chapter, and all compounds reported in chapters 5-7, were undertaken during this work.

In order to develop conditions for determination of enantiopurity, genuine racemic samples of each of the *cis* thiopyrans and the *trans* sulofolanes are required for method development. Usually, racemic samples of products derived from α-diazoketones are generated through use of the standard rhodium acetate catalyst. However, Flynn has demonstrated that, for the α-diazo-β-oxo sulfones, the product distribution is very different when rhodium acetate is employed and the *cis* thiopyran is formed at very low levels in the reaction mixtures. Accordingly, Flynn explored the use of other achiral catalysts to lead to the genuine racemic samples. In particular, use of copper(II) triflate proved effective in providing, in modest yields, the racemic *cis* thiopyrans and while the efficiency of these reactions was poor, it successfully provided the racemic samples required for HPLC development. Hydride elimination products were commonly observed as minor components in the H ^{1}NMR spectra of the crude reaction mixtures[1,2] of reactions catalysed by $Cu(OTf)_2$. As chiral HPLC conditions had been previously developed for compound **22**, **24**, **26**, **28**, **30**, **38** (**a**) and **40**, **42** (**b**) by Flynn, generation of racemic material for these compounds was not repeated in this project. However, where relevant the results obtained by Flynn will be included and discussed.

During this work, a sample of novel α-diazo-β-oxo sulfone **45** was cyclised with $Cu(OTf)_2$ (**Table 4.7**, entry 1) to provide the novel racemic thiopyran **145a**.

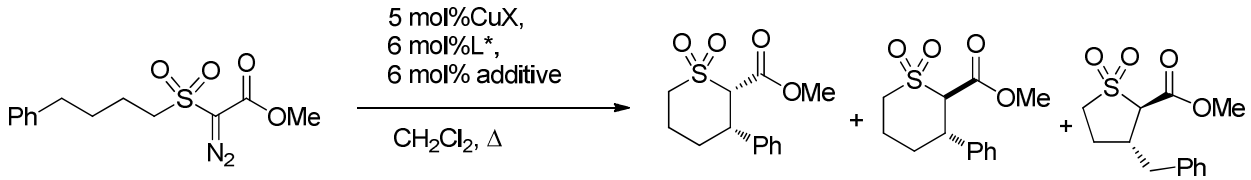
Having established HPLC conditions to enable resolution of the two enantiomers of each of the major C–H insertion products, analysis of the products derived from each of the individual reactions from the catalysts screens was undertaken. As complete chromatographic separation was challenging, in many instances both pure fractions of each of the insertion products and mixed fractions were analysed by chiral HPLC to ensure accurate estimation of enantioselectivity. Isolated examples of enantiomeric disproportionation[17,18] of enantiomers have been seen by the Maguire team with related compounds[16] and as a result, analysis of each fraction is undertaken to ensure % ee recorded reflects the enantioselectivity in each catalysed reaction.

In isolated instances, the enantioselectivity of C–H insertion products that could not be separated from byproducts had to be measured. This involved separation of the

byproducts from the enantiomers of the C–H insertion product using chiral HPLC. This will be discussed in more detail in the specified instances.

4.2 Investigation into the effect of the various catalyst components on the reaction outcome of the asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone 25

As the first part of the investigation, the C–H insertion reactions of α-diazo-β-oxo sulfone **25** were explored, as it is the substrate that gave rise to *cis* thiopyran **26a** with the highest enantiopurity (98% ee), when catalysed using a CuCl-NaBARF-(4*R*)-Ph **20** system, as part of Flynn's original study.[1,2] In this work, the initial aim was to explore the impact that each of the catalytic components have on the outcome of the C–H insertion reaction of α-diazo-β-oxo sulfone **25** (**Scheme 4.7**). Therefore, a variety of bisoxazoline ligands, copper sources and additives were employed. Unless otherwise stated, 5 mol% CuX, 6 mol% additive and 6 mol% bisoxazoline ligand were utilised. In addition, the catalyst was not pre-formed, and reactions were monitored using IR spectroscopy, as previously discussed in **Section 4.1.1**.



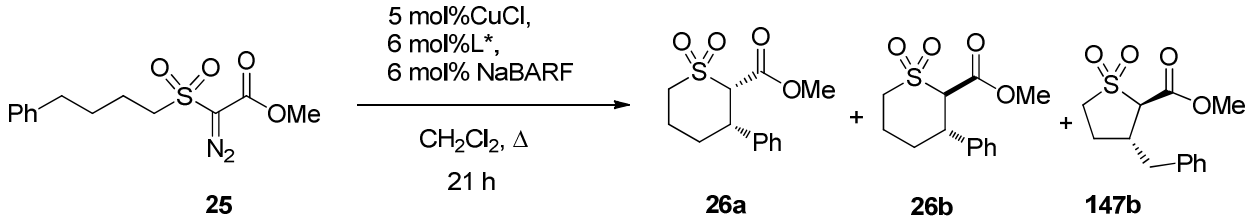
25 **26a** **26b** **147b**

Scheme 4.7

4.2.1 Variation of bisoxazoline ligand

The outcome of the insertion reactions of the methyl ester α-diazo-β-oxo sulfone substrate **25** with variation of the chiral bisoxazoline ligand is presented in **Table 4.1**, clearly indicating the preference for *cis* thiopyran formation as the major insertion product in all cases.

Table 4.1 *Investigation into the copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **25***: a ligand study*



25 **26a** **26b** **147b**

Entry	Ligand	Crude Efficiency[a] (%)	Products[a]			
				cis **26a**	*trans* **26b**	*trans* **147b**
1	(4*R*)-Ph **20**	80–90	**Crude Ratio:** **Purified Yield (%):**	84 52% (>99% ee) (2*S*,3*S*)	7	9
2	(4*R*)-Bn **43**	60–70 [b]	**Crude Ratio:** **Purified Yield (%):**	88 36% (66% ee) (2*S*,3*S*)	9	3
3	(4*R*)-di-Ph **137**	80–90	**Crude Ratio:** **Purified Yield (%):**	81 45% (95% ee) (2*S*,3*S*)	8	11
4	(4*S*)-*t*-Bu **138**	70–80 [b]	**Crude Ratio:** **Purified Yield (%):**	88 33% (71% ee) (2*R*,3*R*)	6	6
5	(3*S*,8*R*) Ind-**44**	60–70	**Crude Ratio:** **Purified Yield (%):**	89 57% (62% ee)[c] (2*R*,3*R*)	8	3
6[d]	-	**Complex mixture**	**Purified Yield (%):**	29%		

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **26a**; δ_H 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**; δ_H 3.74 (3H, s, OCH_3), *trans* thiopyran **26b**; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*]. [^{1}H NMR signal used for calculation of X–H insertion product **148**; δ_H 5.08 (1H, s, SO_2C*H*XCO)].

b. *Approx* 2–4% hydride elimination product **149** observed in the ^{1}H NMR spectra of the crude product.

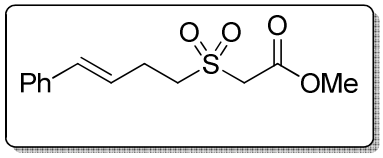
c. Fraction contains *approx* 93% *cis* thiopyran **26a**, 3% *trans* thiopyran **26b**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.86 (s), 4.73 (s). Buckely[7] repeated this experiment more than once and obtained enantioselectivities in the range of 59–68% ee, with 77% ee achieved when the catalyst was pre-formed.

d. Reaction was reported by Flynn, and was carried out with $Cu(OTf)_2$ to generate a racemic sample of *cis* thiopyran **26a** for chiral HPLC development. Hydride elimination product **149** was observed in the crude reaction mixture.

As can clearly be seen in **Table 4.1** the major product was the *cis* thiopyran with minor amounts of the *trans* thiopyran and the *trans* sulfolane detected in the ^{1}H NMR spectra of the crude products, as well as a complex mixture of both identified and unidentified

byproducts (See **Section 4.1.2** and **4.1.3**). Using the copper catalysts, *cis* thiopyran represented typically ≥ 81% of the insertion products with <11% of each of the *trans* sulfolane and *trans* thiopyran; virtually no sensitivity to the nature of the ligand was observed. Relatively high reaction efficiencies were achieved across the board with values typically exceeding 70%. Work previously carried out by Flynn showed that, in contrast, using rhodium acetate, *trans* thiopyran **26b** was the major component, while with rhodium trifluoroacetate only the *trans* sulfolane **147b** was detected within a very complex mixture.[2] Although five-membered ring formation usually dominates in intramolecular C–H insertion reactions of α-diazocarbonyl compounds, the formation of the six-membered thiopyrans is in agreement with reports by Novikov and Du Bois and can be rationalised on the basis of the introduction of the sulfone moiety, impacting on bond lengths and conformation in the transition state of the C–H insertion process.[19,20] With rhodium catalysts, the alteration in selectivity to the sulfolane rather than thiopyran is consistent with a related observation by Novikov and co-workers using $Rh_2(pfb)_4$.[21]

While minor amounts of unidentified byproducts were detected in the ^{1}H NMR spectra of all of the crude reactions mixtures, the presence of hydride elimination product **149** (2–4%) was confirmed in the ^{1}H NMR spectrum of the reaction with (4*R*)-Bn **43** and (4*S*)-*t*-Bu **138** (**Table 4.1**, entries 2 and 4) (**Figure 4.7**). This product was not detected as part of the crude reaction mixtures for cyclisations with the remaining ligands (**Table 4.1**, entries 1, 3-5). This would suggest that the presence of an aryl substituent adjacent to the coordinating nitrogen on the bisoxazoline ligand suppresses the formation of hydride elimination product **149**. A similar trend was observed for the C–H insertion reactions of α-diazo-β-oxo sulfone **61**, where specific ligand-substrate interactions impacted on the amount of byproduct formation (**Chapter 7**, **Section 7.2.2.2**). Flynn reported its presence in a reaction catalysed using copper triflate as the sole catalytic component (**Table 4.1**, entry 6). Byproducts assumed to be linked to a competing hydride transfer have been identified throughout the work reported in this thesis. For a select number of substrates, this process is particularly favourable, for example for C–H insertion reactions of α-diazo-β-oxo sulfone substrate **58** (**Chapter 6**, **Section 6.3.4**). and C–H insertion reactions of α-diazo-β-oxo sulfone **61** (**Chapter 7**, **Section 7.2.2.2**).



149

Figure 4.7

Formation of the hydride transfer product is seen in this case as hydride transfer from the benzylic position competes with the concerted C–H insertion at the same site (**Figure 4.8**). This is consistent with previous finding by Flynn and Slattery, where hydride transfer was proven to be a competing process with C–H insertion.[2,3,22]

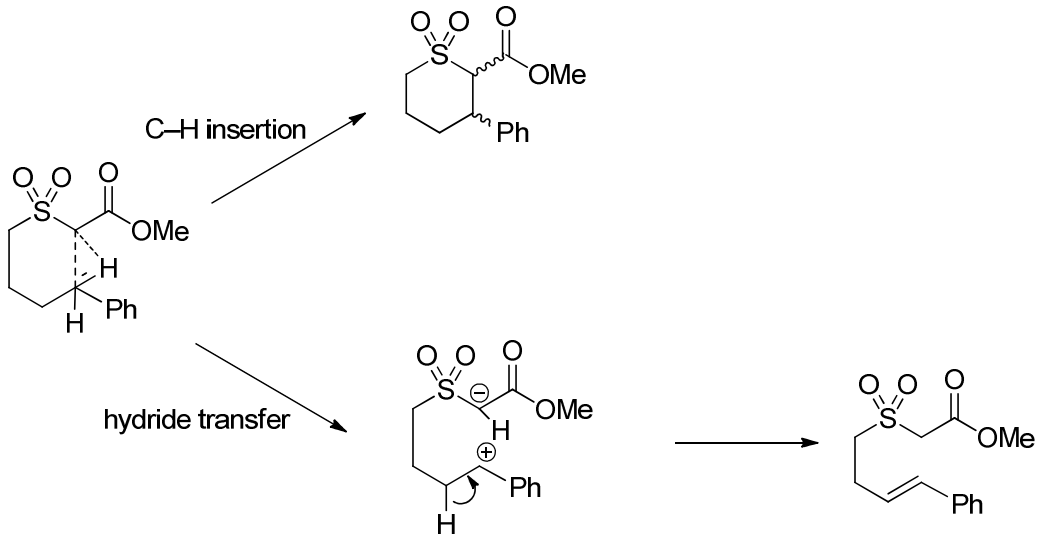


Figure 4.8

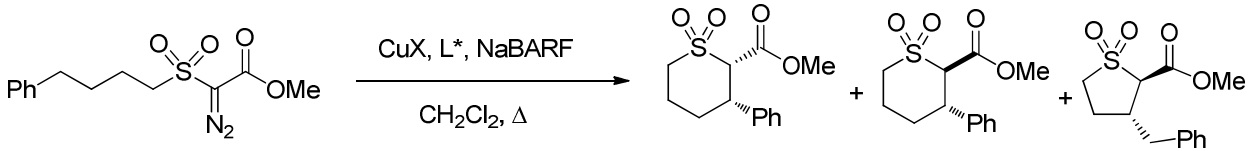
As HPLC conditions had previously been developed by Flynn, using racemic *cis* thiopyran **26a** obtained from a reaction of α-diazo-β-oxo sulfone **25** employing copper triflate, these conditions were again employed in this project (**Table 4.1**, entry 6). The enantiopurity of the *cis* thiopyran **26a** varied considerably with variation of the bisoxazoline ligand; the highest enantioselectivity (>99% ee) was obtained using the phenyl substituted ligand **20**, with enantioselectivity decreasing in the sequence (4*R*)-Ph **20** > (4*R*,5*S*)-di-Ph **137** > (4*S*)-*t*-Bu **138** > (4*R*)-Bn **43** > (3*S*,8*R*)-Ind **44** (**Table 4.1** entries 1-5). Comparison of the outcome of the reaction catalysed by (4*R*)-Ph **20**, (4*R*,5*S*)-di-Ph **137** and the (3*S*,8*R*)-Ind **44** bisoxazoline ligands reveals a very remarkable trend (**Table 4.1**, entries 1, 3, 5). The highest enantiocontrol is achieved with (4*R*)-Ph **20** and (4*R*,5*S*) di-Ph **137** ligands, highlighting the significance of having a phenyl ring adjacent to the coordinating nitrogen in the bisoxazoline ligand structure, leading to effective

enantiocontrol in the C–H insertion. Interestingly, the lowest enantiocontrol is observed for the (3*S*,8*R*)-Ind **44** (**Table 4.1**, entry 5) in which the analogous phenyl substituent is conformationally constrained. Notably, recent work in our lab, by Buckley, has reproduced this result (59–68% ee, with 77% ee achieved when the catalyst was preformed, **Table 4.1**, entry 5).[7] A decrease in enantiocontrol is seen for both (4*S*)-*t*-Bu **138** (71% ee) and (4*R*)-Bn **43** (66% ee) (**Table 4.1**, entries 2 and 4).

4.2.2 Variation of the copper source

The next catalytic component that was investigated was the copper salt. The result of the insertion reactions of methyl ester α-diazo-β-oxo sulfone substrate **25** with variation of the copper salt and the amount of NaBARF used are shown in **Table 4.2**.

Table 4.2 *Investigation into the copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***25****: a copper study*



25 **26a** **26b** **147b**

Entry	**Copper Source**	**NaBARF (mol%)**	**Ligand**	**Time (h)**	**Crude Efficiency[a] (%)**	**Products[a]**			
							***cis* 26a**	***trans* 26a**	***trans* 147b**
1	$CuCl_2$	6	(4*R*)-Ph **20**	3	50–60 [b]	**Crude Ratio:** **Purified Yield (%):**	86 61% (95% ee)[c] (2*S*,3*S*)	4	10
2	$CuCl_2$	12	(4*R*)-Ph **20**	3	70–80[d]	**Crude Ratio:** **Purified Yield (%):**	- 52% (98% ee) (2*S*,3*S*)	-	-
3	$CuCl_2$	6	(4*R*)-Bn **43**	3	70–80 [b]	**Crude Ratio:** **Purified Yield (%):**	88 67% (67% ee)[e] (2*S*,3*S*)	9	3
4	$Cu(OTf)_2$	12	(4*R*)-Ph **20**	2	40–50 [d]	**Crude Ratio:** **Purified Yield (%):**	- 38% (98% ee) (2*S*,3*S*)	-	-
5	$Cu(OTf)_2$	12	(4*R*,5*S*)-di-Ph **137**	2	30–40[b]	**Crude Ratio:** **Purified Yield (%):**	80 32% (94% ee) (2*S*,3*S*)	10	10
6	$Cu(OTf)_2$	12	(4*R*)-Bn **43**	2	30–40[b,d]	**Crude Ratio:** **Purified Yield (%):**	- 28% (66% ee) (2*S*,3*S*)	-	-

7	$Cu(OTf)_2$	12	(4*S*)-*t*-Bu **138**	1.5	50–60[b,d]	**Crude Ratio:** **Purified Yield (%):**	-. 42% (70% ee) (2*R*,3*R*)	**-**	**-**
8	$Cu(OTf)_2$	6	(4*R*)-Ph **20**	6	30–40	**Crude Ratio:** **Purified Yield (%):**	90 11% (97% ee)[f] (2*S*,3*S*)	3	7
9	$Cu(OTf)_2$	**-**	(4*R*)-Ph **20**	1 week	10–20[g]	**Crude Ratio:** **Purified Yield (%):**	87 17% (89% ee)[h] (2*S*,3*S*)	13	-
10	$CuCl_2$	-	(4*R*)-Ph **20**	98	10–20[i]	**Crude Ratio:** **Purified Yield (%):**	~86 48% (79% ee) 31:11:58[j]	~7	~7

a. Efficiency and relative ratios of isomers were calculated using ^{1}H NMR spectra of the crude product mixture using signals for *cis* thiopyran **26a**; δ_H 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**, δ_H 3.74 (3H, s, OCH_3), *trans* thiopyran **26b**; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*]. ^{1}H NMR signal used for calculation of X–H insertion product **148**; δ_H 5.08 (1H, s, SO_2C*H*XCO).

b. *Approx* 1–13% X–H insertion product **148** observed in the ^{1}H NMR spectra of the crude product.

c. Fraction contains *approx* 83% *cis* thiopyran **26a**, 1% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.37-3.48 (m), 3.85 (d, *J* 5.7), 4.69 (s).

d. Presence of and ratios of *trans* sulfolane **147b** and *trans* thiopyran **26b** cannot be accurately estimated due to peak overlap (broad signals).

e. *Approx* 1% X–H insertion product **148** observed in the ^{1}H NMR spectra of the purified product.

f. Purified fraction contains *approx* 70% *cis* thiopyran **26a**, 5% *trans* sulfolane **147b**, as well as uncharacterised material.

g. Reaction was stopped after one week of stirring at reflux. Reaction had not gone to completion, 33% starting material (α-diazocarbonyl **25**) was present.

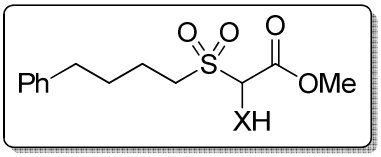
h. Purified fraction contains *approx* 30% *cis* thiopyran **26a**, 1% X–H insertion **148** and 60% starting material (α-diazocarbonyl **25**).

i. Complex mixture containing between 5–7% X–H insertion product **148**.

j. Fraction contains 31% *cis* thiopyran **26a**, 11% X–H insertion product **148** and 58% of the fraction is unknown.

Having investigated the role that the ligand plays in determining the outcome of the enantiopurity of *cis* thiopyran **26a**, the next catalytic component that was investigated was the copper salt. There is a decrease in terms of reaction efficiency seen for both $CuCl_2$ and $Cu(OTf)_2$ when compared to CuCl, (**Table 4.1**, entry 1 *cf.* **Table 4.2** entries 1 and 8) The difference in reaction efficiency is more remarkable for $Cu(OTf)_2$, with a decrease from ~80–90% seen for reaction with CuCl to 30–40% efficiency seen for $Cu(OTf)_2$ with reaction for (4*R*)-Ph **20** (**Table 4.1**, entry 1, *cf.* **Table 4.2** entry 8). The C–H insertion product distribution is also consistent with what was seen previously (**Table 4.1**) with *cis* thiopyran **26a** as the major isomer and *trans* thiopyran **26b** and *trans* sulfolane **147b** being present in minor amounts.

Significantly, $CuCl_2$ mediated or $Cu(OTf)_2$ mediated insertion in the absence of NaBARF is particularly poorly efficient (**Table 4.2**, entries 9 and 10). When the amount of NaBARF is increased from 6 to12 mol%, an increase in reaction efficiency is observed, both with $Cu(OTf)_2$ (**Table 4.2**, entries 7–8) and with $CuCl_2$ (**Table 4.2**, entries 1–2). This is consistent with a recent report by Zhou and co-workers of a palladium mediated O–H insertion.[23] Interestingly, when CuCl was not employed as the copper source, a number of additional byproducts were observed in the ^{1}H NMR spectra of the crude reaction mixtures of a number of reactions presented in **Table 4.2**, of these, X–H insertion product **148**, which was discussed in **Section 4.1.3**, was the most prevalent, being present in quantities of up to 13% of the total reaction products (**Table 4.2**, entries 1, 3 5–7). Throughout this thesis, this widely occurring byproduct is referred to as the X–H insertion product (**Figure 4.9**), although recently it appears that the structure is most likely chloride abstraction.



148

Figure 4.9

Variation in reaction time is strongly dependant on the starting copper salt; generally reaction with $CuCl_2$ proceeds more quickly than reaction with CuCl and results in a modest improvement in recorded yield of *cis* thiopyran **26a**. (**Table 4.1**, entries 1–5, *cf*

Table 4.2 entries 1–3). The same observation can also be made for the use of $Cu(OTf)_2$ (**Table 4.1**, entries 1–4, *cf* **Table 4.2** entries 4–7). Thus, the oxidation state of copper appears to be the critical factor.

Remarkably, the enantioselectivity depended almost completely on the ligand and displayed little or no sensitivity to the copper salt employed, (**Table 4.1**, entries 1–4 *cf* **Table 4.2** entries 1, 3, 4–7) indicating the active catalyst species is likely to be identical, irrespective of the precursor. Operationally, there is a benefit to using the more stable $CuCl_2$, due to decreased reaction times, which was discovered late in the study.

4.2.3 Variation of the Additive

The positive effect of the inclusion of the additive NaBARF in a variety of reactions has been noted by a number of groups.[24–32] It was reported by Zhou and co-workers that it caused an enhancement in enantioselectivity in O–H as well as N–H insertion reactions. In fact in certain instances no enantioinduction was observed in its absence, with up to 99% ee being achieved in its presence (**Figure 4.10**).[5,6,23,33]

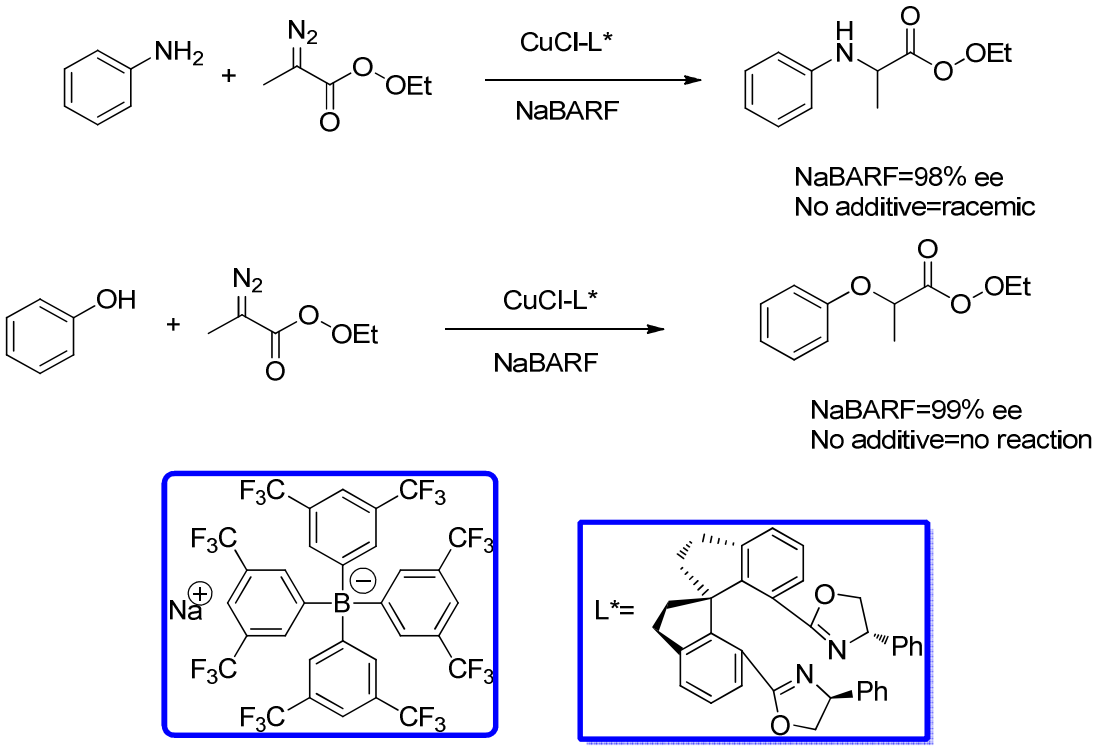
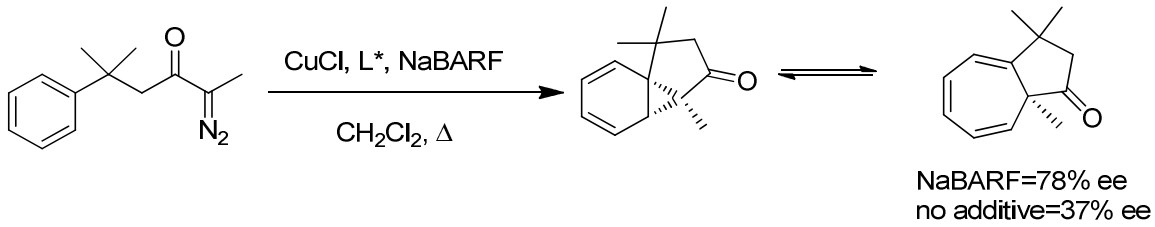


Figure 4.10

An improvement in enantioselectivity was also reported for the Buchner reaction in the presence of NaBARF, with an increase from 37% to 78% ee observed when NaBARF is employed (**Scheme 4.8**).[34]



Scheme 4.8

Fraile and co-workers had carried out extensive research into the role that counterions play in the enantioselectivity of copper catalysed intermolecular cyclopropanation.[35,36] Theoretical and experimental results indicate that there are different catalyst geometries in the presence or absence of strongly coordinating counterions. In the presence of the strongly coordinating chloride counterion, the catalyst adopts a boat confirmation, whereas, in its absence it adopts a planar geometry. The planar catalyst geometry is desirable in order to achieve high enantioselectivities in the intermolecular cyclopropanation reaction (**Figure 4.11**). In addition, removal of chloride results in decreased bond lengths.

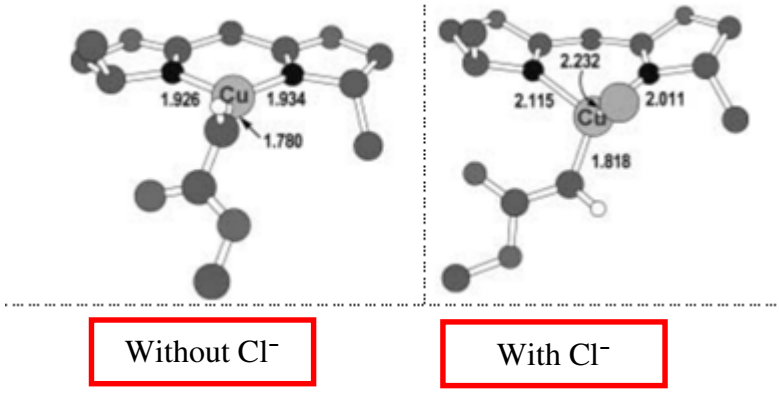


Figure 4.11[35]

In relation to the CuCl-NaBARF-L* catalyst system, one of the key roles that NaBARF is believed to play is to provide a "naked metal" sodium cation, which is available to abstract the chloride anion. The removal of the chloride anion then allows for the formation of the ideal planar catalyst geometry. This process is aided by the weakly coordinating nature of the BARF anion (**Figure 4.12**).[37,38]

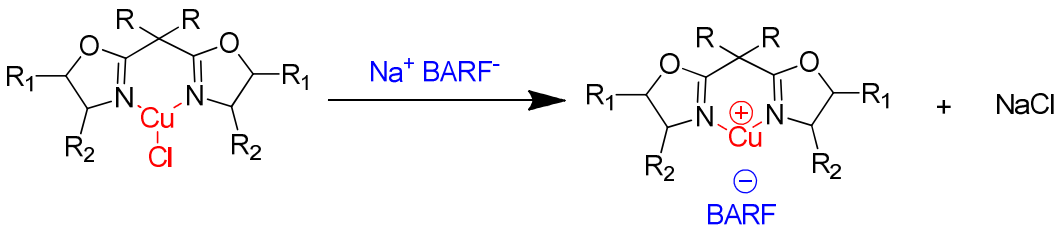
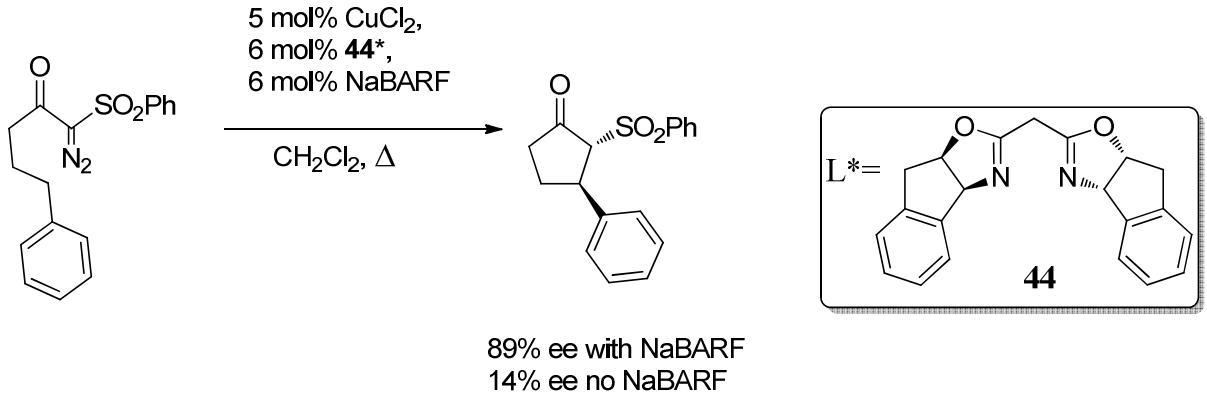


Figure 4.12

In the cyclopentanone series, Slattery *et al.* reported achieving enantioselectivities of up to 89% ee in the presence of NaBARF with the (3*S*,8*R*)-Ind ligand **44** and 14% ee for the same ligand in the absence of the additive (**Table 4.3**).[39–41] These results are consistent with the Fraile model. Slattery subsequently carried out an investigation into the role that the additive NaBARF was playing to cause such an increase in enantioselectivity. As part of this investigation, a variety of different additives were employed instead of NaBARF. As can be seen in **Table 4.3**, both $NaPF_6$ and KBARF (**Table 4.3**, entries 3 and 6) give rise to cyclopentanones with similar levels of enantioselectivities as seen for NaBARF. However, the remaining salts all give rise to decreased enantioselectivity ranging from 11–71% ee, with $NaBF_4$ resulting in the lowest value (**Table 4.3**, entry 5). It is worth mentioning that the salts have varying levels of solubility in dichloromethane. During the course of the study, Slattery noticed the appearance of a white residue on the reaction flask after reaction completion, when using NaBARF. Analysis of this residue, using PXRD analysis, revealed the white solid to be sodium chloride.[1,39,40] This observation supports the theory that the role of NaBARF is to provide a "naked" sodium metal cation to abstract the chloride anion and form NaCl.

The counterion effect is most likely related to the solubility of the sodium cation rather than direct effect of the anion. It is possible that the extent of hydration of the sodium cation is influenced by the nature of the counterion.

Table 4.3 *Effect of the additive NaBARF on the outcome of the enantioselectivity for the cyclopentanone series.*[39,40]

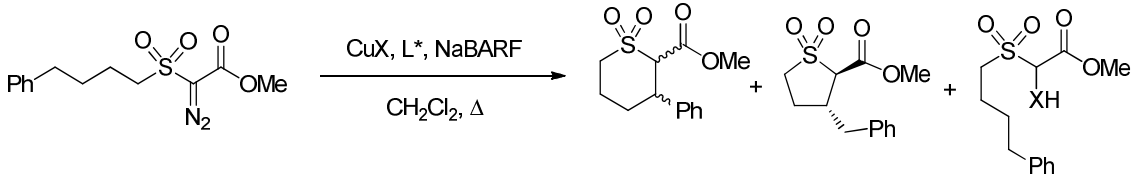


Entry	Additive	Time (h)	Yield (%)[a]	ee (%)[b]
1	-	21	62	14
2	NaBARF	2	87	89
3	$NaPF_6$	4	66	83
4	$NaB(C_6H_5)_4$	5	77	25
5	$NaBF_4$	20	63	11
6	KBARF	2	59	91
7	KPF_6	20	43	35
8	$LiPF_6$	5	78	71

a. Purified using column chromatography.
b. Enantioselectivity measured using chiral HPLC.

As part of this investigation, the additive study was extended to the α-diazo-β-oxo-sulfone series. The results of this study are presented in **Table 4.4**.

Table 4.4 *Investigation into the copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone **25**: an additive study*[39,40]



25 **26 (a and b)** **147b** **148**

Entry	Additive	Ligand	Time (h)	Crude Efficiency [a]	Crude Ratio: Purified Yield (%)[b] (% ee)[c]	Product ratios[a] 26a 148	26b	147b	
1	$LiPF_6$	(4*R*)-Ph **20**	19	**-** [d]	**Crude Ratio:** **Purified Yield (%): 47%** **(% ee)**	- 82% (83% ee)	**-** **-**	**-** **-**	**-** 8%
2	$LiPF_6$	(4*R*)-Bn **43**	21	**-**[d]	**Crude Ratio:** **Purified Yield (%): 35%** **(% ee)**	**-** 30% (69% ee)	**-** 7%	**-** **-**	**-** 4%
3	$NaPF_6$	(4*R*)-Bn **43**	6	30–40[e]	**Crude Ratio:** **Purified Yield (%): 48%** **(% ee)**	76 70 (73% ee)	14 **-**	10 **-**	**-**[e] 5

4	$NaPF_6$	(4*R*)-Ph **20**	6	30–40[e]	**Crude Ratio:** **Purified Yield (%): <u>38%</u>** **(% ee)**	80 71% (97% ee)	11 **-**	9 **-**	**-**[e] 3%
5	KBARF	(4*R*)-Ph **20**	3	50–60[e]	**Crude Ratio:** **Purified Yield (%): <u>46%</u>** **(% ee)**	89 80% (98% ee)	3 -	8 -	-[e] 1%
6	KBARF	(4*R*)-Bn **43**	2	60–70[e]	**Crude Ratio:** **Purified Yield (%): <u>51%</u>** **(% ee)**	94 90% (62% ee)	3 -	3 -	**-**[e] 1%
7	KPF_6	(4*R*)-Ph **20**	30	30–40[e]	**Crude Ratio:** **Purified Yield (%): <u>45%</u>** **(% ee)**	~ 80 72% (92% ee)	~10 -	~10 -	**-**[e] 8%
8	KPF_6	(4*R*)-Bn **43**	48	30–40[e]	**Crude Ratio:** **Purified Yield (%): <u>48%</u>** **(% ee)**	~77 52% (70% ee)	~16 7%	~7 -	**-**[e] 2%
9	$NaB(C_6H_5)_4$	(4*R*)-Ph **20**	56	<10[f]	**Crude Ratio:** **Purified Yield (%): <u>4%</u>** **(% ee)**	- 12%[g]	- -	- -	**-**[f] 45%
10	$NaB(C_6H_5)_4$	(4*R*)-Bn **43**	56	0[h]	**Crude Ratio:** **Purified Yield (%):** **(% ee)**	-	**-**	**-**	**-**
11	$NaBF_4$	(4*R*)-Ph **20**	24	<10[e]	**Crude Ratio:**	~80	~10	~10	-[e]

					Purified Yield (%): <u>43%</u> (% ee)	22% (93% ee)	**-**	**-**	40%
12	$NaBF_4$	(4*R*)-Bn **43**	48	10–20[e]	**Crude Ratio:** **Purified Yield (%) <u>22%</u> (% ee)**	~80 30%[g]	~ 10 **-**	~10 **-**	-[e] 21%
13	-	(4*R*)-Ph **20**	98	10–20[e]	**Crude Ratio:** **Purified Yield (%): <u>48%</u> (% ee)**	~86 31% (79% ee)	~7 -	~7 -	-[e] 11%
14	-	(4*R*)-Bn **43**	1 week	-[i]	**Crude Ratio:** **Purified Yield (%):** **(% ee)**	**-**	-	**-**	**-**

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **26a**; δ_H 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**, δ_H 3.74 (3H, s, OC*H*$_3$), *trans* thiopyran **26b**; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*]. Estimations of the quantities of XH insertion product **148** in the crude and purified mixtures are made using the following spectral data: ^{1}H NMR signal used for calculation of X–H insertion product **148**; δ_H 5.08 (1H, s, SO_2C*H*XCO). The amount of X–H insertion product is not included in the crude efficiency and therefore is not calculated as part of the relative ratios of isomers in the crude product.

b. The purified yields presented in the above Table are given for a mixture of compounds. The % of this mixture that can be accounted for is presented above.

c. Enantioselectivity (%) is reported for *cis* thiopyran **26a**. Additional signals present in the HPLC traces have been assigned to X–H insertion product **148**.

d. ^{1}H NMR spectra of the crude product not obtained due to hazardous nature of $LiPF_6$, the crude material was immediately purified by flash chromatography.

e. Complex mixture containing between 1–10% X–H insertion product **148**.

f. ^{1}H NMR analysis of the crude mixture reveals a complex mixture of products, largely unidentified. Reaction efficiencies and relative ratios of isomers could not be accurately calculated due to overlapping peaks in the ^{1}H NMR spectra of the crude product. It is estimated that there is *approx* 6% X–H insertion **148** product present.

g. Enantioselectivity not determined.

h. ^{1}H NMR analysis of the crude mixture reveals a complex mixture of products (largely unidentified), and there is no clear evidence for the formation of intramolecular insertion products. It is estimated that there is *approx* 5% X–H insertion **148** product present.

i. Reaction did not occur after one week of stirring at reflux.

A variety of different additives were explored, using two separate bisoxazoline ligands: (4*R*)-Ph **20** and (4*R*)-Bn **43**. In the initial studies with NaBARF (4*R*)-Ph **20** gave rise to *cis* thiopyran **26a** in 98% ee (**Section 4.2.1**, **Table 4.1**) and (4*R*)-Bn **43** resulted in an enantioselectivity of 66% ee for *cis* thiopyran **26a**. As part of this additive study a variety of lithium, sodium and potassium salts were employed. Examination of the ^{1}H NMR spectra of the crude reaction products showed some very interesting trends. Reaction efficiency suffers greatly when NaBARF is not used as the additive. Reaction efficiency decreases in the order NaBARF~KBARF>$NaPF_6$~KPF_6>$NaBF_4$~$NaB(C_6H_5)_4$~no additive (**Table 4.4**, **Figure 4.13**). Reaction efficiencies as high as 80–90% have been observed when NaBARF was employed; however, they fall to as low as ~10–20% in the absence of an additive, or when using $NaB(C_6H_5)_4$ or $NaBF_4$. In fact, for the (4*R*)-Bn **43** the reaction did not proceed after 1 week of stirring under reflux in the absence of an additive (**Table 4.4**, entry 14). This demonstrates the crucial role that the NaBARF additive plays in the efficiencies of the copper catalysed C–H insertion reactions of α-diazo-β-oxo-sulfones to synthesise *cis* thiopyran products. When the reaction efficiency decreases, a number of byproducts form instead, most of which have not been characterised; however, X–H insertion product **148** (**Figure 4.9**) has been detected in the majority of reactions presented in **Table 4.4**.

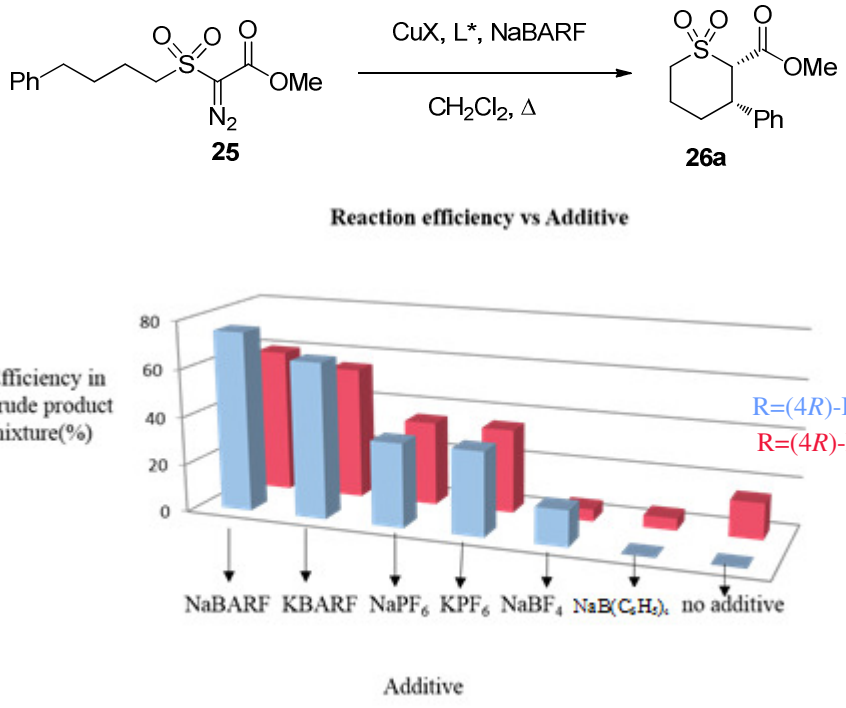


Figure 4.13 *Effect of variation of additive on reaction efficiency in the synthesis of* cis *thiopyran* **26a**

Separation of X–H insertion byproduct **148** from *cis* thiopyran **26a** proved extremely difficult. In most instances, only partial separation was achieved, which proved problematic as chiral HPLC analysis had to be conducted on *cis* thiopyran products. Up until this point, the method developed by Flynn for chiral HPLC analysis had proved successful in the analysis of the enantiopurity of *cis* thiopyran **26a**. However, it was discovered that when X–H insertion product **148** was present, it co-eluted with one of the enantiomers of the *cis* thiopyran product, and would therefore interfere with the results of this study. Alternative HPLC conditions were developed which allowed for separation of X–H insertion product **148**, from the enantiomers of *cis* thiopyran **26a**, the details of which are in **Appendix I**. This illustrates the importance of either having a clean sample for chiral HPLC analysis or ensuring that all components in the reaction mixture are fully separated on the chiral column.

While the efficiencies of the reactions varied greatly with a change in additive, the enantioselectivities of the *cis* thiopyran product displayed little sensitivity to the nature of the additive (**Table 4.4**, **Figure 4.14**). When the (4*R*)-Ph ligand **20** was used enantioselectivities were in the range of 83–98% ee (**Table 4.4**, entries 1, 4, 5, 7, 11); even in the absence of an additive, 79% ee was still attained for the *cis* thiopyran product **26a** (**Table 4.4**, entry 13). This is in contrast with the cyclopentanone series, where enantioselectivities were seen to change from 14–89% ee on variation of the additive. The enantioselectivity of the reaction product arising from the cyclisation with $NaB(C_6H_5)_4$ could not be measured as an analytically pure sample could not be obtained (**Table 4.4**, entry 9). A similar trend is observed for (4*R*)-Bn ligand **43**, where enantioselectivities ranged from 62–73% ee (**Table 4.4**, entries 2, 3, 6 and 8). A reaction did not occur in the absence of an additive (**Table 4.4**, entry 14) and % ee measurements could not be made for reactions resulting from $NaB(C_6H_5)_4$ or $NaBF_4$ (**Table 4.4**, entries 10 and 12) as not enough material was produced or the material was not analytically pure.

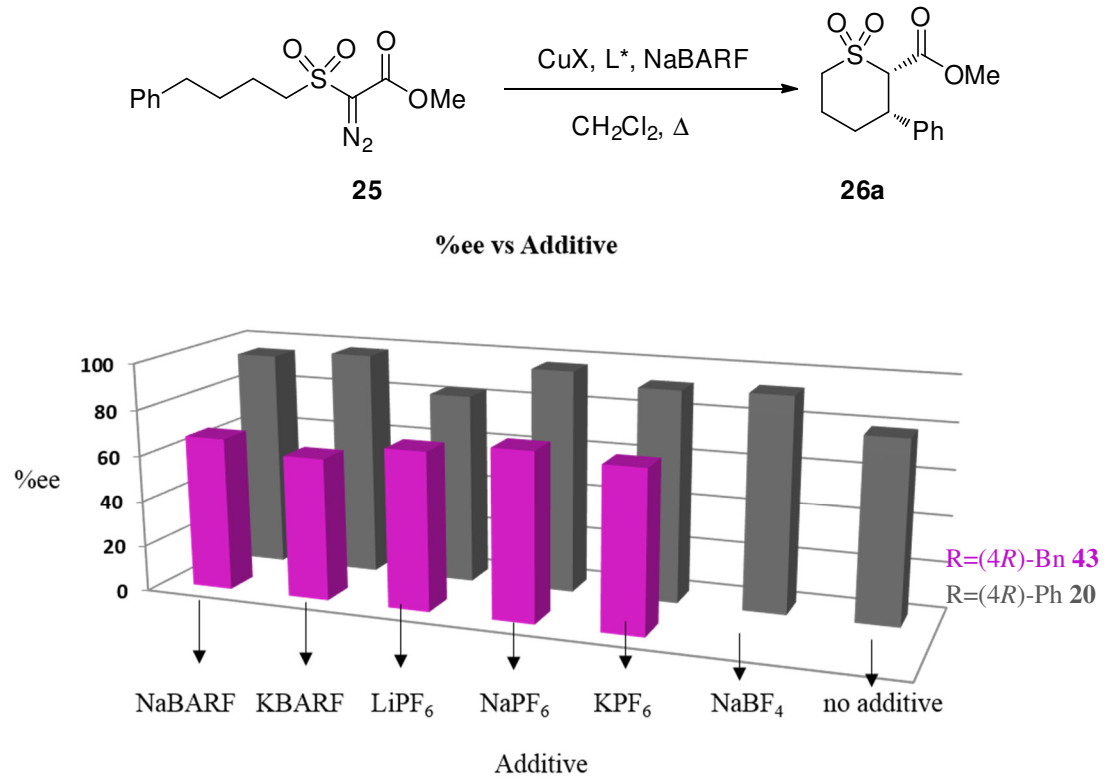


Figure 4.14 *Effect of variation of additive on enantioselectivity of* cis *thiopyran* ***26a***

The result of this study clearly outlines the importance of NaBARF to the success of both the efficiency and enantioselection of the C–H insertion reactions to form *cis* thiopyran compounds.[39,40]

Comparison of Slattery's results with these results, displays an interesting contrast, in that variation of the additive, in cyclopentanone formation displayed little impact on reaction efficiency, but dramatic effect on enantioselectivity,[3] whereas in thiopyran formation, the efficiency was very sensitive to the nature of the additive with just a modest effect on the enantioselectivity (**Figure 4.13** and **Figure 4.14**).

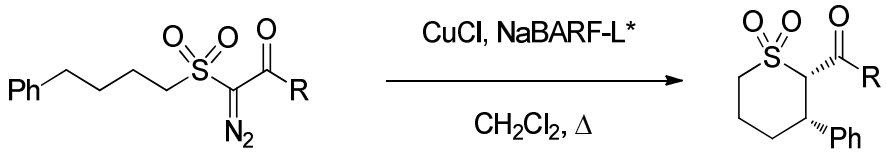
4.3 Exploration of the impact of changing the substrate: variation of carbene carbonyl and C–H insertion site

4.3.1 Exploration of the impact of the carbene carbonyl

In order to explore the impact that the substituent on the carbene carbon has on overall reaction outcome (efficiency, regio- and enantioselectivity), the methyl ester group in compound **25** was replaced with a phenyl and methyl ketone substituent in **23** and **21**.

The site of C–H insertion remained unchanged so as to allow direct comparison with the initial results obtained for methyl ester substrate **25**. The results of this study are summarised in **Table 4.5**, for comparison, results previously described by Flynn are included in **Table 4.5** (**Table 4.5**, entries 5–8).[1,2] With the phenyl ketone derivative **23**, use of either the (4*R*)-Ph **20** or the (4*R*)-Bn **43** bisoxazoline ligands led to crude product mixtures in which only the signals for the *cis* thiopyran could be definitively identified (**Table 4.5**, entries 3 and 5). In contrast the use of the (4*S*)-*t*-Bu **138** and the (4*R*,5*S*)-di-Ph **137** ligands led to additional signals in the ^{1}H NMR spectra of the crude products which are consistent with the formation of the isomeric C–H insertion product *trans* sulfolane and/or *trans* thiopyran (**Table 4.5**, entries 1 and 2). Thus, there is evidence for a modest ligand effect on product distribution. Similarly, with the methyl ketone **21**, while Flynn did not report the formation of additional isomers when (4*R*)-Ph **20** ligand was employed,[1,2] using (4*R*,5*S*)-di-Ph **137**, signals for all three isomers were identified (**Table 4.5**, entries 4 and 6). Both *cis* thiopyran **22a** and *trans* thiopyran **22b** had previously been synthesised and characterised by Flynn, and therefore the presence of these isomers was confirmed.[1,2] However, as a pure sample of *trans* sulfolane **150b** was not isolated by Flynn or as part of this project, its assignment is tentative.

Table 4.5 *Exploration of the impact of the presence of a ketone adjacent to the carbene carbon*



Entry	α-diazosulfone	R	Ligand	*cis* thiopyran	Crude Efficiency[a] (%)	Time (h)	Yield (%)[b]	% ee[c]
1	**23**	Ph	(4*R*,5*S*)-di-Ph **137**	**24a**	>80% [d]	6	41[e]	93% ee (2*S*,3*S*)
2	**23**	Ph	(4*S*)-*t*-Bu **138**	**24a**	>80% [f]	20	51	78% ee (2*R*,3*R*)
3	**23**	Ph	(4*R*)-Bn **43**	**24a**	>70%	20	55	83% ee (2*S*,3*S*)
4	**21**	Me	(4*R*)-di-Ph **137**	**22a**	>90%[g]	21	26[h,i]	73% ee (2*S*,3*S*)
5[j,1,2]	**23**	Ph	(4*R*)-Ph **20**	**24a**	-	6	49	97% ee (2*S*,3*S*)
6[j1,2]	**21**	Me	(4*R*)-Ph **20**	**22a**	-	22	30	85% ee (2*S*,3*S*)
7[j,k]	**23**	Ph	-	**24a**	Complex, contains *cis* : *trans* thiopyran in a 2 :1 mixture.	22	20 *cis*, 11 *trans*	0% ee
8[j,k]	**21**	Me	-	**22a**	Complex	22	29	0% ee

a. Crude efficiency was calculated using the ^{1}H NMR spectra of the crude products, details of which can be found in the experimental section.

b. Yield (%) reported following chromatography on silica gel. The reactions were relatively efficient but the yields obtained reflected challenges in fully separating analytically pure material

c. Enantioselectivity determined using chiral HPLC analysis

d. The calculated crude reaction efficiency includes the presence of two additional compounds; This observation is made due to the presence of two unrelated doublet of doublets in the ^{1}H NMR spectra of the crude product; δ_H 4.60 (dd, *J* 14.0, 11.5) (~5%) and 4.22 (dd, *J* 5.8, 3.7) (~20%). Compound **24a** accounts for ~55% of the crude reaction mixture.

e. A fraction was isolated by chromatography (11 mg), which is *approx* 60% compound **24a**, but contains an additional product (*approx* 30–40%) with a distinct ^{1}H NMR signal; 4.60 ppm (dd, *J* 13.8, 11.1).

f. The calculated crude reaction efficiency includes the presence of an additional compound; This observation is made due to the presence of a doublet of doublets in the ^{1}H NMR spectra of the crude product; 4.60 ppm (dd, *J* 14.0, 11.5) (~20%). Compound **24a** accounts for ~60% of the crude reaction mixture.

g. The presence of three identifiable compounds accounts for *approx.* 90% of this mixture. Using the C(2)*H* signal for all three compounds there is *ca*. 58% compound **22a** (4.21 ppm, dd, *J* 4.2, 3.1), 19% *trans* **22b**, (4.40 ppm, d, *J* 12.1) and 23% *trans* sulfolane **150b** (3.78 ppm, d, *J* 9.1**,** tentatively assigned). In addition the presence of three methyl signals 1.80 ppm (**22a**), 2.19 ppm (*trans* **22b**) and 2.16 ppm (*trans* sulfolane **150b**) confirms the presence of these compounds and their relative ratios.

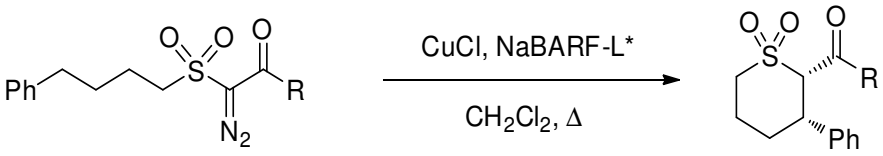
h. A second fraction was isolated (9.30 g, 13%) containing *ca*. 13% *cis* **22a** [4.23 ppm, *J* 4.2, 3.1, C(2)*H*, 1.81 COCH_3] 17% *trans* **22b** [4.35 ppm, *J* 12.1, C(2)*H*, 2.19 COCH_3]and 70% *trans* sulfolane **150b** [3.78 ppm, *J* 9.0, C(2)*H*, 2.20 ppm, COCH_3]-tentative.
i. A ^{1}H NMR spectrum recorded on a sample stored at room temperature after 24 months showed 89% of **22a** remains unchanged, with 11% conversion to *trans* **22b**.
j. Entries 5–8 on **Table 4.5** refer to previously published results and have been included here only for comparison. These results were not repeated during the course of this work.
k. Reactions were carried out previously by Flynn, employing $Cu(OTf)_2$ as a catalyst to generate racemic *cis* thiopyrans **22a** and **24a** for the development of HPLC conditions.

Examination of the ^{1}H NMR spectra of the crude material for all reactions reported in **Table 4.5** showed that, in general, crude reaction mixtures for both compound **22a** and **24a** were complex. However, in all cases ~55–70% of the crude material consisted of *cis* thiopyran product. In certain instances, there was also evidence for the presence of additional isomers, as well as trace amounts of other unidentified byproducts.

Therefore, the nature of the substitution on the bisoxazoline ligand has a minor effect on the regioselectivity of the reaction outcome with (4*R*)-Ph **20** and (4*S*)-*t*-Bu **138** ligands giving only *cis* thiopyran **24a** and (4*R*,5*S*)-di-Ph **137** and (4*R*)-Bn **43** ligands resulting in the formation of other isomers, albeit in minor quantities. All of the yields reported in **Table 4.5** are modest to low, which reflected challenges encountered in the purification process, not the overall efficiency of the C–H insertion reaction.

Flynn had previously determined HPLC conditions for the separation of the enantiomers of *cis* thiopyran **24a** and **22a**, using racemic thiopyran **24a** and **22a** obtained from reactions catalysed by $Cu(OTf)_2$ (**Table 4.5**, entries 7 and 8); these conditions were successfully used in this project. Examining data presented in **Table 4.1** for methyl ester substrate **26a** and data presented in **Table 4.5** for phenyl and methyl ketone compounds **22a** and **24a** a number of comparisons can be drawn. Firstly, it can be seen that the enantioselectivity of the C–H insertion process is relatively insensitive to the nature of the substituent at the diazo carbon (**Figure 4.15**). Thus, using (4*R*)-Ph **20** or (4*R*,5*S*)-di-Ph **137**, the enantioselectivity of the C–H insertion with phenyl ketone α-diazo-β-oxo sulfone **23** (97% and 93% ee respectively) (**Table 4.5**, entries 5 and 1) is comparable to that seen with the methyl ester α-diazo-β-oxo sulfone **25** (98% and 95% ee respectively) (**Table 4.1**, entries 1 and 3), with a slight decrease in the enantiopurity of the methyl ketone *cis* thiopyran **22a** (85% and 73% ee respectively) (**Table 4.5**, entries 6 and 4). Interestingly, with (4*S*)-*t*-Bu **138** and (4*R*)-Bn **43** the trends in terms of enantioselectivity

for phenyl ketone *cis* thiopyran **24a** (78% and 83% ee respectively) (**Table 4.5**, entries 2 and 3) are switched relative to those seen for the methyl ester *cis* thiopyran **26a** (71% and 66% ee respectively) (**Table 4.5**, entries 4 and 2), although the absolute differences are minor.



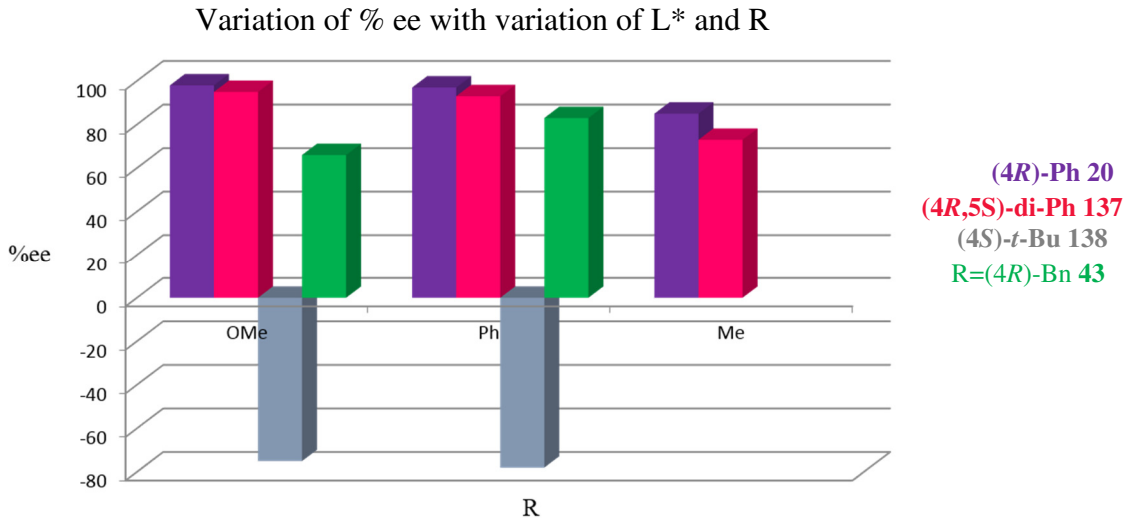


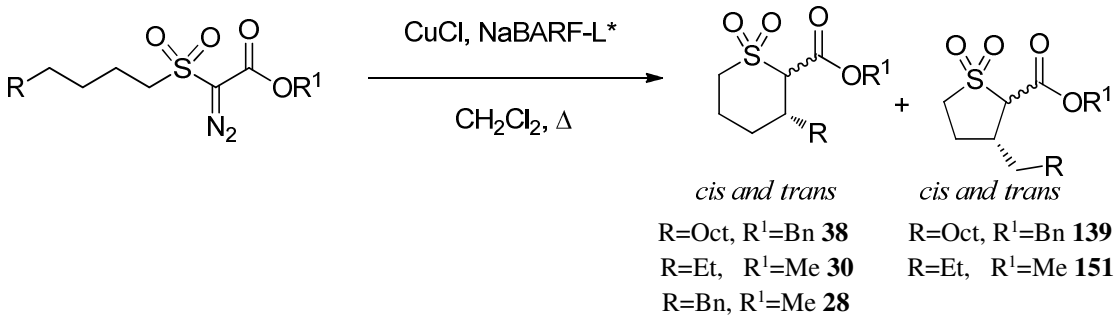
Figure 4.15*

*Note in figures of this nature throughout the thesis downward bars reflect the opposite enantiomeric series, as the ligand employed has the opposite stereochemistry to the others studied.

4.3.2 Exploring the effect of a non-benzylic C–H insertion site

Having examined the effect that changing the nature of the substituent on the carbene carbon has on reaction outcome, the next structural variation explored was varying the substituent at the site of insertion. The outcome of this study is presented in **Table 4.6**. Alkyl and benzyl substituents (compounds **27, 29, 37**) were used for comparison with insertion at the benzylic site in **Table 4.1**. In this study, just the ester derivatives were investigated, to enable direct comparison with the data in **Table 4.1**. In one case, the benzyl ester was employed instead of the methyl ester. Results previously obtained by Flynn have been included **Table 4.6** (entries 11–15) for comparative purposes.

Table 4.6 *Investigation into the impact of variation of a non benzylic site of C–H insertion site for the asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones* **37**, **29** *and* **27**



Entry	α-diazosulfone	R	R^1	Ligand	Crude efficiency (%)[a]	Time (h)	Crude ratio Purified Yield (%) % ee	Products[a,b,c] *cis* thiopyran	*trans* thiopyran	*cis* sulfolane	*trans* sulfolane
1	**37**	Oct	OBn	(4*R*)-di-Ph **137**	80–90[d]	22	**Crude ratio** **Purified Yield (%)**[e] **% ee**	62 12% 79% ee (2*S*,3*R*) **38a**	11 - - **38b**	5 - - **139a**	22 6% - **139b**
2	**37**	Oct	OBn	(4*S*)-*t*-Bu **138**	80–90[d]	21	**Crude ratio** **Purified Yield (%)**[e] **% ee**	60 51% 81% ee (2*R*,3*S*) **38a**	14 10% 59% ee **38b**	4 - - **139a**	22 13% - **139b**
3	**37**	Oct	OBn	(4R)-Bn **43**	80–90[d]	20	**Crude ratio** **Purified Yield (%)**[e] **% ee**	70 51% 80% (2*S*,3*R*)	13 4% 10% ee	- - -	17 13% -

								38a	**38b**	**139a**	**139b**
4	**29**	Et	OMe	(4*R*)-di-Ph **137**	70–80	21	**Crude ratio** **Purified Yield (%)**[e] **% ee**	69 30% >99% ee (2*S*,3*R*) **30a**	9 - - **30b**	- - -	21 9% - **151b**
5	**29**	Et	OMe	(4*S*)-*t*-Bu **138**	80–90	21	**Crude ratio** **Purified Yield (%)**[e] **% ee**	67 49% 92% ee (2*R*,3*S*) **30a**	11 6% 57% ee **30b**	- - -	22 10% - **151b**
6	**29**	Et	OMe	(4*R*)-Bn **43**	80–90	21	**Crude ratio** **Purified Yield (%)**[e] **% ee**	67 56% 87% ee (2*S*,3*R*) **30a**	12 5% 6% ee **30b**	- - -	21 10% - **151b**
7	**27**	Bn	OMe	(4*R*)-Ph **20**	70–80[f]	7	**Crude Ratio** **Purified Yield (%)** **% ee**	- 42% 96% ee (2*S*,3*S*) **28a**	- - -	- - -	- - -
8	**27**	Bn	OMe	(4*R*)-di-Ph **137**	80–90[g]	22	**Crude ratio** **Purified Yield (%)** **% ee**	- 37% 94% ee (2*S*,3*S*) **28a**	- - -	- - -	-
9	**27**	Bn	OMe	(4*S*)-*t*-Bu **138**	80–90[h]	8	**Crude Ratio** **Purified Yield (%)** **% ee**	- 2% 90% ee (2*R*,3*R*) **28a**	- - -	- - -	- - -
10	**27**	Bn	OMe	(4*R*)-Bn **43**	70–80	24	**Crude ratio** **Purified Yield (%)** **% ee**	- 21% 80% ee (2*S*,3*S*) **28a**	- - -	- - -	- - -

11[i1,2]	**37**	Oct	OBn	(4*R*)-Ph **20**	**-**	22[i]	**Crude ratio** **Purified Yield (%)** **% ee**	67 73% 90% ee (2*S*,3*R*) **38a**	13 9% 45% ee **38b**	- - - **139a**	20 17% - **139b**
12[i1,2]	**29**	Et	OMe	(4*R*)-Ph **20**	**-**	16[i]	**Crude ratio** **Purified Yield (%)** **% ee**	- 68% 97% (2*S*,3*R*) **30a**	- - -	- - -	- 13% - **151b**
13[i,2]	**37**	Oct	OBn	-	**Complex mixtures**	18	**Crude ratio** **Yield (%)** **% ee**	- 20%	-	-	-
14[i,2]	**29**	Et	OMe	-	**Complex mixtures**	16	**Crude ratio** **Yield (%)** **% ee**	- 11%	-	-	-
15[i, 2]	**27**	Bn	OMe	-	**Complex mixtures**	15	**Crude ratio** **Yield (%)** **% ee**	- 8%	-	-	-

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product. Full details of how calculations were made for each compound can be found in the experimental chapter.

b. Purification was carried out using column chromatography on silica gel. The reactions were relatively efficient but the yields obtained reflected challenges in fully separating analytically pure material.

c. Enantioselectivities determined using chiral HPLC, details of which are in **Appendix I**.

d. There was ~1% β-oxo-sulfone product **111** present in the crude mixture. Quantities were calculated using ^{1}H NMR spectra of the crude product, additional information can be found in the experimental section.

e. An overall yield is calculated from amounts of each compound in various fractions.

f. Calculated efficiency includes the two unknown compounds; [δ_H 3.63 (d, *J* 9.5)] (*approx* 23%) and [δ_H 3.74 (d, *J* 10.1)] (*approx* 12%). This reaction is a repeat of a reaction previously carried out; there is general agreement between the two results.[1,2]

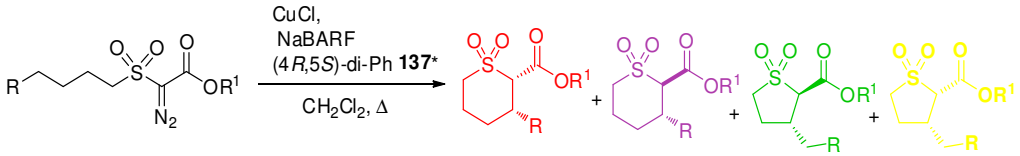
g. Additional signals observed in the ^{1}H NMR spectra of crude product; δ_H 2.27-2.35 (m), 2.37-2.50 (m), 2.76-2.87 (m), 3.02-3.13 (m), 3.14-3.20 (m), 3.23-3.31, (m), 3.37-3.48 (m), 3.63 (d, *J* 9.5), 3.74 (d, *J* 10.1), 3.80 (s). Calculated efficiency includes two unknown compounds; [δ_H 3.63 (d, *J* 9.5)] (*approx* 28%) and [δ_H 3.74 (d, *J* 10.1)] (*approx* 19%).

h. Additional signals observed in the ^{1}H NMR spectra of the crude product; δ_H 2.32-2.49 (m), 2.76-2.81 (m), 2.82-2.89 (m), 3.06-3.15 (m), 3.16-3.30 (m), 3.31-3.48 (m), 3.63 (d, *J* 9.5), 3.74 (d, *J* 10.1) efficiency 80–90%. Calculated efficiency includes two additional compounds; [δ_H 3.63 (d, *J* 9.5)] (*approx* 16%) and [δ_H 3.74 (d, *J* 10.1)] (*approx* 13%).

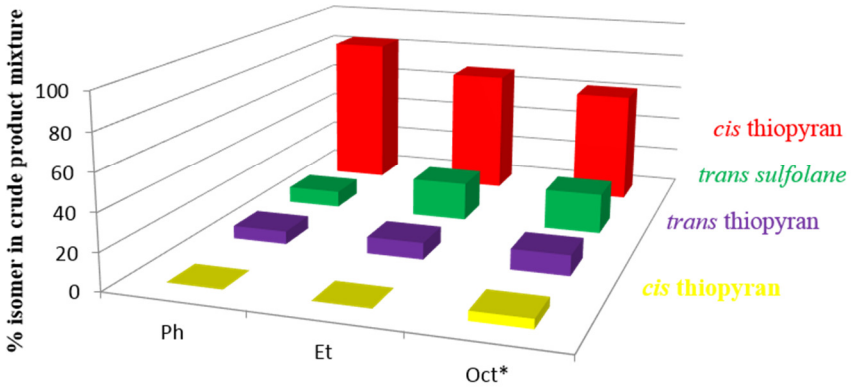
i. Entries 11-15 on **Table 4.6** refer to previously published results and have been included here only for comparison.[1,2] These results were not repeated during the course of this work.

The overall efficiencies of C–H insertion (*ca*. 70–90%) of the α-diazo-β-oxo-sulfones in **Table 4.6** were comparable to those seen for the α-diazo-β-oxo-sulfone **25** in **Table 4.1**. Once again, minor unidentified byproducts were present in the majority of reactions discussed in **Table 4.6**. For reactions with octyl α-diazo-β-oxo sulfone **37**, minor amounts of sulfone **111**, formed by diazo reduction, were present in the majority of the crude reaction mixtures at low level (typically ~1%). Notably, hydride transfer products were not observed in the ^{1}H NMR spectra of the crude product mixtures for α-diazo-β-oxo sulfones **27, 29, 37**, presumably due to the lack of stabilisation of the positive charge.

Interestingly, when the insertion no longer occurs at a benzylic C–H bond, there is an alteration in the isomer ratio (See **Figure 4.16**). On average *cis* thiopyran accounts for 60–70% of the crude product mixture relative to ~80% for insertion at the benzylic position, and while *trans* thiopyran is again present at 9–15%, the relative proportion of *trans* sulfolane is increased at 17–22%, relative to 3–13% for α-diazo-β-oxo-sulfone **25**. This observation is consistent with enhanced efficiency of insertion at the benzylic C–H bond. The type of ester used (benzyl or methyl) did not impact detectably on the relative amounts of the isomeric products (**Table 4.1** and **Table 4.6**). For octyl and ethyl substrates **37** and **29**, the presence of the three major isomers is confirmed as pure samples of all three were obtained and fully characterised. The presence of *cis* sulfolane **139a** was tentatively assigned. The nature of the bisoxazoline ligand does not appear to impact on either the efficiency or the relative amounts of the various isomers for reactions with octyl and ethyl substrates **37** and **29**. While the presence of the *trans* thiopyran and *trans* sulfolane **28b** and **152b** were seen in the ^{1}H NMR spectra for benzyl substrate **27**, it was not possible to fully resolve/quantify these signals (**Table 4.6** entries 7-9). The preference for insertion at a benzylic C–H bond is clearly illustrated in **Figure 4.16**. Otherwise, there is little evidence for sensitivity to alteration of substituent at the site of insertion or indeed on the ester moiety.



Variation in product distribution with variation of substituent adjacent to the insertion site



*=OBn ester, in all other cases OMe ester

Figure 4.16

As illustrated in **Figure 4.17** and **Table 4.6**, the enantioselectivity of the C–H insertion process to form the *cis* thiopyran exhibited little or no sensitivity to variation of substituent at the site of insertion, with the highest enantioselectivities observed with the (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** ligands (90% and 79% ee respectively for octyl *cis* thiopyran **38a**, 97% and >99% ee respectively for ethyl *cis* thiopyran **30a**, 96 and 94% ee respectively for benzyl *cis* thiopyran **28a**) (**Table 4.6**, entries 1, 4, 7–8, 11–12) as described above for compound **25** where the insertion occurs at the benzylic C–H bond. The only point of difference is that, with the benzylic C–H insertion, the sensitivity to variation of the ligand was greater than in the other compounds **27**, **29**, **37** with insertion into an unactivated C–H bond. Thus, with the (4*S*)-*t*-Bu **138** and (4*R*)-Bn **43** ligands, while enantiopurities of methyl ester *cis* thiopyran **26a** dropped to 71% ee and 66% ee respectively, with the alkyl substituents at the site of C–H insertion the enantiopurities with the same ligand were ≥80% (81% and 80% ee respectively for octyl *cis* thiopyran **38a**, 92% and 87% ee respectively for ethyl *cis* thiopyran **30a**, 90 and 90% ee respectively for benzyl *cis* thiopyran **28a**) (**Table 4.6**, entries 2–3, 5–6, 9–10). Again variation of the methyl ester **25** to the benzyl ester **27** had no noticeable effect on enantioselection.

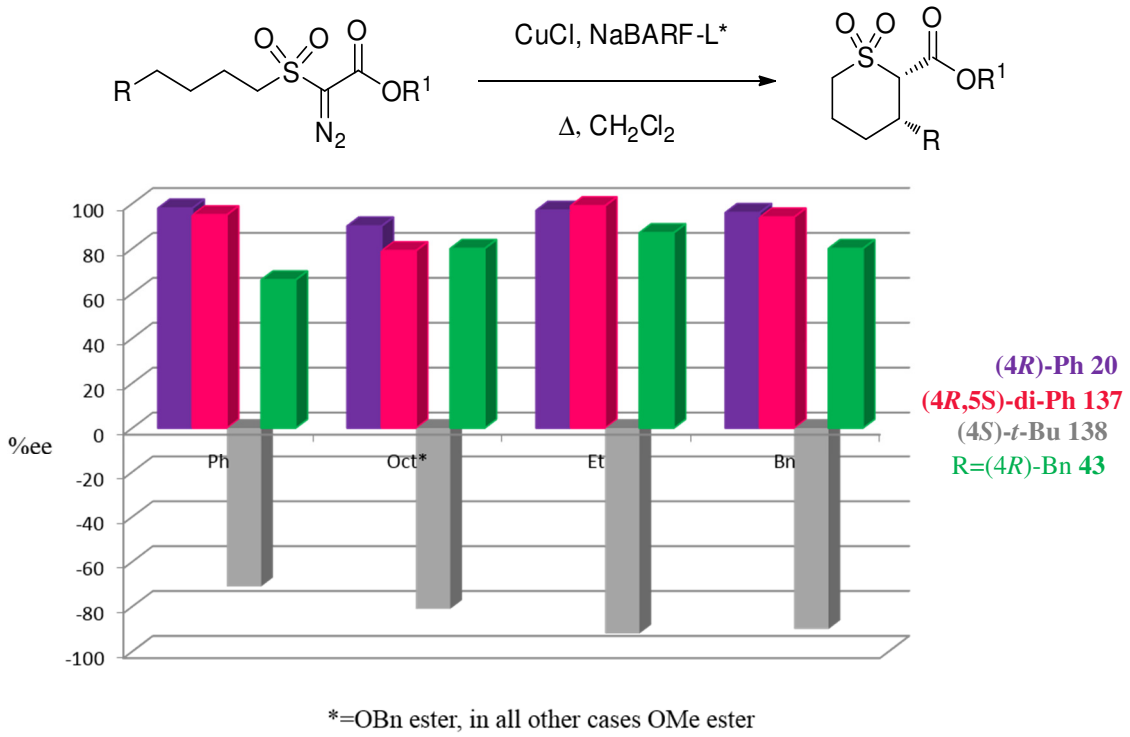


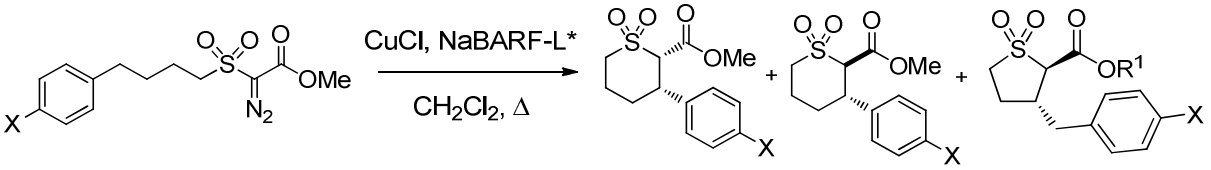
Figure 4.17 *Summary of enantiocontrol achieved with ligands* **20**, **43**, **137**, **138** *for substrates* ***26***, ***28***, ***30***, ***38(a)****; benzylic versus aliphatic C–H insertion site.*

Establishing the enantiopurities of the *trans* thiopyrans **38b** and **30b** isolated as a minor product proved possible; interestingly the enantiopurities were considerably lower for both octyl *trans* thiopyran **38b** (**Table 4.6**, entries 2–3, 11) and ethyl *trans* thiopyran **30b** (**Table 4.6**, entries 5–6) using the best result obtained with (4*S*)-*t*-Bu **138** in both cases with values of 59% ee and 57% ee being obtained for octyl and ethyl *trans* thiopyrans **38b** and **30b** respectively. The use of chiral rhodium catalysts also results in modest enantiopurities for *trans* thiopyrans, with 50% ee being the highest reported value for the synthesis of a *trans* thiopyran employing Rh_2(*S*-PTTL)$_4$ as catalyst.[42]

4.3.3 Exploration of the electronic impact at the site C–H insertion for the asymmetric the copper catalysed reactions of α-diazo-β-oxo sulfones

As there is firm evidence that insertion at the benzylic C–H bond is preferred, investigation of the influence of substituents on the aryl ring was next embarked on, as summarized in **Table 4.7**. Results formerly achieved by Flynn have been presented in **Table 4.7** to enable direct comparison to results achieved in this project (**Table 4.7**, entries 6–8).

Table 4.7 *Investigation into the electronic impact at the site C–H insertion for the asymmetric the copper catalysed reactions of α-diazo-β-oxo sulfone* **45**



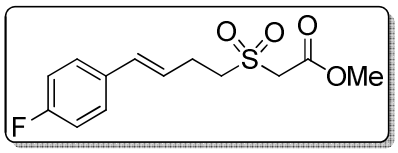
Entry	α-diazosulfone	X	Ligand	Crude efficiency (%)[a]	Time (h)	Crude ratio Purified Yield (%) % ee	*cis* thiopyran	*trans* thiopyran	*trans* sulfolane
1[b]	**45**	F	-	~30%[c]	48	**Crude** **Purified Yield (%)** **% ee**	78 24 (0% ee) **145a**	19 **145b**	3 **153b**
2	**45**	F	(4*R*)-Ph **20**	~75–80%	21	**Crude** **Purified Yield (%)** **% ee**	91 49 (98% ee) (2*S*,3*S*) **145a**	4 - - **145b**	5 - - **153b**
3	**45**	F	(4*R*)-di-Ph **137**	~75–85%	21	**Crude** **Purified Yield (%)** **% ee**	84 55% (98% ee) (2*S*,3*S*) **145a**	7 - **145b**	9 - **153b**
4	**45**	F	(4*S*)-*t*-Bu **138**	75–85%	48	**Crude** **Purified Yield (%)** **% ee**	84 52% (80% ee) (2*R*,3*R*) **145a**	12 -	5 -
5	**45**	F	(4*R*)-Bn **43**	~40%[d]	21	**Crude** **Purified Yield (%)**	84 25%	12 -	5 -

						% ee	(55% ee) (2*S*,3*S*) **145a**		
6[e]	**31**	Me	(4*R*)-Ph **20**	80–90%	5	**Crude** **Purified Yield (%)** **% ee**	**Exclusive product** 64% (96% ee) (2*S*,3*S*) **32a**	-	-
7[e]	**33**	OMe	(4*R*)-Ph **20**	80–90%	22	**Crude** **Purified Yield (%)** **% ee**	80 56% (91% ee) (2*S*,3*S*) **34a**	20 14% 12% ee	-
8[e]	**35**	NO_2	(4*R*)-Ph **20**	Not formed	2.5	**Crude**	Not formed	-	-

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product. Full details of how calculations were made for each compound can be found in the experimental chapter.
b. Catalyst conditions used here were different to the remaining entries on **Table 4.7**. $Cu(OTf)_2$ was the sole catalytic component used, for the purposes of generating a racemic sample.
c. There is approximately 6% hydride abstraction product **154** present in the crude reaction mixture
d. There is evidence for the presence of an X–H insertion product **155** and reduction product **112**.
e. Entries 6-8 on **Table 4.7** refer to previously published results and have been included here only for comparison. These results were not repeated during the course of this work.[1,2]

Previously, studies had been carried out on the effect of having electron donating groups (*p*-methoxy substrate **33** and *p*-methyl substrate **31**) as well as an electron withdrawing group (*p*-nitro substrate **35**) on the aryl ring adjacent to the C–H insertion site.[1,2] Results in this study were obtained using the (4*R*)-Ph ligand **20** (**Table 4.7**, entries 6–8), for comparison to data obtained for unsubstituted substrate **25** (**Table 4.1**, entry 1). There is evidence that both the efficiency of the C–H insertion and its enantioselectivity is sensitive to the electronic nature of the phenyl ring. Thus, in terms of efficiency, the C–H insertion is aided by the presence of electron donating groups, such as methyl and methoxy substituents (**Table 4.7**, entries 6–7), while no insertion is observed when the benzylic C–H bond is deactivated by the *para* nitro substituent (**Table 4.7**, entry 8). Throughout the series, C–H insertion to form the *cis* thiopyran predominates with the *trans* thiopyran and the *trans* sulfolane formed at low levels, similar to those seen for the phenyl derivative **25** in **Table 4.1**. There is some evidence that *cis* thiopyran formation is favored, relative to formation of other isomers, by the presence of the electron donating methyl group (**Table 4.7**, entry 6). In terms of enantioselectivity, there is a slight decrease in enantiopurity of the *cis* thiopyrans bearing the electron donating substituents on the aryl ring (98% ee for unsubstituted substrate **26a**, 96% ee for *p*-methyl **32a** and for 91% ee for *p*-methoxy **34a**) (**Table 4.1**, entry 1, **Table 4.7**, entries 6–7).

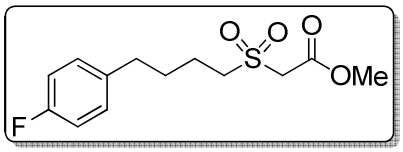
With these initial results in hand, a further substrate modification was explored during this work; the effect of having a weakly electron withdrawing fluorine group at the *para* position on the aryl ring was investigated. In the first instance a reaction was carried out employing $Cu(OTf)_2$ as the sole catalytic component to generate a racemic sample of *cis* thiopyran **145a** for the development of suitable chiral HPLC conditions; this reaction was characterized by a low reaction efficiency (~30%) (**Table 4.7**, entry 1), as was previously observed in the $Cu(OTf)_2$ mediated C–H insertion reactions of several other α-diazo-β-oxo sulfones.[2] Amongst the variety of byproducts present in the crude reaction mixture, hydride abstraction product **154** was identified at a level of ~6% (**Figure 4.18**), which is another typical feature of $Cu(OTf)_2$ mediated reactions. The mode of formation of this product has been previously discussed in **Section 4.1.3**. Chromatographic purification of the crude reaction mixture afforded *cis* thiopyran **145a** in 24% yield, in sufficient quantities for the successful development of chiral HPLC conditions. As *cis* thiopyran **145a** was a novel compound, it was fully characterized employing ^{1}H NMR, ^{13}C NMR, IR spectroscopy and high resolution mass spectrometry.



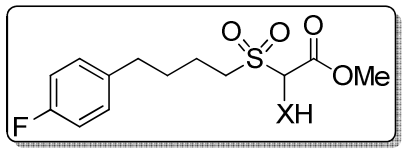
154

Figure 4.18

Results obtained during the course of this work are largely similar to those achieved for unsubstituted substrate **26a** in terms of efficiency, regio and enantioselectivity (**Table 4.7**, entries 2-5 *cf.* **Table 4.1**, entries 1–5). High reaction efficiencies of ≥80% with *cis* thiopyran **145a** accounting for ≥80% of the C–H insertion mixture, with relatively low levels of *trans* thiopyran **145b** and *trans* sulfolane **153b** observed. The one exception to this trend was cyclisation of *p*-fluoro compound **45**, in the presence of benzyl substituted ligand (4*R*)-Bn **43** (**Table 4.7**, entry 5); while the relative formation of all three isomers **145a**, **145b** and **153b** was consistent with the previously observed trend, the reaction efficiency obtained was much lower at ~40%. This may be accounted for by the presence of additional side products; namely β-oxo-sulfone (reduction product **112**) and the presence of an X–H insertion product **155** (**Figure 4.19**).



112



155

Figure 4.19

The best enantioselectivity attained during the course of this ligand study was 98% ee in the presence of phenyl substituted ligand (4*R*)-Ph **20** (**Table 4.7**, entry 2), which is identical to that achieved for aryl compound **26a** (**Table 4.7**, entry 1). As displayed in **Figure 4.20**, the ligand study undertaken for the 4-fluoro series (**Table 4.7**, entries 2–5) exhibits very similar enantioselectivities, across the ligand series, to those seen with the unsubstituted phenyl derivative **26a** with very similar sensitivity to ligand variation (**Table 4.7**, entries 2–5, *cf* **Table 4.1** entries 1–5).

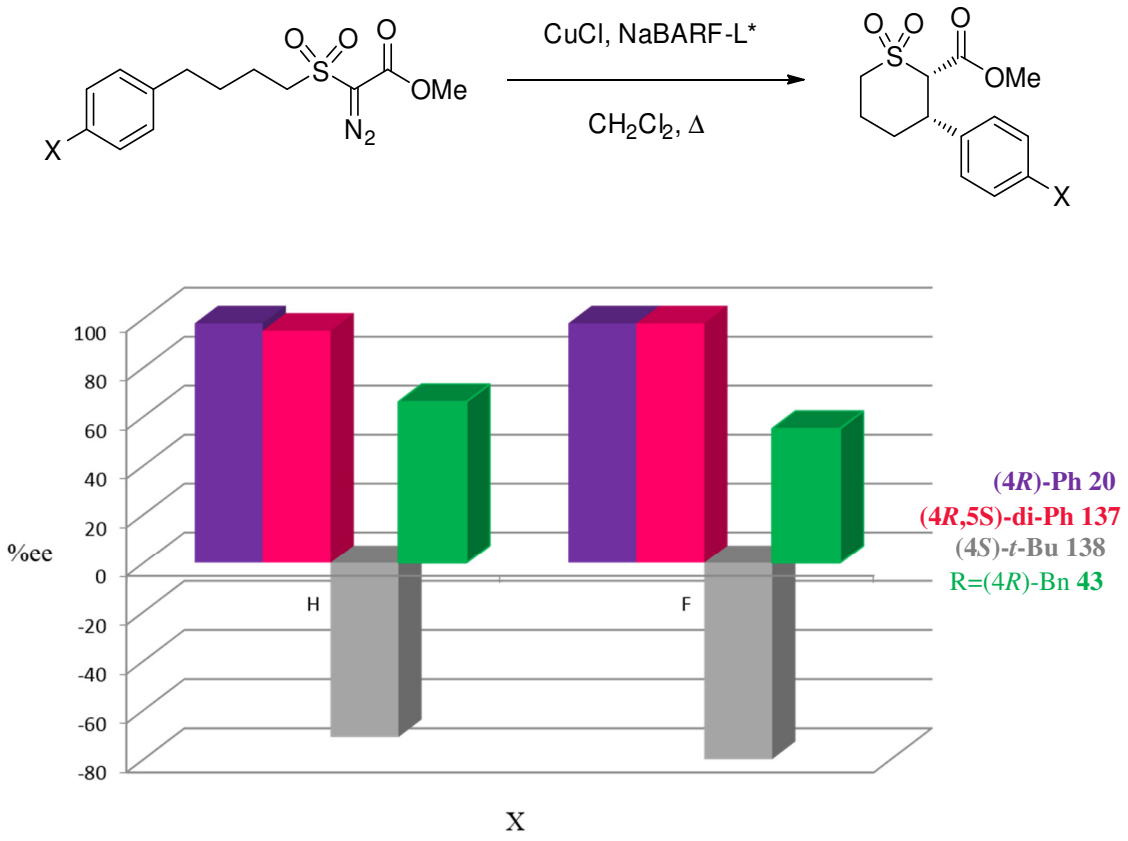
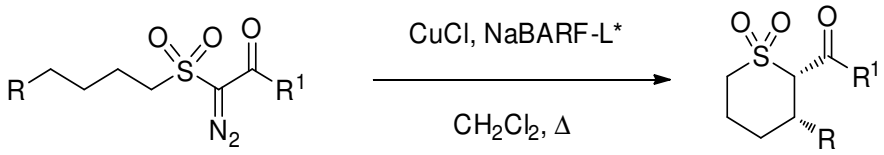
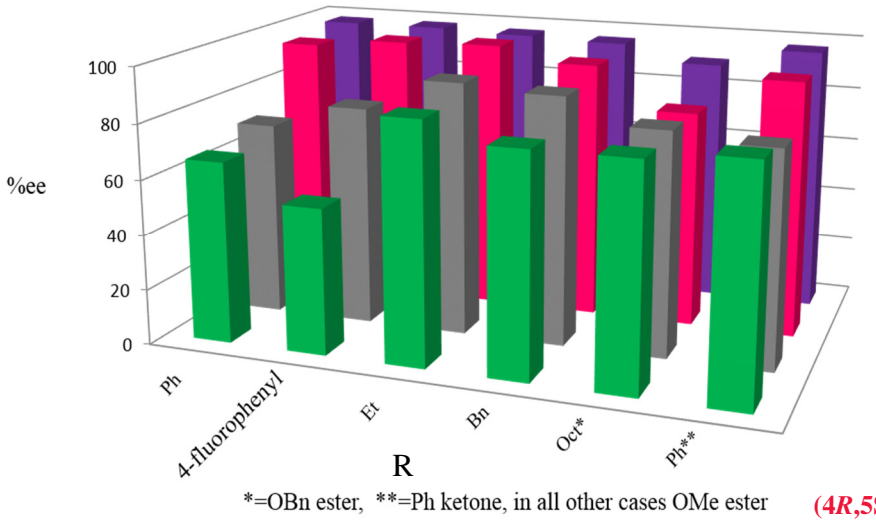


Figure 4.20

The influence of variation of substituents and ligands on enantioselectivity of the C–H insertion to form the *cis* thiopyrans is summarised in **Figure 4.21**, clearly showing the trends discussed above. It is clear that the (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** substituted ligands are superior in terms of enantiocontrol. While the (4*S*)-*t*-Bu **138** and (4*R*)-Bn ligand **43** lead to lower enantioselectivities the sensitivity to ligand variation is dependent on the nature of the substituent at the site of insertion. In contrast, optimum enantioselectivities in the cyclopentanone series were obtained with (4*R*)-Bn ligand **43** (up to 82% ee) and (3*S*,8*R*)-Ind ligand **44** (up to 89% ee), indicating a significant difference in the transition state for the two insertion processes.[3]





(4*R*)-Ph 20
(4*R*,5S)-di-Ph 137
(4*S*)-*t*-Bu 138
R=(4*R*)-Bn **43**

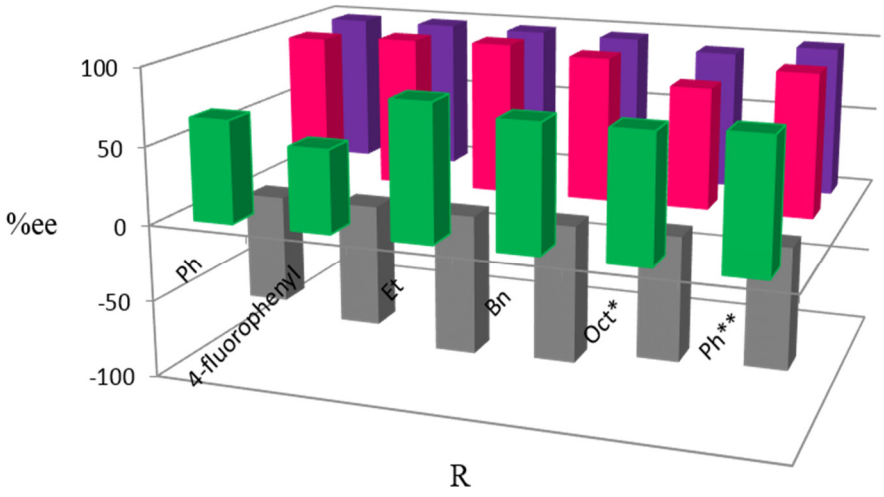
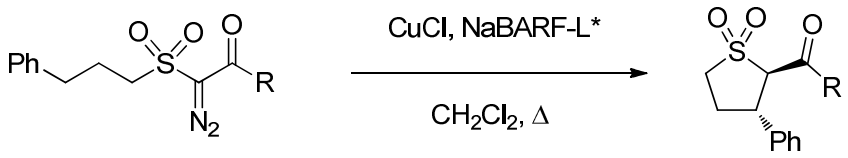


Figure 4.21 *Ligand effect on enantiopurity of* cis *thiopyrans for substrates* ***22***, ***24***, ***26***, ***28***, ***30***, ***38***, ***145***

4.3.4 Effect of shortening the alkyl chain, sulfolane formation

Having investigated the enantioselective C–H insertion process to form the *cis* thiopyrans in detail, attention was next turned to enantioselective C–H insertion to form the sulfolanes **42b** and **40b** from the shorter chain α-diazo-β-oxo-sulfones **41** and **39**, in which six-membered ring formation is impossible. The last four entries on **Table 4.8**, entries 7-10 were not carried out during the course of this work, and come from a previous project.[1,2] Entries 7 and 8 are entered here merely to contrast and compare to results obtained in this project, while entries 9 and 10 refer to reactions employing racemic catalyst that were carried out for the purpose of generating racemic samples of **42b** and **40b** to obtain suitable conditions for chiral HPLC analysis, which were the conditions employed in this project.

Table 4.8 *Asymmetric copper-bisoxazoline catalysed reactions of α-diazo-β-oxo sulfones **41** and **39***



Entry	α-Diazosulfone	Sulfolane	R	L*	Time (h)	Crude Efficiency (%)[a]	*trans* Sulfolane Yield (%) (% ee)
1	**39**	**40b**	OEt	(4*R*,5*S*)-di-Ph **137**	48	80-90 **(50:50, *cis*:*trans*)**	69 (65% ee) (2*R*,3*S*)
2	**39**	**40b**	OEt	(4*S*)-*t*-Bu **138**	3	80–90	61 (0% ee) (2*S*,3*R*)
3	**39**	**40b**	OEt	(4*R*)-Bn **43**	26	80–90	53 (5% ee) (2*R*,3*S*)
4	**41**	**42b**	Me	(4*R*,5*S*)-di-Ph **137**	21	70–80	19 (36% ee) (2*R*,3*S*)
5	**41**	**42b**	Me	(4*S*)-*t*-Bu **138**	26	80–90	53 (51% ee) (2*S*,3*R*)
6	**41**	**42b**	Me	(4*R*)-Bn **43**	21	80–90	33 (59% ee) (2*R*,3*S*)
7[b]	**39**	**40b**	OEt	(4*R*)-Ph **20**	5	complex	57 (60% ee)[b] (2*R*,3*S*)
8[b]	**41**	**42b**	Me	(4*R*)-Ph **20**	3	~60	40 (40% ee)[b] (2*R*,3*S*)
9[b,c]	**39**	**40b**	OEt	-		11	0
10[b,d]	**41**	**42b**	Me	-		43	0

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product. Full details of how calculations were made for each compound can be found in the experimental chapter.
b. Entries 7-10 on **Table 4.8** refer to previously published results and have been included here only for comparison. These results were not repeated during the course of this work.
c. Reaction was previously carried out by Flynn employing $Cu(OTf)_2$ as the sole catalytic component for the generation of a racemic sample of *trans* sulfolane **40b**, which was recovered with ~15% impurities.
d. Reaction was previously carried out by Flynn employing $Rh_2(OAc)_2$ in toluene for the generation of a racemic sample of *trans* sulfolane **42b**.

The insertion efficiencies were in line with those seen previously in **Tables 4.1**, **4.5**, **4.6** and **4.7**. As summarised in **Table 4.8**, the enantiopurities achieved for the *trans* sulfolanes **40b** and **42b** (<65 % ee) were appreciably lower than those seen for the *cis* thiopyrans. Interestingly, the effect of varying the ligand in this series was sensitive to the nature of the substituent on the diazosulfone. Thus, for the ethyl ester **40b**, the highest enantioselection was obtained for the (4*R*)-Ph and (4*R*,5*S*)-di-Ph substituted ligands **20** and **137** (60 and 65% ee respectively) (**Table 4.8**, entry 7 and 1), as seen earlier across the thiopyran series (**Figure 4.21**), while employing the (4*S*)-*t*-Bu and (4*R*)-Bn substituted ligands **138** and **43**, led to essentially racemic samples of the sulfolane (**Table 4.8**, entries 2 and 3). Intriguingly, for the methyl ketone substrate **42b**, the best enantioselection was seen with the (4*R*)-Ph **43** (59% ee) and (4*S*)-*t*-Bu **138** (51% ee) ligands (**Table 4.8**, entries 3 and 2) with lower enantiopurities achieved using the phenyl and di-phenyl substituted ligands **20** and **137** (**Table 4.8**, entries 4 and 8). While this switch in ligand effect is interesting, as illustrated in **Figure 4.22**, the absolute differences in terms of enantioselectivity in the methyl ketone series are relatively small, so the contrast in behaviour should not be overstated.

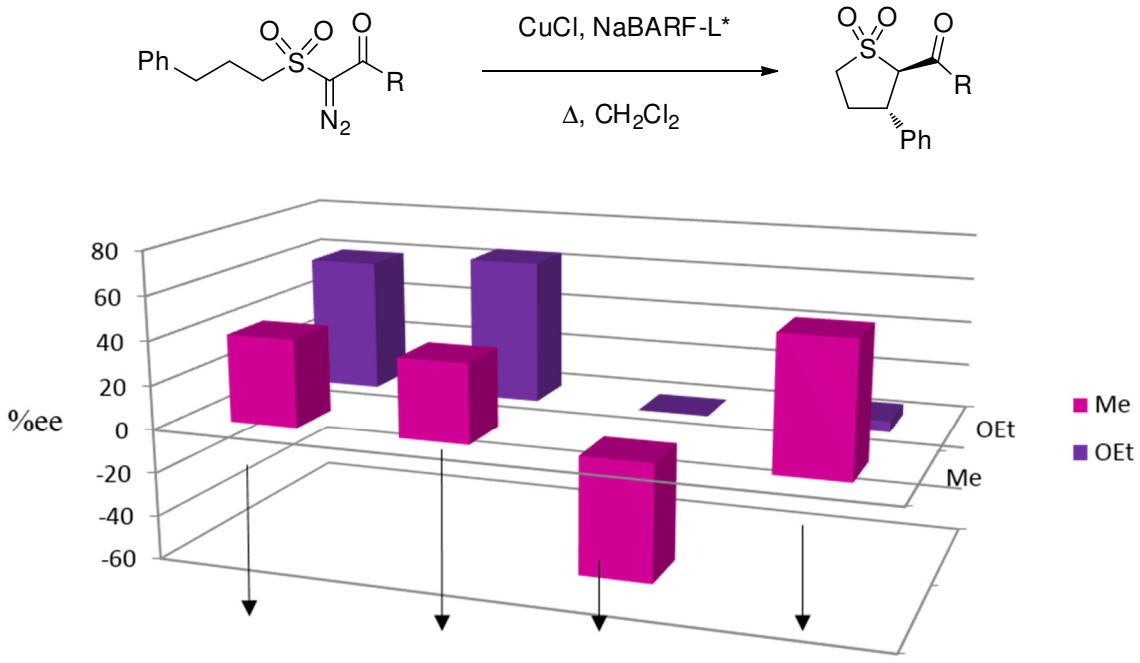
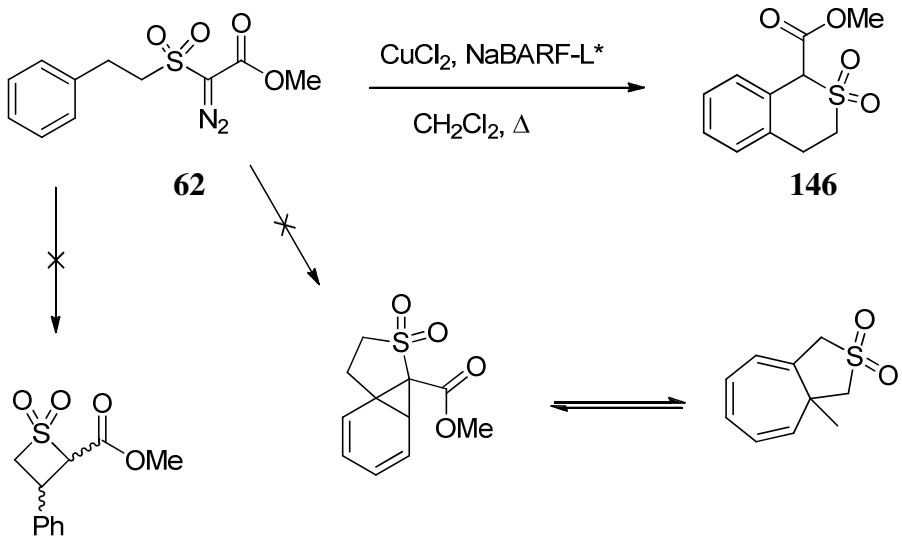


Figure 4.22 *Effect of ligands* **20**, **43**, **137**, **138** *on the enantiopurity of* trans *sulfolane compounds* **42b** *and* **40b**

4.3.5 Impact of a further shortened alkyl chain, dioxothietane formation.

Having explored the synthesis of both thiopyrans and sulfolanes, through C–H insertion reactions of several α-diazo-β-oxo-sulfones, attention was subsequently focused on the potential synthesis of dioxothietanes.



62 **146**

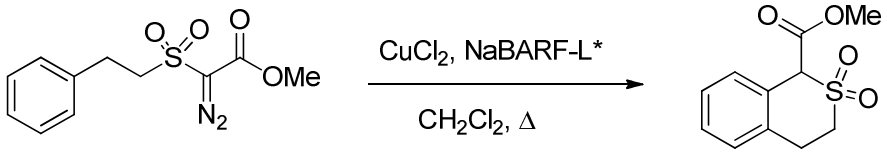
156 **157**

Scheme 4.9

In our previous studies, the presence of four membered rings containing the sulfone moiety had not been detected. Cyclisation of α-diazosulfonyl ester **62** was explored to establish if C–H insertion to form the highly strained dioxothietane could compete with alternative reaction pathways, including aromatic addition to form norcaradiene **157** or aromatic substitution to form fused thiopyran **146**.

Copper catalysed reaction of the short chain α-diazo-β-oxo-sulfone **62** was explored with each of the ligands **20**, **43**, **137**, **138** as shown in **Table 4.9**.

Table 4.9 *Aromatic C–H insertion*



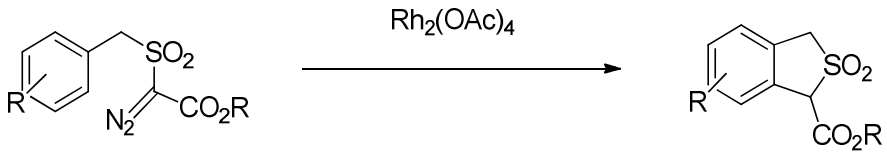
62 **146**

Entry	Crude Efficiency[a]	Ligand	Time (h)	Yield (%)	ee (%)
1	~80–90%	(4*R*)-Ph **20**	2	70	0
2	~85–90%	(4*R*,5*S*)-di-Ph **137**	2	68	0
3	~80–90%	(4*S*)-*t*-Bu **138**	3	69	0
4	~80–90%	(4*R*)-Bn **43**	2	66	0

a. Efficiency and relative ratios of isomers calculated from the ^{1}H NMR spectra of the crude product, details of which can be found in the experimental section.

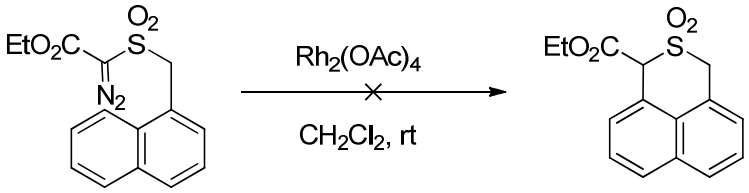
The results of this study clearly show that dioxothietane was not formed when α-diazo-β-oxo sulfone **62** was exposed to copper bisoxazoline catalysts. The main product of these reactions was revealed to be aromatic C–H insertion product **146** (**Scheme 4.9**). The aromatic insertion proceeded efficiently to form methyl isothiochroman-1-carboxylate 2,2-dioxide **146**, with no evidence for C–H insertion at the benzylic position to yield the dioxothietane ring **156** or aromatic addition to form **157** (**Table 4.9**, entries 1–4). As the stereogenic centre in thiochromanone is very labile, the product was obtained in racemic form (**Table 4.9**, entries 1–4). A deliberate racemic sample of product **146** was not prepared in this work, however, HPLC analysis of all four samples showed the presence of two peaks, obtained in a 50:50 ratio in all cases. Durst and co-workers reported a similar rhodium catalysed aromatic addition to form 1-carboalkoxy-l,3-

dihydrobenzo[b]thiophene-2,2-dioxides derivatives from benzylsulfone precursors (**Scheme 4.10**).[43]



Scheme 4.10

However, when Novikov and co-workers attempted a similar transformation, insertion into an aromatic C–H bond was not observed (**Scheme 4.11**).[19]



Scheme 4.11

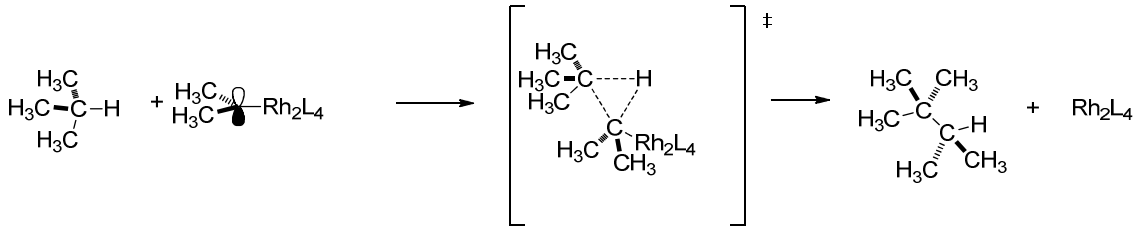
4.4 Concluding remarks

Excellent enantioselectivities were achieved for the asymmetric copper-bisoxazoline catalysed C–H insertion reaction of a range of α-diazo-β-oxo sulfones, in the synthesis of *cis* thiopyrans building on an exciting preliminary study within our research team. It was discovered that each of the catalytic components of the CuX-additive-ligand mixture plays an essential role in the successful outcome of C–H insertion reactions leading to *cis* thiopyrans; the copper source has an impact on reaction time, the additive affects the reaction efficiency, and the nature of the bisoxazoline ligand impacts on the enantiopurity of the *cis* thiopyran products. *cis* Thiopyrans are the major reaction products, but minor amounts of other isomers are also formed, the extent of which is substrate dependant. *cis* Thiopyran formation is most effective through insertion into a benzylic C–H bond; when the site of insertion is not benzylic, greater amounts of *trans* sulfolane products are formed. In substrates where C–H insertion to form *cis* thiopyran is not possible due the absence of an appropriate C–H bond, *trans* sulfolanes are formed instead, however with significantly lower enantiopurities. When insertion cannot proceed to form either *cis* thiopyrans or *trans* sulfolanes, insertion to form four membered rings is not seen, but

instead aromatic C–H insertion results. In general, the highest enantioselectivity in *cis* thiopyran formation is seen through use of the bisoxazoline ligands bearing phenyl (4*R*)-Ph **20** or di-phenyl (4*R*,5*S*)-di-Ph **137** substituents.

4.5 Copper and rhodium catalysts- mechanism of C–H insertion and transition states.

A transition metal catalysed C–H insertion reaction of a diazo compound is generally believed to proceed *via* three main steps; firstly the nucleophilic diazo substrate attacks the catalyst, which after nitrogen extrusion results in metal carbene formation.[8] Steps two and three are C–H activation and C–C bond formation and are believed to occur in a single step. A detailed discussion of the mechanism of rhodium(II) catalysed C–H insertion reactions of diazo substrates has appeared numerous times in the literature. Doyle and co-workers proposed a mechanism where the electrophilic metal carbenes p-orbital overlaps with the σ-orbital of the C–H bond undergoing insertion, followed by formation of the C–C and C–H bond as Rh_2L_4 catalyst dissociates as depicted in **Scheme 4.12**.[44] This mechanism is characterised by a three centred, two electron concerted transition state.



Scheme 4.12[44]

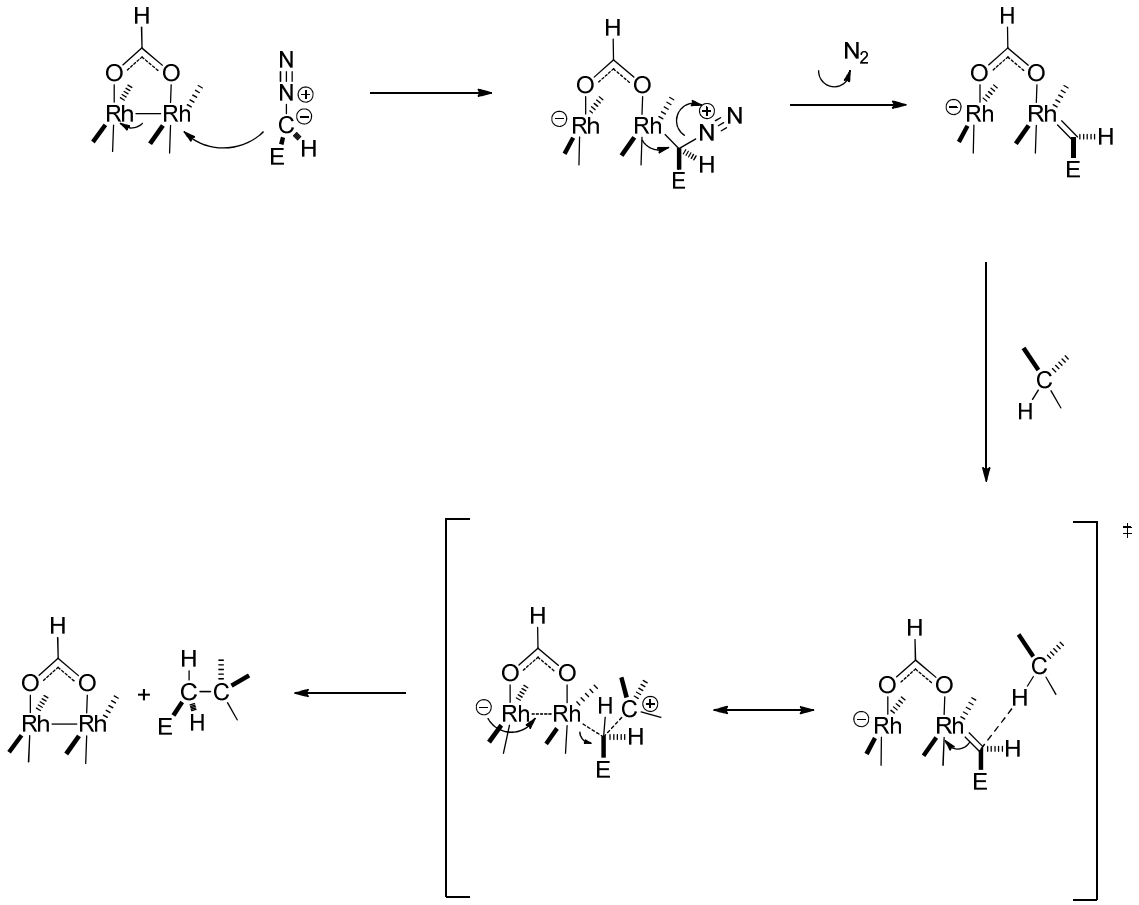
Taber and co-workers proposed a four centred transition state where an interaction between a rhodium atom and the hydrogen atom was proposed (**Scheme 4.13**).[45]



Scheme 4.13[45]

A more accurate transition state model was put forward by Nakamura and co-workers, which was based on high level computational studies. Initially, the diazo compound

interacts with the rhodium complex, resulting in cleavage of the Rh–Rh bond. An electrophilic metal carbene is formed following nitrogen extrusion brought about by back donation by rhodium. A hydride is then transferred from the alkane to the carbene atom, a C–C bond is generated and the Rh–Rh bond re-forms, resulting in production of the C–H insertion product (**Scheme 4.14**).[46]



Scheme 4.14[46]

In addition to these factors, there are a number of additional features to be considered for the intramolecular C–H insertion reaction. Taber and Nakamura have proposed models to explain the preferential five-membered ring formation of these reactions. Nakamura proposed a half chair transition state conformation, leading to C–H insertion (**Figure 4.23**). Nakamura explained the preferential *trans* stereochemistry by reasoning that, in the model leading to the *trans* isomer, the insertion centre substituent lies in the more stable pseudoequatorial position, while in the model leading to the *cis* isomer, the substituent occupies the sterically hindered axial position (**Figure 4.23**). This leads to an energy gap between the two transition states, which accounts for the preferred *trans* pathway. This observation will be discussed in again Chapter 6, where *trans* ɣ-lactams products are formed.

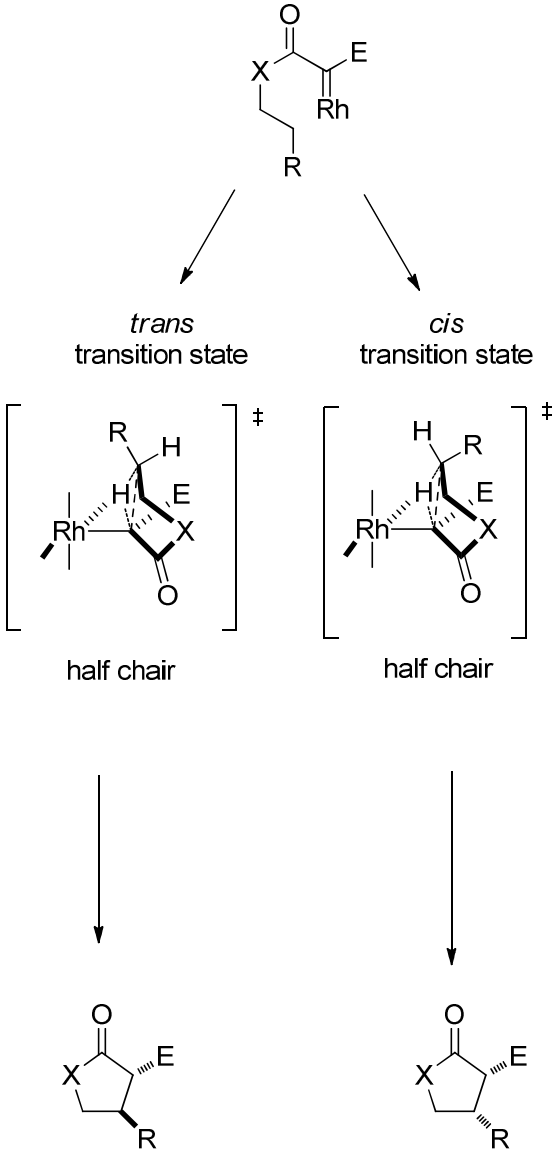


Figure 4.23

In certain instances, five-membered rings are not the preferred outcome. For instance as earlier discussed in this chapter, when α-diazo-β-oxo sulfone compounds undergo copper catalysed C–H insertion, six-membered thiopyran rings are the major reaction products, while formation of five-membered sulfolanes is possible. This has been rationalised due to the bond angles and geometry around the C-SO_2-C bond.[20] In general, *trans* sulfolanes and *cis* thiopyrans are the major reaction products for the copper catalysed reactions. Flynn explained this using the following diagrams.[2]

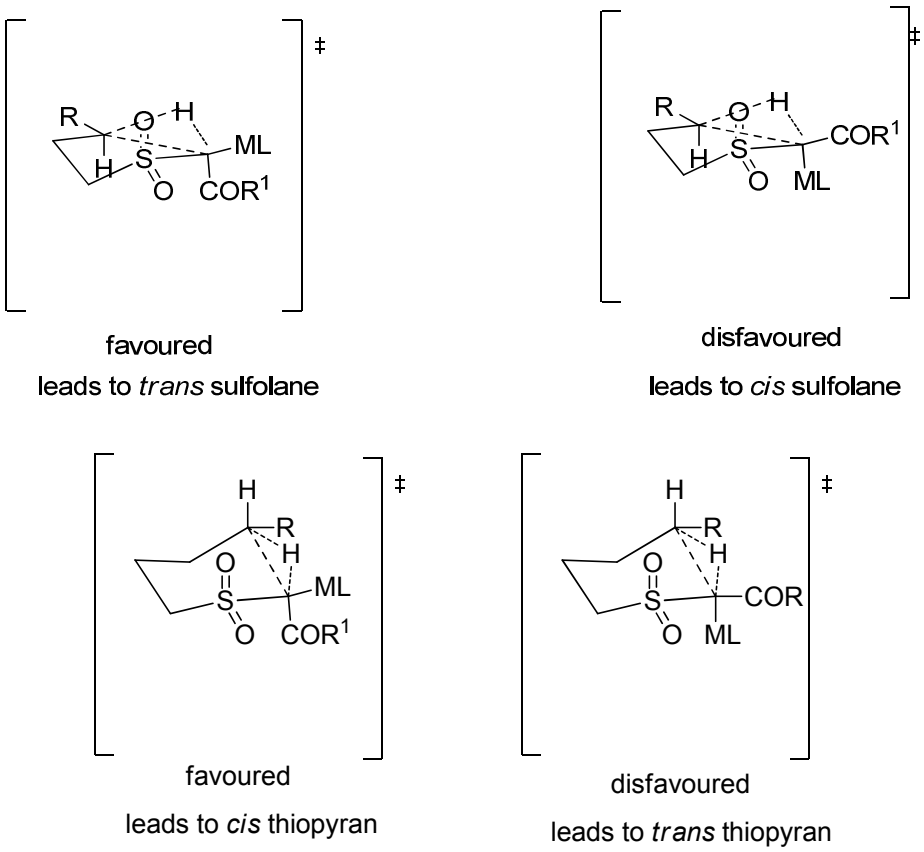


Figure 4.24

Both transition states proceed *via* a pseudo chair conformation. At the site of C–H insertion, the alkyl substituent R adopts the less sterically hindered equatorial position and the diastereoselectivity is then determined by the relative stability of the transition states illustrated in **Figure 4.24**; it appears that the bulky metal catalyst in the pseudo equatorial position is preferred.

In contrast to the rhodium catalysed reaction, the mechanism of the copper catalysed C–H insertion reaction is poorly studied. Transition state models for the copper catalysed intramolecular C–H insertion reactions of α-diazocarbonyl compounds which lead to cyclopentanone, thiopyran and sulfolane formation have been proposed by Slattery and Flynn, in an attempt to better understand factors that lead to high enantiocontrol.[2,3] As a basis for these proposed models, examination of the well-studied transition state model of copper-bisoxazoline catalysed cyclopropanation reaction was undertaken in an attempt to rationalise the C–H insertion reaction. Following on from an early model proposed by Pflatz and co-workers, Fraile and co-workers carried out theoretical studies to propose a model to explain the stereochemical outcome of the reaction.[36,47]

Following formation of the carbenoid complex (ligand)Cu=CHCO$_2$Me, there is approach of the alkene substrate, with subsequent insertion into the alkene double bond. In the proposed model, steric factors largely dictate the adopted geometry of the complex; it is desirable for the R groups on the ligand to avoid interactions with the ester group. Therefore, the carbene substituents adopt a perpendicular position to the copper-bisoxazoline ligand plane. The alkene can approach the Cu=C-C plane from two positions; the *Re* or the *Si* face. The stereochemical outcome of the reaction (*R* or *S*) is dictated by which face the alkene attacks from. The two possible modes of attack are presented in **Figure 4.25**. In this instance, interaction between the oxygen atom of the ester and the "R" substituents of the bisoxazoline ligand is the main steric factor for the basis of the stereochemical outcome of this reaction. As more steric hindrance is encountered from the *Si* face, attack from the *Re* face is preferred as shown in **Figure 4.25**.[36,47,48]

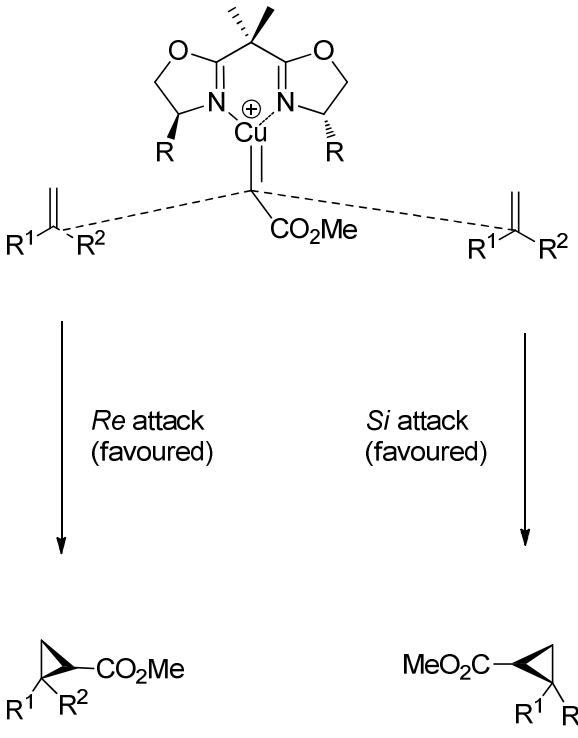


Figure 4.25 *adapted from ref* [36]

Slattery and Flynn applied this logic to the C–H insertion reactions of α-diazo-β-oxo sulfone compounds. As can be seen in **Figure 4.26**, the C–H bond can approach either one of the two non-equivalent faces of the chiral carbene complex. The diastereoselectivity is controlled by the orientation of the R group of the diazo precursor, which can be *cis* or *trans* with respect to the carbonyl substituent. Insertion occurs into one of the two prochiral hydrogens, the bond into which it inserts is dictated by the steric effects of the R substituent. The enantioselectivity is determined by facial selectivity of the carbenoid, *i.e.* the reacting C–H may approach from either the *Re* of the *Si* face, each one leading to a different enantiomer.

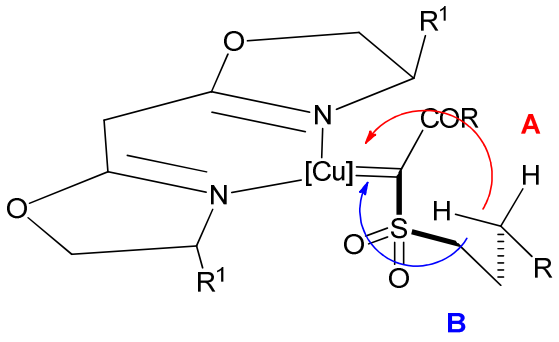
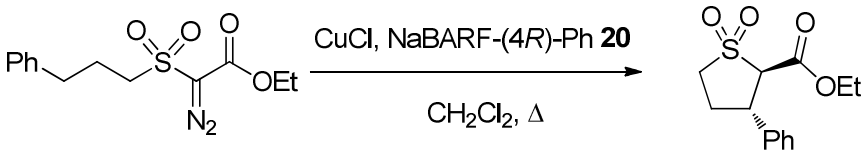


Figure 4.26

The absolute stereochemistry of the *trans* sulfolane compound **40b** was previously determined by Flynn. For reaction of ethyl ester diazo ester **39** in the presence of CuCl-NaBARF-(4*R*)-Ph **20** (**Scheme 4.15**), the absolute stereochemistry of the resulting sulfone compound **40b** was determined to be 2*R*,3*S*. The absolute stereochemistry of the methyl ketone *trans* sulfolane **42b** was then assigned by analogy.

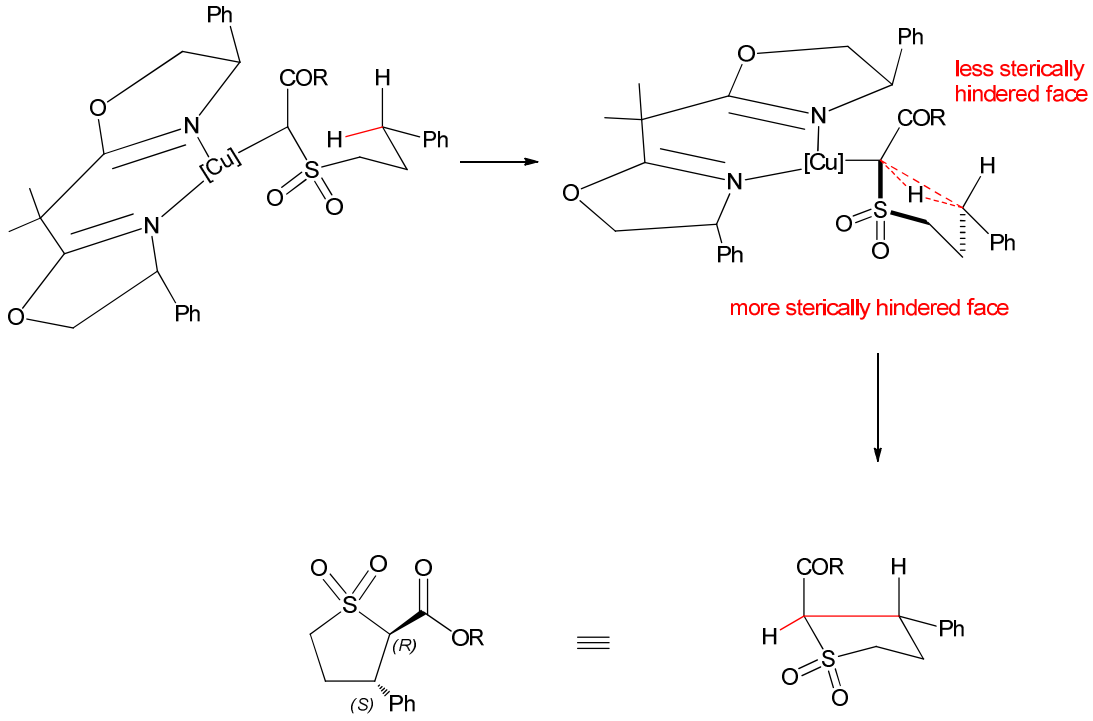


39 **40b**

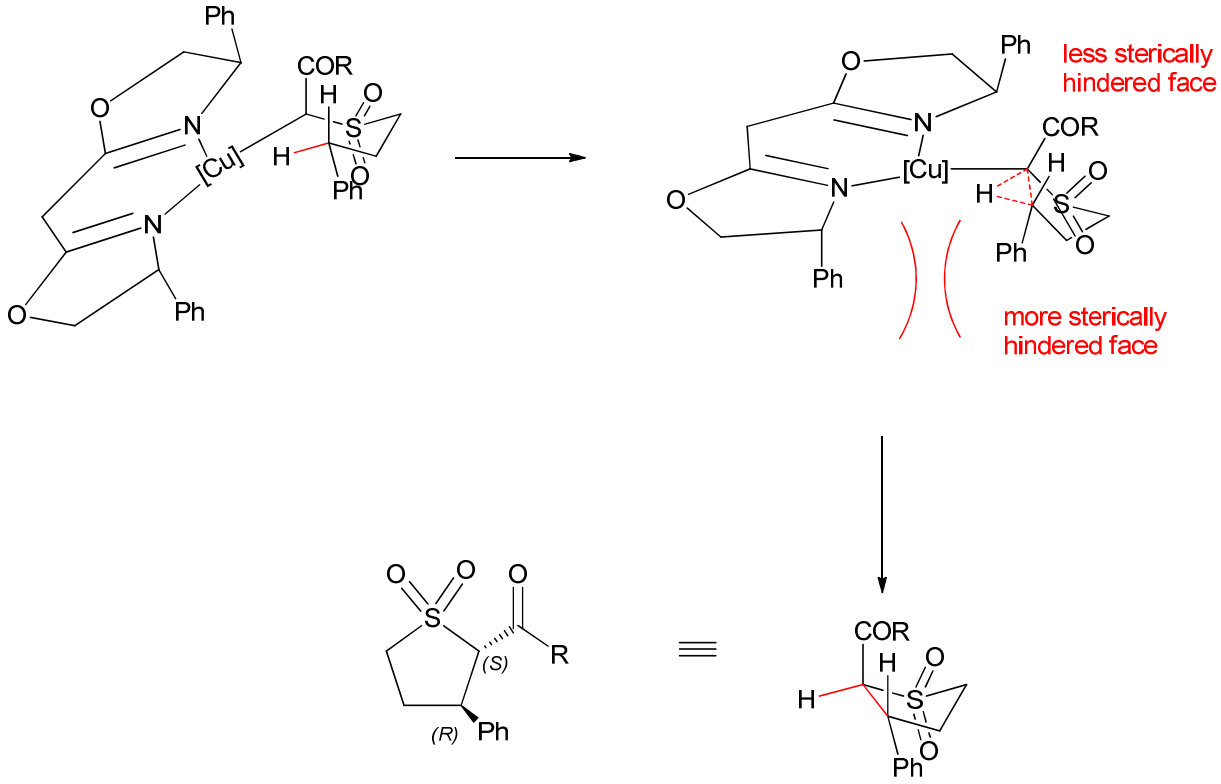
Scheme 4.15

The origin of enantioselectivity for the *trans* sulfolane compounds, arising from reaction in the presence of CuCl-NaBARF-(4*R*)-Ph **20**, can be rationalised through examination of the following transition state models. In the favoured transition state, illustrated in

Figure 4.27, the reacting C–H is approaching from the less sterically hindered face of the carbene. Unfavourable steric interactions, illustrated in the disfavoured transition state, account for the fact that C–H insertion is not likely to occur from this face.



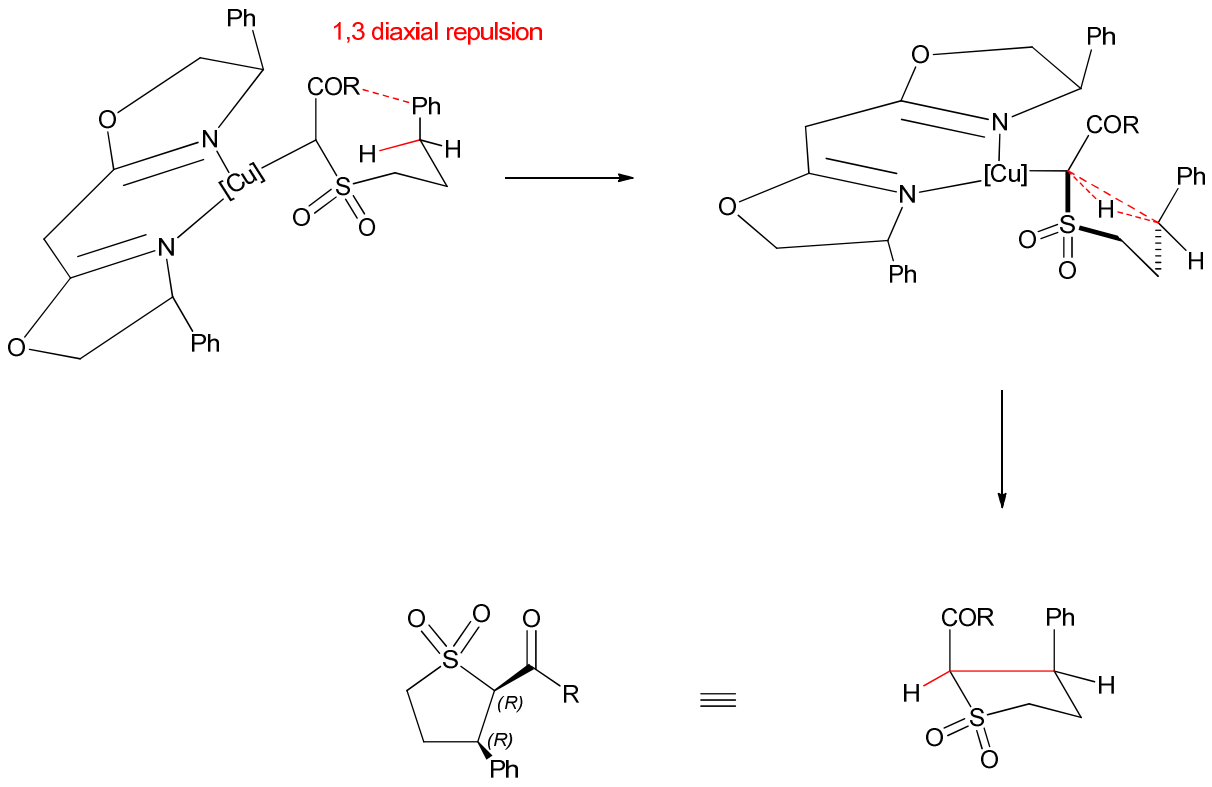
Favoured transition state: *the reacting C-H bond approaches from the less sterically hindered face of the carbenoid, leading to sulfolane with the observed stereochemistry*



Disfavoured transition state: *the reacting C-H appraoches the more sterically hindered face of the carbenoid leading to the "wrong" enantiomer.*

Figure 4.27

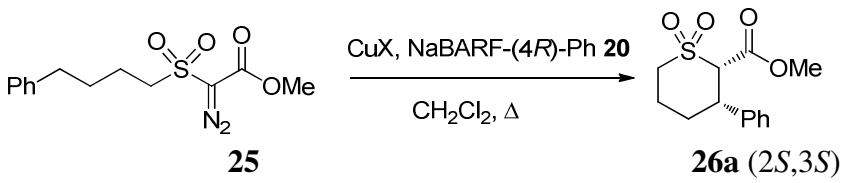
The diastereselectivity of this reaction can also be rationalised by examining the transition state depicted in **Figure 4.28**. The transition state leading to *cis* sulfolanes involves unfavourable 1,3 steric interactions, which are not present in the transition state leading to *trans* sulfolanes.



Transition state leading to the *cis* isomer: *Insertion may occur into two C-H bonds; when the bulky Ph group occupies the axial position, the* cis *iomer arises and when the bulky Ph group occupies the equatorial position the* trans *isomer arises. As can be seen above, unfavourable steric interactions occur when the Ph group is in the axial position thus making the cis isomer the disfavoured diasteromer.*

Figure 4.28

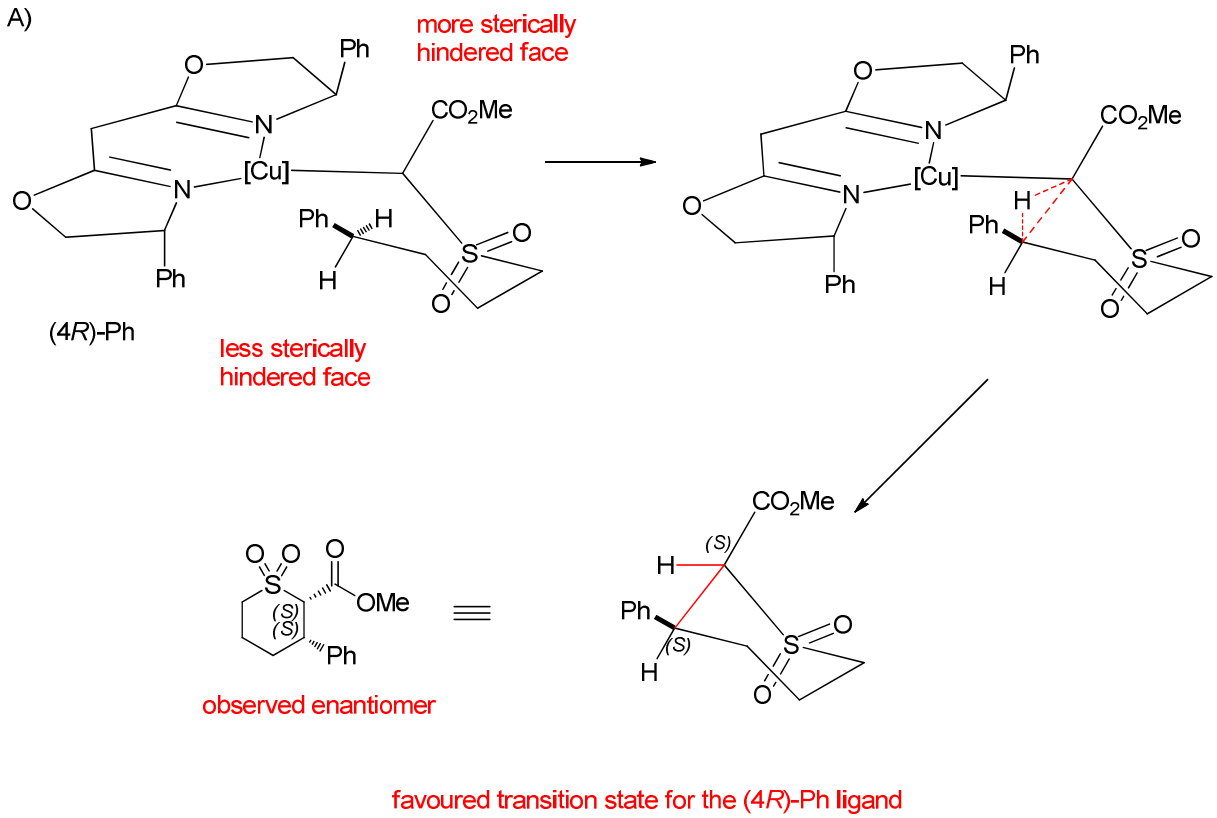
Excellent enantiocontrol is observed for the *cis* thiopyran series. Flynn determined the absolute stereochemistry of methyl ester *cis* thiopyran **26a** to be 2*S*,3*S* when methyl ester α-diazo-β-oxo sulfone **25** underwent C–H insertion, catalysed by CuCl-NaBARF-(4*R*)-Ph **20** (**Scheme 4.16**).



25 **26a** (2*S*,3*S*)

Scheme 4.16

The origin of the absolute stereochemistry can be understood on examination of the transition state, leading to this compound **26a** [**Figure 4.29 (A)**]. There are a few notable differences for the transition state leading the six-membered rings compared to five-membered ring systems. The extra length of the chain means that it cannot proceed through the same transition state as the sulfolane/cyclopentanone. The transition state twists such that the phenyl group at the end of the chain occupies the empty quadrant on the same face of the ligand plane as the ester substituent of the carbene. This physically causes the C–H insertion to proceed *via* the opposite face of the carbene to transition states leading to five-membered ring products. As can be seen in **Figure 4.29 (B)**, unfavourable steric interactions between the two phenyl groups disfavour the formation of the *trans* diastereomer. **Figure 4.29 (C)** illustrates for the enantiomer of the ligand that the formation of the (*S*,*S*) product is not favoured (*ergo* for the (4*R*)-Ph ligand the (*R*,*R*) product is *not* observed.]



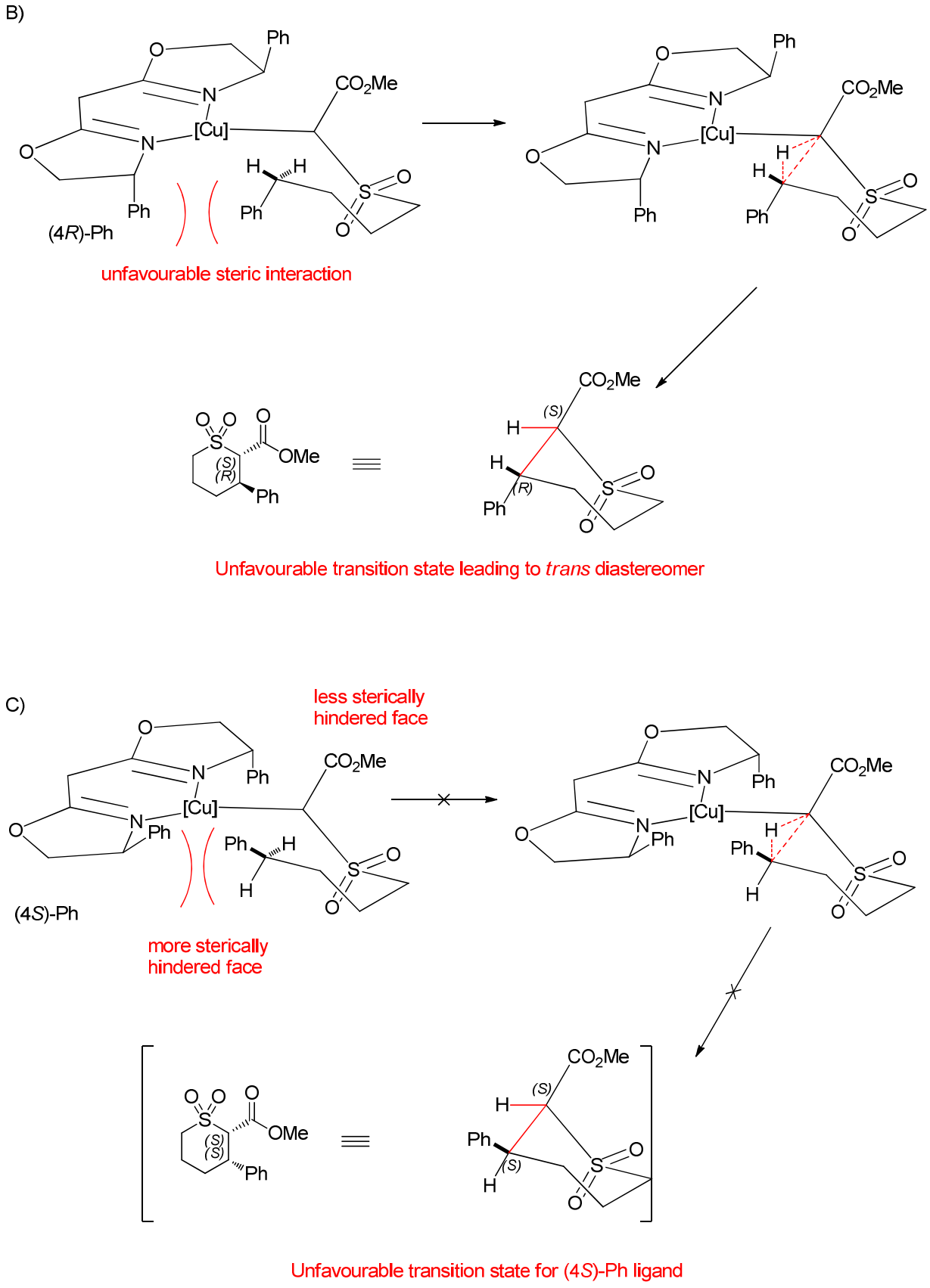

B)
(4R)-Ph
unfavourable steric interaction
Unfavourable transition state leading to trans diastereomer
C)
less sterically hindered face
(4S)-Ph
more sterically hindered face
Unfavourable transition state for (4S)-Ph ligand

Figure 4.29

4.6 Experimental

4.6.1 Purification of crude reaction mixtures

All crude reaction mixtures were purified using flash column chromatography. Purification of crude reaction material where the reactions were extremely efficient and were exceedingly selective was a relatively straight forward task, with separation of the product from the catalyst being the only real goal. However, if a reaction proceeded with a low efficiency and with a poor selectivity, the purification process was more challenging as individual isomers had to be separated from one another, as well as any byproducts. Both chromatography carried out by hand, as well as automated chromatography was employed during this project, the latter producing better overall separation. The ability to carry out slow gradual gradient elution is thought to be the main reason for this.

In general, analysis of the fractions of purified material was troublesome. The use of TLC analysis in conjunction with UV detection on the Varian gave moderate success. However, in general, the compounds were poorly UV active and visualisation of spots by staining TLC plates proved largely ineffective. Potassium permanganate was the stain that gave the most positive results. If results using these techniques was inconclusive, the individual fractions were concentrated and analysed using ^{1}H NMR spectroscopy. Full separation of isomers was not always possible, however, a pure fraction of material was generally obtained, in addition to mixed fractions. Except for a few isolated cases, separation of insertion products from byproducts was not problematic. It was necessary to use whatever means possible to obtain pure samples, as these had to be further analysed using chiral HPLC to determine enantiopurity. All compounds were obtained as colourless oils or white solids and were analysed using ^{1}H NMR spectroscopy, IR spectroscopy and chiral HPLC. In the case of novel compounds ^{13}C NMR spectroscopy and high resolution mass spectrometry were also used to analyse the compounds. Where relevant/possible elemental analysis and melting points were also obtained.

4.6.2 Copper and rhodium catalysed C–H insertion reactions of α-diazocarbonyl compounds

The following C–H insertion reactions gave rise to regioisomers and diastereomers (*cis* and *trans*). Throughout, *cis* isomers have been labelled as **a** and *trans* isomers have been

labelled as **b**. This method of naming *cis* isomers as **a** and *trans* isomers as **b** is used in subsequent Chapters 5-7, including for lactams and for cyclopropanes.

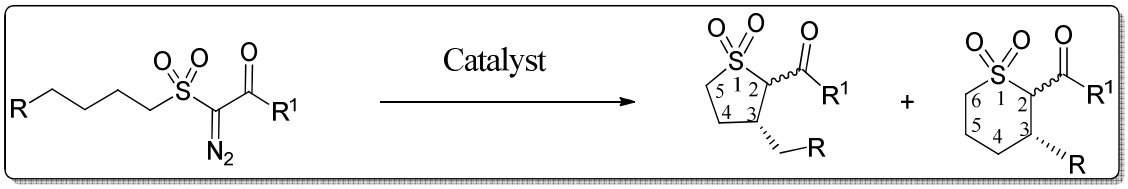


Figure 4.30

Within the copper C–H insertion reactions, enantioselection was achieved using a variety of commercially available bisoxazoline ligands; (+)-2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxzoline] **20**, (+)-2,2′-isopropylidenebis[(4*R*)-4-benzyl-2-oxzoline] **43**, 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxzoline] **138**, 2,2′-methylenebis[(4*R*, 5*S*)-4,5-diphenyl-2-oxazoline] **137**, (3aS,3′aS,8aR,8′aR)-2,2′- methylenebis[3a,8a-dihydro-8H-indeno[1,2-d]oxazole] **44** (**Figure 4.31**).

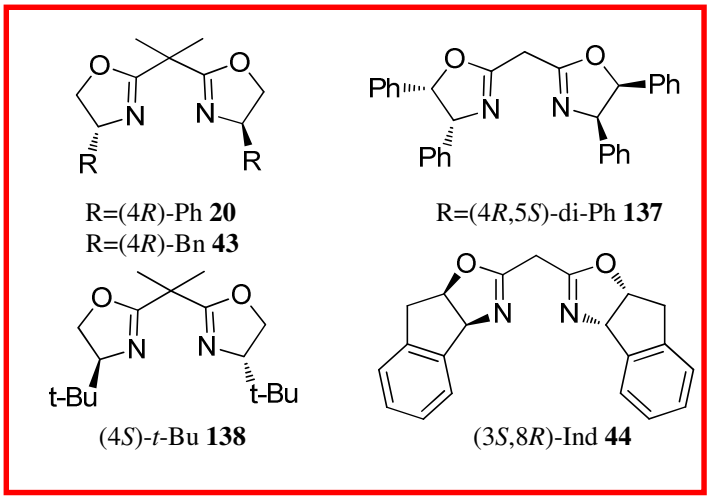


Figure 4.31

Occasionally commercially available chiral pybox ligands and semicorrin ligand were employed for the copper catalysed C–H insertion reactions and commercially available rhodium catalysts were also employed **Figure 4.32**.

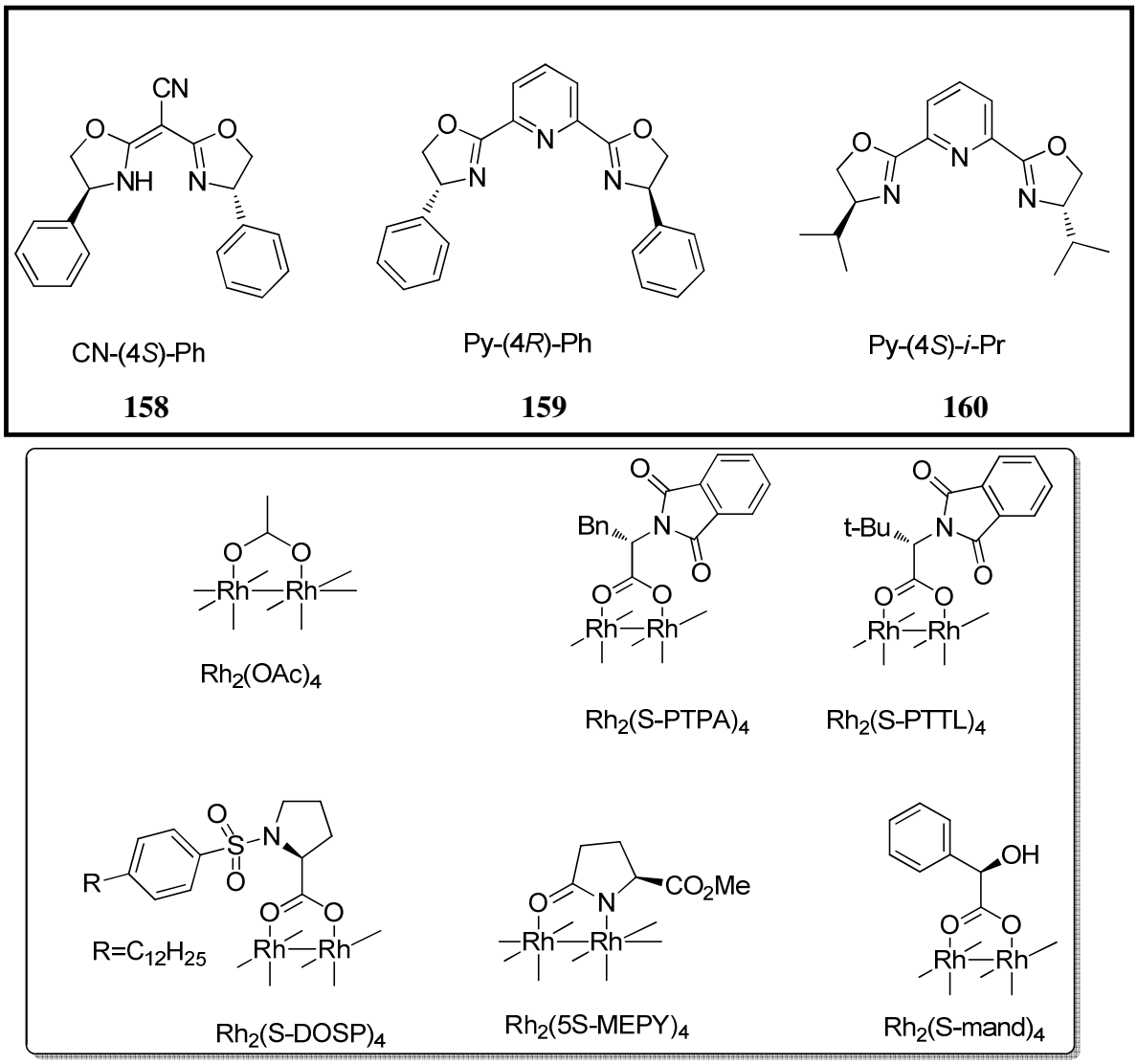


Figure 4.32

Note: shorthand ligand names used for convenience

Seven main modes of catalyst formation and α-diazocarbonyl addition were employed throughout this work;

Method A: Asymmetric copper catalysed intramolecular C–H insertion reactions: Direct addition.

The copper source, the additive and the chiral ligand were suspended/dissolved in distilled dichloromethane. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this. The contents of the reaction flask were then heated directly to reflux under an atmosphere of nitrogen. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^1H NMR spectroscopy. The crude product mixture was then adsorbed onto silica. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~ 2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

Method B: Asymmetric copper catalysed intramolecular C–H insertion reactions: Pre-forming the catalyst

The copper source, the additive and the chiral ligand were suspended/dissolved in doubly distilled dichloromethane, heated to reflux under an atmosphere of nitrogen and stirred under reflux for 2 h. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this over ~ 20 min. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^1H NMR spectroscopy. The crude product mixture was then adsorbed onto silica. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

Method C: Achiral copper catalysed intramolecular C–H insertion reactions- [$Cu(OTf)_2$]

$Cu(OTf)_2$ (5 mol%) was suspended/dissolved in dichloromethane at room temperature. The resulting mixture was heated to reflux under an atmosphere of nitrogen. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this over ~ 5 min. The progress of the reaction was monitored by IR spectroscopy; the reaction was

deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^1H NMR spectroscopy. The crude product mixture was then adsorbed onto silica gel. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

Method D: Racemic copper catalysed intramolecular C–H insertion reactions

The copper source, the additive and the chiral ligands [(3*S*,8*R*)-Ind **44** and (3*S*,8*R*)-Ind **161** in a 1:1 ratio] were suspended/dissolved in distilled dichloromethane, heated to reflux under an atmosphere of nitrogen and stirred at reflux for 2 h. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this over ~ 20 min. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^1H NMR spectroscopy. The crude product mixture was then adsorbed onto silica gel. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~ 2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

Method E: Achiral rhodium catalysed C–H insertion reactions

$Rh(OAc)_4$ (1 mol%) was suspended/dissolved in dichloromethane at room temperature. The resulting mixture was heated to reflux under an atmosphere of nitrogen. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this over ~ 5 min. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^1H NMR spectroscopy. The crude product mixture was then adsorbed onto silica gel. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~ 2.5 g) and

subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

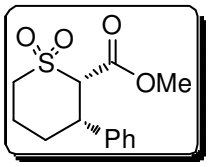
Method F: Chiral rhodium(II) catalysed intramolecular C–H insertion reactions

A chiral rhodium(II) catalyst (1 mol%) was dissolved in dichloromethane at 0 °C. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this over ~ 20 min. The mixture was slowly allowed to warm to room temperature over 6 hours while stirring. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was concentrated under reduced pressure to give the crude product, which was then analysed by ^{1}H NMR spectroscopy. The crude product mixture was then adsorbed onto silica gel. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

Method G: Chiral rhodium(II) catalysed reaction intramolecular C–H reaction

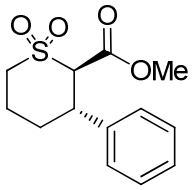
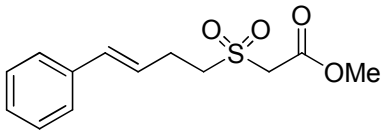
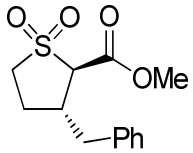
A chiral rhodium(II) catalyst (1 mol%) was dissolved in dichloromethane at 0 °C. A solution of the α-diazocarbonyl compound in distilled dichloromethane was added to this over ~ 20 min. The mixture was slowly allowed to warm to room temperature over 6 hours while stirring. Stirring was maintained at room temperature for 30 hours and was then heated to reflux until reaction completion. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^{1}H NMR spectroscopy. The crude product mixture was then adsorbed onto silica gel. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

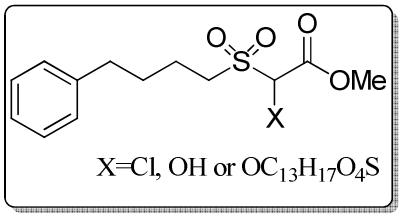
(2*S*,3*S*)-Methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis* 26a[1,2]



CuCl (1.65 mg, 16 μmol), methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **25** (100 mg, 0.34 mmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (17.9 mg, 20.2 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (9.80 mg, 20.2 μmol) were added to dichloromethane (10 mL). The mixture was heated to reflux and stirred under reflux under an inert atmosphere for 21 h, in accordance with **Method A**. The solution was cooled and concentrated under reduced pressure. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 80–90% efficient (9% *trans* sulfolane: 84% *cis* thiopyran: 7% *trans* thiopyran). Following purification by flash chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*S*,3*S*)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis* **26a** (49 mg, 53%) was isolated as a white solid. Spectroscopic characteristics are consistent to those previously reported; mp 119-120 °C (Lit 116-118 °C)[1,2]; $[\alpha]_D^{20}$ +97.5 (*c*, 1.0 CH_2Cl_2), (Lit $[\alpha]_D^{20}$ +103.8, for 98% ee)[1,2], >99% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (KBr): 2952, 2931 (CH), 1726 (CO), 1323, 1295, 1116 (SO_2); δ_H ($CDCl_3$, 400 MHz): 1.86 [1H, apparent dq, *J* 13.9, 3.3, one of C(4)H_2], 2.13–2.35 [2H, m, C(5)H_2], 2.61 [1H, apparent qd, *J* 13.4, 3.8 one of C(4)H_2], 3.05 [1H, apparent dq, *J* 14, 3.2, one of C(6)H_2], 3.54 (3H, s, OCH_3), 3.62–3.74 [2H, m, one of C(6)H_2 and C(3)*H*], 3.99 [1H, dd, *J* 4.5, 2.9, C(2)*H*], 7.16–7.20 (2H, m, Ar*H*), 7.26–7.36 (3H, m, Ar*H*).

Table 4.10 *Additional products were observed in the ^{1}H NMR of the crude products from the cyclisations of methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate* **25** *(previously characterised).*[2]

Entry	Compound	Characteristic signals in ^{1}H NMR
1	 **26b**	δ_H 3.19–3.32 [1H, m, one of C(6)H_2], 3.58 (3H, s, OCH_3), 4.16 [1H, d, *J* 12.1, C(2)*H*]
2	 **149**	δ_H 6.12–6.25 [1H, m, C(3′)H], 6.54 [1H, d, *J* 15.8, C(4′)*H*]
3	 **147b**	δ_H 2.71–2.83 (1H, m, one of ArCH_2), 2.87–2.97 (1H, m, one of ArCH_2), 3.26 [1H, ddd *J* 1.6, 7.0, 12.7, one of C(5)H_2] 3.74 (3H, s, OCH_3).



An additional compound was sometimes observed in the ^{1}H NMR spectra of the crude products from the cyclisations of methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **25**. This compound was occasionally isolated as a less polar fraction than the cyclised product **148**, as a colourless oil; ν_{max}/cm^{-1} (film): 1752 (C=O), 1334, 1117 (SO_2); δ_H (500 MHz, $CDCl_3$): 1.77–1.86 [2H, m, C(3′)H_2], 1.89–1.99 [2H, m, C(2′)H_2], 2.68 [2H, t, *J* 7.5, C(4′)H_2], 3.24–3.35 [1H, m, one of C(1′)H_2], 3.39–3.49 [1H, m, one of C(1′)H_2], 3.91 (3H, s, COOCH_3), 5.08 [1H, s, SO_2C*H*(OR)CO], 7.13–7.23 (3H, m, Ar*H*), 7.24–7.31 (2H, m, Ar*H*); δ_C (125.8 MHz, $CDCl_3$): 20.54 [CH_2, *C*(2′)H_2], 30.12 [CH_2, *C*(3′)H_2], 35.24 [CH_2, *C*(4′)H_2], 48.99 [CH_2, *C*(1′)H_2], 54.51 (CH_3, O*C*H_3), 68.97 [CH, SO_2*C*H(OR)CO], 126.13 (CH, aromatic, *C*H), 128.36 (CH, aromatic, *C*H × 2), 128.50 (CH, aromatic, *C*H × 2), 141.01 (C, aromatic, *C*), 163.16 (C, *C*O).

At this stage it is unclear if the product is the α-hydroxy sulfone **162**, the symmetrical ether **163** or the chlorine abstraction product **164**.

Table 4.11 As*ymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **25** *(Method A)*

Entry	Copper Source	NaBARF (mol%)	Ligand	Time (h)	Crude Efficiency [a] (%)	Products[a]			
							trans : sulfolane[a] **147b**	*trans* : thiopyran [a] **26b**	*cis* thiopyran[a] **26a**
1	CuCl	6	(4*R*)-Ph **20**	21	80–90[b]	**Crude Ratio: Purified Yield (%):**	9	7	84 52% (>99%ee)[c] (2*S*,3*S*)
2	CuCl	6	(4*R*)-Bn **43**	21	60–70[d]	**Crude Ratio: Purified Yield (%):**	3	9	88 36% (66%ee)[c] (2*S*,3*S*)
3	CuCl	6	(4*R*,5*S*)-di-Ph **137**	21	80–90[e]	**Crude Ratio: Purified Yield (%):**	11	8	81 45% (95%ee)[c] (2*S*,3*S*)
4	CuCl	6	(4*S*)-*t*-Bu **138**	21	70–80[f]	**Crude Ratio: Purified Yield (%):**	6	6	88 33% (71%ee)[c] (2*R*,3*R*)
5	CuCl	6	(3*S*,8*R*)-Ind **44**	21	60–70[g]	**Crude Ratio: Purified Yield (%):**	3	8	89 57% (62%ee)[h,c] (2*R*,3*R*)
6	$CuCl_2$	6	(4*R*)-Ph **20**	3	50–60[i]	**Crude Ratio: Purified Yield (%):**	10	4	86 61% (95%ee)[j,k] (2*S*,3*S*)
7	$CuCl_2$	12	(4*R*)-Ph **20**	3	70–80[l]	**Crude Ratio: Purified Yield (%):**	-[1]	-[1]	-[1] 52% (98%ee)[c]

									(2*S*,3*S*)
8	$CuCl_2$	6	(4*R*)-Bn **43**	3	70–80[m]	**Crude Ratio:** **Purified Yield (%):**	3	9	88 67% (67%ee)[n,k] (2*S*,3*S*)
9	$Cu(OTf)_2$	12	(4*R*)-Ph **20**	2	40–50[o]	**Crude Ratio:** **Purified Yield (%):**	-[o]	-[o]	-[o] 38% (98%ee)[c] (2*S*,3*S*)
10	$Cu(OTf)_2$	12	(4*R*,5*S*)-di-Ph **137**	2	30–40[p]	**Crude Ratio:** **Purified Yield (%):**	10	10	80 32% (94%ee)[c] (2S,3S)
11	$Cu(OTf)_2$	12	(4*R*)-Bn **43**	2	30–40[q]	**Crude Ratio:** **Yield (purified):**	-[q]	-[q]	-[q] 28% (66%ee)[c] (2*S*,3*S*)
12	$Cu(OTf)_2$	12	(4*S*)-*t*-Bu **138**	1.5	50–60[r]	**Crude Ratio:** **Purified Yield (%):**	**-**[r]	**-**[r]	-[r] 42% (70%ee)[c] (2*R*,3*R*)
13	$Cu(OTf)_2$	6	(4*R*)-Ph **20**	6	30–40[s]	**Crude Ratio:** **Purified Yield (%):**	7	3	90 11% (97%ee)[t,u] (2*S*,3*S*)
14	$Cu(OTf)_2$	**-**	(4*R*)-Ph **20**	1 week	10–20[v]	**Crude Ratio:** **Purified Yield (%):**	-	13	87 17% (89%ee)[w,u] (2*S*,3*S*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **26a**; δ_H 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**; δ_H 3.74 (3H, s, OCH_3), *trans* thiopyran **26b**; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*].

b. Additional 10–20% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 1.70–1.81 (m) 3.34 (s), 3.39–3.44 (m), 3.80–3.91 (m).

c. HPLC condition set one used to determine % ee (**Appendix I**).

d. Additional 30–40% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 1.70–1.81 (m), 3.34–3.39 (m), 3.40–3.48 (m), 3.78–3.84 (m), 3.87–3.97 (m), 4.34 (s). In addition there is *approx* ~2% hydride-elimination **149** present in the crude material.

e. Additional 10-20% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 1.69–1.80 (m), 3.34 (s), 3.39–3.48 (m), 3.78–3.84 (m), 3.85–3.96 (m).

f. Additional 20-30% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 1.70–1.79 (m), 3.34 (s), 3.39–3.49 (m), 3.78–3.97 (m). In addition there is *approx* ~4% hydride-elimination **149** present in the crude material.

g. Additional 20–30% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 3.34–3.46 (m), 3.78–3.96 (m), 4.44 (s), 4.78 (s), 9.41 (s).

h. Fraction contains *approx* 93% *cis* thiopyran **26a**, 3% *trans* thiopyran **26b**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.86 (s), 4.73 (s).

i. Additional 40–50% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 2.02–2.13 (m), 2.48 (s), 3.35 (s), 3.80–3.89 (m), 3.90–3.97 (m), 4.43 (s), 9.41 (s). In addition there is *approx* ~3% X–H insertion product **148** present in the crude material.

j. Fraction contains *approx* 83% *cis* thiopyran **26a**, 1% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.37–3.48 (m), 3.85 (d, *J* 5.7), 4.69 (s).

k. HPLC condition set two used to determine % ee (**Appendix I**).

l. Presence of and ratios of *trans* sulfolane **147b** and *trans* thiopyran **26b** cannot be accurately estimated due to peak overlap (broad signals). Additional 20–30% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 1.65–1.79 (m), 3.30 (s), 3.76–3.88 (m), 4.82 (s).

m. Additional 20-30% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 2.43 (s), 2.48 (s), 3.40–3.46 (m), 3.76–3.87 (m), 3.88–3.94 (m). In addition there is *approx* ~1% X–H insertion product **148** present in the crude material.

n. Fraction contains 97% *cis* thiopyran **26a**, *approx* 1% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.84–3.87 (m), 4.69 (s). Additional less polar fraction obtained (6 mg) obtained with the following spectral characteristics; δ_H 1.69–1.82 (m), 1.87–1.99 (m), 2.61–.69 (m), 3.07–3.15 (m), 3.21–3.28 (m), 7.11–7.39 (m). Minor peaks are also observed in this fraction at 2.40 (s), 2.44 (s), 2.48 (s), 2.98–3.03 (m), 3.16–3.18 (m), 3.29–3.33 (m), 3.62–3.68 (m), 3.73–3.79 (m), 3.81 (s), 3.90 (s), 3.91(s), 4.29–4.33 (m), 4.42 (s).

o. Presence of and ratios of *trans* sulfolane **147b** and *trans* thiopyran **26b** cannot be estimated due to peak overlap (broad signals). Additional 60–70% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 3.27–3.41 (m), 3.32–3.45 (m), 3.77–3.94 (m), 4.41 (s), 9.41 (s). In addition there is *approx* ~7% X–H insertion product **148** present in the crude material.

p. Additional 70–80% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 2.48 (s), 3.36–3.44 (s), 3.76–3.93 (m), 4.88 (s), 5.05 (s), 5.45 (s), 5.50 (s), 5.75 (d, *J* 5.7), 6.15 (d, *J* 8.5), 6.3 (d, *J* 8.7), 6.78-7.10 (m), 8.89 (s), 9.41 (s). In addition there is *approx* ~13% X–H insertion product **148** present in the crude material.

q. Presence of and ratios of *trans* sulfolane **147b** and *trans* thiopyran **26b** cannot be estimated due to peak overlap (broad signals). Additional 30–40% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 1.58–1.69 (m), 3.30 (s), 3.32–3.45 (m), 3.77–3.96 (m), 4.68–4.87 (m), 9.41 (s). In addition there is *approx* ~1% X–H insertion product **148** present in the crude material.

r. Presence of and ratios of *trans* sulfolane **147b** and *trans* thiopyran **26b** cannot be estimated due to peak overlap (broad signals). Additional 50–60% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 3.77–3.94 (m), 4.47–4.54 (m), 4.57–4.64 (m), 5.87–5.95 (m), 8.34 (s), 9.41 (s). In addition there is *approx* ~1% X–H insertion product **148** present in the crude material.

s. Additional 70–80% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 3.08–3.13 (m), 3.23–3.30 (m), 3.80–3.86 (m, with a singlet present at 3.94 ppm), 4.41–4.46 (m), 4.53–4.62 (m), 5.03–5.06 (m). In addition there are complex overlapping signals; δ_H 1.51–2.10 (m), 2.19–2.50 (m), 2.51–2.89 (m).

t. Purified fraction contains *approx* 70% *cis* thiopyran **26a**, 5% *trans* sulfolane **147b**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.81 (s), 3.82–3.89 (m), 3.91 (s), 3.94 (s). Additional less polar fraction obtained (2 mg) obtained, containing *approx* 20% *cis* thiopyran **26a**, in addition to the following spectral characteristics; δ_H 1.67–1.84 (m), 1.85–1.96 (m), 2.55–2.74 (m), 3.08–3.13 (m), 3.22–3.28 (m), 3.81 (s), 4.41 (s), 7.11–7.39 (m).

u. HPLC condition set three used to determine % ee (**Appendix I**).

v. Reaction was stopped after one week of stirring under reflux. Reaction had not gone to completion, 33% starting material (α-diazocarbonyl **25**) was present. Additional 40–50% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 3.74–3.95 (m), 4.35–4.87(m), 5.25–5.36 (m), 5.58–5.69 (m), 5.93 (s), 6.22 (s), 6.42 (s), 9.40 (s). In addition there are complex overlapping signals; δ_H 1.73–1.94 (m), 2.52–2.73 (m), 2.98–3.45 (m).

w. Purified fraction contains *approx* 30% *cis* thiopyran **26a**, 1% X–H insertion product **148** and 60% starting material (α-diazocarbonyl **25**). Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.91 (d, *J* 2.4), 4.05 (s), 3.94 (s), 3.96 (s), 5.64 (s), 9.41 (s). Additional less polar fraction obtained (3 mg) obtained, containing *approx* 1% X–H insertion product **148**, in addition to the following spectral characteristics being present; δ_H 1.69–1.84 (m), 1.87–1.96 (m), 2.58–2.70 (m), 3.07–3.13 (m), 3.23–3.30 (1H, m), 7.14–7.31 (m). Minor peaks observed; δ_H 2.89–2.99 (m), 3.37–3.42 (m), 3.54 (s), 3.81 (s), 3.86 (s), 3.90 (s), 3.93 (s), 4.42 (s).

Table 4.12 Asy*mmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **25***, variation of additive (Method A)*

Entry	**Additive**	**Ligand**	**Time (h)**	**Crude Efficiency** [a]		Products[a]		
						trans **sulfolane** [a] **147b**	***trans*** **thiopyran**[a] **26b**	***cis*** **thiopyran**[a] **(2*S*,3*S*) 26a**
1	**$LiPF_6$**	(4*R*)-Ph **20**	19	-[b]	**Crude Ratio:** **Purified Yield (%):**	**-**[b]	**-**[b]	-[b] 47% (83% ee)[c,d]
2	**$LiPF_6$**	(4*R*)-Bn **43**	21	-[b]	**Crude Ratio:** **Purified Yield (%):**	-[b]	**-**[b]	-[b] 35% (69% ee)[d,e]
3	**$NaPF_6$**	(4*R*)-Bn **43**	6	30–40[f]	**Crude Ratio:** **Purified Yield (%):**	10	14	76 48% (73% ee)[d,g]

4	**$NaPF_6$**	(4*R*)-Ph **20**	6	30–40[h]	**Crude Ratio:** **Purified Yield (%):**	9	11	80 38% (97% ee)[d,i]
5	**KBARF**	(4*R*)-Ph **20**	3	50–60[j]	**Crude Ratio:** **Purified Yield (%):**	8	3	89 46% (98% ee)[k,l,m]
6	**KBARF**	(4*R*)-Bn **43**	2	60–70[n]	**Crude Ratio:** **Purified Yield (%):**	3	3	94 51% (62% ee)[d,l,o]
7	**KPF_6**	(4*R*)-Ph **20**	30	30–40[p]	**Crude Ratio:** **Purified Yield (%):**	~10	~10	~ 80 45 (92% ee)[d,q]
8	**KPF_6**	(4*R*)-Bn **43**	48	30–40[r]	**Crude Ratio:** **Purified Yield (%):**	~7	~16	~77 48 (70% ee)[s,d]
9	**$NaB(C_6H_5)_4$**	(4*R*)-Ph **20**	56	<10[t]	**Crude Ratio:** **Purified Yield (%):**	-[t]	-[t]	-[t] 4%[u]
10	**$NaB(C_6H_5)_4$**	(4*R*)-Bn **43**	56	0[v]	**Crude Ratio:** **Purified Yield (%):**	-[v]	-[v]	-[v] -[w]
11	**$NaBF_4$**	(4*R*)-Ph **20**	24	<10[x]	**Crude Ratio:** **Purified Yield (%):**	~10	~10	~80 43% (93% ee)[m,y]
12	**$NaBF_4$**	(4*R*)-Bn **43**	48	10–20[z]	**Crude Ratio:** **Purified Yield (%):**	~10[z]	~ 10	~80 22%[aa]
13	**-**	(4*R*)-Ph **20**	98	10–20[bb]	**Crude Ratio:** **Purified Yield (%):**	~7	~7	~86 48% (79% ee)[m,cc]
14	**-**	(4*R*)-Bn **43**	1 week	-[dd]	**Crude Ratio:**	-[dd]	-	-[dd]

				starting material only	**Purified Yield (%):**			

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **26a**; δ_H 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**, δ_H 3.74 (3H, s, OCH_3), *trans* thiopyran **26b**; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*].

b. ^{1}H NMR spectra of the crude product not obtained due to hazardous nature of $LiPF_6$, the crude material was immediately purified by flash chromatography.

c. ^{1}H NMR spectra of the purified product contains 82% *cis* thiopyran **26a**, 8% X–H insertion product **148** {^{1}H NMR signal used for calculation of X–H insertion product; δ_H 5.08 [1H, s, SO_2C*H*(OR)CO], and an additional unknown compound; δ_H 3.87 (s), (additional peaks may be present but may not be observed to overlapping signals in the ^{1}H NMR spectra). Additional peaks are observed in the HPLC trace which have been assigned to the X–H insertion product **148**.

d. HPLC condition set two used to determine % ee (**Appendix I**).

e. ^{1}H NMR spectra of the purified product contains 30% *cis* thiopyran **26a**, 7% *trans* thiopyran **26b**, 4% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified fraction; δ_H 3.36–3.45 (m), 3.80–3.96 (m), 4.66–4.71 (m), 5.49 (s), 5.64 (s), 5.86–5.91 (m). Additional peaks may be present but may not be observed to overlapping signals in the ^{1}H NMR spectra. Additional peaks are observed in the HPLC trace some of which have been assigned to the X–H insertion product **148**.

f. Complex mixture of products. Contains 6% X–H insertion product **148**. Additional 60–70% of crude material may be accounted for by the presence of additional peaks observed the ^{1}H NMR spectra of the crude product; δ_H 3.40–3.48 (m), 3.79–3.89 (m), 3.89–3.94 (m), 4.06–4.15 (m), 4.30 (s), 4.43 (s), 4.64 (s), 4.69 (s), 4.84 (s), 4.87 (s), 4.93 (s), 5.65 (s), 5.93 (s), 9.40 (s).

g. Fraction contains *approx* 70% *cis* thiopyran **26a**, 5% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 1.68–1.84 (m), 1.91–1.97 (m), 3.37–3.45 (m), 3.85 (s), 3.86 (s), 4.69 (s).

h. Additional 60–70% of crude material may be accounted for by the presence of additional peaks observed inthe ^{1}H NMR spectra of the crude product; δ_H 3.35–3.47 (m), 3.76–3.87 (m), 3.88–3.948 (m), 4.25 (s), 4.64 (s), 4.69 (s), 4.84 (s), 4.87 (s), 4.92 (s), 5.65 (s), 5.93 (s), 9.40 (s). In addition there is *approx* ~7% X–H insertion product **148** present in the crude material.

i. Fraction contains *approx* 71% *cis* thiopyran **26a**, 3% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.37–3.48 (m), 3.85 (s), 3.86 (d, *J* 4.1), 3.92 (s), 4.69 (s). Two additional fractions obtained. The least polar fraction obtained (4%) obtained has the following spectral characteristics; δ_H 1.69–1.82 (m), 1.87–1.99 (m), 2.61–2.69 (m), 3.07–3.15 (m), 3.21–3.28 (m), 7.11–7.39 (5m). Minor peaks are also observed in this fraction at 2.40 (s), 2.48 (s), 2.98–3.03 (m), 3.16–3.18 (m), 3.62–3.68 (m), 3.73–3.79 (m), 3.81 (s), 3.90 (s), 3.91(s), 4.29–4.33 (m). The more polar fraction contained X–H insertion product **148** (4%).

j. Additional 40–50% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.38–2.46 (m), 2.48 (s), 2.86–2.95 (m), 3.35–3.46 (m), 3.77–3.88 (m), 3.89–3.96 (m), 4.70 (s), 9.40 (s). In addition there is *approx* ~1% X–H insertion product **148** present in the crude material.

k. Fraction contains *approx* 80% *cis* thiopyran **26a**, 1% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.85 (s), 4.69 (s).

l. HPLC condition set one used to determine % ee (**Appendix I**).

m. HPLC condition set three used to determine % ee (**Appendix I**).

n. Additional 30–40% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.43 (s), 2.48 (s), 3.35 (s), 3.36–3.47 (m), 3.78–3.89 (m), 3.95 (s), 4.69 (s). In addition there is *approx* ~3% X–H insertion product **148** present in the crude material.

o. Fraction contains *approx* 90% *cis* thiopyran **26a**, 1% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.35 (s), 3.85 (s), 3.86 (s), 4.70 (s).

p. Additional 60–70% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.55–2.77 (m), 3.14–3.48 (m), 3.76–3.95 (m), 3.96 (s), 4.84 (s), 4.86 (s), 5.65 (s), 5.93 (s), 9.40 (s). In addition there is *approx* ~6% X–H insertion product **148** present in the crude material.

q. Fraction contains *approx* 72% *cis* thiopyran **26a**, 8% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.85 (s), 3.86 (s), 3.87 (s), 4.70 (s). An additional less polar fraction was obtained (4%), which contained 70% X–H insertion product **148** and 10% *cis* thiopyran **26a**. Additional peaks observed in the ^{1}H NMR spectra of this fraction include; δ_H 3.81 (s), 3.83 (s), 3.85 (s), 3.86 (s), 3.87 (s), 4.09 (s), 4.41 (s).

r. Additional 60–70% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.35–3.49 (m), 3.76–3.97 (m), 4.43 (s), 4.84 (s), 4.86 (s), 5.65 (s), 5.93 (s), 9.40 (s), 11.1 (s) In addition there is *approx* ~7% X–H insertion product **148** present in the crude material.

s. Fraction contains *approx* 52% *cis* thiopyran **26a**, 7% *trans* thiopyran **26b**, 2% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.85 (s), 3.86 (s), 3.87 (s), 4.70 (s). Two additional less polar fractions obtained. The least polar fraction obtained (3%) obtained has the following spectral characteristics; δ_H 1.69–1.82 (3H, m), 1.87–1.99 (1H, m), 2.60–2.68 (2H, m), 3.07–3.14 (m), 3.20–3.28 (2H, m), 7.07–7.38 (5H, m). Minor peaks observed in this fraction; δ_H 2.40 (s), 3.90 (s), 3.92 (s). The more polar fraction (4%) contains *approx* 50% X–H insertion **148**, 22% *cis* thiopyran **26a**. Additional peaks observed in the ^{1}H NMR spectra of this fraction include; δ_H 3.85 (s), 3.86 (s), 3.92 (s), 4.10 (s).

t. ^{1}H NMR analysis of the crude mixture reveals a complex mixture of products, largely unidentified. Reaction efficiencies and relative ratios of isomers could not be accurately calculated due to overlapping peaks in the ^{1}H NMR spectra of the crude product. (A series of overlapping multiplets 1.50–2.70 and 3.00–4.10 ppm appear in ^{1}H NMR spectra of the crude product.) It is estimated that there is *approx* 6% X–H insertion **148** product present. There are additional signals present in the ^{1}H NMR spectra of the crude product; δ_H 5.03 (s), 5.05 (s), 5.64 (s), 9.41 (s).

u. Fraction contains *approx* 12% *cis* thiopyran **26a** and 45% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.85 (s), 4.70 (s). Two additional less polar fractions obtained. The least polar fraction obtained (3%) obtained has the following spectral characteristics; δ_H 1.69–1.82 (3H, m), 1.87–1.99 (1H, m), 2.60–2.68 (2H, m), 3.07–3.14 (m), 3.20–3.28 (2H, m), 7.07–7.38 (5H, m). Minor peaks observed in this fraction; δ_H 2.40 (s), 3.90 (s), 3.92 (s). The more polar fraction (4%) contains *approx* 50% X–H insertion **148**, 22% *cis* thiopyran **26a**. Additional peaks observed in the ^{1}H NMR spectra of this fraction include; δ_H 3.85 (s), 4.68 (s).

v. ^{1}H NMR analysis of the crude mixture reveals a complex mixture of products (largely unidentified), and there is no clear evidence for the formation of intramolecular insertion products. A series of overlapping complex multiplets 1.30–2.10, 2.11–2.80, 2.90–4.40 ppm appear in ^{1}H NMR spectra of the crude product. It is estimated that there is *approx* 5% X–H insertion **148** product present. There are additional signals present in the ^{1}H NMR spectra of the crude product; δ_H 4.69 (s), 4.84 (s), 4.87 (s), 5.03 (s), 5.05 (s), 5.42 (s), 5.48 (s), 5.64 (s).

w. Two fractions of unidentified material isolated. Signals in the ^{1}H NMR of the first fraction (9 mg) are as follows; δ_H 1.72–1.85 (2H, m), 1.86–2.03 (2H, m), 2.67 (2H, t, *J* 7.4), 3.13–3.30 (1H, m), 3.34–3.42 (1H, m), 3.91 (1H, s), 7.12–7.34 (5H, m). Minor peaks are also present in this fraction; δ_H 2.89–2.95 (m), 3.54 (s), 3.75 (s), 3.77 (s), 3.81 (s),

3.85 (s), 3.86 (s), 5.64 (s). ^{1}H NMR analysis of the more polar of the two fractions (5 mg) reveals the following signals; δ_H 1.74–2.07 (2H, m), 2.58–2.76 (1H, m), 3.05–3.43 (1H, m), 7.11–7.35 (5H, m). There are additional signals present in the ^{1}H NMR spectra of the crude product; δ_H 3.73 (s), 3.75 (s), 3.77 (s), 3.81(s), 3.82 (s), 3.85 (s), 3.87 (s), 3.91 (s), 3.93 (s), 3.97 (s), 4.63 (s), 5.07 (s), 5.48 (s), 5.64 (s), 7.68–7.72 (m), 7.81–7.85 (m).

x. Additional 90% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.81 (s), 3.84–3.87 (m), 3.88–3.94 (m), 4.70 (s), 5.64 (s), 5.92 (s), 9.40 (s), 9.70. Additional signals may be present but cannot be distinguished due to large amount of signal overlap from 1.40–2.10 and 2.90–3.88 ppm. In addition there is *approx* ~10% X–H insertion product **148** present in the crude material.

y. Fraction contains *approx* 22% *cis* thiopyran **26a** and 40% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.85 (s), 3.86 (s), 4.70 (s).

z. Additional 90% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.81–3.96 (m), 4.07–4.18 (m), 4.26–4.33 (m), 4.21 (s) 4.64 (s), 4.69 (s), 5.64 (s), 5.92 (s), 9.40 (s), 11.10 (s). Additional signals may be present but cannot be distinguished due to large amount of signal overlap from 1.40–2.20 and 2.90–3.90 ppm. In addition there is *approx* ~9% X–H insertion product **148** present in the crude material. Ratio of *trans* thiopyran **26b** estimated due to peak overlap.

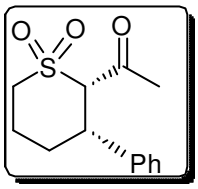
aa. Fraction contains *approx* 30% *cis* thiopyran **26a** and 21% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.84 (s), 3.85 (s), 3.86 (s), 3.91 (s), 3.92 (s), 4.69 (s), 5.64 (s). Enantioselectivity cannot be accurately determined from HPLC trace.

bb. Additional 80–90% of crude material may be accounted for by the presence of additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.81–3.97 (m), 4.29 (s), 4.31 (s), 4.41 (s), 4.69 (s), 4.83 (s), 5.03 (s), 5.64 (s), 5.92 (s), 6.39 (s). Additional signals may be present but cannot be distinguished due to large amount of signal overlap from 1.40–2.20 and 3.00–3.90 ppm. In addition there is *approx* ~10% X–H insertion product **148** present in the crude material.

cc. Fraction contains *approx* 31% *cis* thiopyran **26a**, 11% X–H insertion product **148**. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.37–3.42 (m), 3.85 (s), 4.69 (s). Two additional fractions obtained. (this fraction had been re-purified from a fraction obtained from an earlier attempt at chromatographic purification, however was not obtained in a higher degree of purity.) Two less polar fractions obtained from original column. The more polar fraction contained X–H insertion product **148** (8 mg), the less polar fraction had the following signals in the ^{1}H NMR spectra; δ_H 1.68–1.83 (3H, m), 1.86–1.99 (1H, m), 2.59–2.86 (2H, m), 3.05–3.12 (m), 3.21–3.30 (2H, m), 7.05–7.39 (5H, m). Minor peaks observed in this fraction; δ_H 2.41 (s), 2.94–3.02 (m), 3.13–3.19 (m), 4.06–4.14 (m), 4.15–4.28 (m), 4.30–4.38 (m), 7.47–7.51 (m).

dd. No reaction occurred after one week of stirring at reflux.

(2*S*,3*S*)-1-(Phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)ethanone *cis* 22a[1,2]

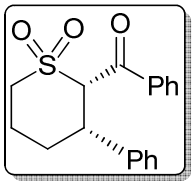


The title compound was prepared according to the procedure described for (2*S*,3*S*)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis*-**26a**, using 1-(4-phenylbutylsulfonyl)-1-diazopropan-2-one **21** (80 mg, 0.28 mmol), CuCl (1.38 mg, 14.0 μmol), NaBARF (15.0 mg, 17 μmol), bi*s*oxazoline ligand (4*R*,5*S*)-di-Ph **137** (7.79 mg, 17 μmol) in dichloromethane (15 mL), stirred while heating under reflux for 21 h, in accordance with Method **A.** ^{1}H NMR spectroscopy of the crude mixture showed a complex mixture of products. The presence of three identifiable compounds accounts for *approx.* 90% of this mixture. Using the C(2)*H* signal for all three compounds there is *circa* 58% compound **22a** (4.21 ppm, dd, *J* 4.2, 3.1), 19% *trans thiopyran* **22b**, (4.40 ppm, d, *J* 12.1) and 23% *trans* sulfolane **150b** (3.78 ppm, d, *J* 9.1**,** tentatively assigned). In addition the presence of three methyl signals, 1.80 ppm (*cis* thiopyran **22a**), 2.19 ppm (*tran*s thiopyran **22b**) and 2.16 ppm (*trans* sulfolane **150b**) confirms the presence of these compounds and their relative ratios. Following purification, by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*S*,3*S*)-1-(phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)ethanone *cis* **22a** (18.4 mg, 26%) was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1,2] mp 113–115 °C (Lit 114–116 °C);[1,2] $[\alpha]_D^{20}$ +56.3 (*c* 0.103 in CH_2Cl_2) (Lit[1,2] $[\alpha]_D^{20}$ +42.4 for 85% ee); 73% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (KBr): 1717 (CO), 1453 (C=C, Ar), 1362, 1314, 1297, 1119 (SO_2), 762, 702 (CS); δ_H ($CDCl_3$, 300 MHz): 1.77–1.87 [4H, m, one of C(4)H_2 incorporating at 1.81, 3H, s, COCH_3], 2.13–2.21 [1H, m, one of C(5)H_2], 2.22–2.37 [1H, m, one of C(5)H_2], 2.56 [1H, apparent qd, *J* 13.4*,* 3.4, one of C(4)H_2], 3.02 [1H, apparant dq, *J* 13.9, 3.2, one of C(6)H_2], 3.50–3.71 [2H m, C(3)*H* and one of C(6)H_2], 4.21 [1H, dd, *J* 4.2, 3.1, C(2)*H*], 7.17–7.24 (2H, m, Ar*H*), 7.27–7.40 (3H, m Ar*H*).

A second fraction was isolated (9.30 g, 13%) containing *circa* 13% *cis* thiopyran **22a** [4.23 ppm, dd, *J* 4.2, 3.1, C(2)*H*, 1.81 ppm, s, COCH_3] 17% *trans* thiopyran **22b** (4.35 ppm, d, *J* 12.1, C(2)*H*, 2.19 ppm, s, COCH_3) and 70% *trans* sulfolane **150b** [3.78 ppm, d, *J* 9.0, C(2)*H*, 2.20 ppm, s, COCH_3]. The assignment of *trans* sulfolane **150b** is tentative.

Note; A ^{1}H NMR spectrum recorded on a sample stored at room temperature after 24 months showed 89% of *cis* **22a** remains unchanged, with 11% conversion to *trans* **22b**.

(2*S*,3*S*)-2-Benzoyl-3-phenyl-1, 1-dioxo-hexahydrothiopyran *cis* 24a[1,2]



The title compound was prepared according to the procedure described for (2*S*,3*S*)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis*-**26a**, using 2-(4-phenylbutylsulfonyl)-2-diazo-1-phenylethanone **23** (100 mg, 0.29 mmol), CuCl (1.78 mg, 14.5 μmol), NaBARF (15.9 mg, 18 μmol) and bisoxazoline ligand (4*R*)-Bn **43** (6.34 mg, 18 μmol) in dichloromethane (12 mL), stirred while heating under reflux for 20 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude mixture showed that compound **24a** was the major product, with an additional compound present (30–40%); the presence of a signal, which appears to be doublet of doublets at 4.60 ppm is observed. Following purification, by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*S*,3*S*)-2-benzoyl-3-phenyl-1,1-dioxo-hexahydrothiopyran *cis*-**24a** (50 mg, 55%) was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1,2] mp 187–188 °C (Lit 189–191 °C);[1,2] $[\alpha]_D^{20}$ +50.1 (*c* 1.02 in CH_2Cl_2); 83% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (KBr): 2959 (CH), 1668 (CO), 1595, 1446, (C=C, Ar), 1321, 1298, 1230, 1207, 1122 (SO_2), 759, 701 (CS); δ_H ($CDCl_3$, 300 MHz): 1.88 [1H, apparent dq, *J* 13.8, 3.2, one of C(4)H_2], 2.15–2.46 [2H, m, C(5)H_2], 2.72 [1H, apparent qd, *J* 13.3, 4.0, one of C(4)H_2], 3.08 [1H, apparent dq, *J* 13.8, 3.2, one of C(6)H_2], 3.77–3.94 [2H, m, one of C(6)H_2 and C(3)*H*], 5.07 [1H, dd, *J* 4.5, 2.7, C(2)*H*], 7.04–7.18 (5H, m, Ar*H*), 7.19–7.30 (2H, m, Ar*H*), 7.37–7.48 (3H, m, Ar*H*).

Table 4.13 Asy*mmetric copper-bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***23****(Method* ***A****)*

Entry	Ligand	Time (h)	Crude Efficiency[a]	Yield (%)	%ee	$[\alpha]_D^{20}$
1	(4*R*)-Bn **43**	20	>70% **24a**	55	83 (2*S*,3*S*)	+50.1 (*c* 0.40)
2	(4*R*,5*S*)-di-Ph **137**	6	>80% (all included ~60% **24a**) Majority **24a**, two additional compounds observed in crude,[b] which may be some of the other insertion products but this is not confirmed. One additional compound obtained as a mixed fraction.[c]	41	93 (2*S*,3*S*)	+89.1 (*c* 0.40)
3	(4*S*)-*t*-Bu **138**	20	>80% (all included-~60%**24a**) Mixture containing majority **24a**, one additional compound in crude; doublet of doublets at 4.60 ppm (~20%)	51	78 (2*R*,3*R*)	-62.5 (*c* 0.10)

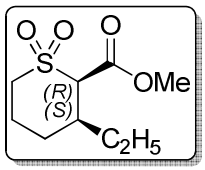
a. Efficiency calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **24a**; δ_H 5.07 (1H, dd, *J* 4.5, 2.7).

b. In the crude product two additional compounds were observed. This observation is made due to the presence of two unrelated doublet of doublets in the ^{1}H NMR spectra of the crude product; δ_H 4.60 (dd, *J* 14.0, 11.5) (~5%) and 4.22 (dd, *J* 5.8, 3.7). (~20%)

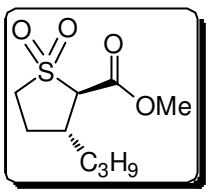
c. A fraction was isolated by chromatography (11 mg), which is *approx*. 60% compound **24a**, but contains an additional product *approx* 30–40% with a distinct ^{1}H NMR signal; 4.60 (dd, *J* 13.8, 11.1)

Note; A ^{1}H NMR spectrum recorded on a sample after 24 months, stored at room temperature showed no change in compound **24a**.

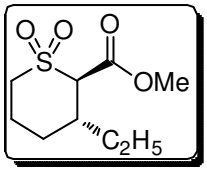
(2*R*,3*S*)-Methyl 2-(3-ethyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis* 30a, methyl 2-(3-propyl-1,1-dioxo-tetrahydrothiophen-2-yl)carboxylate *trans* 151b and methyl 2-(3-ethyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *trans* 30b[1,2]



The title compounds were prepared according to the procedure described for (2*S*,3*S*)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis*-**26a**, using methyl 2-diazo-2-(hexylsulfonyl)acetate **29** (200 mg, 0.81 mmol), CuCl (3.99 mg, 40.3 μmol), NaBARF (42.8 mg, 48.4 μmol) and bisoxazoline ligand (4*S*)-*t*-Bu **138**, (14.2 mg, 48.4 μmol) in dichloromethane (35 mL), stirred while heating under reflux for 21 h, in accordance with Method **A**. The ^{1}H NMR spectrum of the crude reaction mixture shows a mixture of products, including *cis* (2*R*,3*S*) **30a**, *trans* **151b** and *trans* **30b**. Following purification, by column chromatography on silica gel, using gradient ethyl acetate-hexane (0:100-10:90-20:80-40:60-80:20) as eluent (2*R*,3*S*)- **30a** (86 mg, 48%) was isolated as the least polar fraction, as a clear oil. Spectroscopic characteristics are consistent with those previously reported;[1,2] 92% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (film): 2938 (CH), 1736 (CO), 1321, 1296, 1161 (SO_2); δ_H ($CDCl_3$, 400 MHz): 0.97 [3H, t, *J* 7.4, C(2′)H_3], 1.24–1.45 [2H, m, C(1′)H_2], 1.63–1.87 [2H, m, C(4)H_2], 1.99–2.19 [2H, m, C(5)H_2], 2.22–2.34 [1H, m, C(3)*H*], 2.95 [1H, apparent dq, *J* 13.9, 3.2, one of C(6)H_2], 3.53–3.64 [1H, m, one of C(6)H_2], 3.80 (3H, s, OCH_3), 3.89 [1H, dd, *J* 4.4, 3.0, C(2)*H*].



The more polar fraction (*trans* sulfolane **151b**) (18 mg, 11%) was isolated as a white solid; ν_{max}/cm^{-1} (KBr): 2940 (CH), 1732 (CO), 1319, 1269 (SO_2); δ_H ($CDCl_3$, 400 MHz): 0.93 [3H, t, *J* 7.2, C(3′)H_3], 1.22–1.62 [4H, m, C(2′)H_2 and C(1′)H_2], 1.74–1.87 [1H, m, one of C(4)H_2], 2.33–2.42 [1H, m, one of C(4)H_2], 2.73–2.86 [1H, m, C(3)*H*], 3.09 [1H, overlapping ddd, appears as dt, *J* 12.8, 7.0, one of C(5)H_2], 3.27 [1H, ddd, *J* 12.9, 7.0, 2.0, one of C(5)H_2], 3.58 [1H, d, *J* 9.6, C(2)*H*], 3.86 (3H, s, OCH_3).



The most polar fraction (*trans* thiopyran **30b**) (11 mg, 6%) was isolated as a white solid; 57% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (KBr): 2946 (CH), 1729 (CO) 1317, 1293, 1129 (SO_2); δ_H ($CDCl_3$, 400

MHz): 0.94 [3H, t, *J* 7.5, C(2′)H_3], 1.19–1.40 [2H, m, one of C(1′)H_2 and one of C(4)H_2], 1.46–1.58 [1H, m, one of C(1′)H_2], 2.01–2.21 [3H, m, one of C(4)H_2 and C(5)H_2], 2.31–2.45 [1H, m, C(3)*H*], 2.87–2.98 [1H, m, one of C(6)H_2], 3.21 [1H, apparent dt, *J* 14.1, 4.0, one of C(6)H_2], 3.69 [1H, d, *J* 10.5, C(2)*H*], 3.85 (3H, s, OCH_3).

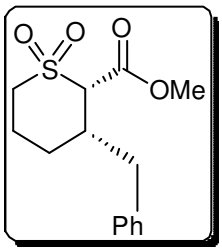
Table 4.14 Asy*mmetric copper-bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **29** *(Method A)*

Entry	Time (h)	Ligand	Crude Efficiency (%)[a]	Product[a]			
					cis **thiopyran 30a :**	***trans*** **thiopyran 30b :**	***trans*** **sulfolane[a] 151b**
1	21	(4*S*)-*t*-Bu **138**	80–90	**Crude Ratio:** **Purified Yield(%):** **Overall Yield[b]**	67 : 48% (92% ee) (2*R*, 3*S*) 49%	11 : 6% (57% ee)[c]	22 11%[d] 10%
2	21	(4*R*)-Bn **43**	80–90	**Crude Ratio:** **Purified Yield(%):** **Overall Yield[b]**	67 : 38% (87% ee) (2*S*, 3*R*) 56%	12 : 5% (6% ee)[e]	21 14%[f], 8%[g] 10%
3	21	(4*R*,5*S*)-di-Ph **137**	70–80	**Crude Ratio:** **Purified Yield(%):** **Overall Yield[b]**	69 : 21% (>99% ee) (2*S*, 3*R*) 30%	9 : -[h]	21 18%[i] 9%

a. Efficiencies and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_3, *cis* thiopyran **30a**; δ_H 3.80 (3H, s, OCH_3), *trans* thiopyran **30b**; δ_H 3.85 (3H, s, OCH_3), *trans* sulfolane **151b**; δ_H 3.86 (3H, s, OCH_3).
b. Overall Yield is calculated from amounts of each compound in various fractions.
c. The first eluting enantiomer of the *trans* isomer **30b** at 30.3 min is the minor enantiomer, the second eluting enantiomer of the *trans* isomer **30b** at 36.7 min the major enantiomer using chiral column Cell-4.
d. Two fractions obtained. The first fraction accounts for 67% mass; this contains 90% *trans* sulfolane **151b**, 10% *cis* thiopyran **30a**, The second fraction accounts for 33% mass; this contains 98% *trans* sulfolane **151b**, 2% *cis* thiopyran **30a**.
e. The first eluting enantiomer of the *trans* isomer **30b** at 30.3 min is the major enantiomer, the second eluting enantiomer of the *trans* isomer **30b** at 36.7 min is the minor enantiomer using chiral column Cell-4.
f. Contains *approx* 83% *cis* thiopyran **30a** and 17% *trans* sulfolane **151b**.

g. Contains *approx* 10% *cis* thiopyran **30a** and 90% *trans* sulfolane **151b**.
h. Not isolated after column chromatography.
i. Contains 51% *trans* sulfolane **151b**, 49% *cis* thiopyran **30a**.

(2*S*,3*S*)-Methyl 2-(3-benzyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis* 28a[1,2]



The title compound was prepared according to the procedure described for (2*S*,3*S*)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis*-**26a**, using methyl 2-diazo-2-(5-phenylpentylsulfonyl) acetate **27** (100 mg, 0.32 mmol), CuCl (1.58 mg, 16.1 μmol), NaBARF (17.1 mg, 19.3 μmol) bisoxazoline ligand (4*R*)-Bn **43**, (6.99 mg, 19.3 μmol) in dichloromethane (15 mL), stirred while heating under reflux for 24 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude mixture showed that *cis* **28a** was the major product (*circa* 70–80%). Following purification, by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*S*,3*S*)-methyl 2-(3-benzyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis* **28a** (19 mg, 21%) was isolated as a colourless oil. Spectroscopic characteristics are consistent with those previously reported; [1,2] $[\alpha]_D^{20}$ +35.8 (*c* 0.123 in CH_2Cl_2); 80% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (film): 2932 (CH), 1732 (CO), 1455, 1437 (C=C, Ar), 1322, 1249, 1168, 1117 (SO_2), 749, 703 (CS); δ_H ($CDCl_3$, 300 MHz): 1.55–1.71 [1H, m, one of C(4)H_2], 1.83–2.19 [3H, m, C(5)H_2 and one of C(4)H_2], 2.47–2.78 [3H, m, 2H of CH_2Ar and C(3)*H*], 2.89–3.01 [1H, m, one of C(6)H_2], 3.48–3.63 [1H, m, one of C(6)H_2], 3.79–3.89 [4H, m, C(2)*H* incorporating at 3.85, 3H, s, OCH_3], 7.06–7.22 (2H, m, Ar*H*), 7.23–7.40 (3H, m, Ar*H*).

Table 4.15 *Asymmetric copper bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo-sulfone* **27** *(Method* ***A****)*

Entry	**Ligand**	**Time (h)**	**Crude Efficiency[a] (total) (%)**	**Crude (%) Purified Yield (%)**	***cis* thiopyran 28a (2*S*,3*S*)**
1	(4*R*)-Bn **43**	24	70–80[b]	**Crude (%):** **Purified Yield (%):**	70–80% 21% (80% ee) (2*S*,3*S*) $[\alpha]_D^{20}$ +35.8 (*c* 0.123)
2	(4*R*,5*S*)-di-Ph **137**	22	80–90[c]	**Crude (%):** **Purified Yield (%):**	45% 37% (94% ee) (2*S*,3*S*)
3	(4*S*)-*t*-Bu **138**	8	80–90[d]	**Crude (%):** **Purified Yield (%):**	58% 22% (90% ee) (2*R*,3*R*) $[\alpha]_D^{20}$ -39.3 (*c* 0.37)
4	(4*R*)-Ph **20**	7	70–80[e]	**Crude (%):** **Purified Yield (%):**	41% (2*S*,3*S*) 12% (96% ee)

a. Efficiencies calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **28a**; one of C(6)H_2, δ_H 3.48–3.63 ppm. Two additional compounds were occasionally observed in the cyclisations of methyl 2-diazo-2-(5-phenylpentylsulfonyl) acetate **27**. A compound with a signal at 3.63 (d, *J* 9.5) and a compound with a signal at 3.74 (d, *J* 10.1) have tentatively been assigned to the *trans* sulfolane **152b** and *trans* thiopyran **28b** isomers (Exact assignments of each signal to each compound have not been made.) Neither compounds **152b** or **28b** have been isolated after purification and are not fully characterised. They have been taken into account in the calculation of crude efficiencies where relevant.

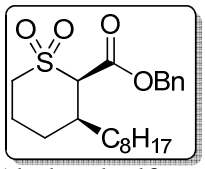
b. Additional signals observed in the ^{1}H NMR spectra of crude product; δ_H 2.36–2.54 (m), 2.79–2.84 (m), 3.04–3.41 (m).

c. Additional signals observed in the ^{1}H NMR spectra of crude product; δ_H 2.27–2.35 (m), 2.37–2.50 (m), 2.76–2.87 (m), 3.02–3.13 (m), 3.14–3.20 (m), 3.23–3.31, (m), 3.37–3.48 (m), 3.63 (d, *J* 9.5), 3.74 (d, *J* 10.1), 3.80 (s). Calculated efficiency includes two additional compounds present in ^{1}H NMR spectra of the crude product; compound [δ_H 3.63 (d, *J* 9.5)] (*approx* 28%), and compound [δ_H 3.74 (d, *J* 10.1)] (*approx* 19%) present in ^{1}H NMR spectra of the crude product. (See footnote a)

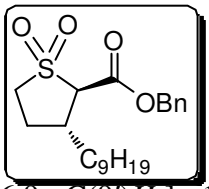
d. Additional signals observed in the ^{1}H NMR spectra of the crude product; δ_H 2.32–2.49 (m), 2.76–2.81 (m), 2.82–2.89 (m), 3.06–3.15 (m), 3.16–3.30 (m), 3.31–3.48 (m), 3.63 (d, *J* 9.5), 3.74 (d, *J* 10.1), efficiency 80–90%. Calculated efficiency includes two additional compounds present in ^{1}H NMR spectra of the crude product; compound [δ_H 3.63 (d, *J* 9.5)], (*approx* 16%) and compound p [δ_H 3.74 (d, *J* 10.1)] (*approx* 13%). (See footnote a).

e. Additional signals observed ^{1}H NMR spectra of crude product; δ_H 2.28–2.51 (m), 2.76–2.89 (m), 3.02–3.20 (m), 3.23–3.33 (m), 3.63 (d, *J* 9.5), 3.74 (d, *J* 10.1), 3.80 (s), 3.87–3.96 (m). Calculated efficiency includes two additional compounds present in ^{1}H NMR spectra of the crude product; compound [δ_H 3.63 (d, *J* 9.5)] (*approx* 23%), and compound[δ_H 3.74 (d, *J* 10.1)]. (*approx* 12%) (See footnote a).

Benzyl 2-(3-nonyl-1,1-dioxo-terahydrothiophen-2-yl)carboxylate *trans* 139b and benzyl 2-(3-octyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis* (2*R*,3*S*) 38a, *trans* (+) 38b[1,2]



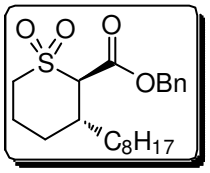
The title compounds were prepared according to the procedure described for (2*S*,3*S*)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate *cis*-**26a** using benzyl 2-diazo-2-(dodecylsulfonyl) acetate **37** (200 mg, 0.49 mmol), CuCl (2.42 mg, 24.5 μmol), NaBARF (26.0 mg, 29.3 μmol) and bisoxazoline ligand (4*S*)-*t*-Bu **138** (8.63 mg, 29.3 μmol) in dichloromethane (30 mL), stirred while heating under reflux for 21 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx*. 80–90% efficient. The ^{1}H NMR spectrum shows a mixture of products, including *trans*-**139b,** *cis* (2*S*,3*R*)-**38a** and *trans* (-)-**38b**. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (0:100–10:90–20:80–40:60–80:20) as eluent (2*R*,3*S*)-**38a** (96 mg, 51%) was isolated as the least polar fraction as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1,2] mp 42-43 °C; $[\alpha]_D^{20}$ -23.7 (*c* 0.12 in CH_2Cl_2) (Lit[1,2] $[\alpha]_D^{20}$ +16.1, for 90% ee-opposite major enantiomer), 82% ee (determined by chiral-HPLC); ν_{max}/cm^{-1}(KBr): 2957, 2927, 2855 (CH), 1720 (CO), 1467, 1458 (C=C, Ar), 1326, 1295, 1256, 1172, 1119 (SO_2), 871, 851, 750, 698 (CS); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 7.0, C(8′)H_3], 1.10–1.36 [14H, m, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2, C(2′)H_2, C(1′)H_2], 1.57–1.66 [1H, m, one of C(4)H_2], 1.70–1.83 [1H, m, one of C(4)H_2], 1.99–2.19 [2H, m, C(5)H_2], 2.29–2.41 [1H, m, C(3)*H*], 2.90–2.97 [1H, m, one of C(6)H_2], 3.59 [1H, apparent dt, *J* 13.6, 4.6, one of C(6)H_2], 3.90 [1H, dd, *J* 4.4, 2.9, C(2)*H*], 5.14 (1H, d, H_A of AB system, *J* 12.1, CH_2Ar), 5.30 (1H, d, H_B of AB system, *J* 12.1, CH_2Ar), 7.33–7.39 (5H, m, Ar*H*)



The more polar fraction **139b** (24 mg, 13%) was isolated as a white solid; mp 73–74 °C; ν_{max}/cm^{-1}(KBr): 2925 (CH), 1743 (CO), 1311, 1280 (SO_2), 745, 719, 697 (CS); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 6.9, C(9′)H_3], 1.17–1.35, 1.35–1.52 [16H, m, C(8′)H_2, C(7′)H_2, C(6″)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2, C(2′)H_2, C(1′)H_2], 1.74–1.87 [1H, m, one of C(4)H_2], 2.32–2.41 [1H,

m, one of C(4)H_2], 2.71–2.84 [1H, m, C(3)*H*], 3.09 [1H, apparent td, *J* 12.8, 6.9, one of C(5)H_2], 3.26 [1H, ddd, *J* 12.8, 6.8, 1.7 one of C(5)H_2], 3.61 [1H, d, *J* 9.5, C(2)*H*], 5.20–5.34 (2H, m, CH_2Ar), 7.29–7.43 (5H, m, Ar*H*).

This fraction also contains *approx*. 4% reduction product **111**, signals in ^{1}H NMR spectra appears at δ_H 3.98 (2H, s, SCH_2CO), 1.35–1.50 [18 H, m, C(11′)H_2, C(10′)H_2, C(9′)H_2, C(8′)H_2, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2].



The most polar fraction **38b** (18 mg, 10%) was isolated as a white solid; mp 88–89 °C (Lit 86–88°C);[1,2] $[\alpha]_D^{20}$ -10.0 (*c* 0.1 in CH_2Cl_2) (Lit $[\alpha]_D^{20}$ +3.9, for 45% ee-opposite major enantiomer);[1,2] 59% ee (determined by chiral-HPLC); ν_{max}/cm^{-1}(KBr): 2927, 2855 (CH), 1729 (CO), 1457 (C=C, Ar), 1314, 1272, 1195, 1131 (SO_2), 699 (CS); δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 7.0, C(8′)H_3], 1.09–1.38 [15H, m, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2, C(2′)H_2, C(1′)H_2 and one of C(4)H_2], 2.00–2.18 [3H, m, C(5)H_2 and one of C(4)H_2], 2.36–2.47 [1H, m, C(3)*H*], 2.85–2.94 [1H, m, one of C(6)H_2], 3.21 [1H, apparent dt, *J* 14.1, 4.2, one of C(6)H_2], 3.68 [1H, d, *J* 10.5, C(2)*H*], 5.28 (2H, s, CH_2Ar), 7.29–7.42 (5H, m, Ar*H*).

Table 4.16 *Asymmetric copper bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo-sulfone* ***37*** *(Method* ***A****)*

Entry	**Ligand**	**Time (h)**	**Crude Efficiency (%)[a,b]**		**Products[a]**			
					cis **: sulfolane[a, c,d]**	***cis*** **thiopyran [a,c]:**	***trans*** **thiopyran [a,c] :**	***trans*** **sulfolane[a,c]**
1	(4*S*)-*t*-Bu **138**	21	80–90	**Crude Ratio:** **Purified Yield (%)** **Overall Yield[g]**	4 : -	60 : 51% (81% ee)[e] (2*R*, 3*S*) 51% $[\alpha]_D^{20}$ -23.7(*c* 0.12)	14 : 10% (59% ee) 10% $[\alpha]_D^{20}$ -10.0 (*c* 0.1)	22 13%[f] 13%
2	(4*R*)-Bn **43**	20	80–90[h]	**Crude Ratio** **Purified Yield (%)** **Overall Yield[n]**	- :	70 : 49% (80% ee)[i] (2*S*, 3*R*) 51% $[\alpha]_D^{20}$ +13.64 (*c* 0.11)	13 : 4% (10% ee)[j] $[\alpha]_D^{20}$ +9.5 (*c* 0.1)	17 10%, 6%[k] 13%

3	(4*R*,5*S*)- di-Ph **137**	22	80–90	**Crude Ratio** **Purified Yield (%)** **Overall Yield[n]**	5 : -	62 : 12% (79% ee)[l] (2*S*, 3*R*) 12%	11 : -[m]	22 7%[n] 6%

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **139a**, δ_H 3.92 [1H, d, *J* 6.5, C(2)*H*], *cis* thiopyran **38a**, δ_H 3.90 [1H, dd, *J* 4.4, 2.9, C(2)*H*]; *trans* thiopyran **38b**, δ_H 3.68 [1H, d, *J* 10.5, C(2)*H*]; *trans* sulfolane **139b**, δ_H 3.61 [1H, d, *J* 9.5, C(2)*H*].

b. ~1% reduction product **111** observed in all ^{1}H NMR spectra of crude products; δ_H 3.98 (2H, s, SCH_2CO).

c. Estimation due to peak overlap.

d. Signal in ^{1}H NMR spectra for *cis* sulfolane **139a**; δ_H 3.92 [1H, d, *J* 6.5, C(2)*H*], otherwise not fully characteristed.

e. The enantioselectivity of 81% ee is based on a weighted average. The enantioselectivity and the relative masses of each fraction(s)are given as follows; Fraction one-84% ee, 7% mass (baseline impurity), fraction two-82% ee, 63% mass, fraction three-78% ee, 30% mass (contains 95% *cis* thiopyran **38a**, 5% *trans* sulfolane **139b**).

f. Three fractions of product were obtained. The % yield is given for all three fractions combined. Fraction one (42% mass) contains 78% *trans* sulfolane **139b**, 11% *cis* thiopyran **38a**, 6% *cis* sulfolane **139a** and 5% reduction product **111**, fraction two (56% mass) contains 97% *trans* sulfolane **139b**, 3% reduction product **111**, fraction three (2% mass), contains 97% *trans* sulfolane **139b** and 3% reduction product **111**.

g. Overall Yield is calculated from amounts of each compound in various fractions.

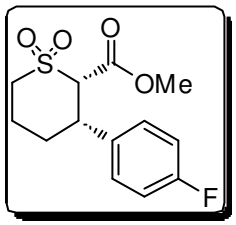
h. Unidentified peaks observed in product ^{1}H NMR spectra of the crude product; δ_H 4.68 (s), 8.05–8.11 (m), 8.16–8.25 (m), 8.69 (s).

i. The enantioselectivity of 80% ee is based on a weighted average. The enantioselectivity and the relative masses of each fraction(s) are given as follows; fraction one-84% ee, 19% mass (baseline impurity), fraction two-82% ee, 50% mass, fraction three-74% ee, 31% mass (contains 93% *cis* thiopyran **38a**, 7% *trans* sulfolane **139b**, decrease in % ee may be due to overlapping peaks).

j. Two fractions were obtained, fraction one (12% mass) contains 95% *trans* thiopyran **38b**, 5% aldehyde δ_H 9.42 (s), fraction two (88% mass, clean). Enantioselectivity measured on fraction two.

k. Two fractions obtained. Fraction one (10%) contains *approx* 61% *trans* sulfolane **139b**, 27% *cis* thiopyran **38a**, 7% reduction product **111** (5% baseline/unknown). Fraction two (6%) contains 95% *trans* sulfolane **139b** and 5% reduction product **111**.
l. Contains 94% *cis* thiopyran **38a**, 3% *trans* sulfolane **139b** and 3% *cis* sulfolane **139a**.
m. Not isolated after chromatography.
n. Contains *approx* 84% *trans* sulfolane **139b**, 14% *cis* thiopyran **38a** and 2% reduction product **111**.

(2*S*,3*S*)-Methyl 3-(4-fluorophenyl)tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide *cis* 145a



Methyl 2-diazo-2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate **45** (100 mg, 31.8 mmol) in dichloromethane (5 mL) was directly added to CuCl (1.57 mg, 16 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (16.92 mg, 19 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (6.35 mg, 19 μmol) in dichloromethane (10 mL). The mixture was heated to reflux directly following addition and stirred under reflux under an inert atmosphere for 21 h (in accordance with Method **A**). The solution was then cooled and concentrated under reduced pressure. ^{1}H NMR spectroscopy of the crude product showed the reaction was *approx* 75–85% efficient (91% *cis* thiopyran **145a**: 4% *trans* thiopyran **145b**: 5% *trans* sulfolane **153b**) Following purification, by flash chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*S*,3*S*)-methyl 3-(4-fluorophenyl)tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide *cis* **145a** (45 mg, 49%) was isolated as a white solid; mp 155–156 °C; $[\alpha]_D^{20}$ +92.0 (*c*, 1.0 CH_2Cl_2) 98% ee (determined by chiral-HPLC); (Found C, 54.57; H 5.31; S, 11.44, $C_{13}H_{15}O_4FS$ requires C, 54.53; H, 5.28; S, 11.20%); ν_{max}/cm^{-1} (KBr): 2956, 2939 (CH) 1735 (CO), 1512 (C=C, Ar), 1317, 1114 (SO_2) 840; δ_H ($CDCl_3$, 300 MHz): 1.84 [1H, apparent dq, *J* 13.6, 3.2, one of C(4)H_2], 2.10–2.36 [2H, m, C(5)H_2], 2.58 [1H, apparent qd, *J* 13.2, 3.9, one of C(4)H_2], 3.05 [1H, apparent dq, *J* 14.1, 3.4, one of of C(6)H_2], 3.56 (3H, s, OCH_3), 3.61–3.73 [2H, m, one of C(6)$H_2$and C(3)*H*], 3.96 [1H, dd, *J* 4.5, 2.9 C(2)*H*], 6.95–7.07 (2H, m, Ar*H*), 7.12–7.23 (2H, m, Ar*H*); δ_c ($CDCl_3$, 75.5 MHz): 22.9, 23.8 [2 × CH_2, *C*(4)H_2, *C*(5)H_2], 43.8 [CH, *C*(3)H], 47.8 [CH_2, *C*(6)H_2], 52.7 (CH_3, O*C*H_3), 70.4 [CH, *C*(2)H], 115.8 [2 × ArCH, d, $^2J_{CF}$ 21.4, *C*(3')H, *C*(5')H], 128.6 [2 × ArCH, d, $^3J_{CF}$ 8.1, *C*(2')H, *C*(6')H], 135.3 [C, d, $^4J_{CF}$ 3.3, *C*(1')], 162.1 [C, $^1J_{CF}$ 246.9, *C*(4')], 166.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{16}O_4FS$ [M+H] $^+$, 287.0753. Found 287.0767.

Stereochemistry assigned by analogy

Copper catalysed reactions of ethyl 2-diazo-2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate **45** yielded (2*S*,3*S*)-methyl 3-(4-fluorophenyl)tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide *cis*-**145a** as the major

product. Additional products were observed in the crude mixtures. The following table (**Table 4.17**) shows these products and signals from ^{1}H NMR spectroscopy. Not every product listed appears in the mixture of every cyclisation and the relative amounts vary. These products are not fully characterised but their assignments are made on the basis of the analogous compound.[1]

Table 4.17

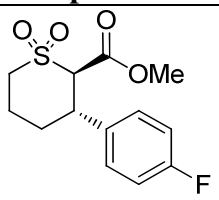
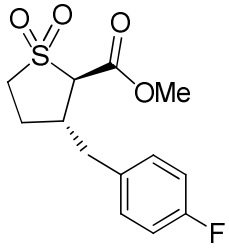
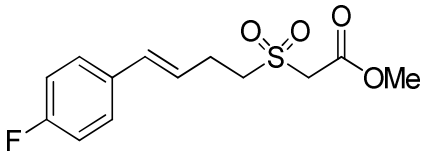
Entry	Compound	^{1}H NMR
1	 **145b**	δ_H 3.59 (3H, s, OCH_3), 4.10 [1H, d, *J* 12.1, C(2)*H*].
2	 **153b**	δ_H 2.68–2.75 (1H, m, H_A of CH_2Ar), 2.85–2.91 (1H, m, H_B of CH_2Ar), 3.28 [1H, ddd, *J* 12.3, 7.1, 1.5, H_B of CH_2Ar C(5)H_2], 3.75 (3H, s, OCH_3).
3	 **154**	δ_H 6.05–6.15 [(1H, m, C(3′)*H*], 6.50 [1H, d, *J* 15.8, C(4′)*H*].

Table 4.18 *Copper bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo-sulfone* **45** *(Method A)*

Entry	Ligand	Time (h)	Crude Efficiency[a]	Crude Ratio (*cis* thiopyran **145a**: *trans* thiopyran **145b** : *trans* sulfolane **153b**)[a]	(*cis* thiopyran **145a**)		
					Yield (%)	% ee	$[\alpha]_D^{20}$
1	(4*R*)-Ph **20**	21	~75–85%	91 : 4 : 5	49	98 (2*S*,3*S*)	+92 (*c* 1.000)
2	(4*R*,5*S*)-di-Ph **137**	21	~75–85%	84 :7 : 9[b]	55	98 (2*S*,3*S*)	
3	(4*S*)-*t*-Bu **138**	48	~75–85%	84 : 12 : 5[b]	52	80 (2*R*,3*R*)	-68.5 (*c* 1.000)
4	(4*R*)-Bn **43**	21	~37% Complex Mixture of Products	84 : 12 : 5	25[c]	53 (2*S*,3*S*)	
5	$Cu(OTf)_2$[d]	48	~30% efficient. Complex mixture Hydride elimination **154** ~6%	78 : 19 : 2	24	-	-

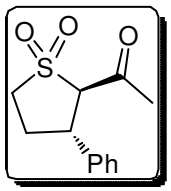
a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_3, *cis* thiopyran **145a**; δ_H 3.56 (3H, s, OCH_3), *trans* thiopyran **145b**; δ_H 3.59 (3H, s, OCH_3), *trans* sulfolane **153b**; δ_H 3.75(3H, s, OCH_3). (see **Table 4.17**)

b. A shift in the singlet for *trans* thiopyran **145b** was observed in the ^{1}H NMR spectra of the crude product of ***entries* 2** and **3** from δ_H 3.59 (3H, s, OCH_3) (entries 1, 4 and 5) to δ_H 3.57 (3H, s, OCH_3) (entries 2 and 3). Therefore the presence of *trans* thiopyran **145b** in the crude mixture of products is interpreted cautiously.

c. A less polar mixed fraction was obtained with the following characteristics; (5 mg) δ_H 1.67-2.01 (m), 2.53–2.74 (m), 3.24–3.34 (m), 3.37–3.43 (m), 3.43–3.49 (m), 3.56 (s), 3.86 (s), 3.91 (s), 6.93–7.33 (m) (90% reduction product **112** +10% X–H insertion **155**).

d. Method C was employed.

(2*R*,3*S*)-1-(3-Phenyl-1, 1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans* 42b[1,2]



CuCl (1.10 mg, 11.2 μmol), 1-(phenylpropylsulfonyl)-1-diazopropan-2-one **41** (60.00 mg, 0.23 mmol), sodium tetrakis[3, 5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.97 mg, 13.5 μmol) and bisoxazoline ligand (4*R*)-Bn **43** (4.90 mg, 13.5 μmol) were added to dichloromethane (12 mL). The mixture was heated to reflux and stirred while heating under reflux for 21 h, in accordance with Method **A**. The solution was cooled and concentrated under reduced pressure. ^{1}H NMR spectroscopy of the crude product showed that greater than 90% of compound **42b** was present. Following purification, by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*R*, 3*S*)-1-(3-phenyl-1,1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans* **42b** (17.6 mg, 33%) was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1,2] mp 129–131 °C (Lit 118–120 °C); [1,2] $[\alpha]_D^{20}$ +63.8 (*c* 0.112 in CH_2Cl_2) (Lit[1,2] $[\alpha]_D^{20}$ +49.9, for 40% ee), 59% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (KBr): 1714 (CO), 1605, 1497, 1458, 1412 (C=C, Ar), 1365, 1296, 1169, 1122 (SO_2), 753, 702 (CS); δ_H ($CDCl_3$, 300 MHz): 2.24–2.43 [4H, m, one of C(4)H_2 incorporating 3H, s at 2.37, COCH_3], 2.45–2.59 [1H, m, one of C(4)H_2], 3.18 [1H, apparent td, *J* 12.9, 6.9 H_A of C(5)H_2], 3.42 [1H, ddd, *J* 12.9, 6.9, 1.7 one of C(5)H_2], 3.97–4.10 [1H, m, C(3)*H*], 4.17 [1H, d, *J* 9.8, C(2)*H*], 7.23–7.41 (5H, m, Ar*H*).

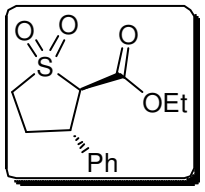
Note; A ^{1}H NMR spectrum recorded on a sample after 24 months stored at room temperature showed no change in compound **42b**.

Table 4.19 *Asymmetric copper-bisoxazoline catalysed C–H insertion reaction of α-diazo-β-oxo sulfone* **41** *(Method **A**)*

Entry	Ligand	Time (h)	Crude Efficiency[a]	Yield (%)	ee (%)	$[\alpha]_D^{20}$
1	(4*R*)-Bn **43**	21	>90% **42b**	33	59 (2*R*,3*S*)	+63.8(*c* 0.112)
2	(4*R*,5*S*)-di-Ph **137**	21	>80% **42b**	19	36 (2*R*,3*S*)	-
3	(4*S*)-*t*-Bu **138**	26	>90% **42b**	53	51(3*R*,2*S*)	-76.6 (*c* 0.113)

a. Efficiency calculated using C(2)*H,* δ_H 4.17 [1H, d, *J* 9.8, C(2)*H*].

(2*R*,3*S*)-Ethyl 2-(3-phenyl-1, 1-dioxo-tetrahydrothiophen-2-yl)carboxylate *trans* 40b[1,2]



The title compound was prepared according to the procedure described for (2*R*,3*S*)-1-(3-phenyl-1,1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans* **42b** using 2-diazo-2-(3-phenylpropylsulfonyl) acetate **39** (100 mg, 0.34 mmol), CuCl, (1.67 mg, 16.9 μmol), NaBARF (17.9 mg, 20.2 μmol) and bisoxazoline ligand (4*R*)-Bn **43**, (7.32 mg, 20.2 μmol) in dichloromethane (15 mL), stirred while heating under reflux for 26 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude product showed that greater than 90% of compound **40b** was present. Following purification, by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*R*,3*S*)-ethyl 2-(3-phenyl-1, 1-dioxo-tetrahydrothiophen-2-yl)carboxylate *trans*-**40b** (43 mg, 53%) was isolated as a white solid. Spectroscopic characteristics are consistent with those previously reported;[1,2] mp 95-97 °C (Lit 94-96 °C);[1,2] $[\alpha]_D^{20}$ +1.7 (*c* 1.0 in CH_2Cl_2) (Lit[1,2] $[\alpha]_D^{20}$ +21.3, for 60% ee); 5% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (KBr) 1739 (CO), 1456 (C=C, Ar), 1380, 1317, 1277, 1195, 1123 (SO_2), 759, 702 (CS); δ_H ($CDCl_3$, 300 MHz) 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 2.26-2.43 [1H, m, one of C(4)H_2], 2.46-2.59 [1H, m, one of C(4)H_2], 3.23 [1H, apparent dt, *J* 12.9, 6.9, one of C(5)H_2], 3.45 [1H, ddd, *J* 12.9, 6.8, 1.6, one of C(5)H_2], 3.89-4.08 [2H, m, C(2)*H* and C(3)*H*], 4.12-4.39 (2H, m, OCH_2CH_3), 7.24-7.44 (5H, m, Ar*H*).

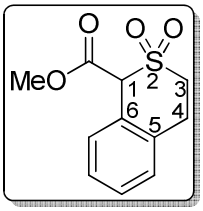
Table 4.20 *Asymmetric copper-bisoxazoline catalysed C–H insertion reaction of α-diazo-β-oxo sulfone* **39** *(Method* ***A****)*

Entry	Ligand	Time (h)	Crude Efficiency (%)[a]	Yield (%)	% ee	$[\alpha]_D^{20}$
1	(4*R*)-Bn **43**	26	>90% **40b**	53	5 (2*R*,3*S*)	+1.7 (*c* 1.000)
2	(4*R*,5*S*)-di-Ph **137**	48	> 90% (1 :1) (**40a** : **40b**)	69	65 (2*R*,3*S*)	+42.3 (*c* 0.122)
3	(4*S*)-*t*-Bu **138**	3	>90% **40b**	61	0 (2*S*,3*R*)	-

a. Efficiency calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H* and C(3)*H*, *trans* sulfolane **40b**; δ_H 3.89-4.08 [2H, m, C(2)*H* and C(3)*H*].

Note; A ^{1}H NMR spectrum recorded on a sample, stored at room temperature for 30 months showed no change in compound.

Methyl isothiochroman-1-carboxylate 2,2-dioxide 146



The title compound was prepared according to the procedure described for (2*R*,3*S*)-1-(3-phenyl-1,1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans*-**42b** using methyl 2-diazo-2-(phenethylsulfinyl)acetate **62** (80 mg, 0.30 mmol), $CuCl_2$ (2.0 mg, 15 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (15.7 mg, 18 μmol) and bisoxazoline ligand (4*R*,5*S*)-di-Ph **137** (8.2 mg,18 μmol) in dichloromethane (20 mL), stirred while heating under reflux for 2 h. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 80–90% efficient. Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, methyl isothiochroman-1-carboxylate 2,2-dioxide **146** (49 mg, 68%) was isolated as a white solid; mp 118–119 °C; 0% ee (determined by chiral HPLC); ν_{max}/cm^{-1} (KBr): 2936 (CH), 1736 (CO), 1429 (C=C, ArH), 1321, 1312, 1298, 1121 (SO_2), 740 (CS); δ_H ($CDCl_3$, 600 MHz): 3.22 (1H, dddd, *J* 14.1, 5.1, 3.8, 2.6 one of SO_2CH_2), 3.43–3.59 (2H, m, $SO_2CH_2CH_2$), 3.84 (3H, s, OCH_3), 3.93–4.01 (1H, ddd, *J* 14.1, 11.4, 5.7, one of SO_2CH_2), 4.99 (1H, d, *J* 2.5, SO_2CH), 7.11–7.14 (1H, m, Ar*H*), 7.24–7.29 (2H, m, Ar*H*), 7.31–7.36 (1H, m, Ar*H*); δ_c ($CDCl_3$, 150.9 MHz) 29.0 (CH_2, $SO_2CH_2CH_2$), 45.9 (CH_2, SO_2CH_2), 53.8 (CH_3, OCH_3), 67.8 (CH, SO_2CH), 127.4 (CH, aromatic *C*H), 128.1 (C, aromatic *C*), 129.3 (CH, aromatic *C*H), 130.0 (CH, aromatic *C*H), 130.1 (CH, aromatic *C*H), 132.0 (C, aromatic, *C*), 166.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}O_4S$ $[M+H]^+$, 241.0535. Found 241.0527.

Assignments made with aid of 2D NMR experiments.

Table 4.21 *Copper catalysed C–H insertion reaction of α-diazo-β-oxo sulfone* **62** *(Method **A**)*

Entry	Crude Efficiency[a]	Ligand	Time (h)	Yield (%)	% ee
1	~85–90%[b]	(4*R*,5*S*)-di-Ph **137**	2	68	0
2	~80–90%	(4*R*)-Bn **43**	2	66	0
3	~80–90%	(4*S*)-*t*-Bu **138**	3	69	0
4	~80–90%[c]	(4*R*)-Ph **20**	2	70[d]	0

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for **146** C(2)*H*; δ_H 4.99 [1H, d, *J* 2.5, SO_2CH].
b. Additional product observed in the ^{1}H NMR spectra of the crude product; δ_H 5.44 (d, *J* 9.4), 6.16 (d, *J* 9.7), 6.23 (d, *J* 7.9), 6.37–6.45 (m), 6.91 (d, *J* 7.8).
c. Additional product observed the ^{1}H NMR spectra of the crude product; δ_H 5.71 (dd, *J* 4.3, 8.9), 6.37–6.45 (m), 6.5–6.65 (m) 6.78 (dd, *J* 5.6, 11.6).
d. Additional product observed in the ^{1}H NMR spectra of the pure product; δ_H 4.16 (t, *J* 8.0), 4.67 (dd, *J* 8.4, 10.1), 5.23 (dd, *J* 7.8, 10.0), 5.68–5.75 (m).

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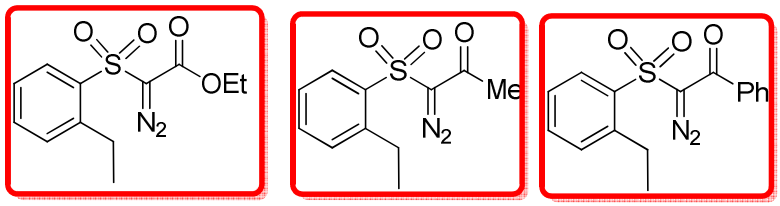
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Chapter Five
C–H insertion reactions of α-diazo-β-oxo sulfones bearing a non flexible linker

"*Or watch the things you gave your life to, broken, And stoop and build 'em up with worn-out tools*……" Rudyard Kipling

5.1 Introduction

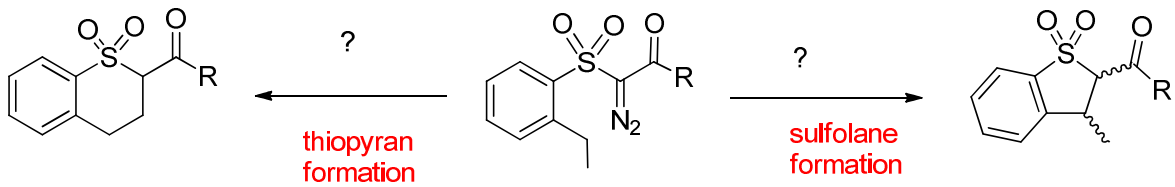
The general features of transition metal catalysed C–H insertion reactions of α-diazocarbonyl compounds have been discussed in Chapters 2 and 4.[1–16] Based on our observation of excellent enantiocontrol in C–H insertion reactions of α-diazo-β-oxo sulfones using a freely rotating alkyl chain (up to 98% ee),[17–23] we wished to explore the scope of this reaction when less flexible linker chains were present. The α-diazo-β-oxo sulfones **54**–**56** were selected for investigation where a rigid aryl ring replaces the flexible alkyl chain. (**Figure 5.1**)



54 **55** **56**

Figure 5.1

These substrates were particularly interesting as insertion can occur at either the benzylic site to form a sulfolane or at the methyl group to form a thiopyran. Our previous results indicated that thiopyran formation is favoured over sulfolane formation when both are possible. On the other hand insertion at a benzylic C–H bond is favoured (**Scheme 5.1**). Accordingly substrates **54**–**56** allow further exploration of these trends.



Scheme 5.1

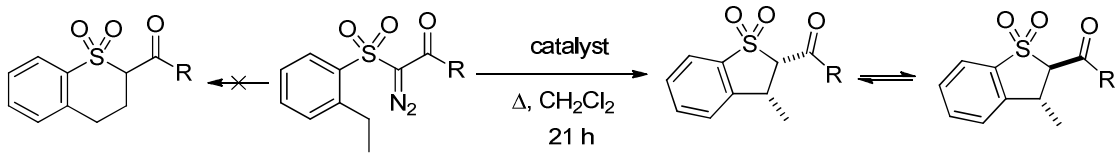
As the highest enantiocontrol achieved to date for sulfolane formation was 65% ee (**Section 4.3.4**, **Table 4.8**), extending the scope to this fused series could potentially lead to improvement in enantiopurity. The initial challenge was to explore the reaction pathway, to establish if C–H insertion to form the thiopyran or sulfolane is obtained. As

the substituent on the carbonyl had strongly influenced the outcome of the C–H insertion, especially the enantioselectivity, to form the sulfolanes **40b** and **42b**, three derivatives, the α-diazo-α-sulfonyl ethyl ester **54**, α-diazo-α-sulfonyl methyl ketone **55** and α-diazo-α-sulfonyl phenyl ketone **56** were explored, which are shown in **Figure 5.1**.

5.2 Synthesis of racemic samples of substrates 165, 166 and 167

Substrates **54**–**56** were initially exposed to achiral catalysts to generate racemic cyclised products, to explore the pathway followed and to generate racemic samples to allow the development of chiral HPLC conditions so that enantioenriched samples can be accurately analysed. The results of this study are presented in **Table 5.1**. In all cases only the sulfolane was observed, with no evidence for thiopyran formation through insertion into the methyl groups.

Table 5.1 *Achiral catalysed C–H insertion reactions of α-diazo-β-oxo sulfones* **54-56**



Entry	Method	R	M	Crude Efficiency	Yield (%)		*cis* % ee	:	*trans* % ee
1	**C**	OEt	$Cu(OTf)_2$[a] (5 mol%)	~60–70%[b]	29[c]	**Crude:** **Purified:**	50 7 (0% ee) **165a**		50 93 (0% ee) **165b**
2	**E**	Ph	$Rh_2(OAc)_4$ (1 mol%)	~70–80%[d]	40 (80% **167**)[e]	**Crude:** **Purified:**	10 1 **167a**		90 99 (0% ee) **167b**
3	**E**	Me	$Rh_2(OAc)_4$ (1 mol%)	~95%[f]	56	**Crude:** **Purified:**	9 2 **166a**		91 98 (0% ee) **166b**

a. Contains multiple products in the crude mixture, including minor amounts of starting material **54** and X–H insertion product **168**.
b. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_2CH_3, *cis* sulfolane **165a**, δ_H 1.26 (3H, t, *J* 7.1, OCH_2CH_3); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).
c. Additional material present, including X–H insertion product **168**.
d. Efficiency and relative ratios of isomers calculated using the ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **167a**, δ_H 5.45 [1H, d, *J* 5.4, C(2)*H*]; *trans* sulfolane **167b**, δ_H 5.02 [1H, d, *J* 6.9, C(2)*H*].
e. Purified product was not 100% pure, and contained ~20% of unidentified material.

f. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **166a**, δ_H 4.44 [1H, d, *J* 6.5, C(2)*H*]; *trans* sulfolane **166b**, δ_H 4.17 [1H, d, *J* 7.0, C(2)*H*].

α-Diazo-α-sulfonyl ethyl ester **54** was the first substrate to undergo transition metal catalysed intramolecular C–H insertion. The reaction was carried out with 5 mol% $Cu(OTf)_2$ in refluxing dichloromethane and was monitored using IR analysis; the disappearance of the diazo stretch at ν_{max} 2126 cm^{-1} (C=N$_2$) after 21 hours indicated that the reaction was complete; however, examination of the ^{1}H NMR spectra of the crude reaction mixture revealed that a trace amount of starting α-diazo-β-oxo sulfone **54** was present, in addition to minor amounts of X–H insertion product **168**, the most likely structure of which is chloride abstraction product **169** (**Figure 5.2**) (This has previously been discussed in **Chapter 4**, **Section 4.1.3**).

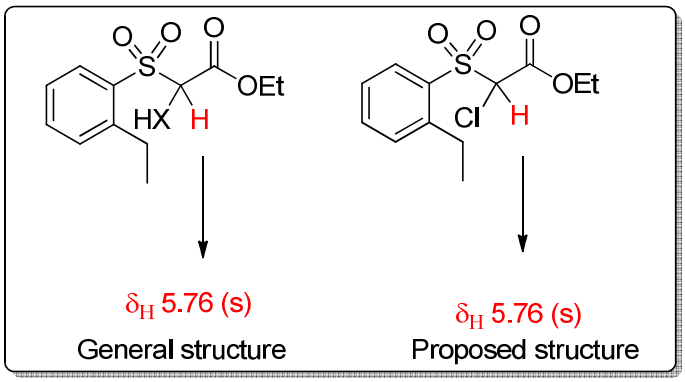
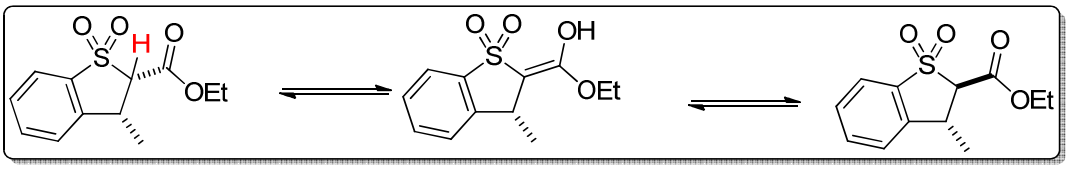


Figure 5.2

Further study of the ^{1}H NMR spectrum showed a moderate reaction efficiency of ~60–70% for C–H insertion which contained a mixture of *cis* and *trans* sulfolane in a ratio of 50 : 50. There was no evidence in the crude reaction mixture for thiopyran formation. Thus, insertion was preferred into the benzylic position rather than at the methyl group, to form the thiopyran. During purification, using column chromatography on silica gel, epimerisation of the *cis* sulfolane **165a** to the *trans* sulfolane **165b** isomer occurred, presumably via an enol intermediate (**Scheme 5.2**).



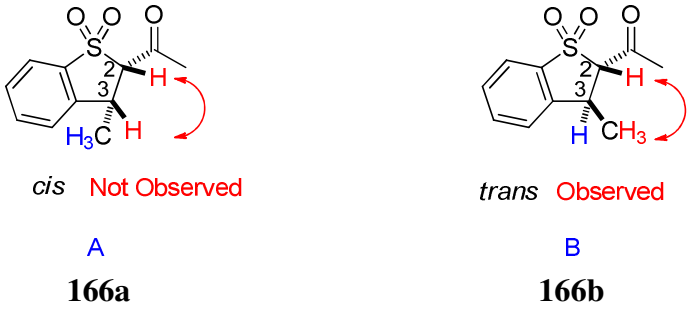
Scheme 5.2

This effect has previously been observed in the cyclopentanone series and is due to the acidic nature of C(2)*H*.[24] The purified mixture contained both *cis* sulfolane and *trans* sulfolane isomers in a ratio of 7 : 93, and was isolated as a colourless oil in a relatively poor yield of 29% (**Table 5.1**, entry 1). HPLC conditions were developed, that allowed full separation of the diastereomeric mixture, ensuring that enantioselectivities of both *cis* and *trans* sulfolane products could be measured.

$Rh_2(OAc)_4$ was used to catalyse the C–H insertion reactions of α-diazo-β-oxo sulfones **55** and **56**. These reactions involved the use of ~1 mol% $Rh_2(OAc)_4$ in refluxing dichloromethane. The disappearance of the diazo stretch at ν_{max} 2117 cm^{-1} (C=N_2) for α-diazo-α-sulfonyl phenyl ketone **56** and at ν_{max} 2115 cm^{-1} (C=N_2) for α-diazo-α-sulfonyl methyl ketone **55** indicated that the reactions were finished. Inspection of the ^{1}H NMR spectra of the crude reaction mixtures showed that there was a moderate difference in reaction efficiency for reaction with α-diazo-α-sulfonyl phenyl ketone **56** and α-diazo-α-sulfonyl methyl ketone **55** with values of 70–80% and ~95% being achieved respectively (**Table 5.1**, entry 2 and 3). However, the diastereomeric ratio of the crude material was essentially the same with the *trans* sulfolane isomer being the major reaction product when α-diazo-α-sulfonyl phenyl ketone **56** and α-diazo-α-sulfonyl methyl ketone **55** underwent C–H insertion (**Table 5.1**, entry 2–3). Following purification of the crude reaction material, there was a noticeable change in the *cis* : *trans* ratio; the *cis* isomer accounted for *approx* 10% of the crude C–H insertion products for both the phenyl ketone derivative and the methyl ketone derivative, while it was present at lower levels (1–2%) in the purified material in both cases (**Table 5.1,** entries 2 and 3), presumably due to epimerisation. These results are in agreement with those previously obtained for the ethyl ester derivative **54** (**Table 5.1**, entry 1). Factors affecting *cis* : *trans* sulfolane ratios observed in the crude reaction mixture of diazo-β-oxo sulfones **54**–**56** will be discussed in more detail later in this Section (**Table 5.2**) and **Section 5.3.2**. Phenyl ketone derivative (1 : 99, *cis* **167a**: *trans* **167b**) and methyl ketone derivative (2 : 98, *cis* **166a** : *trans* **166b**) were isolated in moderate yields, with values of 40% and 56% obtained respectively (**Table 5.1**, entries 2 and 3). In the case of both ketone derivatives **166b** and **167b**, HPLC conditions were developed that allowed the separation of the enantiomers of the major *trans* isomer, however, the minor *cis* isomer was not detected in either case. Each of the three sulfolanes **165**, **166** and **167** (**a** and **b** of each) is a novel compound. In each case,

the *trans* isomer was fully characterised using ^{1}H NMR, ^{13}C NMR and IR spectroscopy in addition to high resolution mass spectrometry.

Determination of the relative stereochemistry of the *cis* and *trans* isomers was made using NMR experiments, namely NOESY and NOE difference. These experiments were carried out on the purified sample of a methyl ketone sulfolane **166b** (**Table 5.1**, entry 3) and the relative stereochemistry of the major isomer was determined to be *trans* **166b**. If the major isomer was *cis* **166a**, the protons on C(2)*H* and C(3)*H* would be expected to correlate to one another in the 2D NOESY spectrum, and a positive NOE effect would be expected in the 1D NOE difference spectrum, as depicted in (A) **Figure 5.3**. In practice, a positive NOE effect was not observed between these two protons, leading to the conclusion that they are *trans* with respect to one another. In addition, in the NOESY spectrum there was evidence for correlation between C(2)*H* and the methyl group at C(3) as depicted in (B) **Figure 5.3**, leading to the conclusion that the *trans* isomer was the major reaction product.



166a **166b**

Figure 5.3

The relative stereochemistry for ethyl ester (*cis* **165a** and *trans* **165b**) and phenyl ketone (*cis* **167a** and *trans* **167b**) sulfolanes was subsequently assigned by analogy. The assignments were based on two key points; firstly the chemical shift of the C(2)*H* proton in the *cis* isomers **165a**, **166a** and **167a** was further downfield than the corresponding *trans* isomers **165b**, **166b** and **167b**, as can be seen in **Figure 5.4** and secondly it was envisaged that the more stable *trans* isomers would be recovered following epimerisation during chromatography.

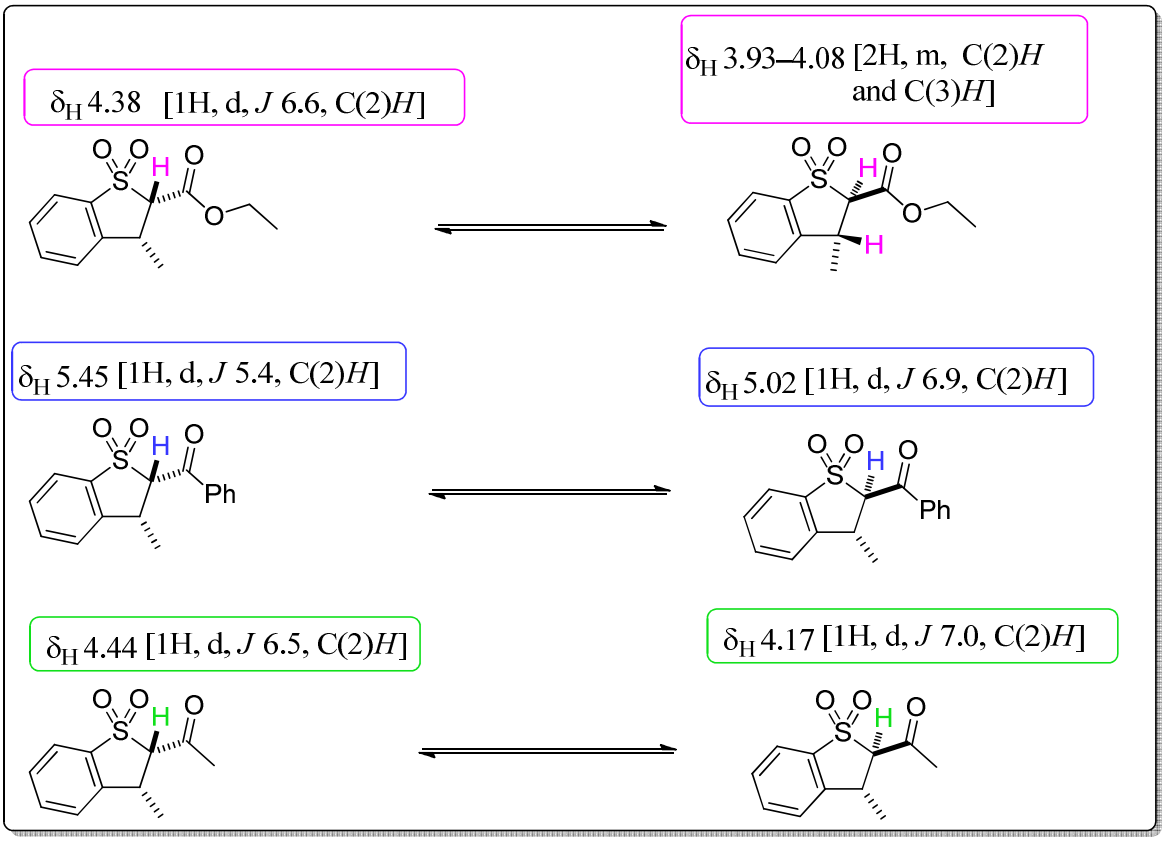


Figure 5.4

Further evidence for the assignment of the relative stereochemistry of these products comes from a crystal structure of carboxylic acid **170b** obtained from hydrolysis of ethyl ester **165b**; this is discussed in greater detail in **Section 5.3.1**.

There are a number of key signals that allow the identification and quantification of the *cis* isomers **165a**, **166a** and **167a** and the *trans* isomers **165b**, **166b** and **167b** in the crude and purified ^{1}H NMR spectra of the cyclisation products. Due to signal overlap, different signals are selected in different cases to ensure accurate measurement of ratios, as depicted in **Figure 5.5**. For reaction mixtures containing ethyl ester sulfolanes *cis* **165a** and *trans* **165b** it is the methyl signal of the ethyl ester group that is used, in practice, to quantify the *cis* : *trans* ratio. For methyl ketone (*cis* **166a** and *trans* **166b**) and phenyl ketone sulfolanes (*cis* **167a** and *trans* **167a**) it is generally the C(2)*H* signal that is used for comparison. These signals were chosen as they are the most distinguishable in the ^{1}H NMR spectra.

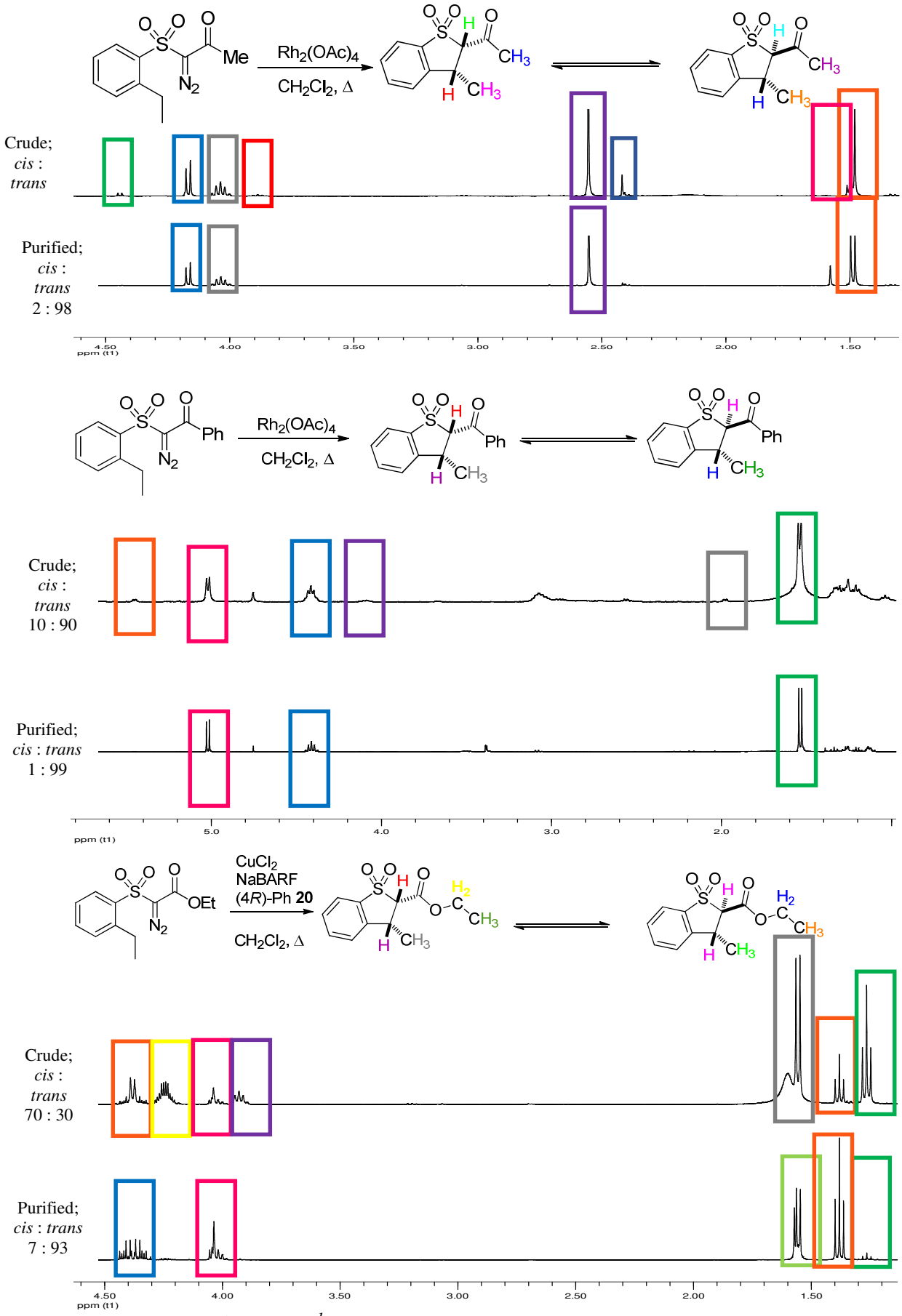
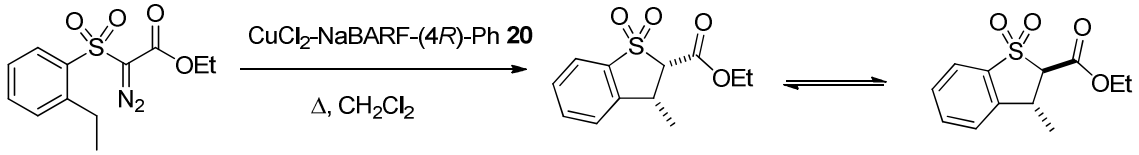


Figure 5.5 *^{1}H NMR spectra recorded in $CDCl_3$ (400 MHz)*

A further study was then conducted to investigate the effects of prolonged heating in dichloromethane on *cis*/*trans* isomerisation. In addition, epimerisation of *cis* **165a** to *trans* **165b** in deuterated chloroform was examined. During the course of the investigation into asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones **54-56** it was found that for reaction of α-diazo-α-sulfonyl ethyl ester **54** catalysed by $CuCl_2$-NaBARF-(4*R*)-Ph **20** the reaction mixture consisted mostly of *cis* sulfolane **165a** (*cis* : *trans*, 89 : 11), which epimerised on silica gel to give nearly entirely *trans* sulfolane **165b** (*cis* : *trans*, 94 : 6) (**Table 5.2**, entry 1). For this reason, as well as the very short reaction time of 2 hours, this was chosen as the model reaction for the isomerisation study. (Additional details of this reaction, such as enantioselectivity *etc* will be discussed in detail in **Section 5.3.1**). This reaction was repeated and was deemed complete after 1 h by IR analysis, at which point a sample was withdrawn and a ^{1}H NMR spectrum in $CDCl_3$ was obtained, to enable determination of the *cis* : *trans* ratio, with the initial sample being held in $CDCl_3$. The reaction mixture was stirred for a further 9 days, during which period aliquots were withdrawn to enable measurements of the *cis* **165a**: *trans* **165b** ratios using ^{1}H NMR.

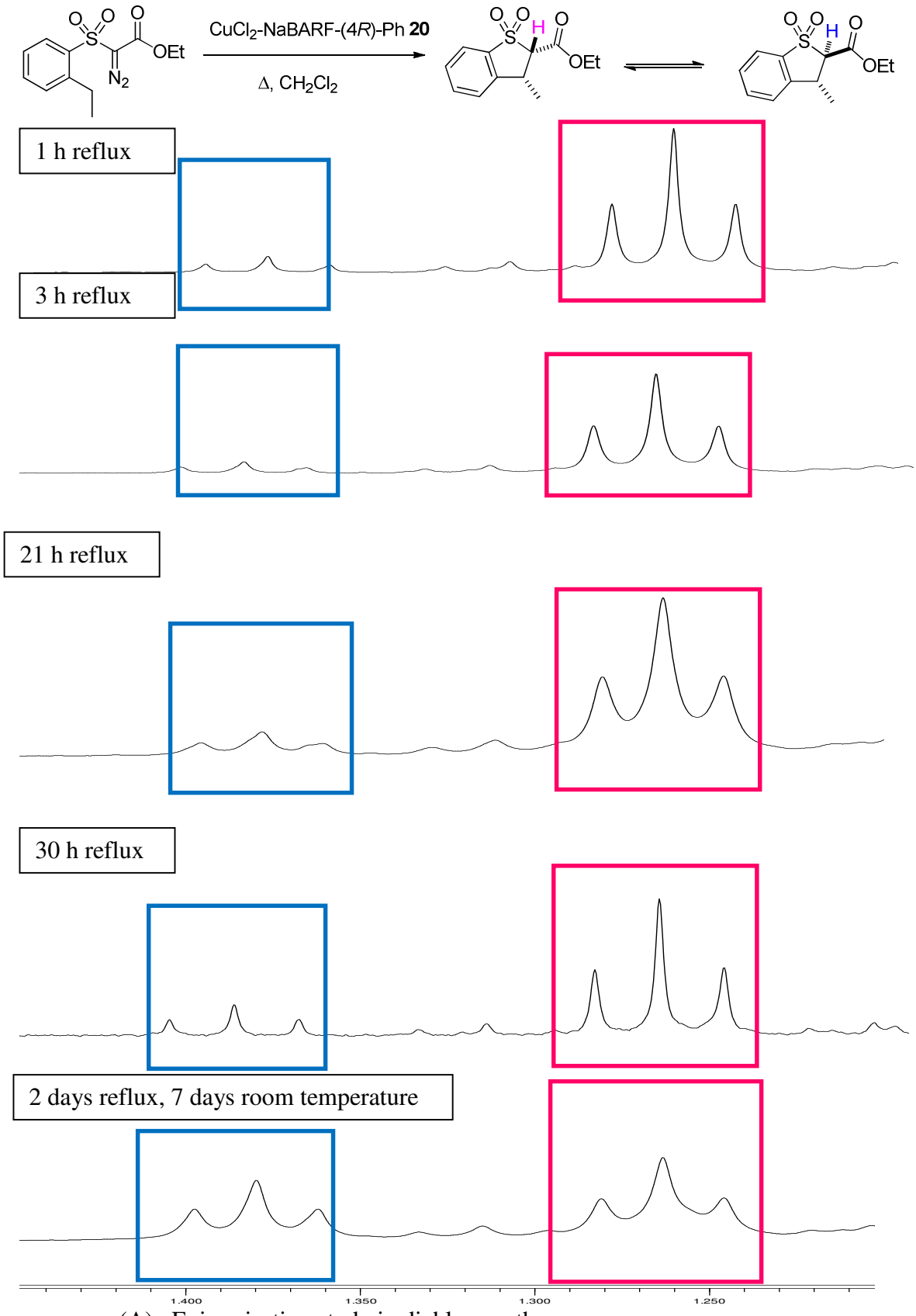
Table 5.2 *Study on factors affecting the ratio of epimerisation of* cis *sulfolane* **165a** *to* trans *sulfolane* **165b**



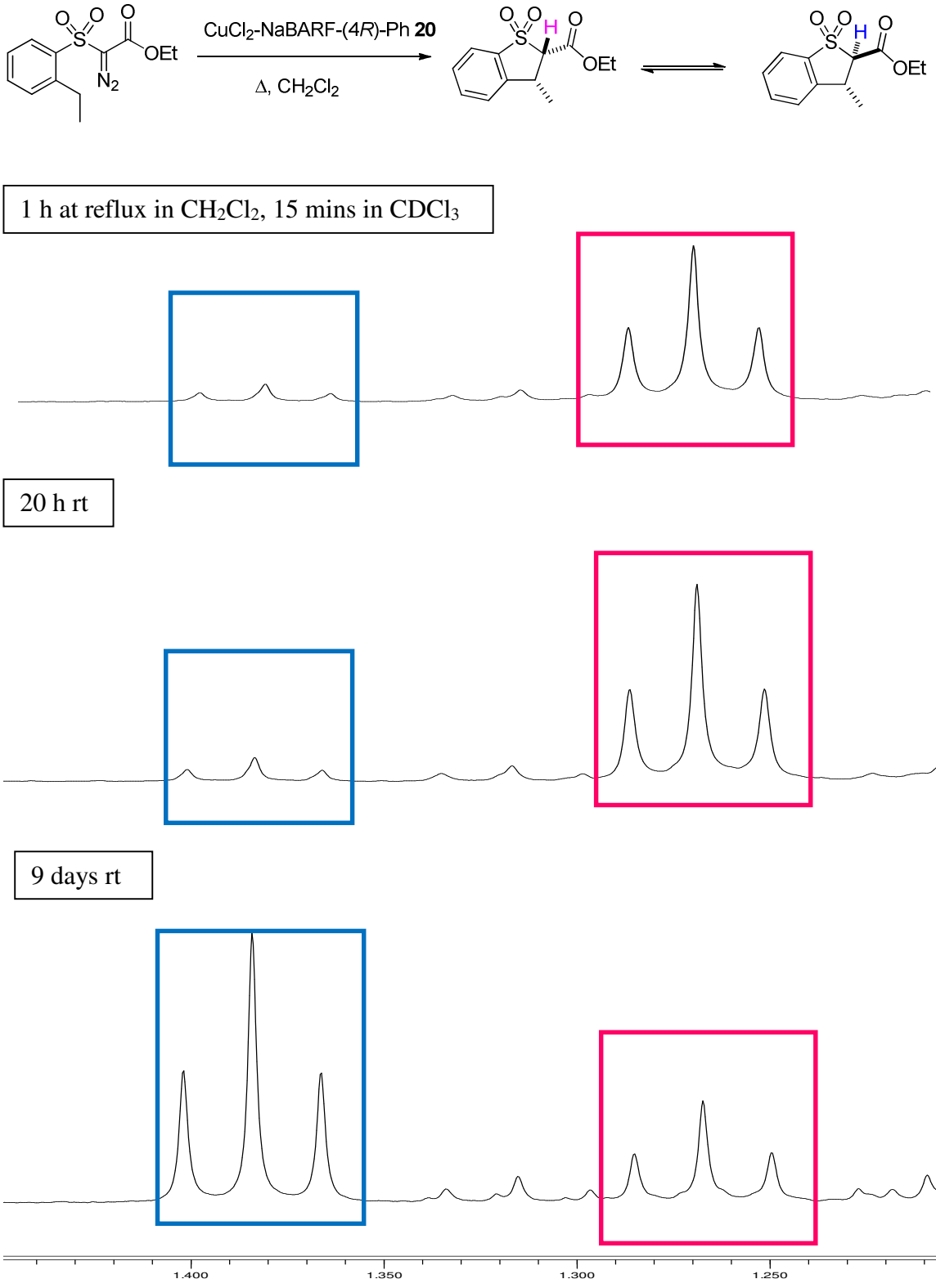
Entry	Time	Solvent	Temperature	*cis* : *trans*[b]
1[a]	1h	CH_2Cl_2	Reflux*	88% : 12%
	20 h	$CDCl_3$	rt	87% : 13%
	9 days	$CDCl_3$	rt	33% : 67%
2	3h	CH_2Cl_2	reflux	87% : 13%
3	21h	CH_2Cl_2	reflux	84% : 16%
4	30h	CH_2Cl_2	reflux	81% : 19%
5	9 days	CH_2Cl_2	2 day reflux, 7 days rt	60% : 40%
6[c]	~0.5 h	Silica gel	Room temperature	**Crude:** 70% :30% **Purified**: 7%:93%

a. The initial sample was held in $CDCl_3$ and two further ^1H NMR spectra of this sample were obtained, one after 20 h in $CDCl_3$ and one after 9 days in $CDCl_3$.
b. Relative ratios of isomers calculated using ^1H NMR spectra of the crude product using signals for OCH_2CH_3, *cis* sulfolane; 1.26 (3H, t, *J* 7.1, OCH_2CH_3) *trans* sulfolane; δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).
c. Results reported here refer to a separate reaction to the one referred to in entries 1-5, and are specifically referring to isomerisation taking place during column chromatography on silica gel. This reaction is reported in full detail in **Table 5.3**, entry 2.
*Spectrum recorded in $CDCl_3$ after *circa* 15 minutes.

Results of this study showed that prolonged heating in dichloromethane causes slow epimerisation from *cis* **165a** to *trans* **165b**, as does extended contact with $CDCl_3$. This slow epimerisation can be clearly seen in **Figure 5.6**. However, epimerisation is much more rapid on contact with silica gel, resulting typically in a 93 : 7 ratio of *trans* : *cis,* which presumably is the thermodynamic ratio.



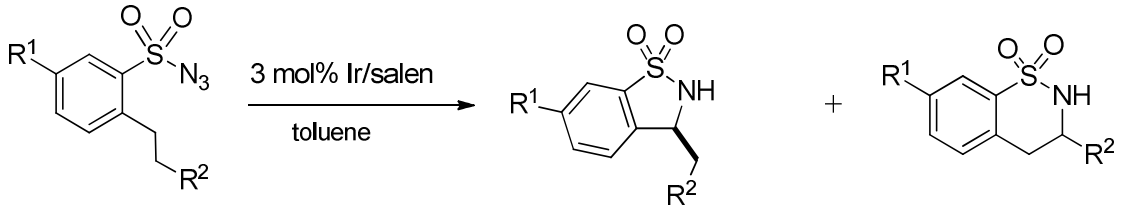
(A) –Epimerisation study in dichloromethane



(B) –Epimerisation study in $CDCl_3$

Figure 5.6 *^1H NMR spectra recorded in $CDCl_3$ (400 MHz)*

While α-diazo-β-oxo sulfones **54-56** are novel compounds, there are structurally similar compounds reported in the literature employed for nitrene insertion to form benzosultams. When 2, 5-diethylbenzenesulfonyl azide **171** underwent C–H bond amination in the presence of several iridium-salen complexes as catalysts, exclusive insertion into the benzylic position was observed to yield product **172**, with no amination occurring at the CH_3 of the ethyl group to give product **173** as illustrated in **Scheme 5.3**.[25] The product distribution here agrees with our findings, for the same potential insertion sites. Enantioselectivities of up to 91% ee were achieved using this catalyst system.



		Ratio (%ee)		**Ratio (%ee)**
R^1=ethyl, R^2=H	**171**	Only (91% ee)	**172**	-(-% ee) **173**
R^1=*n*-propyl, R^2=CH_3	**174**	1 (10% ee)	**175**	> 20 (99% ee) **176**
R^1=H, R^2=Ph	**177**	1 (5% ee)	**178**	2 (98% ee) **179**

Scheme 5.3[25]

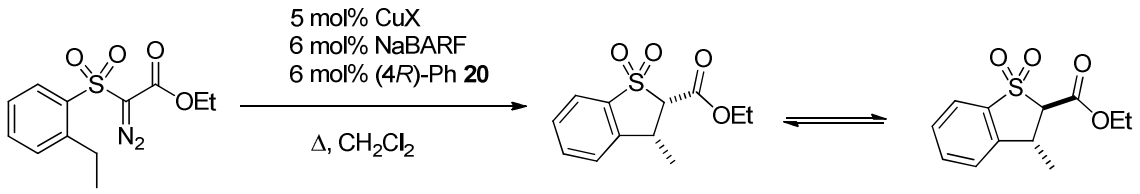
While insertion at the benzylic site is the only pathway seen in the ethyl substituted substrate **171**, extension of the chain resulted in a dramatic shift, favouring the formation of the six membered sultam. This highlights the importance of the nature of the insertion site on the outcome of the reaction (**Scheme 5.3**).

5.3 Asymmetric C–H insertion reactions

5.3.1 Asymmetric intramolecular C–H insertion reactions of α-diazo-β-oxo sulfone 54

α-Diazo-α-sulfonyl ethyl ester **54** was initially selected to undergo asymmetric copper catalysed C–H insertion reactions, as summarised in **Table 5.3**. The initial copper catalysed reaction that was carried out on α-diazo-α-sulfonyl ethyl ester **54** utilised 5 mol% $CuCl_2$, 6 mol% NaBARF and 6 mol% (4*R*)-Ph **20**, which had proved effective in the C–H insertions in the freely rotating systems in Chapter 3. In the first instance, pre-forming the catalyst was not carried out, in line with the experiments undertaken in Chapter 3 and following Flynn's conclusion that pre-forming was not necessary. The outcome of this initial reaction was very promising. Examination of the ^{1}H NMR spectrum of the crude reaction mixture showed an excellent reaction efficiency of ~90% for C–H insertion yielding a mixture of *cis* and *trans* sulfolane in a ratio of 89 : 11. As was the case for reaction of α-diazo-α-sulfonyl ethyl ester **54** with $Cu(OTf)_2$ (**Table 5.3**, entry 1), there was no evidence in the crude reaction mixture for thiopyran formation (**Table 5.3**, entry 1). As previously discussed nearly complete epimerisation of the *cis* to the *trans* isomer occurred upon exposure to silica gel, with *cis* **165a** and *trans* **165b** sulfolanes being isolated as a mixture (*cis* **165a** : *trans* **165b**, 6 : 94) in a very high yield of 91%, far superior to that achieved for the $Cu(OTf)_2$ catalysed reaction, (29%, **Table 5.1**, entry 1). Enantiopurities of both the *cis* and *trans* isomers, as a mixture, were measured using chiral HPLC, and were found to be 82% ee and 80% ee respectively, presumably reflecting the same enantiopurity as the diastereomers are in equilibrium. Similarly in entries 2 and 3 the enantiopurities measured for the *cis* and *trans* isomers are presumably the same although the accuracy of determination of the minor *cis* isomer is probably less than that of the major *trans* isomer. Notably, the enantiopurities of the *trans* isomers are more likely to be an accurate reflection of the overall enantioselection. These values represent the highest enantioselectivity achieved to date for *trans* sulfolane synthesis using copper mediated C–H insertion. (**Table 5.3**, entry 1).

Table 5.3 *Asymmetric copper-bisoxazoline catalysed intramolecular C–H insertion reactions of α-diazo-β-oxo sulfone* **54**



54 **165a** **165b**

Entry	Method	CuX	Time (h)	Crude Efficiency[a]	Yield (%)[b]	Product Ratio	*cis* % ee[c]	:	*trans* % ee[c]
1	**A** catalyst not pre-formed	$CuCl_2$	2	~90%	91	**Crude:** **Purified:**	89 6 (82% ee) (2*S*,3*R*)		11 94 (80% ee) (2*R*,3*R*)
2[d]	**A** catalyst not pre-formed	$CuCl_2$	5	~90%	78	**Crude:** **Purified:**	70 7 (90% ee) (2*S*,3*R*)		30 93 (80% ee) (2*R*,3*R*)
3	**B** pre-formed catalyst	$CuCl_2$	3	~90%	81	**Crude:** **Purified:**	84 8 (86% ee)[e] (2*S*,3*R*)		16 92 (80% ee) (2*R*,3*R*)
4	**B** pre-formed catalyst	CuCl	30	~90%	77	**Crude:** **Purified:**	38 7(-)[f,g]		62 93 (80% ee) (2*R*,3*R*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_2CH_3, *cis* sulfolane **165a**; 1.26 (3H, t, *J* 7.1, OCH_2CH_3) *trans* sulfolane **165b**; δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).

b. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluent, and contains both *cis* and *trans* isomers, in the specified ratios.

c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**. Enantioselectivity was measured on mixed fractions, where both *cis* **165a** and *trans* **165b** isomers were present in the purified material. All four diastereoisomers were separable. The % ee is determined on purified samples by HPLC. The % ee of the *cis* isomer was measured using weak HPLC signals, making measurements less accurate. Therefore, these results should be interpreted with caution.

d. This reaction was carried out using 1 g of α-diazo-β-oxo sulfone **54**, in comparison to the remaining entries where ~50–200 mg of α-diazo-β-oxo sulfone **54** were employed.

e. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -29.0 (*c*, 1.0 CH_2Cl_2)

f. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -39.5 (*c*, 1.0 CH_2Cl_2)

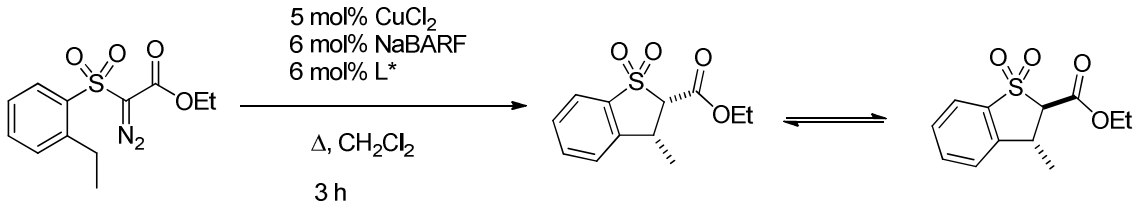
g. Result could not be determined accurately.

Note: General Method **A** and **B** are fully explained in Chapter 4. Briefly General Method **A** refers to all in one addition while General Method **B** refers to pre-forming of the catalyst followed by slow addition of the α-diazocarbonyl compound.

The reaction represented in **Table 5.3** was undertaken a number of times, with minor modifications to investigate the role of catalyst pre-forming for this system (**Table 5.3**, entries 1–2 *cf.* entries 3–4), the role of the copper salt (**Table 5.3**, entries 1–3 *cf.* entry 4) and to investigate the impact of scaling the reaction up to 1 g relative to 50–200 mg (**Table 5.3**, entry 2, *cf.* entries 1, 3–4). As can clearly be seen in **Table 5.3**, reaction efficiency, product yield and the enantiopurities of the products obtained are essentially the same, when using CuCl or $CuCl_2$ as copper sources, with or without catalyst pre-forming and when the reaction scale is varied from 50–200 mg to 1 g. In contrast the reaction time is sensitive to the nature of the copper salt, being much slower with CuCl compared to $CuCl_2$. Similarly, increasing the scale resulted in a slightly longer reaction time. It is evident that longer reaction times result in an alteration in the diastereomeric ratio, resulting in increased proportion of the *trans* isomer in the crude product. As there was no advantage found to pre-forming the catalyst at this stage, and $CuCl_2$ was the copper salt that resulted in the fastest reaction times, conditions in **Table 5.3**, entry 1 were employed for the remaining copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones **54**–**56** in this chapter.

Next, a ligand investigation was carried out using four additional commercially available ligands **43**, **44**, **137**, **138**. The results of this study are presented in **Table 5.4**.

Table 5.4 *Asymmetric copper-bisoxazoline catalysed intramolecular C–H insertion reactions of α-diazo-β-oxo sulfone* ***54***



54 **165a** **165b**

Entry	L*	Crude Efficiency[a]	Yield (%)[b]	Product Ratio	*cis* % ee[c]	:	*trans* % ee[c]
1	(4*R*,5*S*)-di-Ph **137**	~90%	67	**Crude:** **Purified:**	83 14 (83% ee) (2*S*,3*R*)		17 86 (75 % ee) (2*R*,3*R*)
2	(4*R*)-Bn **43**	~90%	75	**Crude:** **Purified:**	32 7 (18% ee) (2*S*,3*R*)		68 93 (15% ee) (2*R*,3*R*)
3	(4*S*)-*t*-Bu **138**	~82%	61	**Crude:** **Purified:**	52 11 (54% ee) (2*R*,3*S*)		48 89 (49% ee) (2*S*,3*S*)
4	(3*S*,8*R*)-Ind **44**	~90%	84	**Crude:** **Purified:**	63 7 (3% ee) (2*R*,3*S*)		37 93 (2% ee) (2*S*,3*S*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_2CH_3, *cis* sulfolane **165a**;1.26 (3H, t, *J* 7.1, OCH_2CH_3); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).

b. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluent, and contains both *cis* and *trans* isomers, in the specified ratios.

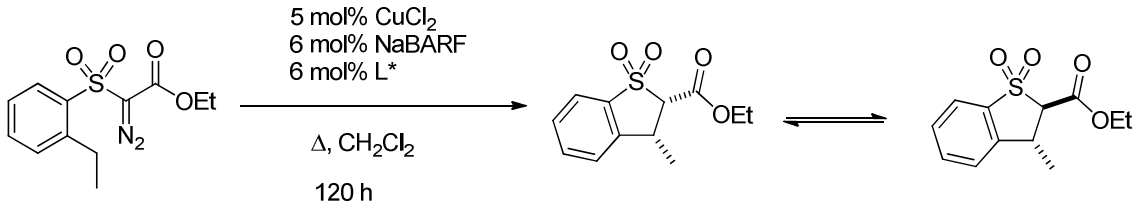
c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**. Enantioselectivity was measured on mixed fractions, where both *cis* **165a** and *trans* **165b** isomers were present in the purified material. All four diastereoisomers were separable. The % ee is determined on purified samples by HPLC. The % ee of the *cis* isomer was measured using weak HPLC signals, making measurements less accurate. Therefore these results should be interpreted with caution.

Reaction efficiencies and isolated yields remained high for sulfolane synthesis, independent of the nature of the bisoxazoline ligand used. (**Table 5.4**, entries 1–4). However, the enantioselectivity and the diastereoselectivity were very sensitive to the nature of the ligand, as summarised in **Table 5.4**. In this study, the variation in the *cis* : *trans* ratio of the crude product mixtures cannot be explained on the basis of reaction time, as each reaction was undertaken for 3 h. Interestingly, the *cis* isomer predominates in the crude product mixture of reactions using the (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** ligands (**Table 5.3**, entry 1 and **Table 5.4**, entry 1), which may suggest that the aryl

substituent on the ligand has an impact. The result of this ligand study showed that both (4*R*)-Ph **20** (**Table 5.3**, entry 1) and (4*R*)-di-Ph **137** (**Table 5.4**, entry 1) gave *trans* sulfolane **165b** with the highest levels of enantiopurity with values of 80% ee and 75% ee being obtained respectively. The remaining ligands showed much poorer enantioinduction, with (4*S*)-*t*-Bu ligand **138** giving rise to *trans* sulfolane **165b** with 49% ee (**Table 5.4**, entry 3) and enantioselectivity falls off dramatically when (4*R*)-Bn **43** and (3*S*,8*R*)-Ind **44** are used with values of <20% ee attained in both instances. (**Table 5.4**, entries 2 and 4). The (4*R*)-Ph ligand **20** proved to be the optimum ligand for yielding C–H insertion products with high levels of enantiopurity, as had been previously observed for thiopyran synthesis. Interestingly, the (3*S*,8*R*)-Ind **44** showed virtually no enantioinduction, with *trans* sulfolane **165b** being obtained in only 2% ee (**Table 5.4**, entry 4). Thus, while the ligand trends mirror those seen in the thiopyran synthesis, with the lowest enantioselectivity seen for the (3*S*,8*R*)-Ind **44** ligand, the extent of decrease in enantioselectivity is much more dramatic in the sulfolane series. This shows once again that while having a phenyl ring present in the ligand structure is essential for high levels of enantioselectivity, it is also important that this phenyl ring has a certain degree of conformational freedom, a similar trend to that reported in for *cis* thiopyran synthesis (**Chapter 4**, **4.2.1**).

Use of commercially available Py-(4*R*)-Ph **159**, Py-(4*S*)-*i*-Pr **160** and CN-(4*S*)-Ph **158** ligands was then explored. The results obtained in this study are presented in **Table 5.5**.

Table 5.5 *Asymmetric copper-semicorrin and copper-pybox catalysed intramolecular C–H insertion reactions of α-diazo-β-oxo sulfone* ***54***



54 **165a** **165b**

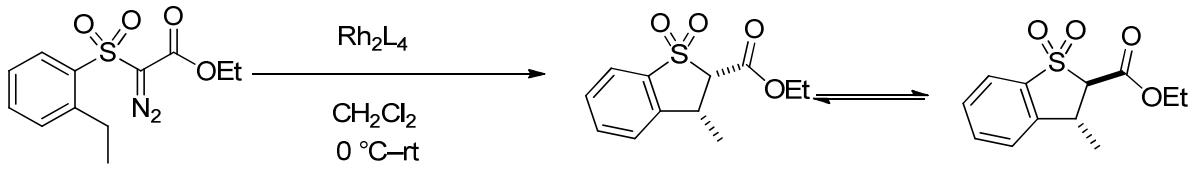
Entry	Ligand	Crude Efficiency[a]	Yield (%)[b]		*cis* **165a** % ee[c]	:	*trans* **165a** % ee[c]
1	CN-(4*S*)-Ph **158**	~80%[d]	35	**Crude:** **Purified:**	33 6 -		67 94 (28% ee)[e] (2*S*,3*S*)
2	Py-(4*R*)-Ph **159**	Starting material only		**Crude:** **Purified:**	- - -		- - -
3	Py-(4*S*)-*i*-Pr **160**	50–60%[f]	26	**Crude:** **Purified:**	10 10 (10% ee)[e]		90 90 (10% ee)[e]

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_2CH_3, *cis* sulfolane **165a**; 1.26 (3H, t, *J* 7.1, OCH_2CH_3) *trans* sulfolane **165b**; δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).
b. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluent, and contains both *cis* and *trans* isomers, in the specified ratios.
c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**. Enantioselectivity was measured on mixed fractions, where both *cis* **165a** and *trans* **165b** isomers were present in the purified material. All four diastereoisomers were separable. The % ee is determined on purified samples by HPLC. The % ee of the *cis* isomer was measured using weak HPLC signals, making measurements less accurate. Therefore these results should be interpreted with caution.
d. The crude material contains ~5% starting material α-diazo-β-oxo sulfone **54**.
e. The enantioselectivity given here is estimated and could not be accurately determined due to peak overlap in the HPLC trace.
f. Contains ~30% starting material α-diazo-β-oxo sulfone **54**.

In contrast to the bisoxazoline ligands, reactions employing ligands **158-160** were characterised by low efficiencies and enantioselectivities (**Table 5.4**, entries 1–3). Reaction with Py-(4*R*)-Ph ligand **159** did not proceed at all after 120 hours of stirring under reflux in dichloromethane (**Table 5.5**, entry 2), while reactions with CN-(4*S*)-Ph **158** and the Py-(4*S*)-*i*-Pr **160** were still not complete after 120 h. (**Table 5.5**, entries 1 and 3). Therefore, neither semicorrin nor pybox ligands are suitable replacements for bisoxazoline ligands for substrates of this type.

After completing the study using chiral copper catalysts, an investigation was carried out using commercially available chiral rhodium catalysts (**Section 4.6.2**, **Figure 4.32**). It has been reported that the use of chiral rhodium catalysts gave poor enantioselectivities in the synthesis of *trans* thiopyrans as discussed Chapter 2.[26] However, no reports exist in the literature for their use in sulfolane systems. In addition, this had not previously been explored in our group.

Table 5.6 *Chiral rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***54***



54 **165a** **165b**

Entry	Method	Rh_2L_4	Time (h)	Crude Efficiency[a]	Yield (%)[b]	Product Ratios	*cis* % ee[c]	:	*trans* % ee[c]
1	**F**	Rh_2(*S*-PTTL)$_4$ 0 °C-rt	6	80–90%	44	**Crude:** **Purified:**	58 7 (20% ee) (2*S*,3*R*)		42 93 (30% ee) (2*R*,3*R*)
2	**F**	Rh_2(*S*-PTPA)$_4$ 0 °C-rt	6	80–90%	61	**Crude:** **Purified:**	62 5 (13% ee) (2*S*,3*R*)		48 95 (16% ee) (2*R*,3*R*)
3	**F**	Rh_2(*S*-DOSP)$_4$ 0 °C-rt	2	80–90%	52	**Crude:** **Purified:**	50 8		50 92 (8% ee) (2*S*,3*S*)
4	**G**	Rh_2(*S*-MEPY)$_4$ 0 °C-rt-Δ	30,90[d]	50–60%[e]	25	**Crude:** **Purified:**	47 10 (0% ee)		53 90 (2% ee)[f] (2*R*,3*R*)
5	**F**	Rh_2(*S*-mand)$_4$ 0 °C-rt	6	80–90%	58	**Crude:** **Purified:**	45 7 (5% ee) (2*R*,3*S*)		55 93 (6% ee) (2*S*,3*S*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_2CH_3, *cis* sulfolane **165a**, 1.26 (3H, t, *J* 7.1, OCH_2CH_3); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).

b. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluent, and contains both *cis* and *trans* isomers , in the specified ratios.

c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**. Enantioselectivity was measured on mixed fractions, where both *cis* **165a** and *trans* **165b** isomers were present in the purified material. All four diastereoisomers were separable. The

% ee is determined on purified samples by HPLC. The % ee of the *cis* isomer **165a** was measured using weak HPLC signals, making measurements less accurate. Therefore these results should be interpreted with caution

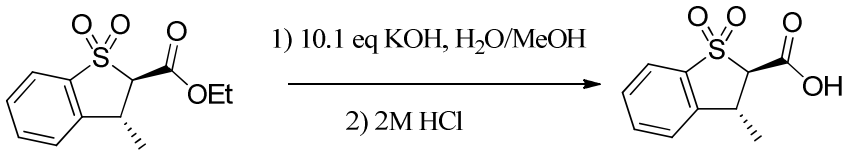
d. Reaction was not complete after 30 h, and was subsequently heated under reflux for an additional 90 hours.
e. Contains ~25% starting material α-diazo-β-oxo sulfone **54**.
f. The enantioselectivity given here is estimated and could not be accurately determined due to peak overlap in the HPLC trace.

Reactions of α-diazo-β-oxo sulfone **54** with rhodium catalysts display very similar efficiencies and regioselectivities to those with seen for reactions with the copper catalysts, with no evidence for competing thiopyran formation in any case, as previously discussed (**Tables 5.3** and **5.4**). Efficiencies were generally high, with values of 80–90% being achieved in most cases. (**Table 5.6**, entries 1–3, 5). The exception to this was the use of $Rh_2(MEPY)_4$, which gave rise to a reaction efficiency of 50–60%, and still contained ~25% starting material after prolonged stirring under reflux (**Table 5.6**, entry 4). This was consistent with the decreased catalytic activity of $Rh_2(MEPY)_4$ and carboxamidates in general. Each of the catalysts gave rise to sulfolane as a mixture of *cis* **165a** and *trans* **165b** isomers. Interestingly, the variation in diastereomeric ratio was much less than in the rhodium series than in the copper series (**Table 5.4** and **Table 5.6**). Once again epimerisation on silica occurred, which gave predominately *trans* **165b** as the major product after purification.

Enantioselectivities were low, when compared to reactions carried out with CuCl-NaBARF-(4*R*)-Ph **20** and CuCl-NaBARF-(4*R*,5*S*)-di-Ph **137**. The highest enantioselectivity, of 30% ee, was achieved for Rh_2(*S*-PTTL)$_4$ (**Table 5.6**, entry 1), with all other rhodium catalysts giving enantioselectvities lower than 20% ee (**Table 5.6**, entries 2–5). Once again, the copper- NaBARF-bisoxazoline catalysts are found to be superior to rhodium catalysts for C–H insertion reactions in the synthesis of sulfolane compounds. Furthermore, the sensitivity of the diastereomeric ratio and enantiopurity to the nature of the bisoxazoline ligand is indicative of strong ligand-substrate interactions in the transition state of the copper mediated C–H insertion.

The ethyl ester sulfolane **165b** was isolated as a colourless oil. With the objective of determining the absolute stereochemistry of this series, hydrolysis of the ester to the carboxylic acid was explored, in an attempt to obtain a crystalline solid for X-ray analysis. Conversion of the ester **165b** to the acid **170b** was successfully achieved using potassium hydroxide in aqueous methanol, the results of which are presented in **Table 5.7**.

Table 5.7 *Conversion of ethyl ester **165b** to carboxylic acid **170b** results from **Table 5.3**, entry 2*



97 : 3
trans : *cis*
80% ee-*trans*

(2*R*,3*R*)
95:5
trans : *cis*
78% ee-*trans*

Entry	Ester 165b (*trans : cis*) (% ee-*trans*)	Yield (%)	Product Ratio	Acid[a]	
				cis[b] (**170a**)	*trans* (**170b**)
1	80%[c] (93 : 7) (2*R*,3*R*) ***Table 5.3**, entry 2*	78%	Ratio (% ee)	5(-)[b]	95 (78% ee)
2	0% (93 : 7) **Table 5.1**, entry 1	65%	Ratio (% ee)	8(-)[b]	92 (0% ee)

a. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for *cis* sulfolane **170a**; δ_H 4.46 [1H, d, *J* 6.8 C(2)H], *trans* sulfolane **170b**; δ_H 4.13 [1H, d, *J* 7.3, C(2)*H*].

b. Peaks for *cis* sulfolane **170a** not detected during HPLC analysis.

c. Result obtained from a reaction catalysed using (4*R*)-Ph ligand **20**.

Conversion of ethyl ester **165b** to carboxylic acid **170b** was carried out twice; once on a racemic sample of sulfolane **165b** and once on an enantioenriched sample. A racemic sample of carboxylic acid sulfolane **170b** was required for the development of chiral HPLC conditions. Thus, the retention of stereochemical integrity on hydrolysis could be confirmed both in terms of % ee (HPLC) and % de (^{1}H NMR). Good yields of carboxylic acid **170b** were obtained in both cases (**Table 5.7**, entries 1 and 2). The enantioenriched carboxylic acid **170b** synthesised was initially isolated as a colourless oil, which after several days of storage at room temperature solidified to a white solid. Upon slow recrystallisation from IPA, a crystalline white solid suitable for X-ray crystal structure analysis was obtained and gave rise to the crystal structure shown in **Figure 5.7**.

Recrystallisation provided a crystal that was 95% ee (crystal dissolved after X-ray determination and re-injected in HPLC) and therefore, presumably, the X-ray presented the structure of the major enantiomer. It is not surprising that a small amount of the minor enantiomer was not detected during X-ray analysis as crystallography is an average technique for a bulk sample and therefore minor components of the bulk sample may not necessarily be detected. The structure was determined as (2*R*,3*R*) as illustrated in **Figure 5.7**; the crystal was re-dissolved for HPLC analysis to confirm that the crystal was the major enantiomer present.

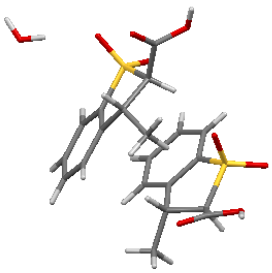
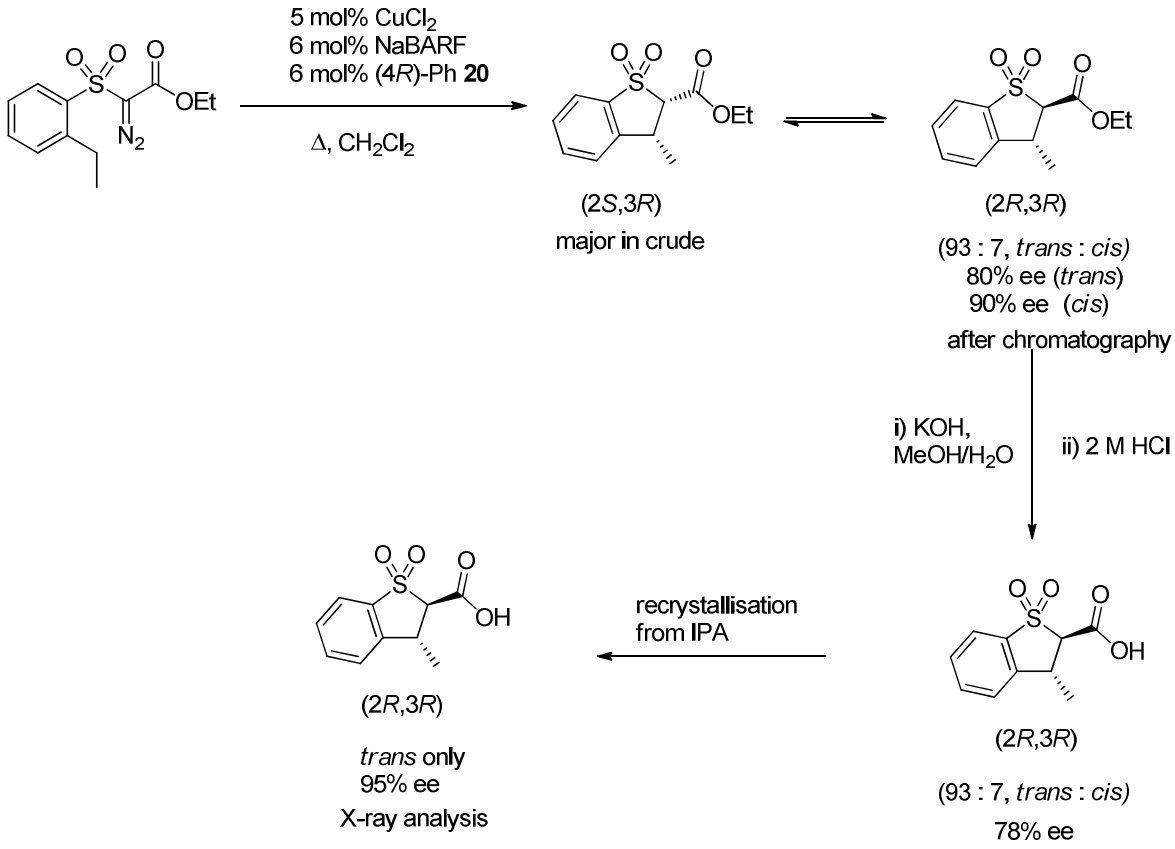


Figure 5.7 *A view of **170b** showing the structure and relative stereochemistry. Anisotropic displacement parameters are drawn at the 30% probability level.*[27]

There are a few noteworthy points about the crystal structure that was obtained. Firstly the structure obtained is a hydrate, containing two molecules of sulfone to one molecule of water. Water is a bridge between the crystallographically independent sulfolane molecules *via* O–H····O=S hydrogen bonding. The carboxylic acid of one of the independent sulfolane molecules is utilising O–H····O=S hydrogen bonding with the sulfone group of the second independent sulfolane molecule. The carboxylic acid of the other independent sulfolane molecule is involved in O–H····O hydrogen bonds with the water molecule.[27]

With this information in hand the following sequence of events were established; C–H insertion of α-diazo-β-oxo sulfone **54** in the presence of (4*R*)-Ph **20** resulted in the initial formation predominantly of *cis* sulfolane **165a**, which was assigned (2*S*,3*R*) stereochemistry on the basis of the crystal structure of carboxylic acid **170b** (**Scheme**

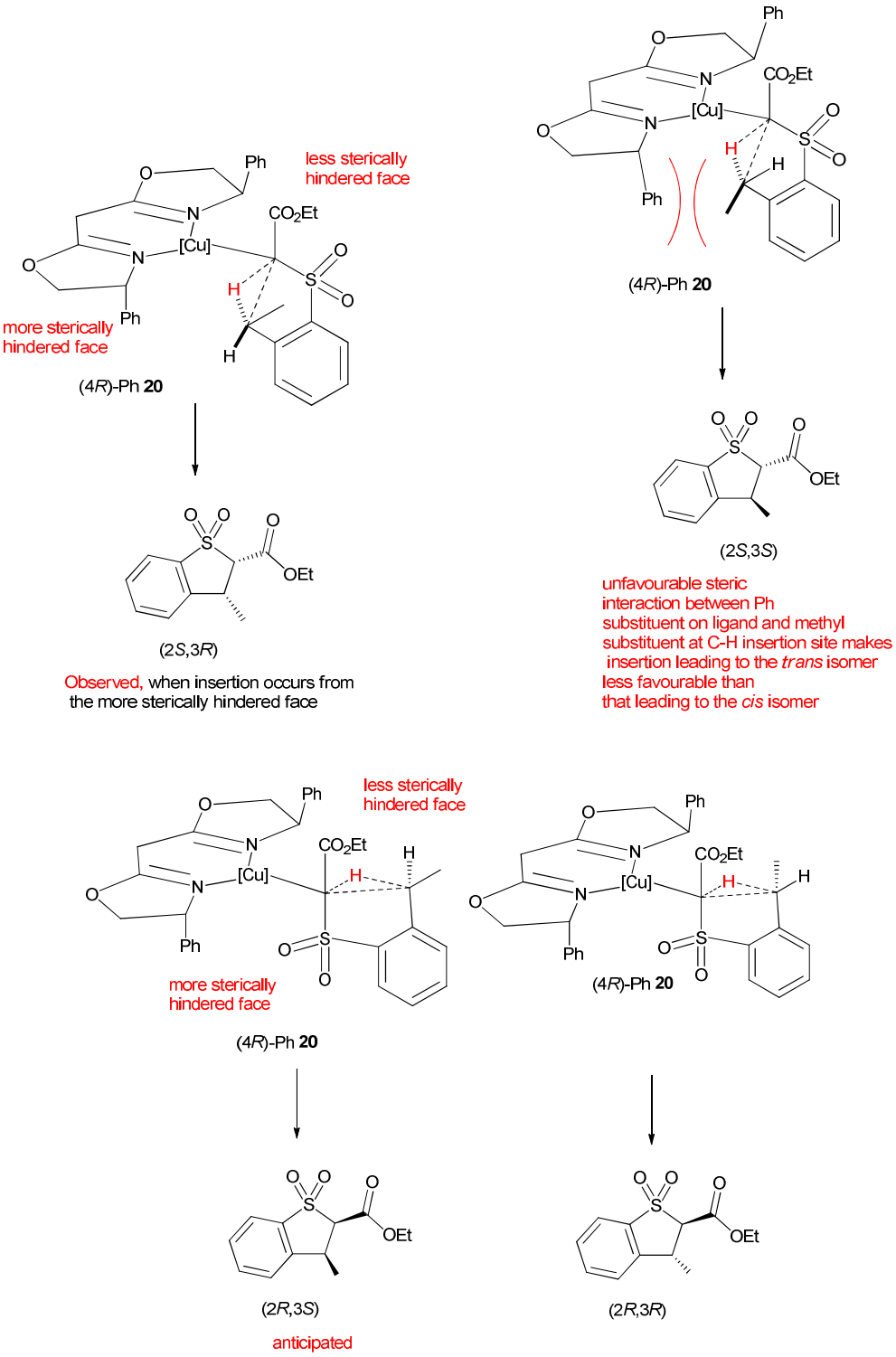
5.4); epimerisation of *cis* sulfolane **165a** then occurred on silica gel to give predominately *trans* sulfolane **165a** with (2*R*,3*R*) stereochemistry (80% ee, **Table 5.3**, entry 2), which upon saponification gave rise to carboxylic acid **170b** with (2*R*,3*R*) stereochemistry (78% ee).



Scheme 5.4

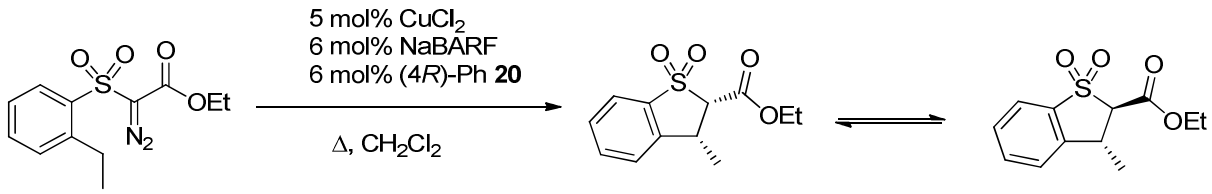
Therefore, the proposed transition state of the copper catalysed C–H insertion reaction of α-diazo-β-oxo sulfone **54** must explain the formation of *cis* sulfolane (2*S*,3*R*) initially. The proposed transition states for the formation of *cis* sulfolane **165a** are shown in **Scheme 5.5**. Transition state models for the formation of *trans* sulfolanes and *cis* thiopyrans were previously discussed in Chapter 4, **Section 4.5**. For the "non-fused" *trans* sulfolanes, a transition state model was proposed where the reacting C–H bond approached the carbene carbon from the least hindered face. Following this model, the anticipated transition state is in agreement with the one observed experimentally. However, when the same logic is applied to the fused systems, the absolute stereochemistry is not in agreement with the predicted absolute stereochemistry.

Therefore, an assumption can be made that insertion is occurring from the more hindered face of the carbene. It is possible that specific substrate ligand interactions are responsible for this outcome. However, it should be noted that there is a possibility that in certain instances the *trans* sulfolane may be forming initially, for this reason transition states leading to the formation of the *trans* isomer are included in **Scheme 5.5**.



Scheme 5.5

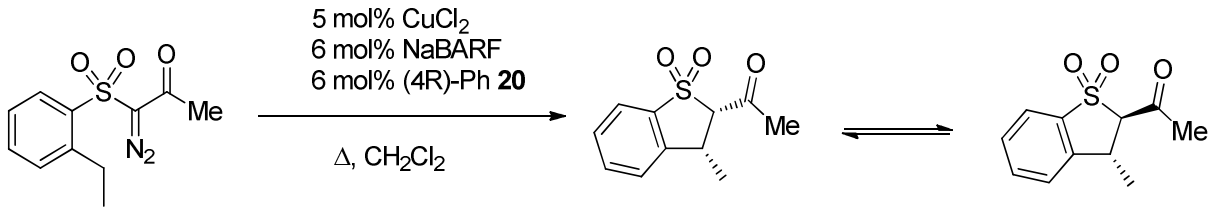
The assignment of the absolute stereochemistry of the methyl ketone **166b** and the phenyl ketone **167b** *trans* sulfolanes were subsequently made by analogy to the ethyl ester *trans* sulfolane **165b**, using specific rotation data. The specific rotation of *trans* sulfolane **165b** is negative $[\alpha]_D^{20}$ -29.0 (*c*, 1.0 CH_2Cl_2) from a reaction obtained with (4*R*)-Ph **20**. The absolute stereochemistry of this compound was determined to be (2*R*,3*R*) through the use of crystallography studies as was previously discussed. The rotation of methyl ketone **166b** was also negative $[\alpha]_D^{20}$ -2.0 (*c*, 0.1 CH_2Cl_2) from a reaction employing (4*R*)-Ph **20**, therefore its absolute chemistry was assigned as (2*R*,3*R*) by analogy. For phenyl ketone *trans* sulfolane **167b**, a positive specific rotation $[\alpha]_D^{20}$ +16.0 (*c*, 0.1 CH_2Cl_2) was obtained through use of (3*S*,8*R*)-Ind **44**. Therefore, in this instance the absolute stereochemistry was assigned as (2*S*,3*S*). A discussion of the assignment of the absolute stereochemistry of **165b**, **166b** and **167b** will appear in **Appendix II**.



165b (2*R*,3*R*) by X-ray

7 : 93 *cis* : *trans*, 80% ee *trans*

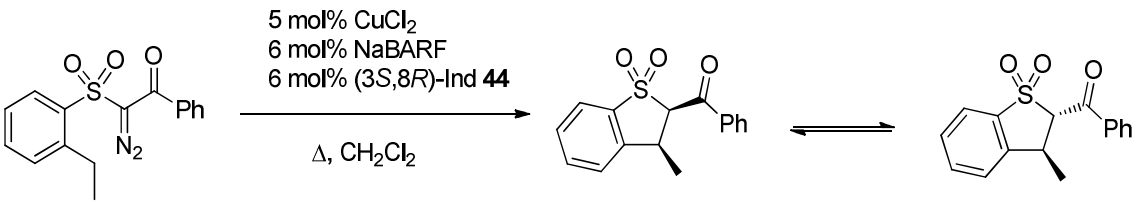
$[\alpha]_D^{20}$ -29.0 (*c*, 1.0 CH_2Cl_2)



166b (2*R*,3*R*)

2 : 98 *cis* : *trans,* 64 % ee *trans*

$[\alpha]_D^{20}$ -2.0 (*c*, 0.1 CH_2Cl_2).



167b (2*S*,3*S*)

7 : 93 *cis* : *trans,* 13 % ee *trans*

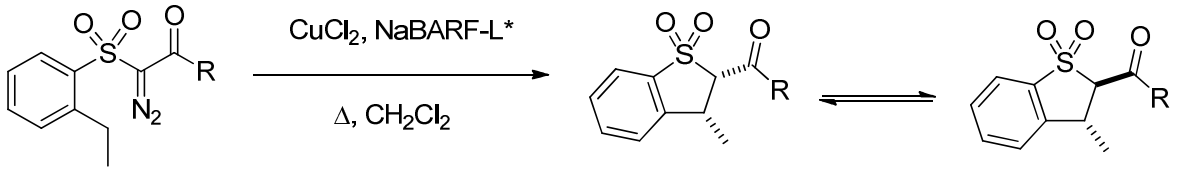
$[\alpha]_D^{20}$ +16.0 (*c*, 0.1 CH_2Cl_2).

Scheme 5.6

5.3.2. Asymmetric copper catalysed C–H insertion reaction of α-diazo-β-oxo sulfones 55 and 56

After completing our initial studies on α-diazo-ester **54**, our attention was then focused on the analogous methyl ketone **55** and phenyl ketone **56** diazo derivatives to investigate the effects of variation of the substituents on the carbonyl group. Reactions of these substrates were catalysed using five commercially available bisoxazoline ligands **20**, **43**, **44**, **137**, **138**. Racemic samples of both compounds were generated using $Rh_2(OAc)_4$, as previously discussed in **Section 5.2**.

Table 5.8 *Asymmetric copper-bisoxazoline catalysed C–H insertion reactions of α-diazo-β-oxo sulfones* ***55*** *and* ***56***



56, R=Ph
55, R=Me

167a R=Ph
166a R=Me

167b R=Ph
166b R=Me

Entry	α-diazosulfone	R	L*	Time (h)	Crude Efficiency (%)	Combined Yield (*cis* and *trans*) (%)[a]	Product Ratio	*cis* % ee	:	*trans* % ee[b]
1	**56**	Ph	(4*R*)-Ph **20**	5	~65%[c]	38[d]	**Crude ratio:** **Purified ratio:**	9 1		91 99[e] (71% ee) (2*R*,3*R*)
2	**56**	Ph	(4*R*,5*S*) di-Ph **137**	3	~72%[c]	50[f]	**Crude ratio:** **Purified ratio:**	54 1		46 99 (70% ee)[g,h] (2*R*,3*R*)
3	**56**	Ph	(4*S*)-*t*-Bu **138**	21	~70%[c]	55	**Crude ratio:** **Purified ratio:**	42 1		58 99[i] (39% ee) (2*S*,3*S*)
4	**56**	Ph	(3*S*,8*R*)-Ind **44**	24	~65%[c]	42	**Crude ratio:** **Purified ratio:**	7 1		93 99 (13% ee)[j] (2*S*,3*S*)
5	**56**	Ph	(4*R*)-Bn **43**	50	~65%[c]	48	**Crude ratio:**	Trace		>99

							Purified ratio:	1		99 (12% ee)[k] (2*R*,3*R*)
6	**55**	Me	(4*R*)-Ph **20**	3	>90%[l]	65	**Crude ratio:** **Purified ratio:**	2 2		98 98 (64% ee)[m] (2*R*,3*R*)
7	**55**	Me	(4*R*,5*S*) di-Ph **137**	7	~55%[l,n]	42	**Crude ratio:** **Purified ratio:**	2 1		98 99 (76% ee)[o,p] (2*R*,3*R*)
8	**55**	Me	(4*S*)-*t*-Bu **138**	30	41% starting material left, of remaining 59%;43% efficient[l]	38	**Crude ratio:** **Purified ratio:**	2 2		98 98 (12% ee) (2*S*,3*S*)
9	**55**	Me	(3*S*,8*R*)-Ind **44**	5	~60–70%[l,q]	45	**Crude ratio:** **Purified ratio:**	5 2		95 98 (16% ee)[r,s] (2*R*,3*R*)
10	**55**	Me	(4*R*)-Bn **43**	4	~70%[l]	60	**Crude ratio:** **Purified ratio:**	4 1		96 99 (13% ee) (2*R*,3*R*)

a. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane as eluent, and contains both *cis* and *trans* isomers, in the specified ratios.

b. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**, absolute stereochemistry was assigned by analogy to ethyl ester sulfolane **165b**, details of which can be found in **Appendix II**.

c. Efficiency and relative ratios of isomers calculated using the ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **167a**, δ_H 5.45 [1H, d, *J* 5.4, C(2)*H*]; *trans* sulfolane **167b**, δ_H 5.02 [1H, d, *J* 6.9, C(2)*H*].

d. Additional less polar fraction isolated after chromatography (3 mg); δ_H 1.27–1.34 (m), 2.98–3.16 (m), 6.14 (s), 7.30–7.44 (m), 7.49–7.58 (m), 7.58–7.69 (m), 7.91–7.95 (m), 8.02–8.08 (m)

e. Compound **167b** eluted over six fractions, The enantiopurity of the contents of the last fraction differs slightly to that of the first five fractions, indicating enantiomer self-disproportionation. The enantioselectivity of 71% ee is based on a weighted average. The enantiopurity and the relative mass of each fraction(s) are given as follows; fractions one-five,70% ee, 84% mass (99% *trans,* 1% *cis*), fraction six, 80% ee, 14% mass (100% *trans*).

f. Additional less polar fraction isolated after purification; δ_H 1.30 (t, *J* 7.5), 3.00–3.19 (sym m), 6.14 (s), 7.32–7.46 (m), 7.49–7.57 (m), 7.59–7.68 (m), 7.93 (dd , *J* 1.3, 8.1), 8.05 (2H, dd, *J*. 1.3, 8.4)

g. Compound **167b** eluted over five fractions. The enantiopurity of the contents of the last fraction differs slightly to that of the first four fractions, indicating enantiomer self-disproportionation .The enantioselectivity of 70% ee is based on a weighted average. The enantiopurity and the relative masses of each fraction(s) are given as follows; fractions one-four, 68% ee, 70% mass (99% *trans,* 1% *cis*), fraction five, 75% ee, 30% mass (>99% *trans,* trace *cis*)

h. Rotation measured on combined mixed fraction-$[\alpha]_D^{20}$ -104.5 (*c*, 0.1 CH_2Cl_2), measured on fraction five (see g).

i. Rotation measured on combined mixed -$[\alpha]_D^{20}$ +73.5 (*c*, 0.1 CH_2Cl_2).

j. Rotation measured on combined mixed -$[\alpha]_D^{20}$ +16.0 (*c*, 0.1 CH_2Cl_2)..

k. Rotation measured on combined mixed -$[\alpha]_D^{20}$ +26.8 (*c*, 0.276 CH_2Cl_2), the direction of specific rotation is inconsistent with HPLC data.

l. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **166a**, δ_H 4.44 [1H, d, *J* 6.5, C(2)*H*]; *trans* sulfolane **166b**, δ_H 4.17 [1H, d, *J* 7.0, C(2)*H*].

m. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -2.0 (*c*, 0.1 CH_2Cl_2).

n. Additional peaks observed in ^{1}H NMR spectra of the crude product; δ_H 4.27 (dd, *J* 4.1, 10.2), 4.68 (s), 4.93 (s), 5.12 (s), 7.79–8.10 (m), 8.05–8.12 (m), 8.18–8.23 (m).

o. Compound **166b** eluted over three fractions. The enantioselectivity of the contents of each fraction differs slightly indicating enantiomer self-disproportionation. The enantioselectivity of 76% ee is based on a weighted average. The enantioselectivity and the relative mass of each fraction are given as follows; fraction one, 80% ee, 21% mass (100% *trans*), fraction two, 74% ee, 67% mass (98% *trans*, 2% *cis*), fraction three, 66% ee, 12% mass (*cis* isomer absent, impurities present).

p. Rotation measured on mixed fraction: $[\alpha]_D^{20}$ -2.0 (*c*, 0.1 CH_2Cl_2), measured on fraction one (see o).

q. Additional peaks observed in ^{1}H NMR spectra of the crude product; δ_H 3.01–3.11 (m), 5.13 (s).

r. Enantioselectivity observed was opposite to that predicted, confirmed by rotation.

s. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -1.167 (*c*, 0.3 CH_2Cl_2).

.

On changing the carbonyl group from an ethyl ester to a methyl or phenyl ketone substituent, the major reaction product is once again a sulfolane, which is consistent with results obtained for reactions with achiral catalysts (**Section 5.2**, **Table 5.1**). There is a noticeable decrease in reaction efficiency for C–H insertion for methyl ketone and phenyl ketone compounds **55** and **56** (~50–70%) (**Table 5.8**) when compared with ethyl ester compound **54** (80–90%) (**Table 5.3** and **Table 5.4**). In general, there was evidence in the ^{1}H NMR spectra of the crude product mixtures for additional byproduct formation, which were largely unidentified. However, there is evidence for X–H insertion product **180** being present in additional purified mixed fractions (**Table 5.8**, entries 1 and 2) and X–H insertion product **181** was potentially detected in certain crude reaction mixtures (**Table 5.8**, entries 7 and 9) (**Figure 5.8**). This is in contrast to cyclisations involving ethyl ester α-diazo-β-oxo sulfone **54**, where an X–H insertion product was only detected in a $Cu(OTf)_2$ catalysed reaction and not in copper-bisoxazoline catalysed C–H insertion reactions (**Table 5.3** and **5.4**)

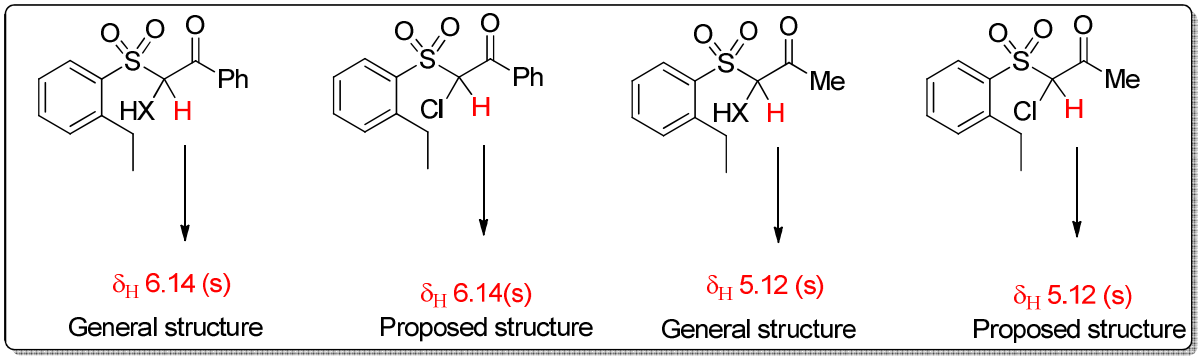


Figure 5.8

In addition to a change in reaction efficiencies, there is also an appreciable difference in the *cis* : *trans* ratios seen in the ^{1}H NMR spectra of the cyclisation of ethyl ester compound **54** and that of phenyl and methyl ketone compounds **56** and **55**. Generally, the *cis* isomer was the minor reaction component of the crude reaction mixture for reactions of methyl ketone and phenyl ketone substrates **55** and **56**, which is opposite to what was observed for reactions employing ethyl ester substrate **54**, where the *cis* isomer was the main component of the crude reaction mixture (**Table 5.8** and **Table 5.4**). However, notable amounts of the *cis* isomer **167a** were observed in the ^{1}H NMR spectra of the crude reaction material for reactions of phenyl ketone **56**, with (4*R*,5*S*)-di-Ph **137** and (4*S*)-*t*-Bu **138**, where essentially 50 : 50 mixtures of *cis* : *trans* were seen (**Table 5.8**, entries 2 and 3). Epimerisation to *trans* **167b** occurs on contact with silica gel in cases where the *cis*

isomer is present in the crude mixture. For methyl ketone substrate **55** the *cis* isomer **166a** is only observed in small amounts in the crude products for all ligands (**Table 5.8**, entries 6–10). Presumably the different rates of epimerisation are related to the pKa of the of the C(2)*H*. Examination of Evans' pKa tables[28] reveals the following pKa values (**Figure 5.9**). This observation can be rationalised on the basis of the acidity of the α-proton, with the ketones having a slightly lower pKa than the corresponding ester and accordingly undergoing more rapid epimerisation to the thermodynamically favoured *trans* isomer. However, it is likely that the kinetic product is the *cis* isomer in line with the results seen for the ethyl ester. This is particularly important when attempting to develop transition state models. Interestingly, at equilibrium typically 7% of the *cis* isomer of the ester is seen, while for the ketones approximately 1–2% of the *cis* isomer is seen after chromatography.

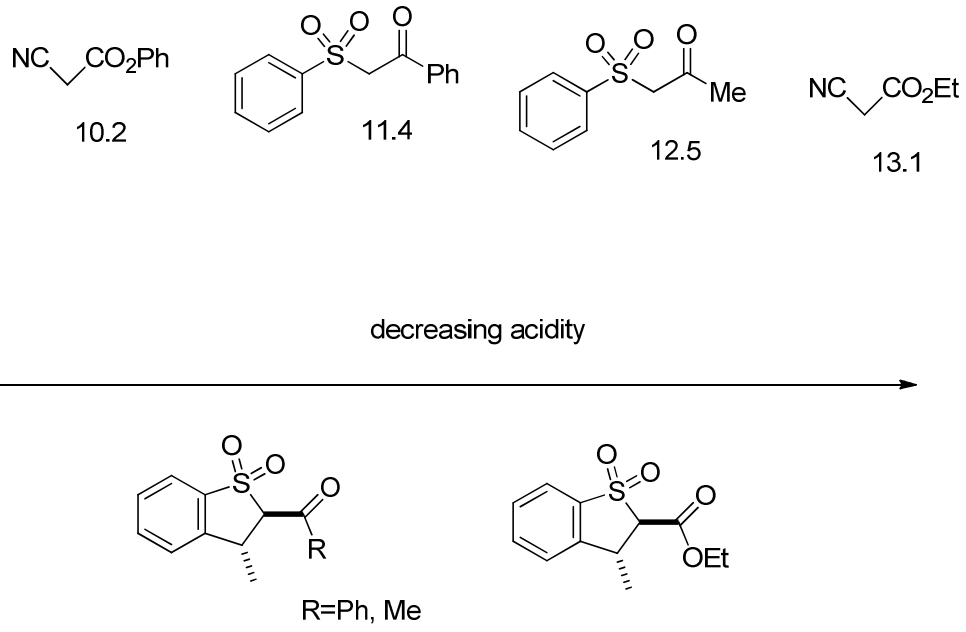
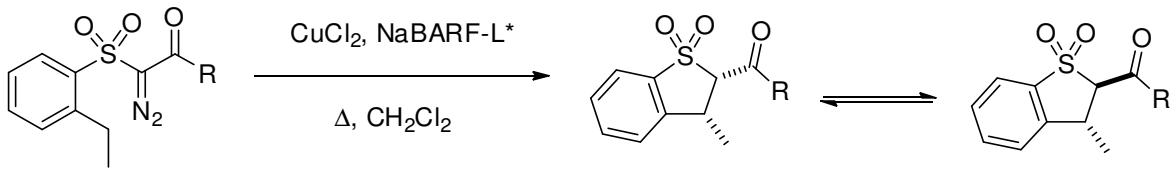


Figure 5.9

In terms of enantioselectivities, the values obtained for both *trans* ketone substrates **167b** and **166b** are largely similar to those obtained for *trans* ethyl ester **165b**, with either (4*R*)-Ph **20** or (4*R*,5*S*) di-Ph **137** ligands giving the best results, (64–76% ee) (**Table 5.8**, entries 1-2, 6-7) with all other ligands giving remarkably lower enantioinduction (**Table 5.8**, 12–39% ee). This effect can clearly be seen in **Figure 5.10**. There was some evidence for enantiomeric disproportionation (discussed in **Chapter 4**, **Section 4.1.4**). The enantioselectivities of *trans* sulfolane **167b** arising from reactions of phenyl ketone α-

diazo-β-oxo sulfone **56** (**Table 5.8**, entries 1–2, see footnotes) and methyl ketone α-diazo-β-oxo sulfone **55** (**Table 5.8**, entries 7, see footnote) were measured across several fractions, with slight variations evident across individual fractions. This may be due to enantiomeric disproportionation, however, as the *cis* : *trans* ratios and the purities of the individual fractions vary, this may also be responsible for the observed result. While the direction of the enantioselectivity using the (3*S*,8*R*)-Ind **44** ligand with the methyl ketone was in the opposite sense to that expected based on the ligand configuration, as the absolute enantioselectivities are small, this is not believed to be significant.

Significantly, however, the ligand trends are remarkably consistent across each of the three substrates, with the optimum asymmetric induction seen with (4*R*)-Ph **20** or (4*R*,5*S*)-di-Ph **137** series.



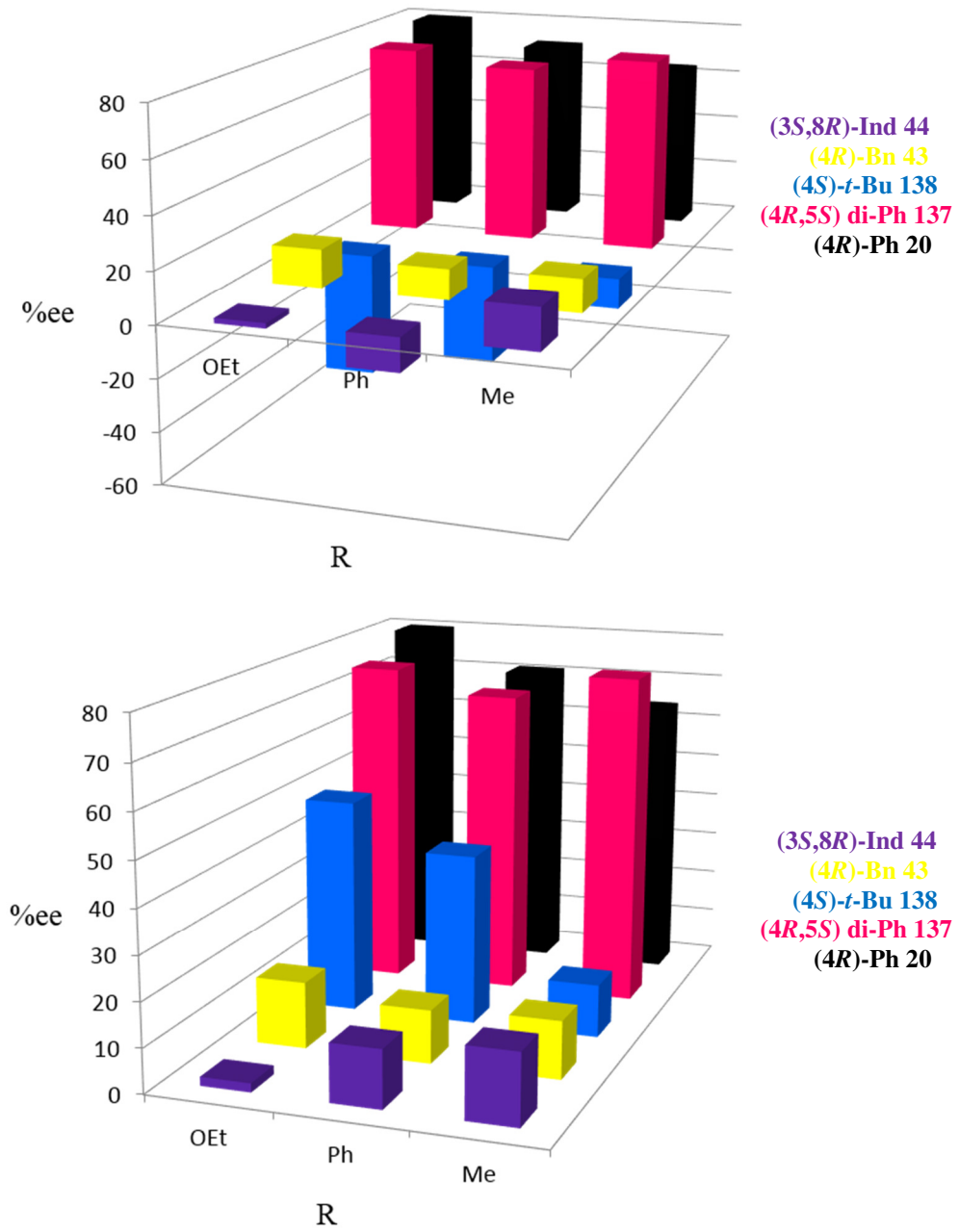


Figure 5.10 *Bisoxazoline ligand effect on enantiopurity of trans sulfolanes for substrates* **165b, 166b** and **167b**

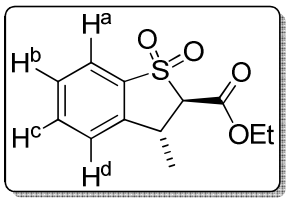
This effect is in contrast to the other *trans* sulfolanes, where ketone and ester compounds show different trends based on the ligands employed (**Chapter 4**, **Section 4.3.4**, **Figure 4.22**). It is interesting to compare these trends with those seen for simple sulfolane formation (**Figure 4.22**, **Chapter 4**), where the influence of the ligand on enantioselectivity varied on changing from an ethyl ester to a methyl ketone. In contrast, in the formation of the thiopyran derivatives, ligand trends were again comparable across the methyl ester and phenyl and methyl ketones (**Figure 4.15**, **Chapter 4**).

5.4 Conclusions

C–H insertion to generate fused sulfolanes can be effected using either rhodium or copper catalysts for the first time. Enantioselectivities of up to 80% ee have been achieved, using copper-bisoxazoline catalysts, with the best results seen with (4*R*)-Ph **20** and (4*R*,5*S*) di-Ph **137** and the absolute stereochemistry has been confirmed for **165b**. Enantioselectivities using chiral rhodium catalysts were lower. While detailed rationalisation is complicated by epimerisation of the initially formed *cis* sulfolanes to the thermodynamically more favoured *trans* sulfolanes, it is particularly interesting to note that ligand trends across the ethyl ester-methyl/phenyl ketone were consistent in this series, in contrast to the patterns seen with the simple sulfolanes.

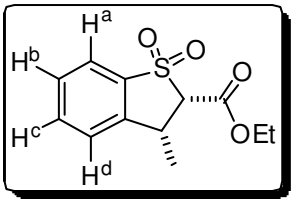
5.5 Experimental

(2*R*,3*R*) Ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1, 1-dioxide 165b



The title compound was prepared according to the procedure described for (2*R*,3*S*)-1-(3-phenyl-1,1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans* **42b** using ethyl 2-diazo-2-[(2-ethylphenyl)sulfonyl]acetate **54** (150 mg, 0.53 mmol), $CuCl_2$ (3.53 mg, 26.6 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (28mg, 31.9 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (10.6 mg, 31.9 μmol) in dichloromethane (20 mL), stirred while heating under reflux for 2 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 90% efficient (89% *cis* **165a**: 11% *trans* **165b**). Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*R*,3*R*) ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1,1-dioxide (6% *cis* **165a**, 94% *trans* **165b**) (130 mg, 91%) was isolated as a colourless oil (*cis* **165a** -82% ee, *trans* **165b** -80%); (determined by chiral-HPLC); The following spectral characteristics are reported for *trans* **165b**. ν_{max}/cm^{-1} (film): 1741 (CO), 1317, 1282, 1251, 1213, 1180 (SO_2), 761 (CS); δ_H ($CDCl_3$, 300 MHz): 1.37 (3H, t, *J* 7.1, OCH_2CH_3), 1.55 [3H, d, *J* 6.70, C(1′)H_3], 3.93–4.08 [2H, m, C(2)*H* and C(3)*H*], 4.17–4.47 (2H, sym m, OCH_2CH_3), 7.39–7.57 (2H, overlapping dd and ddd, appears as m, ArH^d and ArH^b), 7.64 (1H, ddd, *J* 7.6, 7.6, 1.1 ArH^c), 7.71 (1H, d, *J* 7.9 ArH^a); δ_C ($CDCl_3$, 75.5 MHz): 14.1 (CH_3, OCH_2CH_3), 18.7 [CH_3, C(1′)H_3], 35.7 [CH, *C*(3)H], 62.9 (CH_2, OCH_2CH_3), 72.3 [CH, *C*(2)H], 121.6 (CH, aromatic *C*H), 125.4 (CH, aromatic *C*H), 129.0 (CH, aromatic *C*H), 134.1 (CH, aromatic *C*H), 137.4 (C, aromatic *C*), 140.3 (C, aromatic *C*), 164.0 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{15}O_4S$ $[M+H]^+$, 255.0691. Found 255.0688. m/z (ESI+): 255.2 $[M+H]^+$.

*Assignments made with aid of 2D NMR experiments, which included HETCOR and COSY. The absolute stereochemistry was assigned by analogy with respect to carboxylic acid **170b**.*



^{1}H NMR spectral characteristics of *cis* **165a** were determined from the spectra of the crude product; δ_H ($CDCl_3$, 400 MHz): 1.26 (3H, t, *J* 7.1, OCH_2CH_3), 1.55 [3H, d, *J* 7.1, C(1′)H_3], 3.92 [1H, apparent quint, *J* 6.8, C(3)*H*], 4.16–4.32 (2H, m,

OC*H*$_2$CH$_3$), 4.38 [1H, d, *J* 6.6 C(2)*H*] 7.40–7.54 (2H, m, Ar*H*^{d} and Ar*H*^{b}), 7.59–7.66 (1H, m, Ar*H*^{c}), 7.71 (1H, d, *J* 7.1 Ar*H*^{a}).

Mixtures of *cis* **165a** and *trans* **165b** are seen in the ^{1}H NMR spectra of the crude product of cyclisations of ethyl 2-diazo-2-[(2-ethylphenyl)sulfonyl]acetate **54**. Purification on silica gel causes epimerisation of *cis* **165a** to *trans* **165b**. A study was carried out on the rate of epimerisation of *cis* **165a** to *trans* **165b** in $CDCl_3$ and in CH_2Cl_2. A reaction was set up identical to that reported for ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1,1-dioxide **165b**. The reaction was deemed complete after 1 h, at which point a ^{1}H NMR spectrum was obtained. The reaction mixture was stirred for a further 9 days, during which period measurements of the *cis* **165a** : *trans* **165b** ratios were measure using ^{1}H NMR analysis.

Table 5.9 *Investigation into the rate of epimerisation of **165a** to **165b**; solvent and heat effects*

Entry	**Time**	**Solvent**	**Temperature**	***cis* 165a : *trans* 165b** [b]
1[a]	1h	CH_2Cl_2	reflux	88% : 12%
2	20 h	$CDCl_3$	rt	87% : 13%
3	9 days	$CDCl_3$	rt	33% : 67%
4	3h	CH_2Cl_2	reflux	87% : 13%
5	21h	CH_2Cl_2	reflux	84% : 16%
6	30h	CH_2Cl_2	reflux	81% : 19%
7	9 days	CH_2Cl_2	2 day reflux, 7 days rt	60% : 40%

a. The initial ^{1}H NMR of the crude mixture was kept in $CDCl_3$. Two further ^{1}H NMR were measured for this sample, one after 20 h in $CDCl_3$ and one after 9 days in $CDCl_3$.
b. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH$_2$C*H*$_3$; *cis* sulfolane **165a**, δ_H 1.26 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$).

Reactions were monitored using IR spectroscopy for the first six hours. The reaction was deemed to be complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. If starting material remained after six hours the reaction was heated under reflux overnight, at which point monitoring of the reaction commenced again.

Table 5.10 *Copper and rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **54**

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency[a]	Yield (%)[b]	Crude ratios[a] Purified ratios[a]	*cis* **165a** %ee[c]	:	*trans* **165b** %ee[c]
1	**A**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	2	~90%	91	**Crude ratio:** **Purified ratio:**	89 6 (82% ee) (2*S*,3*R*)		11 94 (80% ee) (2*R*,3*R*)
2[d]	**A**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	5	~90%	78	**Crude ratio:** **Purified ratio:**	70 7 (90% ee) (2*S*,3*R*)		30 93 (80% ee) (2*R*,3*R*)
3	**C**	$Cu(OTf)_2$[e]$/\Delta$	-	21	~60–70%	29[f]	**Crude ratio:** **Purified ratio:**	50 7 (0% ee)		50 93 (0% ee)
4	**A**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	3	~90%	84	**Crude ratio:** **Purified ratio:**	63 7 (3% ee) (2*R*,3*S*)		37 93 (2% ee) (2*S*,3*S*)
5	**A**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	3	~90%	75	**Crude ratio:** **Purified ratio:**	32 7 (18% ee) (2*S*,3*R*)		68 93 (15% ee) (2*R*,3*R*)
6	**A**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	3	~82%	61	**Crude ratio:** **Purified ratio:**	52 11 (54% ee) (2*R*,3*S*)		48 89 (49% ee) (2*S*,3*S*)

7	**A**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	3	~90%	67	**Crude ratio:** **Purified ratio:**	83 14 (83% ee) (2*S*,3*R*)		17 86 (75% ee) (2*R*,3*R*)
8	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	3	~90%	81	**Crude ratio:** **Purified ratio:**	84 8 (86% ee)[g] (2*S*,3*R*)		16 92 (80% ee)[g] (2*R*,3*R*)
9	**B**	CuCl/Δ	(4*R*)-Ph **20**	30	~90%	77	**Crude ratio:** **Purified ratio:**	38 7 (-)[h]		62 93 (80% ee)[i] (2*R*,3*R*)
10	**B**	$CuCl_2/\Delta$	CN-(4*S*)-Ph **158**	120	~80%[j]	35	**Crude ratio:** **Purified ratio:**	33 6		67 94 (28% ee)[k] (2*S*,3*S*)
11	**B**	$CuCl_2/\Delta$	Py-(4*R*)-Ph **159**	120	Starting material only	-	**Crude ratio:** **Purified ratio:**	- - -		- - -
12	**B**	$CuCl_2/\Delta$	Py-(4*S*)-*i*-Pr **160**	120	50–60%[l]	26	**Crude ratio:** **Purified ratio:**	10 10 (10% ee)[k]		90 90 (10% ee)[k]
13	**F**	Rh_2(*S*-PTTL)$_4$ 0 °C-rt	-	6	-	44	**Crude ratio:** **Purified ratio:**	58 7 (20% ee) (2*S*,3*R*)		42 93 (30% ee) (2*R*,3*R*)
14	**F**	Rh_2(*S*- PTPA)$_4$ 0 °C-rt	-	6	80–90%	61	**Crude ratio:** **Purified ratio:**	62 5 (13% ee) (2*S*,3*R*)		48 95 (16% ee) (2*R*,3*R*)
15	**F**	Rh_2(*S*- DOSP)$_4$ 0 °C-rt	-	2	80–90%	52	**Crude ratio:** **Purified ratio:**	50 8		50 92 (8% ee) (2*S*,3*S*)

16	**G**	Rh_2(*S*- MEPY)$_4$ 0 °C-rt-Δ	-	120	50–60%[m]	25	**Crude ratio:** **Purified ratio:**	47 10 (0% ee)		53 90 (2% ee)[k] (2*R*,3*R*)
17	**F**	Rh_2(*S*- mand)$_4$ 0 °C-rt	-	6	80–90%	58	**Crude ratio:** **Purified ratio:**	45 7 (5% ee) (2*R*,3*S*)		55 93 (6% ee) (2*S*,3*S*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for OCH_2CH_3; *cis* sulfolane **165a**, δ_H 1.26 (3H, t, *J* 7.1, OCH_2CH_3); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH_2CH_3).

b. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluent, and contains both *cis* and *trans* isomers, in the specified ratios.

c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**. Enantioselectivity was measured on mixed fractions, where both *cis* **165a** and *trans* **165b** isomers were present in the purified material. All four diastereoisomers were separable. The % ee is determined on purified samples by HPLC. The % ee of the *cis* isomer **165a** was measured using weak HPLC signals, making measurements less accurate. Therefore these results should be interpreted with caution. The absolute stereochemistry of *trans* isomer **165b** is assigned by analogy to carboxylic acid **170b**, details of which can be found in **Appendix II.**

d. This reaction was carried out using 1 g of α-diazo-β-oxo sulfone **54**, in comparison to the remaining entries where ~50-200 mg of α-diazo-β-oxo sulfone **54** were employed.

e. Multiple products in crude.

f. Additional (less polar) fraction obtained; *approx* 60% α-diazo-β-oxo-sulfone **54**, ~ 40% of this fraction is tentatively assigned as an X–H insertion product **168**; ν_{max}/cm^{-1} 2126 (C=N_2), 1720 (CO); δ_H ($CDCl_3$, 400 MHz) 3.07 (ddd, *J* 1.6, 7.3, 14.7), 4.27–4.39 (sym m), 5.76 (s), 7.42–7.53 (m), 7.57 (td, *J* 1.4, 7.6), 8.00 (dd, *J* 1.3, 8).

g. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -29.0 (*c*, 1.0 CH_2Cl_2)

h. Result could not be determined accurately.

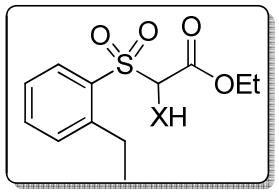
i. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -39.5 (*c*, 1.0 CH_2Cl_2)

j. The crude material contains ~5% starting material α-diazo-β-oxo sulfone **54**.

k. The enantioselectivity given here is estimated and could not be accurately determined due to peak overlap in the HPLC trace.

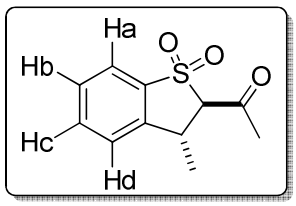
l. Contains ~30% starting material α-diazo-β-oxo sulfone **54**.

m. Contains ~25% starting material α-diazo-β-oxo sulfone **54**.



The presence of δ_H ***5.76 (s) in the*** ^{1}***H NMR spectra of some of the crude products may indicate the presence of an X–H insertion product*** **168**, ***however, this is not confirmed.***

1-(3-Methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl)ethanone 166b

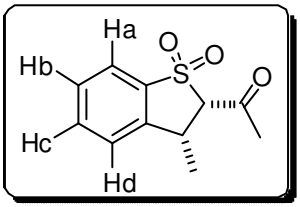


1-Diazo-1-[(2-ethylphenyl)sulfonyl]propan-2-one **55** (100 mg, 0.39 mmol) in distilled dichloromethane was added dropwise over 5 min to a refluxing solution of $Rh_2(OAc)_4$ (~1 mg) in distilled dichloromethane (20 mL), stirred while heating under reflux for 21 h, in accordance with **Method E**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 95% efficient (9% *cis* **166a**: 91% *trans* **166b**). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80) as eluent, 1-(3-methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl)ethanone (2% *cis* **166a**, 98% *trans* **166b**) (49 mg, 56%) was isolated as a colourless oil; 0 % ee (*trans* **166b**) (determined by chiral HPLC); The following spectral characteristics are reported for *trans* **166b**. ν_{max}/cm^{-1} (film): 2912 (CH), 1726 (CO), 1647, 1595 (C=C, Ar), 1299, 1209, 1173, 1126 (SO_2), 768 (CS); δ_H ($CDCl_3$, 400 MHz): 1.49 [3H, d, *J* 7.0, C(1′)H_3], 2.55 (3H, s, COCH_3), 4.04 [1H, apparent quint, *J* 7.0, C(3)*H*], 4.17 [1H, d, *J* 7.0, C(2)*H*], 7.44–7.52 (2H, overlapping dd and ddd, appears as m, ArH^d and ArH^b), 7.64 (1H, ddd, *J* 7.6, 7.6, 1.1, ArH^c), 7.70 (1H, d, *J* 7.8 ArH^a); δ_C ($CDCl_3$, 150.9 MHz): 18.7 [CH_3, *C*(1′)H_3], 31.1 [CH_3, CO*C*H_3], 34.3 [CH, *C*(3)H], 78.5 [CH, *C*(2)H], 121.5 (CH, aromatic *C*H), 125.5 (CH, aromatic *C*H), 129.0 (CH, aromatic *C*H), 134.2 (CH, aromatic *C*H), 137.0 (C, aromatic *C*), 140.8 (C, aromatic *C*), 195.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}O_3S$ $[M+H]^+$, 225.0585. Found 225.0584.

NOSEY and NOE difference experiments were conducted to establish relative stereochemistry

The title compound was prepared according to the procedure described for (2*R*,3*S*)-1-(3-phenyl-1,1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans* **42b** using 1-diazo-1-[(2-ethylphenyl)sulfonyl]propan-2-one **55** (80 mg, 0.32 mmol), $CuCl_2$ (2.1 mg, 16 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (16.8 mg, 19 μmol) and bisoxazoline ligand (4*R*)-Bn **43** (6.9 mg, 19 μmol) in dichloromethane (20 mL), stirred while heating under reflux for 21 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 70% efficient (4% *cis*: 96% *trans*). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80) as eluent, 1-[(2*R*,3*R*)-3-methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl]ethanone (1% *cis* **166a**, 99% *trans* **166b**) (42

mg, 60%) was isolated as a colourless oil; 10% ee (*trans* **166b**) (determined by chiral HPLC). Spectral characteristics are identical to those reported above.

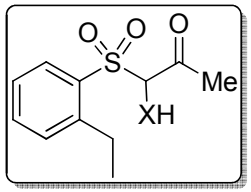


The following signals appear in ^{1}H NMR spectra of the crude product and are tentatively assigned to *cis* **166a**; δ_H ($CDCl_3$, 400 MHz): 1.51 [3H, d, *J* 5.4, C(1′)H_3], 2.42 (3H, s, COCH_3), 3.89 [1H, apparent quint *J* 6.5, C(3)*H*], 4.44 [1H, d, *J* 6.5, C(2)*H*].

Table 5.11 *Asymmetric copper-bisoxazoline and rhodium acetate catalysed C-H insertion reactions of α-diazo-β-oxo sulfone* **55**

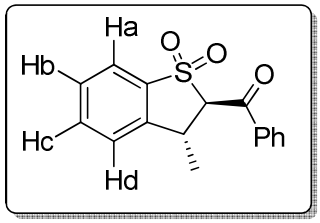
Entry	Method	M	Ligand	Time (h)	Crude Efficiency[a]	Yield (%)[b]	Crude ratios[a] Purified ratios[a]	*cis* % ee[c]	:	*trans* % ee[c]
1	**A**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	3	>90%[d]	65[e]	**Crude ratio:** **Purified ratio:**	2 2		98 98 (64% ee)[f] (2*R*,3*R*)
2	**A**	$CuCl_2/\Delta$	(4*R*,5*S*) di-Ph **137**	7	~55%[g]	42	**Crude ratio:** **Purified ratio:**	2 1		98 99 (76% ee)[h,i] (2*R*,3*R*)
3	**A**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	30	41% starting material left, [j] of remaining 59%;43% efficient	38	**Crude ratio:** **Purified ratio:**	2 2[j]		98 98[j] (12% ee) (2*S*,3*S*)
4	**A**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	5	~60–70% [k]	45[d,l]	**Crude ratio:** **Purified ratio:**	5 2		95 98 (16% ee)[m,n] (2*R*,3*R*)
5	**A**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	4	~70%	60	**Crude ratio:** **Purified ratio:**	4 1		96 99 (13% ee) (2*R*,3*R*)
6	**E**	$Rh_2(OAc)_4/\Delta$	-	21	~95%	56[d]	**Crude ratio:** **Purified ratio:**	9 2		91 98 (0% ee)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*; *cis* sulfolane **166a**, δ_H 4.44 [1H, d, *J* 6.5, C(2)*H*]; *trans* sulfolane **166b**, δ_H 4.17 [1H, d, *J* 7.0, C(2)*H*].
b. Yield (%) refers to material purified using column chromatography on silica gel using ethyl acetate : hexane (5:95–10:90–20:80) as eluent, and contains both *cis* **166a** and *trans* **166b** isomers, in the specified ratios.
c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**, absolute stereochemistry was assigned by analogy, with respect to ethyl ester **165b**, details of which can be found in **Appendix II**.
d. White solid, (mp 73–74°C).
e. Additional peaks observed in ^{1}H NMR spectra of the crude product; δ_H 2.41 (d, *J* 4.14), 4.28 (dd, *J* 4.1, 10.2), 4.34 (d, *J* 7.1).
f. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -2.0 (*c*, 0.1 CH_2Cl_2).
g. Additional peaks observed in ^{1}H NMR spectra of the crude product; δ_H 4.27 (dd, *J* 4.1, 10.2), 4.68 (s), 4.93 (s), 5.12 (s), 7.79–8.10 (m), 8.05–8.12 (m), 8.18–8.23 (m).
h. Compound **166**, eluted over three fractions. The enantiopurity of the contents of each fraction differs slightly indicating enantiomer self-disproportionation. The enantiopurity of 76% ee is based on a weighted average. The enantiopurity and the relative mass of each fraction are given as follows; fraction one-90% ee, 21% mass (100% *trans* **166b**), fraction two-74% ee, 67% mass (98% *trans* **166b**, 2% *cis* **166a**), fraction three 66% ee, 12% mass (*cis* isomer **166a** absent, impurities present).
i. Rotation measured on mixed fraction: $[\alpha]_D^{20}$ -2.0 (*c*, 0.1 CH_2Cl_2).
j. Impurity(ies) observed in ^{1}H NMR spectra of the crude and purified product. Signals listed for ^{1}H NMR of purified product; δ_H 1.83 (d, *J* 6.5), 5.70 (s), 6.54 (q, *J* 6.6), 8.03 (d, *J* 7.1)
k. Additional peaks observed in ^{1}H NMR spectra of the crude product; δ_H 3.01–3.11 (m), 5.12 (s).
l. Additional peaks observed in the ^{1}H NMR of the crude product; δ_H 2.41 (d, *J* 4.1), 3.06 (q, *J* 7.5), 4.28 (dd, *J* 4.1, 10.2), 7.86–7.97 (m).
m. Enantioselectivity observed was opposite to that predicted, confirmed by rotation.
n. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -1.167 (*c*, 0.3 CH_2Cl_2).

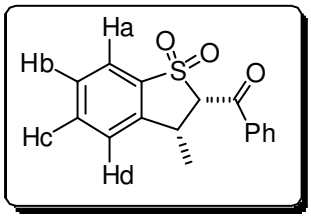


The presence of δ_H ***5.12 (s) in the*** ^{1}***H NMR spectra of some of the crude products may indicate the presence of an X–H insertion product*** **181***, however, this is not confirmed.*

[(2*R*,3*R*)-3-Methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl](phenyl)methanone 167b



The title compound was prepared according to the procedure described for (2*R*,3*S*)-1-(3-phenyl-1,1-dioxo-tetrahydrothiophen-2-yl)ethanone *trans* **42b** using 2-diazo-2-[2-(ethylphenyl)sulfonyl]-1-phenylethanone **56** (100 mg, 0.32 mmol), $CuCl_2$ (2.2 mg, 16 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (16.9 mg, 19 μmol) and (4*R*)-Ph **20** (6.4 mg,19 μmol) in dichloromethane (25 mL), stirred while heating under reflux for 5 h, in accordance with Method **A**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 65% efficient (9% *cis*: 91% *trans*). Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, [(2*R*,3*R*)-3-methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl](phenyl)methanone (1% *cis* **167a**, 99% *trans* **167b**) (34 mg, 38%) was isolated as a colourless oil; 71% ee (*trans* **167b)** (determined by chiral HPLC); ν_{max}/cm^{-1} (film): 2922, 2851 (CH), 1684 (CO), 1597 (C=C, Ar), 1309, 1156 (SO_2), 751 (CS); δ_H ($CDCl_3$, 400 MHz): 1.54 [3H, d, *J* 7.0, C(1′)H_3], 4.41 [1H, apparent quint, *J* 6.9, C(3)H], 5.02 [1H, d, *J* 6.9, C(2)H], 7.46–7.60 (4H, m, Ar*H*), 7.63–7.72 (3H, m, Ar*H*), 8.19–8.22 (2H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 18.8 [CH_3, *C*(1′)H_3], 35.7 [CH, *C*(3)H], 73.8 [CH, *C*(2)H], 121.6 (CH, aromatic *C*H), 125.4, 129.1 (× 2), 129.5 (× 2), 134.2, 134.6 (6 signals seen for 7 aromatic *C*H carbons), 136.3 (C, aromatic *C*), 137.3 (C, aromatic *C*), 141.2 (C, aromatic *C*), 188.2 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{15}O_3S$ $[M+H]^+$, 287.0742. Found 287.0732.



The following signals appear in ^{1}H NMR spectra of the crude product and are tentatively assigned to *cis* **167a**; δ_H ($CDCl_3$, 400 MHz): 1.81 [3H, d, *J* 6.3, C(1′)H_3], 4.09 [1H, apparent quint, *J* 6.4, C(3)*H*], 5.45 [1H, d, *J* 5.4, C(2)*H*].

Assignments made with aid of a 2D NMR experiment (COSY)

Table 5.12 *Asymmetric copper-bisoxazoline and rhodium acetate catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **56**

Entry	**Method**	**M**	**Ligand**	**Time (h)**	**Crude Efficiency[a]**	**Yield (%)[b]**	**Crude ratios[a] Purified ratios[a]**	***cis*** **% ee[c]**	**:**	***trans*** **% ee[c]**
1	**A**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	5	~65%	38[d] (oil)	**Crude ratio:** **Purified ratio:**	9 1[e]		91 99[e] (71% ee) (2*R*,3*R*)
2	**A**	$CuCl_2/\Delta$	(4*R*,5*S*) di-Ph **137**	3	~72%[f]	50[g] (oil)	**Crude ratio:** **Purified ratio:**	54 1		46 99 (70% ee)[h,i] (2*R*,3*R*)
3	**A**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	21	~70%	55[j] (solid)	**Crude ratio:** **Purified ratio:**	42 1[j]		58 99[j,k] (39% ee) (2*S*,3*S*)
4	**A**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	24	~65%[l]	42 (solid)[m]	**Crude ratio:** **Purified ratio:**	7 1		93 99 (13% ee)[n] (2*S*,3*S*)
5	**A**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	50	~65%	48 (solid)	**Crude ratio:** **Purified ratio:**	Trace 1		>99 99 (12% ee)[o] (2*R*,3*R*)
6	**E**	$Rh_2(OAc)_4/\Delta$	-	21	~70–80%	40	**Crude ratio:** **Purified ratio:**	10 1		90 99 (0% ee)

						(80% **167b**) (solid)				

a. Efficiency and relative ratios of isomers calculated using the ^{1}H NMR spectra of the crude product using signals for C(2)*H*; *cis* sulfolane **167a**, δ_H 5.45 [1H, d, *J* 5.4, C(2)*H*]; *trans* sulfolane **167b**, δ_H 5.02 [1H, d, *J* 6.9, C(2)*H*].

b. Yield (%) refers to material purified by column chromatography on silica gel using ethyl acetate : hexane (10 : 90) as eluent, and contains both *cis* **167a** and *trans* **167b** isomers, in the specified ratios.

c. Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in **Appendix I**, absolute stereochemistry was assigned by analogy with respect to ethyl ester sulfolane **165b**, details of which can be found in **Appendix II**.

d. Additional less polar fraction isolated after chromatography (3 mg); δ_H 1.27–1.34 (m), 2.98–3.16 (m), 6.14 (s), 7.30–7.44 (m), 7.49–7.58 (m), 7.58–7.69 (m), 7.91–7.95 (m), 8.02–8.08 (m)

e. Compound **167** eluted over six fractions, The enantiopurity of the contents of the last fraction differs slightly to that of the first five fractions, indicating enantiomer self-disproportionation. The enantiopurity of 71% ee is based on a weighted average. The enantiopurity and the relative mass of each fraction(s) are given as follows; fractions one-five 70% ee, 84% mass (99% *trans* **167b**, 1% *cis* **167a**), fraction six 80% ee, 14% mass (100% *trans* **167b**).

f. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.50–2.33 (overlapping peaks, appears as m), 3.77 (s), 3.93 (m), 6.05–6.35 (m), 6.74–6.93 (m).

g. Additional less polar fraction isolated after purification; δ_H 1.30 (t, *J* 7.5), 3.00–3.19 (sym m), 6.14 (s), 7.32–7.46 (m), 7.49–7.57 (m), 7.59–7.68 (m), 7.93 (dd , *J* 1.3, 8.1), 8.05 (2H, dd, *J*. 1.3, 8.4)

h. Compound **167** eluted over 5 fractions. The enantiopurity of the contents of the last fraction differs slightly to that of the first four fraction, indicating enantiomer self-disproportionation. The enantiopurity of 70% ee is based on a weighted average. The enantiopurity and the relative masses of each fraction(s) are given as follows; fractions one-four 68% ee, 70% mass (99% *trans* **167b**, 1% *cis* **167a**), fraction six-75% ee, 30% mass (>99% *trans* **167b**, trace *cis* **167a**)

i. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ -104.5 (c, 0.1 CH_2Cl_2)

j. Additional peaks present in the ^{1}H NMR spectra of the crude and purified product; δ_H 3.78 (s), 3.93 (s), 4.05-4.15 (m).

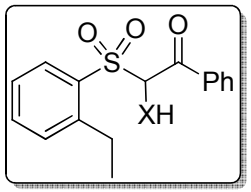
k. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ +73.5 (c, 0.1 CH_2Cl_2)

l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.50–3.33 (overlapping peaks, appears as m), 3.77 (s), 3.93-4.0 (m), 6.14 (s), 6.29 (s), 6.74 (dd, *J* 6.3, 12.7)

m. mp 85–87 °C.

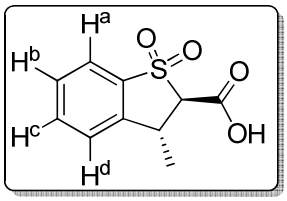
n. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ +16.0 (c, 0.1 CH_2Cl_2).

o. Rotation measured on mixed fraction-$[\alpha]_D^{20}$ +26.8 (c, 0.276 CH_2Cl_2)



The presence of δ_H ***6.14 (s) in the*** ^{1}***H NMR spectra of some of the crude products may indicate the presence of an X–H insertion product*** 180***, however, this is not confirmed.***

(2*R*,3*R*)-3-Methyl-2,3-dihydrobenzo[b]thiophene-2-carboxylic acid 1,1-dioxide 170b

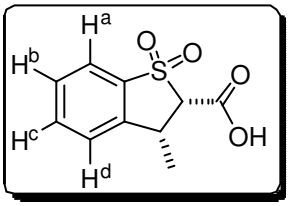


Potassium hydroxide (1.47 g, 26.3 mmol) in distilled water (15 mL) was added to ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1,1-dioxide {*cis* **165a** [90% ee (2*S*,3*R*)] : *trans* **165b** [80%ee (2*R*,3*R*)], 7 : 93}, isolated from reaction reported in **Table 5.10**, entry 2, (0.67 g, 2.6 mmol) in methanol (30 mL) and the resulting solution was stirred for 2 h at room temperature, after which TLC analysis indicated that the reaction was complete. Methanol was removed from the crude reaction mixture by evaporation under reduced pressure, then ethyl acetate (30 mL) and aqueous HCl (15 mL, 2 M, aqueous solution) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$ and concentrated under reduced pressure to yield (2*R*,3*R*) 3-methyl-2,3-dihydrobenzo[b]thiophene-2-carboxylic acid 1,1-dioxide (5% *cis* **170a**, 95% *trans* **170b**) (0.46 g, 78%) as a white crystalline solid; mp 75–76 °C; $[\alpha]_D^{20}$ -35.5 (*c* 1.1, CH_2Cl_2); 78% ee (*trans* **170a**) (determined by chiral-HPLC); (Found: C, 51.50; H, 4.53; $C_{10}H_{10}O_4S.0.5H_2O$ requires C, 51.05; H, 4.71 %); ν_{max}/cm^{-1} (neat): 3176 (OH), 2926 (CH), 1725 (CO), 1281, 1151, 1123 (SO_2), 764 (CS); The following spectral characteristics are reported for *trans* **170b**. δ_H ($CDCl_3$, 600 MHz): 1.57 [3H, d, *J* 7.0, C(1′)H_3], 3.99 [1H, apparent quint, *J* 6.9 C(3)*H*], 4.13 [1H, d, *J* 7.3, C(2)*H*], 7.08 (1H, br s, COO*H*), 7.45–7.54 (2H, overlapping d and t, appears as m, ArH^d and ArH^b), 7.66 (1H, apparent td, *J* 7.6, 1.0 ArH^c), 7.73 (1H, d, *J* 7.8 ArH^a); δ_C ($CDCl_3$, 75.5 MHz): 18.5 [CH_3, *C*(1′)H_3], 35.8 [CH, *C*(3)H], 72.2 [CH, br, *C*(2)H], 121.7 (CH, aromatic *C*H^a), 125.1 (CH, aromatic *C*H^b or *C*H^d), 129.1 (CH, aromatic *C*H^b or *C*H^d), 134.3 (CH, aromatic *C*H^c), 137.0 (C, aromatic *C*), 140.3 (C, aromatic *C*), 167.4 (C, *C*O).

The relative stereochemistry was determined by single crystal X-ray diffraction of a crystalline sample of **170b** recrystallised from IPA.[27] Full Structural details are contained on the accompanying CD.

Crystals of **170b** are triclinic, space group *P*1, formula $C_{20}H_{22}O_9S_2$, M_R = 470.49, *a* = 8.1731(8) Å, *b* = 8.5779(9) Å, *c* = 9.0489(9) Å, α = 74.180(2)°, β = 76.474(2)°, γ = 63.539(2)°, *U* = 541.75(10) Å^3, *F(000)* = 246, μ(Mo Kα) = 0.295 mm^{-1}, *R*(F_o) = 0.024,

for 3965 observed reflections with $I > 2\sigma(I)$, $wR_2(F^2) = 0.056$ for all 4147 unique reflections. Data in the θ range 2.36 – 26.35° were collected on a Bruker APEX DUO diffractometer using Mo Kα radiation, λ = 0.71073 Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom. Full details are given on the accompanying CD.



^{1}H NMR spectral characteristics of *cis* **170a** were determined from spectra of purified product; δ_H ($CDCl_3$, 600 MHz) 1.59 [3H, d, *J* 7.1, C(1′)H_3], 4.46 [1H, d, *J* 6.8, C(2)*H*].

Table 5.13 *Synthesis of* carboxylic acid **170** (**a** and **b**) from ethyl ester **165** (**a** and **b**)

Entry	**Sulfolane** *cis* **165a** : *trans* **165b** (***trans* %ee**)	**Yield (%)**		**Carboxylic acid[a]**	
				***cis* 170a**	***trans* 170b**
1	7: 93 (80% ee)[b]	78%	Ratio (% ee)	5 (-)[c]	95 (78% ee)
2	7: 93 (0% ee)[d]	65%	Ratio (% ee)	8 (-)[c]	92 (0% ee)

a. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals C(2)*H*; *cis* sulfolane, δ_H 4.46 [1H, d, *J* 6.8 C(2)*H*]; *trans* sulfolane, δ_H 4.13 [1H, d, *J* 7.3, C(2)*H*].

b. Starting material obtained from **Table 5.10**, entry 2

c. Peaks for *cis* sulfolane not detected during HPLC analysis.

d. Starting material obtained from **Table 5.10**, entry 3.

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(1) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2904.

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Chapter Six

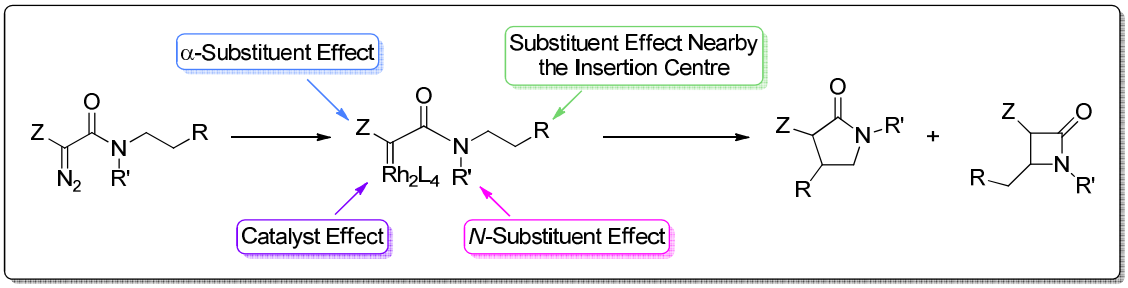
C–H insertion reactions of α-diazo-β-amido sulfones

"If you can talk with crowds and keep your virtue, Or walk with Kings—nor lose the common touch, If neither foes nor loving friends can hurt you…." Rudyard Kipling

6.1 Background

The transition metal catalysed intramolecular C–H insertion reactions of α-diazoacetamides to lead to β- and/or ɣ-lactams is a well-established methodology,[1–11] and has gone from strength to strength since the first report of this reaction by Ponsford and Southgate.[12] The fact that both β- and ɣ-lactams are biologically important compounds makes this transformation very desirable.[1,13–16] While the general mechanistic features that were discussed in Chapter 4, (**Section 4.5**) for transition metal catalysed intramolecular C–H insertion reactions of α-diazocarbonyl compounds apply to the synthesis of lactams,[17] there are additional issues to be considered for the C–H insertion reactions of α-diazoacetamides; of these competition between β- and ɣ-lactam formation is one of the most important. While five membered ring formation is generally the dominant pathway for C–H insertion reactions with α-diazocarbonyl compounds, in the specific case of α-diazoacetamides, competition between β- and ɣ-lactam formation is seen as insertion into the C–H bond adjacent to the nitrogen is facilitated through the activating effect of the nitrogen atom.[7]

As a result of extensive study, by a number of research teams notably those of Doyle,[18–21] Wee, [22,23] Padwa, [24,25] Afonso[7,26,27] and Jung,[16,28] it has been shown that through careful substrate and/or catalyst design that the regioselectivity of C–H insertion reactions of α-diazoacetamides to form either β- or ɣ-lactams can be carefully controlled, potentially leading to highly selective C–H insertion reactions. In relation to substrate design, the effect of the α-substituent, the substituent effect close to the C–H insertion centre and the effect of the *N*-substituent, all have a major impact on whether the β- or ɣ-lactam is the major reaction product, as discussed by Gois and Afonso (**Scheme 6.1**). In addition, the nature of the catalyst employed can affect reaction outcome. A number of catalysts have been successfully utilised for transformations of this type including copper, ruthenium, *etc.*[29–33] However, it has been the use of rhodium catalysts that have dominated the literature over the past 20 years; careful alteration of the ligands on the rhodium catalysts can preferentially lead to either β- or ɣ-lactam formation. The factors that significantly impact the reaction pathway in the Rh(II) catalysed C–H insertion reactions of α-diazoacetamides in lactam formation have been excellently summarised in a review by Gois and Afonso.[7]



Scheme 6.1[7]

Before discussing the outcome of the studies conducted during this project, a brief synopsis of the factors specifically affecting the outcome of C–H insertion reactions of α-diazoacetamides to lead to β- and/or ɣ-lactams will be discussed.

6.1.1 α-Substituent Effect

The α-substituent on the carbene carbon can dramatically alter the electrophilicity of the metal carbene. The more electrophilic the metal carbene, the more reactive it is, which is usually accompanied by a decrease in selectivity. In general, metal carbenoids can be classified as acceptor substituted carbenoids, acceptor/acceptor substituted carbenoids or acceptor/donor substituted carbenoids, where an acceptor group is an electron withdrawing substituent and a donor group is an electron donating group. Examples of diazo precursors to acceptor substituted carbenoids are illustrated in **Figure 6.1**. The presence of an electron withdrawing acceptor group makes the metal carbene more reactive due to increased electrophilicity. In general, metal carbenes or carbenoids derived from α-diazoketones are more reactive than those from α-diazoacetates which in turn have greater reactivity than those generated from α-diazoacetamides.[2,6,7]

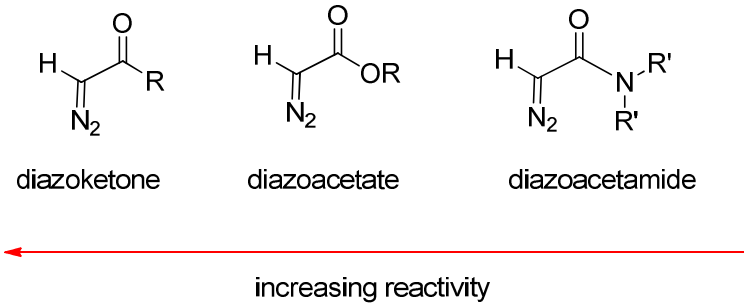


Figure 6.1[6]

Acceptor/acceptor carbenoids possess two electron withdrawing groups α to the diazo carbon. Examples of these are illustrated in **Figure 6.2**, where one of the electron withdrawing groups is an amide substituent. In general, α-diazoacetoacetamides are the most reactive of the diazoacetamides with reactivity decreasing in the order shown in **Figure 6.2**. The presence of two electron withdrawing substituents results in a relatively stable diazo compound, making initial carbene transfer difficult. However, once the carbenoid is formed, the presence of two electron withdrawing groups makes the carbenoid highly electrophilic and therefore it can readily undergo C–H insertion. A highly reactive carbene of this nature would be expected to demonstrate poor selectivity; however, there is literature evidence to the contrary.[6]

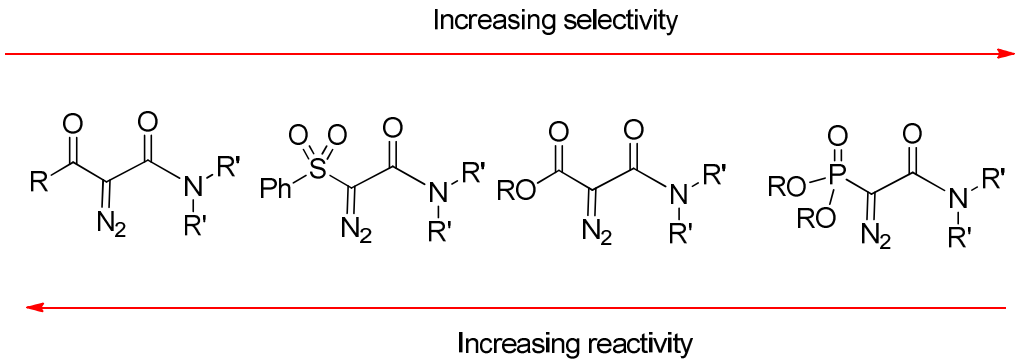
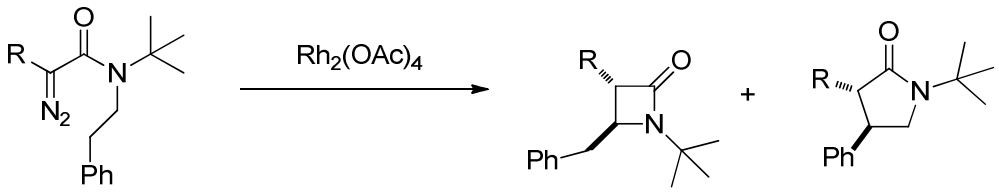


Figure 6.2

Both regio- and stereoselectivity of the C–H insertion reaction can be controlled through careful selection of the α-substituent. This is clearly illustrated in the example presented in **Table 6.1**, where the use of a sulfonyl and a phosphoryl α-substituent result in exclusive ɣ-lactam formation (**Table 6.1**, entries 2 and 3), while use of a methyl ketone substituent results in a much less selective reaction, with both β- and ɣ-lactams being synthesised in approximately equal amounts (**Table 6.1**, entry 1). This may be rationalised by the fact that ketones are more electron withdrawing than sulfonyl and phosphoryl groups, giving rise to a less stable carbenoid, resulting in an earlier transition state and a less selective reaction (**Table 6.1**).[25,26,28]

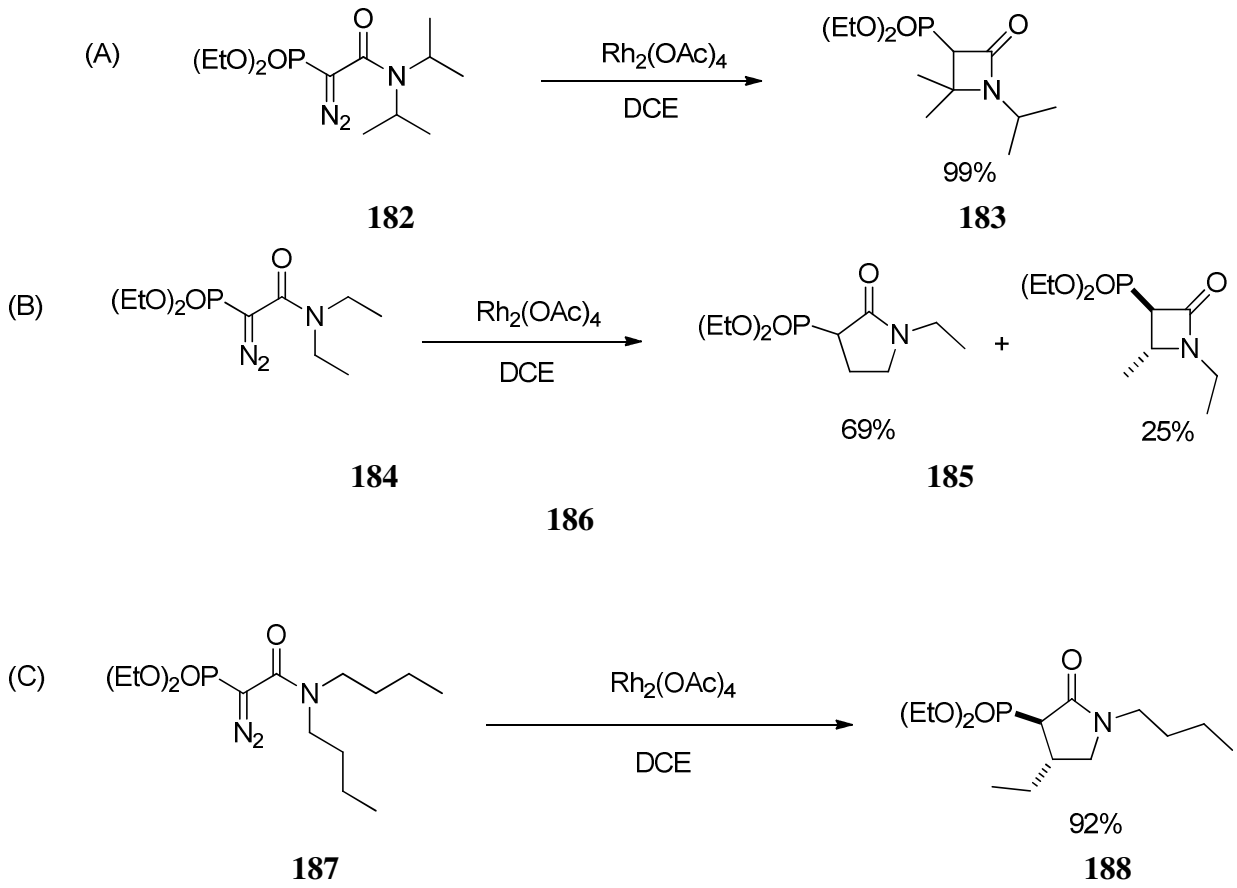
Table 6.1 *Rhodium acetate catalysed C–H insertion reactions of α-diazoacetamides with variation of the α-substituent*[34]



Entry	R	Yield (%)	Ratio	
			β	ɣ
1[25]	$COCH_3$	9	49	51
2[28]	$PhSO_2$	95	none	only
3[26]	$PO(OEt)_2$	81	none	only

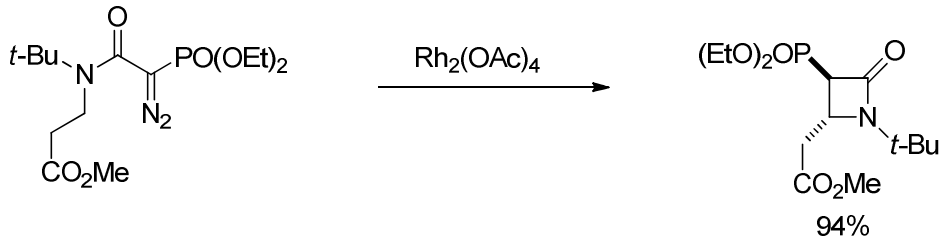
6.1.2 Effect of substituents near to the insertion centre

In determining whether β- or ɣ-lactam dominates the crude reaction mixture of C–H insertion reactions of α-diazoacetamides, it is often the substituent near the potential insertion sites that dictates the reaction outcome. Theoretically, the presence of electron donating groups near to a potential C–H insertion site should activate this site toward insertion. Not only does increased electron density at the site of insertion favour electrophilic attack by a rhodium carbenoid, but electron donating groups α to the C–H bond undergoing insertion may also stabilise the build-up of positive charge at this carbon (A number of potential transition states for C–H insertion have been presented in Chapter 4, **Section 4.5**, for a more thorough discussion of this, this section should be consulted). This effect can be clearly seen in the work presented in **Scheme 6.2**[26,27] A similar product distribution is seen in ionic liquids.[27]



Scheme 6.2[26]

Both the nitrogen atom and the methyl group in (A) are activating for C–H insertion; combining these effects results in exclusive β-lactam **183** formation, as can be seen in the **Scheme 6.2** (A). When the activating effect of the methyl group is removed, ɣ-lactam **185** is the major reaction product (69%) with β-lactam **186** being formed in lower quantities (25%) [**Scheme 6.2** (B)]. Therefore, removing an electron donating methyl group α to the insertion site has a significant impact on the regioselectivity of the reaction. Generally, C–H insertion into a methyl group is not favoured; however, in this case the tendancy towards formation of a five-membered ɣ-lactam product outweighs this preference. The exclusive synthesis of ɣ-lactam **188** in **Scheme 6.2** (C) results from the rhodium acetate catalysed C–H insertion reaction of α-diazoacetamide **187**, where insertion occurs into a methylene group (**Scheme 6.2**). Conversely the presence of an electron withdrawing group α to the C–H site can have a deactivating effect; an ester substituent is an example of such a group.[17,35,36] For example, when α-diazoacetamide **189** undergoes rhodium acetate catalysed C–H insertion reaction, exclusively β-lactam **190** is formed with no evidence for ɣ-lactam formation (**Scheme 6.3**).[26]

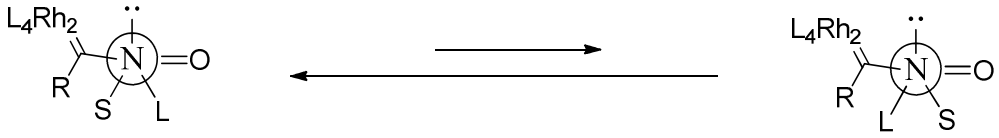


189 **190**

Scheme 6.3[26]

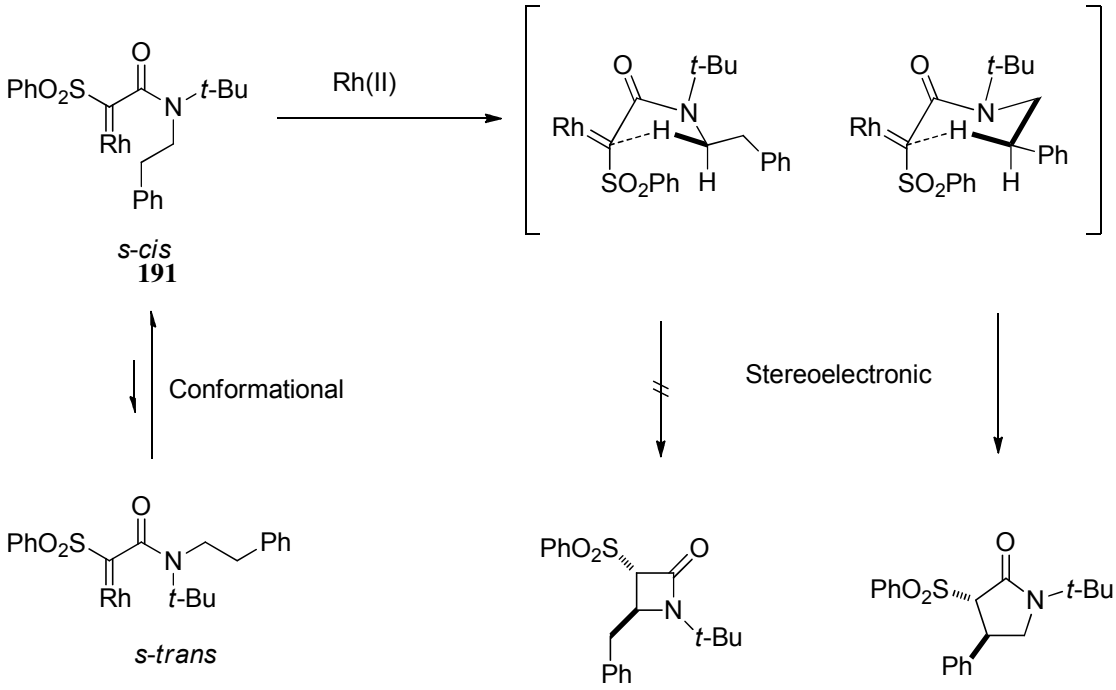
6.1.3 Effect of the *N*-substituent

In cases where the amide functionality is not symmetrical, conformational effects owing to this moiety can have a profound effect on reaction outcome. Doyle and co-workers have rationalised this by stating that the lone pair of electrons on the amide nitrogen interact with the amide carbonyl group thus fixing the amide in a conformation where the smaller *N*-substituent is near in space to the reacting carbene carbon, therefore allowing C–H insertion to proceed at this proximal site (**Scheme 6.4**).[37] Consequently, it is possible to exploit this effect; the introduction of a conformational bias *via* the utilisation of two sterically different *N*-substituents can enhance the regioselectivity of the reaction, causing C–H insertion to occur selectively or exclusively at one of the *N*-substituents.



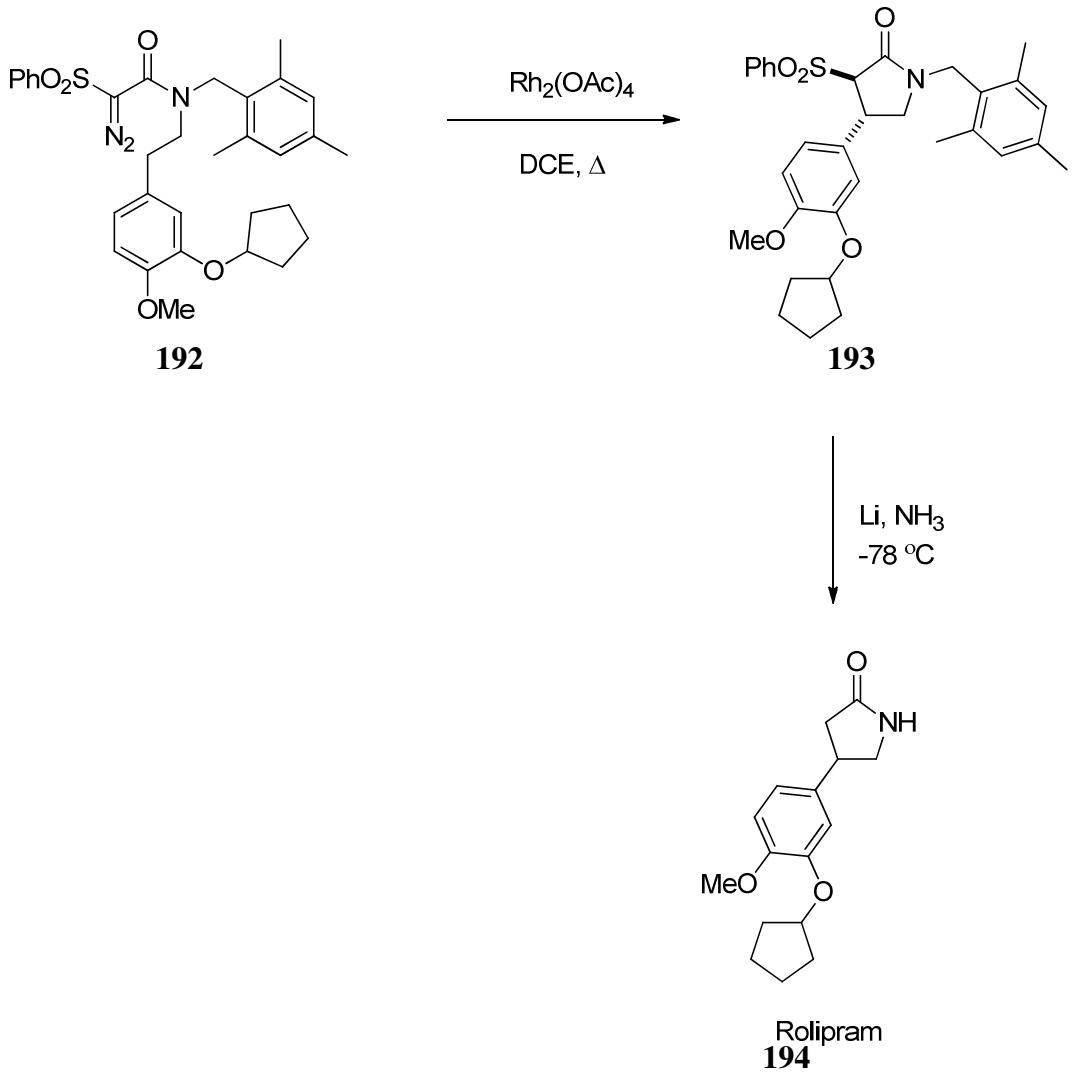
Scheme 6.4[7,37]

This effect has been described numerous times in the literature.[7,20] The following example demonstrates it in action for the rhodium acetate catalysed C–H insertion of α-diazo-α-(phenylsulfonyl) acetamide **191** (**Scheme 6.5**). Due to conformational effects, only the *s-cis* conformation is suitable to undergo C–H insertion reaction, allowing the possibility of either β- or ɣ-lactam formation through the transition states presented in **Scheme 6.5**. In practice insertion occurs *via* the later, more stereoelectronically favourable transition state, to yield the ɣ-lactam product, which has been rationalised by the stabilising effect of the phenylsulfonyl moiety.[28]



Scheme 6.5[28]

A practical use of this effect is where one of the *N*-substituents can be used as a protecting group with insertion occurring exclusively into the other *N*-substituent, which has proved an important synthetic strategy in the synthesis of biologically important targets. Through careful substrate design, Jung and co-workers have demonstrated this in the synthesis of rolipram (**Scheme 6.6**).[38] Rhodium acetate catalysed C–H insertion reaction of α-diazoacetamide **192** led to exclusive formation of ɣ-lactam **193**; cleavage of both the phenylsulfonyl moiety and the *N*-benzyl group occurred simultaneously upon exposure to Li/NH_3 which afforded rolipram **194** in an excellent yield of 90%.[38]



Scheme 6.6[38]

6.1.4 Rhodium catalyst effect

Rhodium(II) carboxylates and carboxamidates are by far the most widely studied transition metal catalysts for the intramolecular C–H insertion reactions of α-diazoacetamides. The regioselectivity of these reactions can largely depend on the nature of the rhodium ligands. In general, catalysts bearing more electron withdrawing ligands are more reactive and thus, reactions employing these ligands usually proceed through an earlier transition state [*e.g.* $Rh_2(pfb)_4$]. The opposite is also true; the more electron donating ligands cause reactions to proceed more slowly; however, these generally result in products arising from a later transition state [*e.g.* $Rh_2(acam)_4$] (**Figure 6.3**).[2,7,39,40]

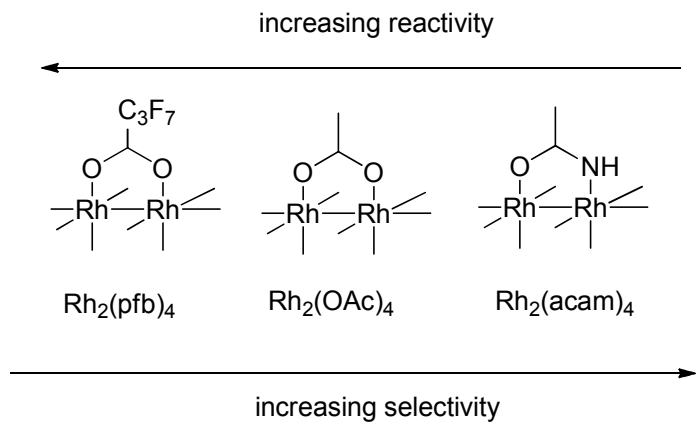
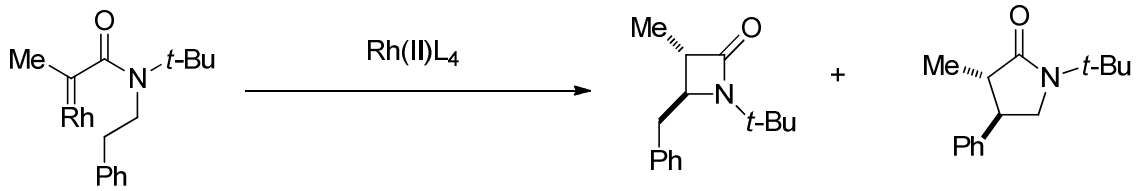


Figure 6.3[6]

The effects that these ligands bearing relatively strongly electron withdrawing ligands have on product distribution can clearly be seen in **Table 6.2**. When $Rh_2(pfb)_4$ catalyst is employed a less selective reaction occurs, with β-lactam **195** being formed as the major product (**Table 6.2**, entry 1). Conversely, when α-diazoacetamide **196** is exposed to the more electron donating $Rh_2(acam)_4$, the reaction is more selective, proceeding through a later transition state, resulting in much higher proportions of ɣ-lactam **197** formation (**Table 6.2**, entry 3). [25]

Table 6.2 *C–H insertion reactions of α-diazoacetamide **196** employing electronically different rhodium catalysts*[25]

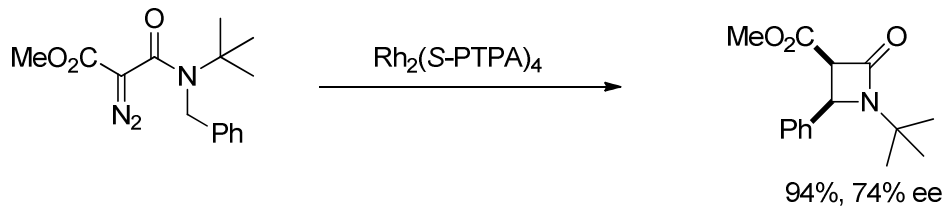


196 **195** **197**

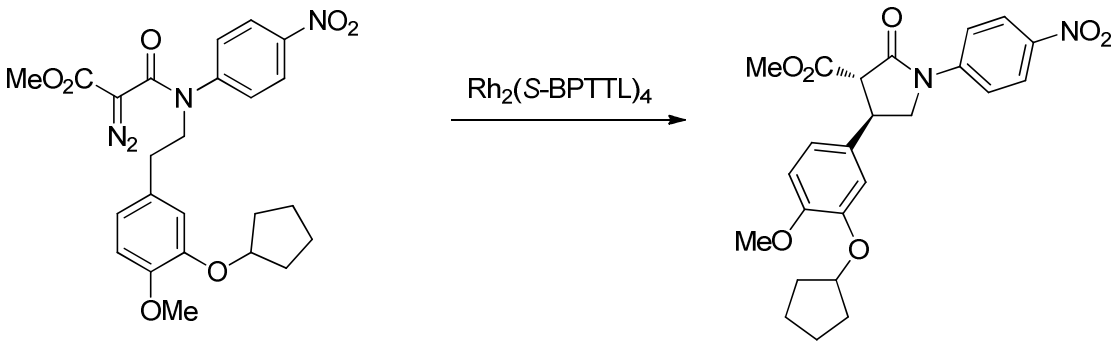
Entry	Catalyst	Yield (%)	β 195	ɣ 197
1	$Rh_2(pfb)_4$	85	56	44
2	$Rh_2(OAc)_4$	94	49	51
3	$Rh_2(acam)_4$	90	30	70

6.1.5 Chiral rhodium catalysts

The use of chiral rhodium(II) catalysts has proven to be a very effective method for the enantioselective synthesis of both β- and ɣ-lactams.[3,5–7] For example, Hashimoto and co-workers reported the synthesis of β-lactam **198** in 74% ee, employing Rh_2(*S*-PTPA)$_4$ as a catalyst and the synthesis of ɣ-lactam **199**, an important intermediate in the synthesis of R-(-)-rolipram, in 88% ee when Rh_2(*S*-BPTTL)$_4$ was utilised as a catalyst (**Scheme 6.7**).[41,42]



200 **198**

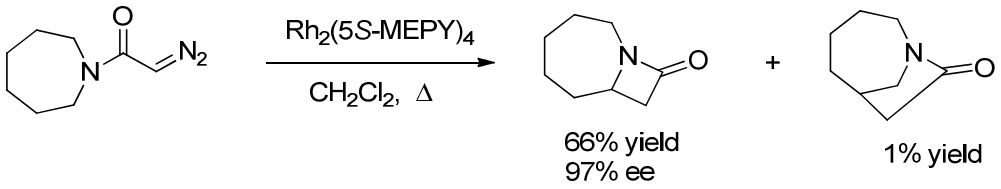


201 **199**

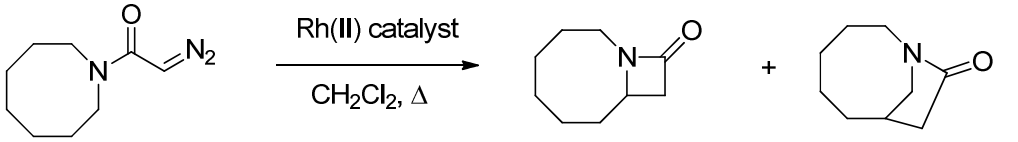
Scheme 6.7[41,42]

When reaction of cyclic terminal α-diazoacetamides are catalysed using rhodium carboxamidate catalysts, very high enantioselectivities have been reported in the synthesis of both β- and ɣ-lactams (**Scheme 6.8**). The synthesis of β-lactam **202** was reported with a value of 97% ee, when Rh_2(5*S*-MEPY)$_4$ was employed as a catalyst. However, when the starting α-diazoacetamide consisted of an eight-membered rather than a seven-membered ring, there was a change in the regioselectivity of the reaction; ɣ-lactam **203** was the major product, isolated in 98% ee with Rh_2(4*S*-MEOX)$_4$ catalyst. The change in regioselectivity has been rationalised by the fact that the seven membered ring

system is much more rigid than the eight membered ring, thus not allowing sufficient orbital overlap to facilitate the formation of a γ-lactam product.[18]



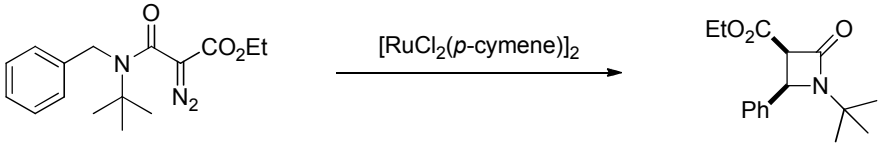
204 **202** **205**

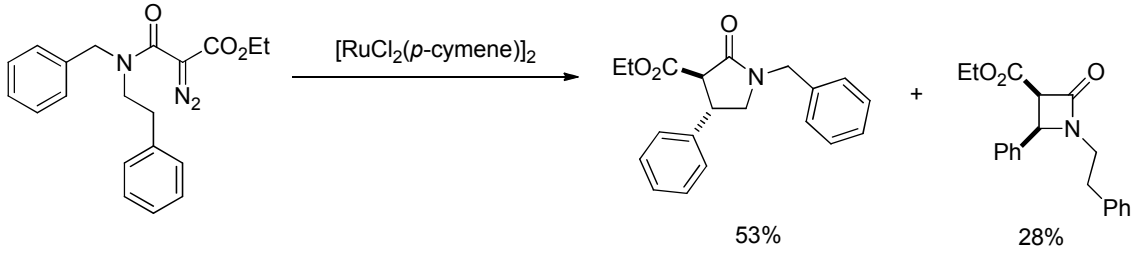


206 **207** **203**

Scheme 6.8[18]

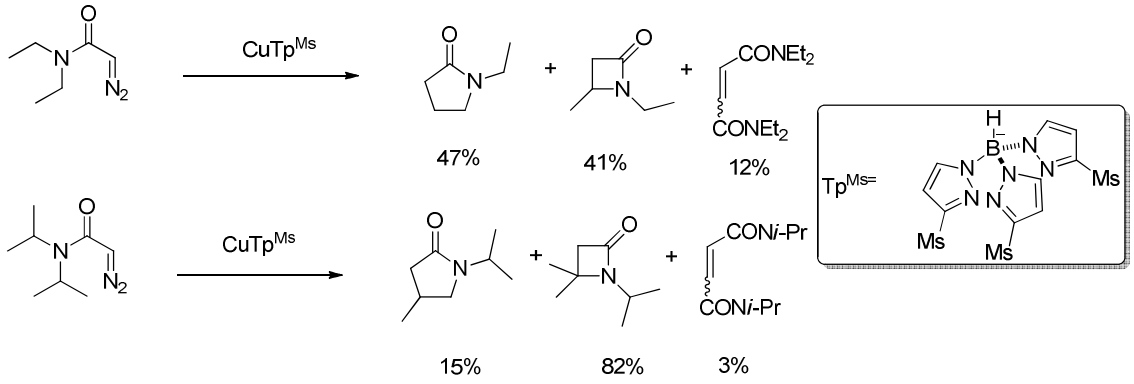
In addition to rhodium, a number of other transition metal catalysts have been reported to successfully catalyse the C–H insertion reactions of α-diazoacetamides. Ruthenium has been successfully utilised in lactam synthesis,[29,32,43] for example, both β- and γ-lactams have been successfully synthesised employing $[RuCl_2(p\text{-cymene})]_2$ as a catalyst (**Scheme 6.9**).[29] Notably *cis* β-lactams are the favoured insertion product for ruthenium catalysed insertion reactions, while generally, rhodium catalysed reactions result in *trans* selectivity.[25,28]





Scheme 6.9[29]

There is also a report demonstrating the effectiveness of achiral copper catalysts for C–H insertion reactions of α-diazoacetamides, as shown in **Scheme 6.10**.[33]

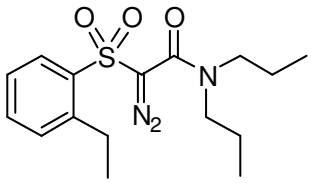


Scheme 6.10[33]

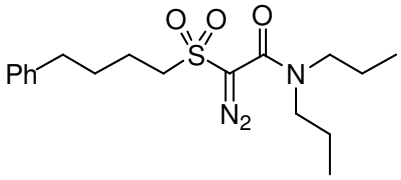
6.2 Chapter Aims

To the best of our knowledge there have been no reports in the literature of asymmetric copper catalysed C–H insertion reactions of α-diazoacetamides. In addition there have only been a limited number of reports of the C–H insertion reactions of α-sulfonyl-α-diazoacetamides.[28,38,44] A thorough discussion of the C–H insertion reactions of α-diazo-β-keto sulfones and α-diazo-β-ester sulfones was included in Chapters 4 and 5. In this chapter we wish to extend this discussion to include C–H insertion reactions of α-diazo-β-amido sulfones. A number of amide groups were chosen for investigation, namely *N*,*N*-dipropyl amides **46, 50, 57** *N*,*N*-diethyl amides **47, 51**, *N*,*N*-dibenzyl amide **53**, in addition to the morpholine amides **48, 49, 52, 58**. A variety of accompanying sulfonyl groups were selected for examination, as illustrated in **Figure 6.4**. The sulfonyl groups were chosen principally to allow exploration of competing C–H insertion pathways, into the sulfonyl substituent to form thiopyrans or sulfolanes or into the amide substituent to form lactams.

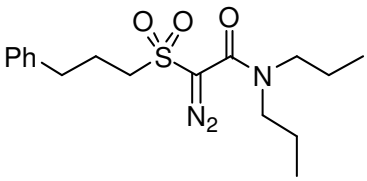
***N*,*N*-dipropyl amide substrates**



57

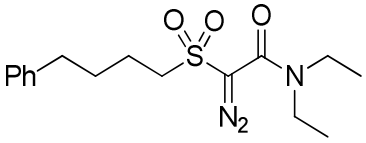


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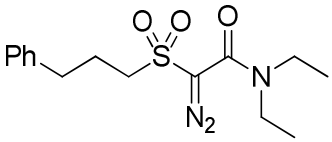


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***N*,*N*-diethyl amide substrates**

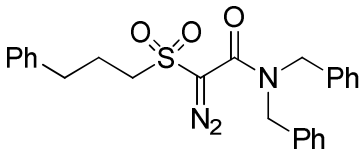


47



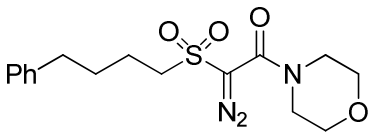
51

***N*,*N*-dibenzyl amide substrate**

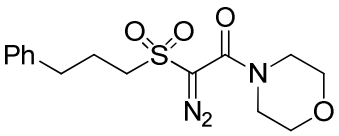


53

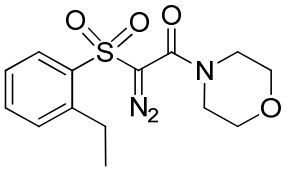
Morpholine amide substrates



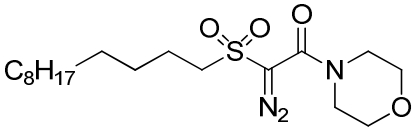
48



52



58



49

Figure 6.4

The most interesting feature of these substrates is the number of potential insertion sites present. The C–H insertion reaction can be envisaged to give sulfolanes/thiopyrans, in line with the reactivity patterns seen for ketone and ester derivatives, or alternatively, insertion can occur into one of the alkyl substituents on the amide functionality, to yield β or ɣ lactams, as illustrated in **Figure 6.5**. In addition, while the majority of the sulfones are alkyl sulfones, inclusion of the two aryl sulfones **57** and **58** provides an opportunity to explore the electronic effect of the α- substituent. As Doyle and co-workers have indicated the importance of conformational effects of α-diazoamides,[20] symmetrically substituted amides were employed to avoid the complications associated with conformational factors. As stated above, while the formation of five-membered rings is usually favoured in C–H insertion reactions, in the specific case of lactam formation, activation of the C–H bond adjacent to the nitrogen can result in β- lactam formation.

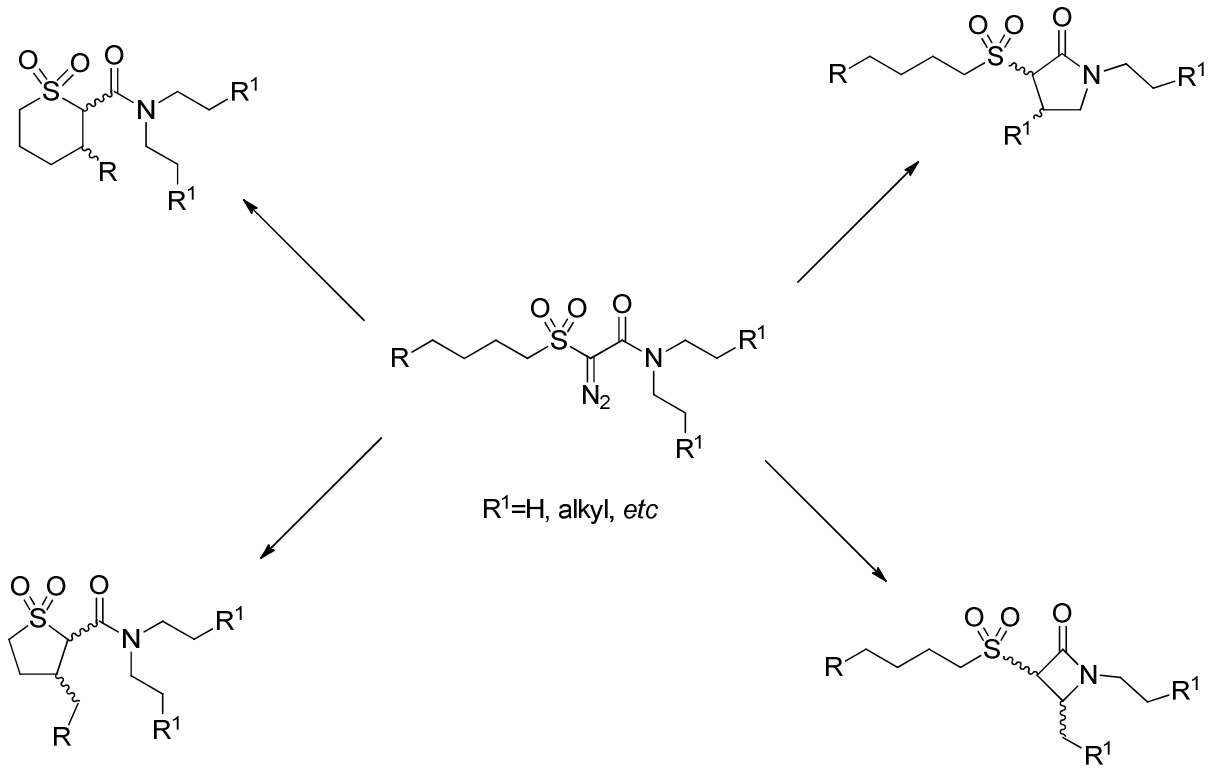
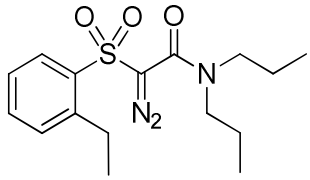


Figure 6.5

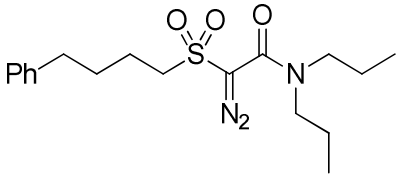
6.3 Results and Discussion

6.3.1 Exploration of substrates that contain *N*,*N*-dipropyl amide.

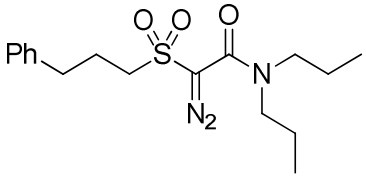
The first series of amides that was selected for investigation was that containing the *N*,*N*-dipropyl amide functionality. Three different sulfonyl substituents were chosen for examination leading to the synthesis of α-diazo-β-amido sulfones **46, 50, 57** (**Figure 6.6**), as discussed in Chapter 3. Keeping the amide group constant and varying the sulfonyl group allows investigation of the impact of the sulfone substituent on both product outcome in terms of regioselectivity, and on the enantiopurity of products formed in the reaction. For substrate **46**, formation of all four isomeric products (sulfolane/thiopyran and β-/ɣ lactam) is potentially possible. While the same is true for substrate **57**, C–H insertion to give thiopyran is unlikely based on results obtained for similar substrates, as discussed in Chapter 5. The formation of thiopyran is impossible for substrate **50** due to the shorter alkyl chain present on the sulfonyl group.



57



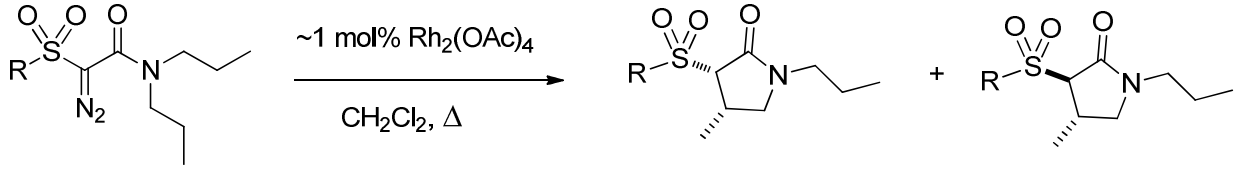
46



50

Figure 6.6

Table 6.3 *C–H insertion reactions of α-diazo-β-amido sulfones* **46, 50, 57** *catalysed by rhodium acetate; investigation of* N,N-*dipropyl amide*[45]



46, 50, 57 **208-210 (a)** **208-210 (b)**

Entry	α-diazo sulfone	R	Time (h)	Crude Efficiency (%)	Yield (%)[a]	Product Ratio:	*cis* (% ee)	*trans* (% ee)
1	**57**	2'-ethylphenyl	18	~80–90%[b]	52	**Crude:** **Pure:**	8 5 (0% ee) **208a**	92 95 (0% ee) **208b**
2	**46**	$Ph(CH_2)_4$	6	>90%[c]	60	**Crude:** **Pure:**	5 5 (0% ee) **209a**	95 95 (0% ee) **209b**
3	**50**	$Ph(CH_2)_3$	2	~80–90%[d]	57	**Crude:** **Pure:**	12 10 (0% ee) **210a**	88 90 (0% ee) **210b**

a. Yield reported after purification using column chromatography on silica gel with ethyl acetate : hexane as eluent. The yield reported is a combined yield for both *cis* and *trans* γ-lactam, which are recovered as a mixed fraction.

b. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using, for example, signals for C(3)*H*, *cis* γ-lactam **208a**, δ_H 3.90 [1H, d, *J* 8.3, C(3)*H*]; *trans* γ-lactam **208b**, δ_H 3.63 [1H, d, *J* 3.9, C(3)*H*].

c. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for $NCH_2CH_2CH_3$, *cis* γ-lactam **209a**, δ_H 0.93 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$); *trans* γ-lactam **209b**, δ_H 0.92 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$). Relative ratios for *cis* and *trans* isomers are estimated due to partial peak overlap.

d. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for $NCH_2CH_2CH_3$, *cis* γ-lactam **210a**, δ_H 0.95 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$); *trans* γ-lactam **210a**, δ_H 0.92 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$). Relative ratios for *cis* and *trans* isomers are estimated due to partial peak overlap.

Initially, C–H insertion reactions of substrates **46**, **50**, **57** were investigated using rhodium acetate as a catalyst. A solution of α-diazoamide, typically 50–100 mg, in dichloromethane was added dropwise to a solution of rhodium acetate (~1 mol%) in dichloromethane at reflux. Reactions were monitored using IR spectroscopy, and, when complete, they were concentrated under reduced pressure whereupon analysis of the crude reaction material was carried out using ^{1}H NMR spectroscopy. In the cases where

reactions were not complete within ~6–7 h, they were heated under reflux overnight (**Table 6.3**, entry 1). Interestingly, for substrates **46**, **50**, **57**, the sole reaction pathway observed was insertion into the CH_2 group β to the nitrogen, leading to ɣ-lactam products exclusively (**Table 6.3**, entries 1–3), with no evidence for sulfolane and/or thiopyran and/or β-lactam formation. The synthesis of ɣ- lactams **208**–**210** (**a** and **b**) using rhodium acetate as a catalyst is a very efficient process with insertion products making up between 80–90% of the crude reaction mixture (**Table 6.3**, 1 and 3), with more than 90% being obtained in one instance (**Table 6.3**, entry 2). ɣ-Lactams **208**–**210** are novel compounds and were fully characterised using ^{1}H NMR, ^{13}C NMR, IR and high resolution mass spectrometry. Both *cis* and *trans* ɣ-lactams were observed in the crude reaction mixture and the products after purification were obtained in essentially the same diastereomeric ratio. The relative stereochemistry of each of the *trans* ɣ-lactams **208**–**210** was assigned with the use of NOESY NMR experiments, and accordingly the stereochemistry of the minor lactam was assigned as *cis*. The assignment of the major diastereomer as *trans* was based on a NOSEY spectrum where an interaction was observed between C(3)*H* and the methyl protons attached to C(4) (**Figure 6.7**). An interaction was not observed between C(3)*H* and C(4)*H* further confirming the trans stereochemistry.

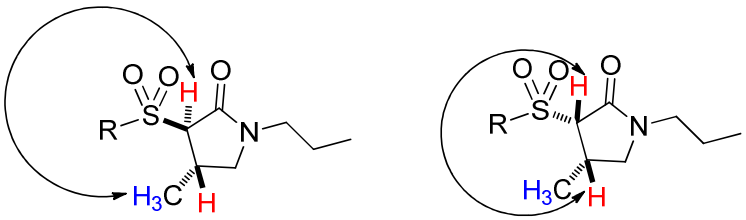
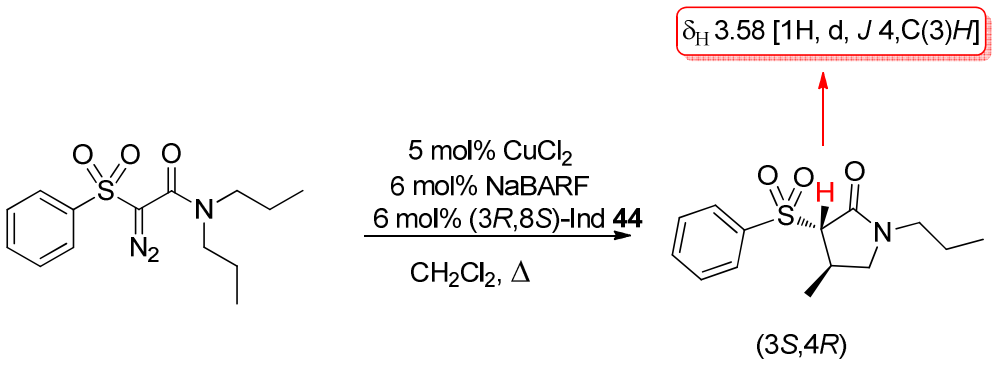


Figure 6.7

Furthermore, Ring has obtained an X-ray crystal structure of the ɣ-lactam **211** formed by C–H insertion reaction of the related α-diazoacetamide **212**, which confirmed the *trans* stereochemistry of the lactam. ^{1}H NMR characteristics of Ring's ɣ-lactam **211** were consistent with those seen for ɣ-lactam **208b**.



212 **211**

Scheme 6.11

The key characteristic signals for the *cis* and *trans* isomers of **208-210** (**a** and **b**) are shown in **Figure 6.8** below.

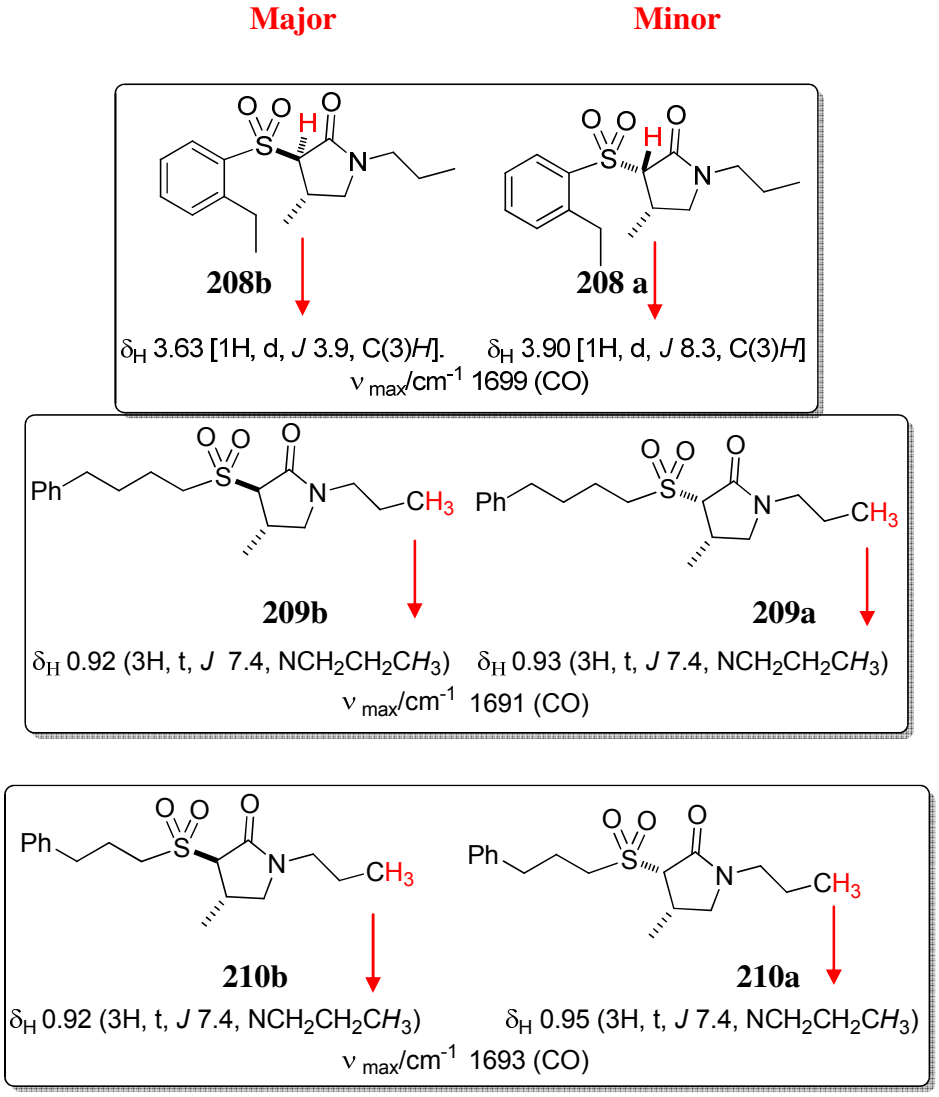


Figure 6.8 *Characteristc carbonyl IR stretches and characteristic ^{1}H NMR signals (in $CDCl_3$) for the identification of* cis *and* trans *γ- lactams* **208-210** (**a** and **b**)

Analysis of the crude reaction mixtures revealed that the major isomer observed for insertion reactions of substrates **46**, **50**, **57** was the *trans* isomer, which constituted more than 88% of the insertion products in all instances (**Table 6.3**, entries 1–3, **Figure 6.9**). After purification, using column chromatography on silica gel, both *cis* and *trans* lactams were isolated as a mixture, with no noticeable change being observed in the overall *cis* : *trans* ratio by ^{1}H NMR (**Figure 6.9**). Modest yields were obtained with values between 52–60% being achieved in all cases (**Table 6.3**, entries 1–3). In future work use of alumina should be considered. As rhodium acetate is an achiral catalyst, the samples of ɣ-lactams obtained allowed development of HPLC conditions for analysis of enantioenriched samples, prepared using chiral catalysts as will be subsequently discussed. Conditions were developed that allowed resolution of the enantiomers of the *cis* and *trans* ɣ-lactams through a single injection.

^{1}H NMR spectra of the crude product and the purified ɣ-lactams are shown in **Figure 6.9**, showing the high efficiency of the C–H insertion process and the selectivity for the formation of the *trans* isomer, with no substantial alteration in the *cis*/*trans* ratio. The outcome with rhodium and copper catalysts is very similar as illustrated in **Figure 6.9**.

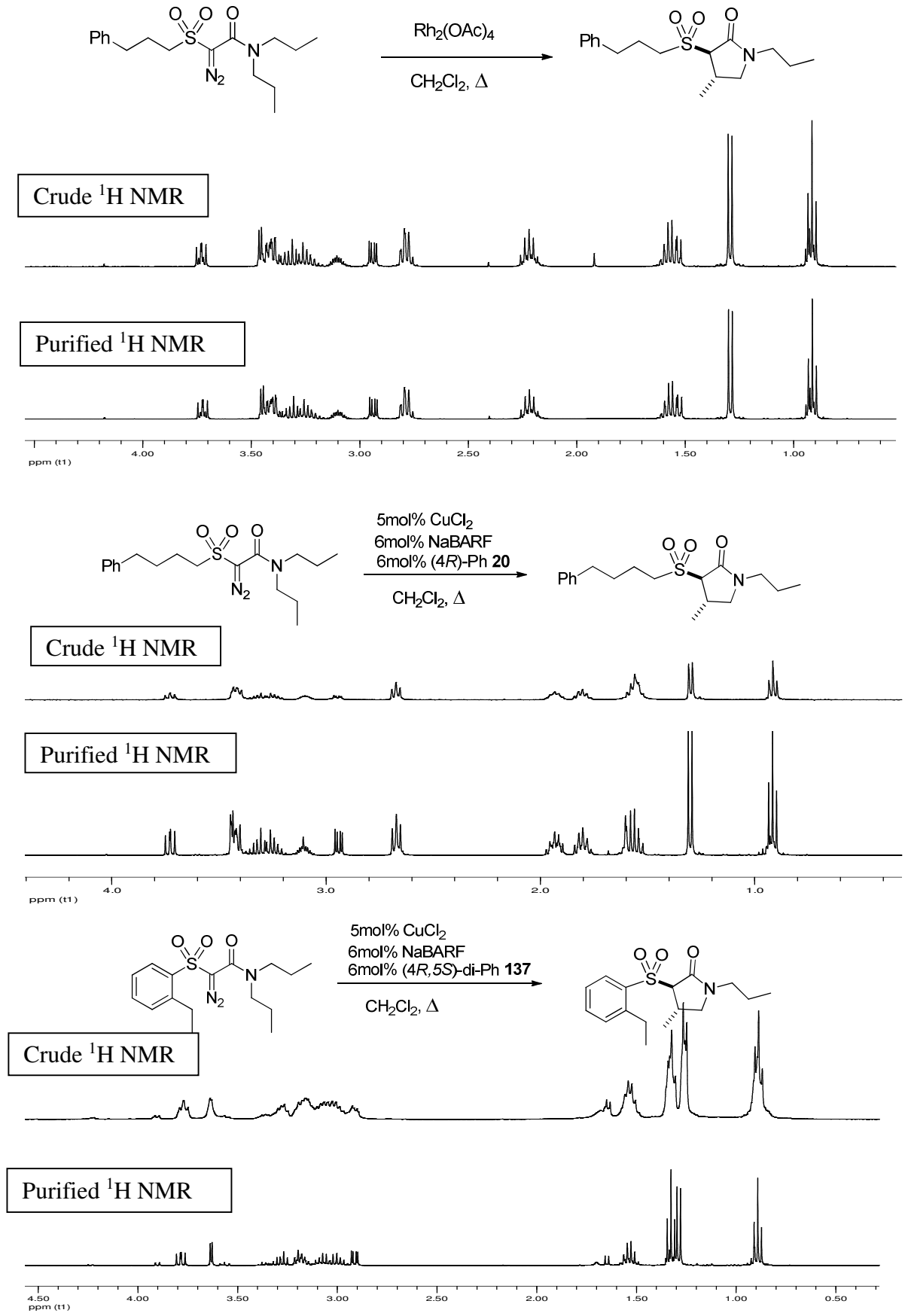
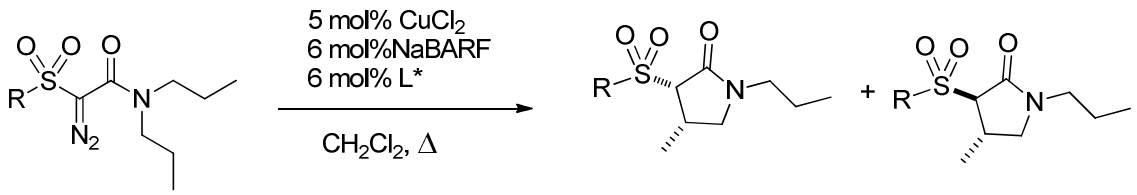


Figure 6.9 ^{1}H NMR ($CDCl_3$, 400 MHz)

Table 6.4 *C–H insertion reactions of α-diazo-β-amido sulfones* ***46, 50, 57*** *catalysed by chiral copper catalysts; investigation of dipropyl amide*[45]



Entry	α-diazosulfone	R	Ligand	Time (h)	Crude Efficiency (%)[b]	Yield (%)[a]	Product Ratio	*cis*[b] (% ee)	*trans*[b] (% ee)
1	**57**	2'-ethylphenyl	(4*R*)-Ph **20**	21	~75–85%	48	**Crude:** **Pure:**	14 10 (43% ee) **208a**	86 90 (48% ee) (3*S*,4*R*) **208b**
2	**57**	2'-ethylphenyl	(4*R*,5*S*)-di-Ph **137**	21	~80–90%	53	**Crude:** **Pure:**	15 7 (53% ee) **208a**	85 93 (34% ee) (3*S*,4*R*) **208b**
3	**57**	2'-ethylphenyl	(4*R*)-Bn **43**	21	~80–90%	59	**Crude:** **Pure:**	12 0 **208a**	88 100 (52% ee) (3*S*,4*R*) **208b**

4	**57**	2'-ethylphenyl	(4*S*)-*t*-Bu **138**	48	~70–80%	45	**Crude:** **Pure:**	8 6 (38% ee) **208a**	92 94 (70% ee) (3*R*,4*S*) **208b**
5[c]	**57**	2'-ethylphenyl	(3*S*,8*R*)-Ind **44**	6	~80–90%	61	**Crude:** **Pure:**	4 - **208a**	96 99 (82% ee) (3*R*,4*S*) **208b**
6	**46**	$Ph(CH_2)_4$	(4*R*)-Ph **20**	21	>90%	49	**Crude:** **Pure:**	3 3 **209a**	97 97 (12% ee) (3*S*,4*R*) **209b**
7	**46**	$Ph(CH_2)_4$	(4*R*,5*S*)-di-Ph **137**	21	>90%	49	**Crude:** **Pure:**	5 5 **209a**	95 95 (3% ee) (3*S*,4*R*) **209b**
8	**46**	$Ph(CH_2)_4$	(4*R*)-Bn **43**	21	>90%	51	**Crude:** **Pure:**	5 0 **209a**	95 100 (45% ee) (3*S*,4*R*) **209b**
9	**46**	$Ph(CH_2)_4$	(4*S*)-*t*-Bu **138**	50	>90%	60	**Crude:** **Pure:**	3 3 **209a**	97 97 (62% ee) (3*R*,4*S*) **209b**
10[d]	**46**	$Ph(CH_2)_4$	(4*S*)-*t*-Bu **138**	21	>90%	52	**Crude:** **Pure:**	8 6 **209a**	92 94 (72% ee) (3*R*,4*S*) **209b**
11	**46**	$Ph(CH_2)_4$	(3*S*,8*R*)-Ind **44**	21	>90%	61	**Crude:** **Pure:**	2 2	98 98 (54% ee) (3*R*,4*S*)

								209a	**209b**
12[d]	**46**	$Ph(CH_2)_4$	(3*S*,8*R*)-Ind **44**	21	>90%	60	**Crude:** **Pure:**	5 2 **209a**	95 98 (67% ee) (3*R*,4*S*) **209b**
13	**50**	$Ph(CH_2)_3$	(4*R*)-Ph **20**	18	~80–90%	76	**Crude:** **Pure:**	5 3 **210a**	95 97(13% ee) (3*S*,4*R*) **210b**
14[d]	**50**	$Ph(CH_2)_3$	(4*R*)-Ph **20**	1	>90%	69	**Crude:** **Pure:**	15 12 **210a**	85 88 (0% ee) (3*S*,4*R*) **210b**
15	**50**	$Ph(CH_2)_3$	(4*R*,5*S*)-di-Ph **137**	30	>90%	67	**Crude:** **Pure:**	15 10 **210a**	85 90 (4% ee) (3*S*,4*R*) **210b**
16	**50**	$Ph(CH_2)_3$	(4*R*)-Bn **43**	31	-[e]	65	**Crude:** **Pure:**	- 1 **210a**	- 99 (48% ee) (3*S*,4*R*) **210b**
17	**50**	$Ph(CH_2)_3$	(4*S*)-*t*-Bu **138**	40	>90%	66	**Crude:** **Pure:**	<10 3 **210a**	>90 97 (67% ee) (3*R*,4*S*) **210b**
18	**50**	$Ph(CH_2)_3$	(3*S*,8*R*)-Ind **44**	16	>90%	58	**Crude:** **Pure:**	<10 1 **210a**	90 99 (61% ee) (3*R*,4*S*) **210b**

a. Yields reported after purification using column chromatography on silica gel.

b. Details of the calculation of reaction efficiencies and relative ratios of isomers is given in **Table 6.3** and can also be found in the Experimental Section.
c. Reaction was repeated on a larger scale (300 mg). The reaction time was 21 h, 64% yield, 78% ee.
d. $Cu(CH_3CN)_4PF_6$ was the copper source used. NaBARF was not employed in these reactions.
e. Data not available.

With racemic samples of ɣ-lactams **208–210** in hand, attention was next focused on copper bisoxazoline catalysed reactions of substrates **46**, **50**, **57**. The catalytic components employed were 5 mol% $CuCl_2$, 6 mol% NaBARF and 6 mol% bisoxazoline ligand. Five commercially available bisoxazoline ligands **20**, **43**, **44**, **137**, **138** were chosen for investigation. The catalyst was preformed for ~2 hours at reflux prior to slow addition of the α-diazo-β-oxo sulfone substrate. This method was applied to all copper catalysed C–H insertion reactions discussed in this chapter. In all instances, high reaction efficiencies were observed (typically 80–90%, **Table 6.4** entries 1–5, 13), with excellent values of > 90% being observed in some instances (**Table 6.4**, entries 6–9, 11, 13, 15–18). These reaction efficiencies are similar to those seen for rhodium acetate catalysed reactions with these substrates (**Table 6.3**, entries 1–3). The product distribution seen for the copper catalysed reactions is comparable to that seen for the rhodium catalysed reactions, namely the *trans* ɣ-lactam is the predominant product, with minor amounts of the *cis* isomer being observed in both the crude and purified products. (**Table 6.4**, entries 1–9, 11, 13, 15–18). Moderate to good reaction yields were observed in all cases, with values between 48% and 76% being obtained. No evidence for competing β-lactam formation or insertion into the sulfonyl group was seen, in line with the rhodium catalysed reactions.

As has been previously discussed in **Section 6.1.3**, formation of ɣ-lactam products occurs *via* a later, more stabilised, transition state than formation of β-lactam products. Jung previously reported that a phenylsulfone moiety α to the carbene carbon plays a crucial role in exclusive ɣ-lactam formation, due to the stabilising effect of the phenylsulfonyl moiety. Presumably, the same effect is at play here; the presence of the sulfone group facilitates the highly regioselective C–H insertion reaction, leading exclusively to the ɣ-lactam products, with the *trans* diastereomer dominating.[28]

There is literature precedent for the selective formation of *trans* ɣ-lactams in the rhodium catalysed intramolecular C–H insertion reactions of α-diazoacetamides. Both Taber and co-workers[46,47] and Nakamura and co-workers[36] have proposed chair like or half chair transition states in an effort to account for this selectivity. Nakamura reasoned that there must be a significant energy gap between the *cis* and *trans* half chair transition states, which allows for the high *trans* selectivity. An adapted, simplified version of this model is presented in **Figure 6.10**. In the transition state leading to *trans* ɣ-lactam formation, the substituent at the insertion centre is in the sterically less hindered equatorial position.

However, in the transition state leading to the *cis* γ-lactam, this substituent suffers from 1,3 diaxial repulsion as it occupies the less stable axial position. Presumably, the same steric factors that determine the *trans* selectivity for the rhodium catalysed C–H insertion reactions are at play for the copper catalysed reactions and account for the results obtained in this project.[7,36,46,47]

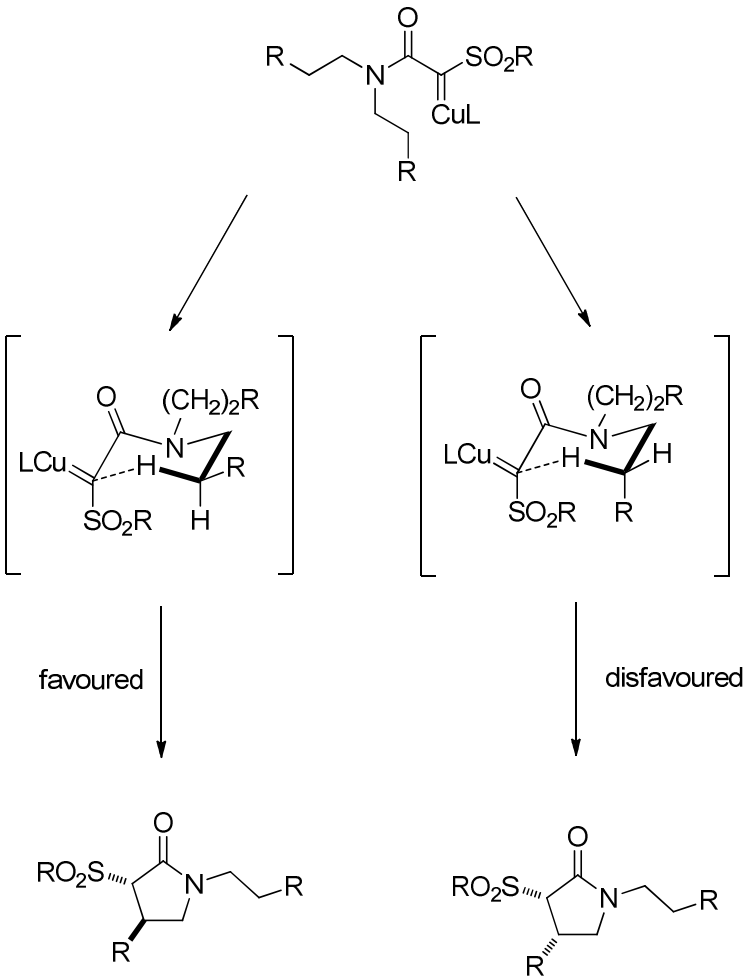


Figure 6.10

The highest enantioselectivity was achieved for 2'-ethylphenyl substrate **208b**, with 82% ee for the *trans* isomer **208b** (**Table 6.4**, entry 5) being attained using the (3*S*,8*R*)-Ind **44** ligand.[45] This marks the highest enantiocontrol for the synthesis of a γ-lactam using chiral copper catalysis to date. The (4*S*)-*t*-Bu **138** ligand gave the next highest level of enantiocontrol with a value of 70% ee being reached (**Table 6.4**, entry 4). In this instance, the enantioselectivity of the *cis* isomer was also measured and was seen to be much lower than that of the *trans* isomer, with a value of 38% ee. For the *trans* isomer, the (4*R*)-Bn **43**, (4*R*)-Ph **20** and the (4*R*,5*S*)-di-Ph **137** gave the poorest enantiocontrol with values of 52% ee, 48% ee and 34% ee being achieved respectively (**Table 6.4**, entries 3, 1 and 2). Enantioselectivities of the *cis* isomer were measured in three cases, with the highest

enanticontrol seen for the (4*R*,5*S*)-di-Ph **137** ligand (53% ee, **Table 6.4**, entry 2) with (4*R*)-Ph **20** ligand giving the next best result at 43% ee (**Table 6.4**, entry 1) while the (4*S*)-*t*-Bu **138** ligand gave the poorest enantiocontrol of 38% ee (**Table 6.4**, entry 4). Therefore, the highest enantiocontrol for the *cis* and *trans* isomers is achieved with different ligands. The observation of different enantiopurities for the *cis* and *trans* γ-lactams indicates that *cis*/*trans* interconversion is unlikely and instead, the *cis*/*trans* ratio reflects the kinetic preference of the insertion. A similar trend is observed for substrate **209b** [$Ph(CH_2)_4$], with the (4*S*)-*t*-Bu **138** ligand giving the best enantiocontrol at 62% ee (**Table 6.4**, entry 9), followed closely by (3*S*,8*R*)-Ind **44** ligand at 54% ee (**Table 6.4**, entry 11), (4*R*)-Bn **43** ligand giving 45% ee (**Table 6.4**, entry 8), (4*R*)-Ph **20** ligand giving 12% ee (**Table 6.4**, entry 6), and (4*R*)-Bn ligand **43** (**Table 6.4**, entry 7) giving 3% ee. Interestingly, when $Cu(CH_3CN)_4PF_6$ is used as a copper source, instead of $CuCl_2$-NABARF, an increase of 62% ee to 72% ee was observed in the presence of the (4*S*)-*t*-Bu **138** ligand (**Table 6.4**, entries 9 and 10) and an increase from 54% ee to 67% ee was seen for (3*S*,8*R*)-Ind **44** ligand (**Table 6.4**, entries 11 and 12). In contrast, for substrate **210b** [$Ph(CH_2)_3$] a decrease in enantioselectivity is seen for $Cu(CH_3CN)_4PF_6$ as a copper source, when compared to $CuCl_2$-NABARF, for (4*R*)-Ph **20** ligand, going from 13 to 0% ee (**Table 6.4**, entries 13 and 14). The enantiocontrol achieved for substrate **210b** [$Ph(CH_2)_3$] with the various ligands in descending order is as follows (4*S*)-*t*-Bu **138** (67% ee) **>** (3*S*,8*R*)-Ind **44** (61% ee) **>** (4*R*)-Bn **43** (48% ee) **>** (4*R*)-Ph **20** (13% ee) > (4*R*,5*S*)-di-Ph **137** (3% ee) (**Table 6.4**, entries 13, 15–18). Therefore, the best ligands for achieving high enantiocontrol in this series are (4*S*)-*t*-Bu **138** and (3*S*,8*R*)-Ind **44**. This trend is clearly illustrated in **Figure 6.11**. This is in contrast to the thiopyran and sulfolane series, where (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** generally give the best enantioselectivities. The nature of the sulfone group is also an important factor in enantiocontrol with the highest values seen for the aryl sulfone **208b**, and slightly lower values being achieved for alkylphenyl substrates **209b** and **210b**. It is also interesting to note that, in general, when $Cu(CH_3CN)_4PF_6$-bisoxazoline is employed as a catalyst, lower enantioselectivities are observed than when a $CuCl_2$-NaBARF-bisoxazoline / CuCl-NaBARF-bisoxazoline catalyst system is employed for C–H insertion reactions and aromatic addition reactions.[48–51] However, certain exceptions to this have been observed and will be discussed in **Section 6.4**.

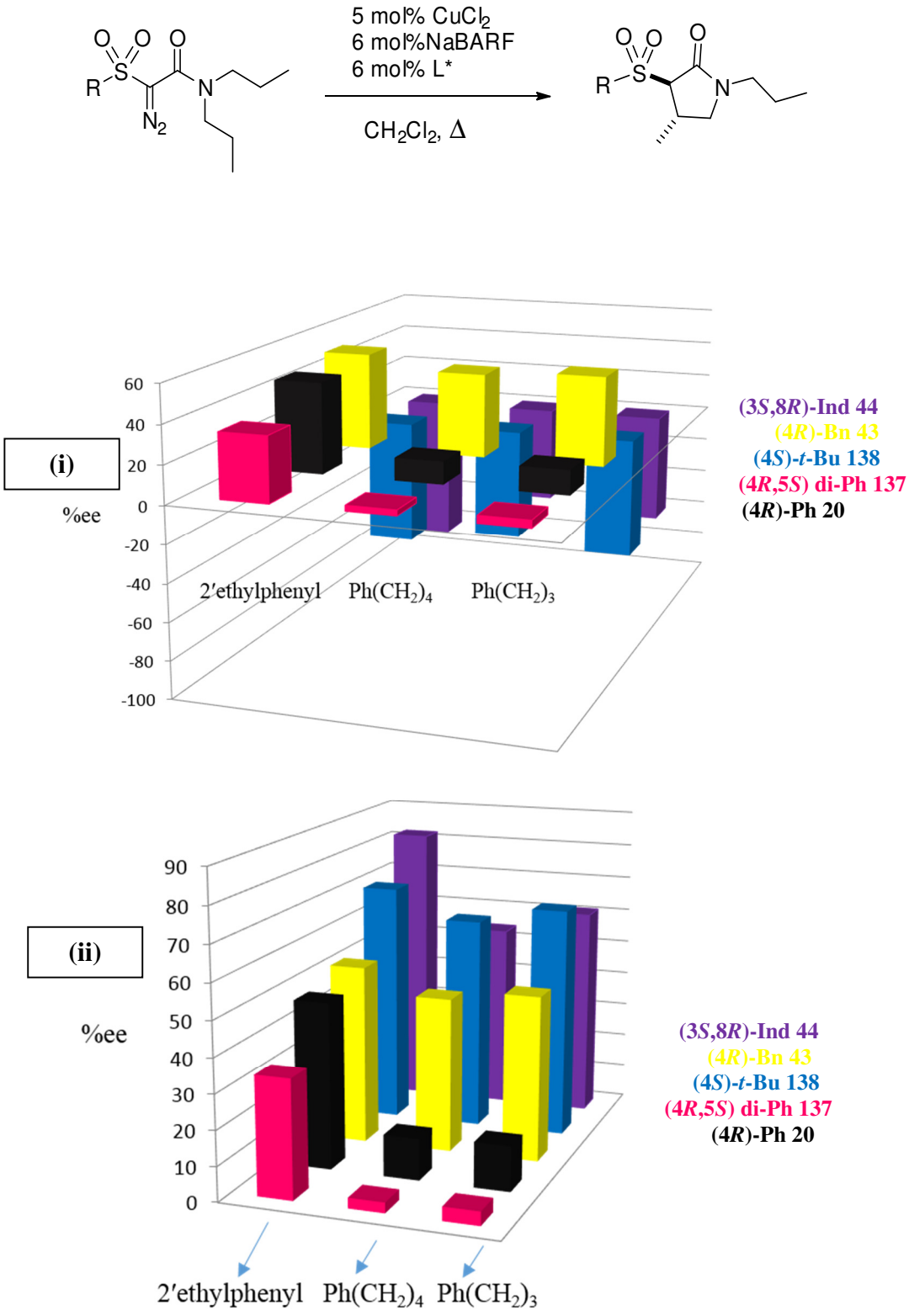
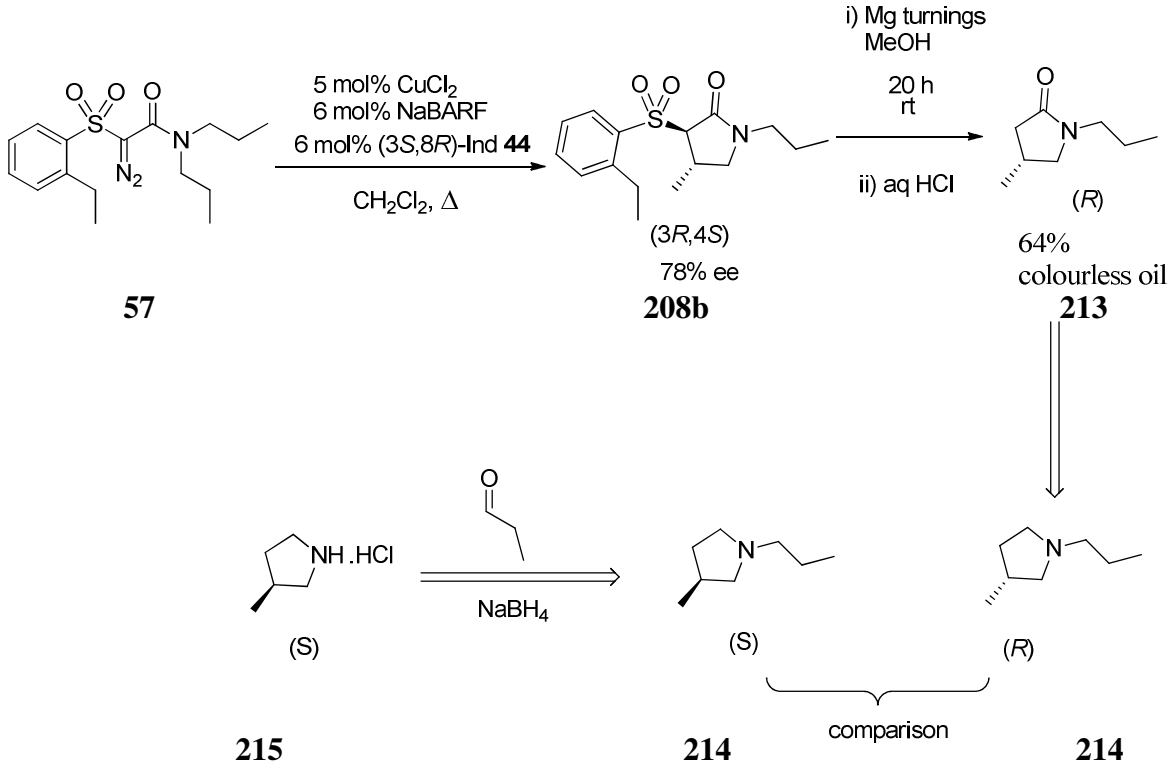


Figure 6.11 *Summary of enantiocontrol achieved for* trans *γ-lactams* **208–210(b)** *using five commercially available bisoxazoline ligands* **20, 43, 44, 137, 138**

*In **Figure 6.11** (i) the direction of enantiocontrol is indicated in addition to the magnitude, in (ii) for convenience only the magnitude of the enantioselectivity is indicated to enable clarity in terms of the ligand effect.*

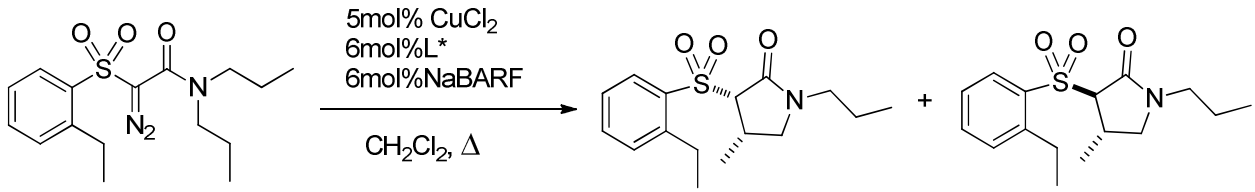
To ensure reproducibility a selection of reactions was repeated (**Table 6.4**, entries 5, 11–14), with essentially the same outcome in terms of efficiency and enantioselectivity. These were selected to confirm the highest enantioselectivity (entry 5) and the impact of variation of the copper salt and counterion (entries 11–14).

Originally, the intention was to reduce the lactam **208b** to the corresponding tertiary amine **213**, to enable comparison of the specific rotation with the data for **214**, thereby confirming the direction of the enantioselection in the C–H insertion process. However, as the absolute stereochemistry was subsequently confirmed crystallographically in a closely related compound,[51] this reaction sequence was not pursued. The sample of ɣ-lactam **208b** (78% ee) obtained from the 300 mg scale up (**Table 6.4**, entry 5, see footnote) was then desulfonylated with magnesium turnings, leading to ɣ-lactam **213** in a 64% yield as colourless oil, demonstrating the synthetic potential of these reaction pathways. (**Scheme 6.12**).



Scheme 6.12

Table 6.5 *C–H insertion reactions of α-diazo-β-amido sulfones* ***57*** *catalysed by chiral copper catalysts*



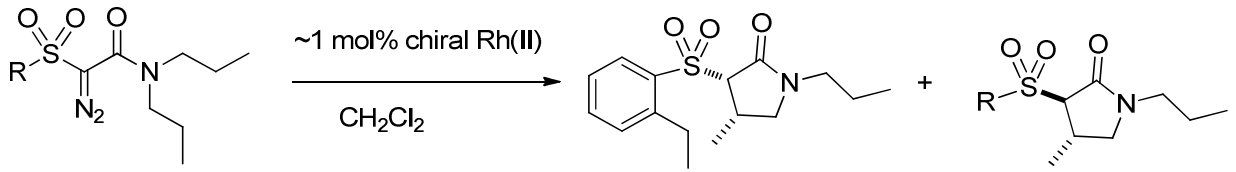
57 **208a** **208b**

Entry	L*	Time (h)	Crude Efficiency (%)[a]	Yield (%)	Product Ratio	*cis* (% ee)	*trans* (% ee)
1	CN-(4*S*)-Ph **158**	30	~70–80%	32	**Crude:** **Pure:**	9 5 (6% ee)	91 95 (4% ee) (3*R*,4*S*)
2	Py-(4*R*)-Ph **159**	21	~60–70%	39	**Crude:** **Pure:**	20 15 (8% ee)	80 85 (3% ee) (3*S*,4*R*)
3	Py-(4*S*)-*i*-Pr **160**	72	~40–50% reaction *approx* 50% complete	22	**Crude:** **Pure:**	26 26 (46% ee)	74 74 (24% ee) (3*R*,4*S*)

a. For details of how the crude efficiency was calculated consult **Tables 6.3** and Experimental section. In addition ,for notes on purification, measurement of enantioselectivity and determination of absolute stereochemistry the Experimental section and **Appendices I** and **II** should be consulted.

A brief study was then conducted using semicorrin ligand **158** and pybox ligands **159** and **160** (shown in **Figure 4.32, Section 4.6.2**) with α-sulfonyl diazoacetamide **57**, as it gave the highest enantiocontrol in the copper-bisoxazoline catalysed reactions (82% ee, **Table 6.4**, entry 5). These ligands did not perform as well as the bisoxazoline ligands, with lower reaction efficiencies (~40–70% **Table 6.5** *cf.* ~90% **Table 6.4**), longer reaction times and much poorer enantioselectivities being achieved. The highest enantiopurity obtained for the *trans* isomer **208b** was 24% ee and 46% ee for the *cis* isomer **208a**, both attained for the Py-(4*S*)-*i*-Pr **160** ligand (**Table 6.5**, entry 3).

Table 6.6 *C–H insertion reactions of α-diazo-β-amido sulfones* **50, 57** *catalysed by chiral rhodium catalysis*[45]



Entry	α-diazo-sulfone	R	Rh(II)	Time (h)	Crude Efficiency (%)[a]	Yield (%)	Product Ratio	% ee *cis*	% ee *trans*
1	**57**	2'-ethylphenyl	Rh_2(*S*-DOSP)$_4$ 0 °C–rt–Δ 30 h, 18 h	48	~80–90%	62	**Crude:** **Pure:** **208a**	22 24 (20% ee)	78 76 (6% ee) (3*R*,4*S*) **208b**
2	**57**	2'-ethylphenyl	Rh_2(5*S*-MEPY)$_4$ 0 °C–rt–Δ 30 h, 42 h	72 (reaction~90 % complete)	~70–80%	25	**Crude:** **Pure:** **208a**	13 7 (-% ee)	87 93 (0% ee) **208b**
3	**57**	2'-ethylphenyl	Rh_2(*S*-mand)$_4$ 0 °C–rt	7	~80–90%	61	**Crude:** **Pure:** **208a**	18 9 (20% ee)	82 91 (27% ee) (3*S*,4*R*) **208b**
4	**57**	2'-ethylphenyl	Rh_2(*S*-PTPA)$_4$ 0 °C–rt	21	~80–90%	59	**Crude:** **Pure:**	23 17 (60% ee)	77 83 (41% ee)

								208a	(3*R*,4*S*) **208b**
5	**57**	2'-ethylphenyl	Rh_2(*S*-PTTL)$_4$ 0 °C–rt	30	>90%	65	**Crude:** **Pure:**	11 11 (75% ee) **208a**	89 89 (71% ee) (3*R*,4*S*) **208b**
6	**50**	$Ph(CH_2)_3$	Rh_2(*S*-PTTL)$_4$ 0 °C–rt	4	~80–90%	74	**Crude:** **Pure:**	10 5 **210a**	90 95 (51% ee) (3*R*,4*S*) **210b**

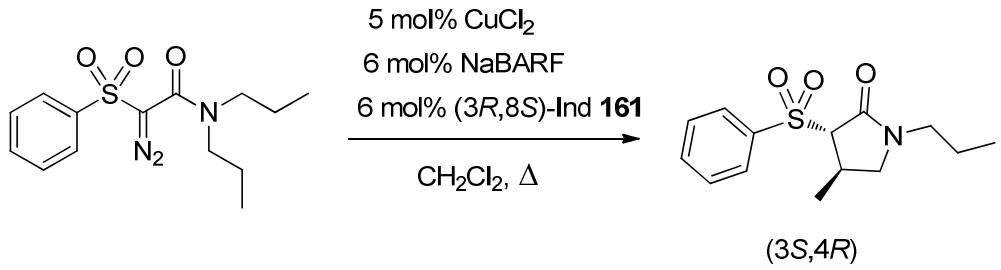
a. For details of how the crude efficiency was calculated consult **Tables 6.3** and the experimental section at the end of this chapter. In addition, for notes on purification, measurement of enantioselectivity and determination of absolute stereochemistry the experimental section and **Appendices I** and **II** should be consulted.
Note: Some of the data in the above **Table 6.6** (entries 1-5), *i.e.* the enantioselectivities for the *trans* ɣ-lactams, have been included in a publication.[45]

.

The synthesis of ɣ-lactams with high enantiocontrol using chiral rhodium catalysts is well established in the literature.[6,7] However, no examples of this exist for the reactions of α-sulfonyl diazoacetamides, with only achiral catalysts described for these compounds.[28,38,44] For comparative reasons, a number of chiral rhodium carboxylates as well as a carboxamidate catalyst were chosen for investigation of the C–H insertion reactions of α-sulfonyl diazoacetamide **57**. Based on literature precedent, rhodium catalysed insertions were undertaken at 0 °C for the α-diazocarbonyl addition, with slow warming to room temperature. Reactions at reflux, for comparison with the copper catalysts, would be of interest for future exploration, although it is unlikely that enhanced enantioselectivities would be observed at high temperatures. For chiral rhodium carboxylate catalysts [Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-mand)$_4$, Rh_2(*S*-PTPA)$_4$ and Rh_2(*S*-PTTL)$_4$] reaction efficiencies were high (~80–90%.) (**Table 6.6**, entries 1, 3–5) and are broadly in line with those seen for the chiral copper catalysts. However, with the exception of Rh_2(*S*-PTTL)$_4$, which gave *trans* ɣ-lactam **208b** in 71% ee (**Table 6.6**, entry 5), all other catalysts gave poor to modest enantioselectivities. While enantiopurities of the minor ɣ-lactam **208a** are recorded in **Table 6.6**, it should be noted that the HPLC signals for these minor peaks are relatively weak and therefore, should be interpreted accordingly. The carboxamidate catalyst, Rh_2(5*S*-MEPY)$_4$, gave rise to the most sluggish reaction of all of the chiral rhodium catalysts, being only one of two rhodium catalysts that required heating to reflux to proceed. [(Rh_2(*S*-DOSP)$_4$ was the other catalyst that required heating to go to completion.] It also gave rise to the poorest enantioselectivity, with 0% ee being achieved. (**Table 6.6**, entry 2). As Rh_2(*S*-PTTL)$_4$ was the best chiral rhodium catalyst in this study, it was also applied to substrate **50**, where it gave rise to 51% ee. (**Table 6.6**, Entry 6). This study demonstrates the superior nature of the chiral copper catalysts to the chiral rhodium catalysts for this series.

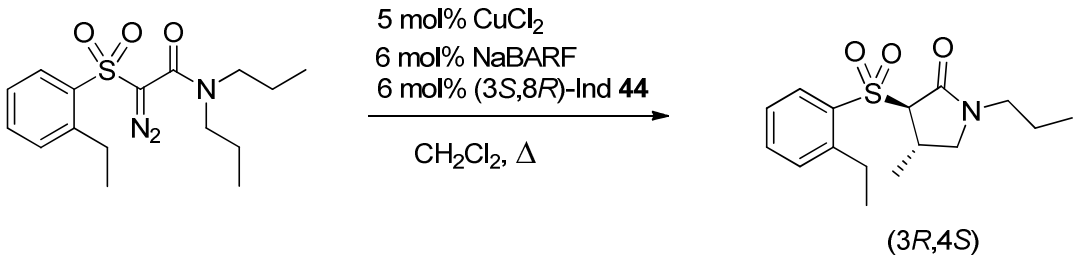
The absolute stereochemistry was not directly determined for this series as all compounds obtained were oils, making structural determination by X-ray crystallography impossible. However, Ring obtained a crystal structure for a similar substrate **211b** and determined the absolute stereochemistry to be (3*S*,4*R*) when (3*R*,8*S*)-Ind **161** ligand was employed.[51] Therefore, the absolute stereochemistry of **208b** was assigned by analogy as (3*S*,4*R*) when (3*S*,8*R*)-Ind **44** ligand was employed. Additional evidence that supports that both α-diazocarbonyl compounds proceed through similar transition states comes from the

optical rotation data of ɣ-lactam **211b** and **208b**; employing (3*R*,8*S*)-Ind **161** results in ɣ-lactam **211b** having a negative specific rotation $[\alpha]_D^{20}$ -9.5 (*c* 0.11, $CHCl_3$, 66% ee) and using (3*S*,8*R*)-Ind **44** leads to ɣ-lactam **208b** having a positive specific rotation $[\alpha]_D^{20}$ +41.11 (*c* 0.09, CH_2Cl_2, 82% ee) (**Scheme 6.13**). By comparing rotation data for **208b**, **209b** and **210b** and the order of elution of enantiomers of **210b** and **209b** on the HPLC, depending on the ligand employed, the absolute stereochemistry of **210b** and **209b** was assigned by analogy to **208b**. More details of the protocol used for assignment of absolute stereochemistry can be found in **Appendix II**.



$[\alpha]_D^{20}$ -9.5 (*c* 0.11, $CHCl_3$, 66% ee)

212 **211b**



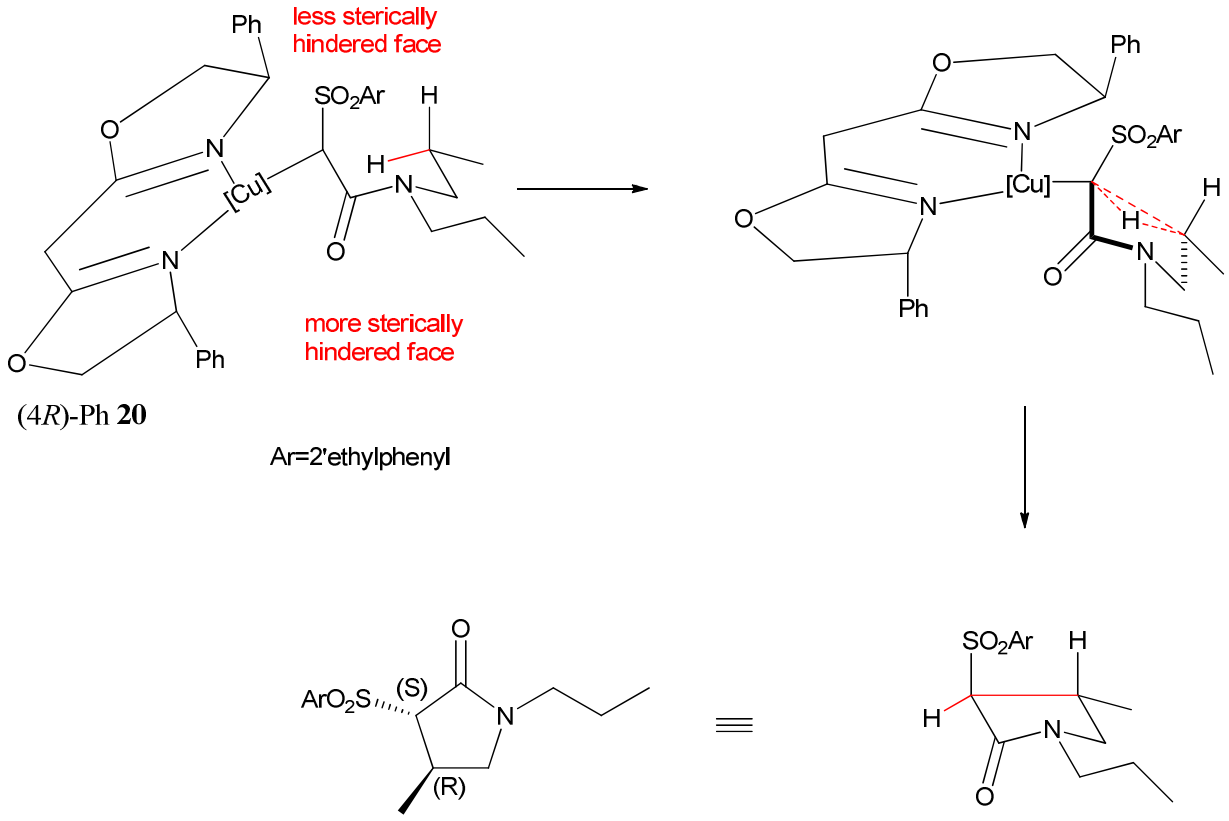
$[\alpha]_D^{20}$ +41.11 (*c* 0.09, CH_2Cl_2, 82% ee)

57 **208b**

Scheme 6.13

A detailed discussion of the transition states of the copper-bisoxazoline mediated intramolecular C–H insertion of α-diazo-β-oxo sulfones appears in Chapter 4 and therefore will not be discussed here. The favoured transition state is drawn in **Scheme 6.14**, illustrated for (4*R*)-Ph ligand **20** and the α-diazo-β-oxo sulfone **57**. As can clearly be seen in **Scheme 6.14**, C–H insertion occurs from the less hindered face of the carbene, leading to the major *trans* ɣ-lactam **208b** with (3*S*,4*R*) stereochemistry, which is consistent with the experimental data. Use of the (3*S*,8*R*)-Ind **44** and (4*S*)-*t*-Bu **138**

ligands resulted in the highest enantioselectivities for this series. Presumably, unfavourable steric interactions prevent insertion from occurring from the more hindered face of the carbene. This transition state can be generalised for the formation of *trans* ɣ-lactams **210b** and **209b**.

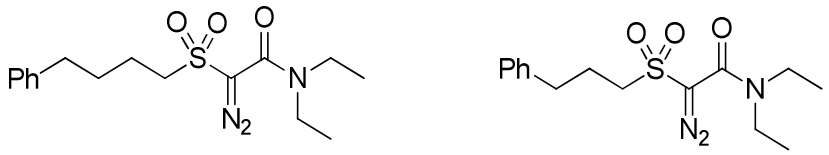


favoured transition state: reacting C-H approaches carbenoid from the less sterically hindered face leading to observed stereochemistry

Scheme 6.14

6.3.2 *N*,*N*-Diethyl amide substrates

Having thoroughly investigated substrates containing the *N*,*N*-dipropyl amides, attention was next focused on the substrates containing an *N*,*N*-diethyl amide. Two substrates were chosen for investigation. Substrate **47** potentially allows for the formation of thiopyran/sulfolane products as well as β- and ɣ- lactams, whereas substrate **51** does not allow thiopyran formation.

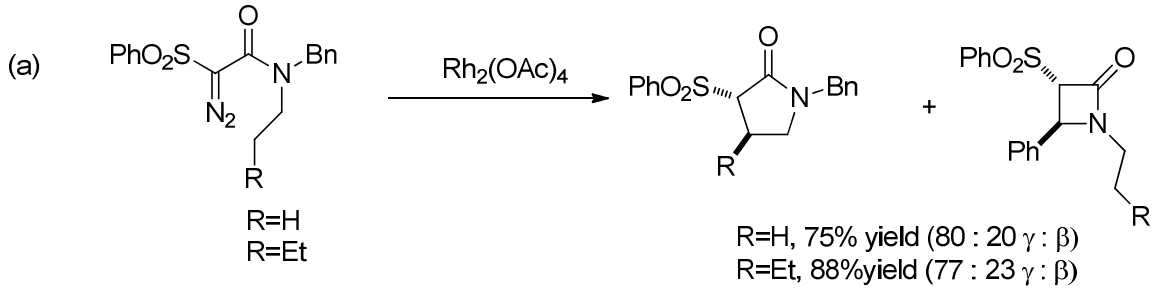


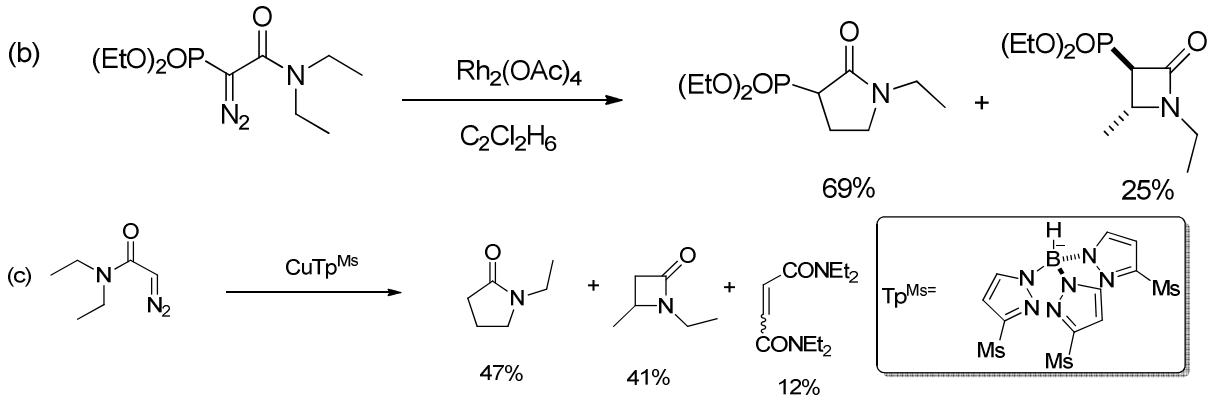
47 **51**

Figure 6.12

Substrate **51**, where formation of a thiopyran product is impossible, was initially chosen for investigation. C–H insertion using rhodium acetate as a catalyst was carried out; the reaction proceeded with excellent efficiency (80–90%) (**Table 6.7**, entry 3), however, the reaction was less selective for the formation of ɣ-lactam than the reaction of the *N*,*N*-dipropyl analogue **50**.

While ɣ-lactam **216** accounts for ~91% of the insertion products, additional isomers resulting from alternative pathways were also formed, including β-lactam **217b** which accounted for 7% of the reaction mixture as well as *trans* sulfolane **218b** which constituted 2% of the crude reaction product mixture. While there was evidence for minor byproduct formation, none of these byproducts were identified. Insertion to form the ɣ-lactam **216** requires insertion at a primary C–H bond which is generally less favoured than insertion at secondary or tertiary C–H bonds. Following the general rules for C–H insertion processes,[35,52–54] this is considered unfavourable and one might expect insertion to proceed into the secondary C–H bond, α- to the activating nitrogen atom. However, there is literature precedent for insertion into the CH_3 of a *N*,*N*-diethyl group. [26,28,55] This product may be observed in this case due to the stabilising effect of the sulfone group on the carbenoid carbon. Some of the literature examples are presented in **Scheme 6.15**.[26,28,55] In the **Scheme 6.15** (a) the ɣ : β ratio reflects the conformational preference in the amide rather than the preference for C–H insertion.





Scheme 6.15[26,28,55]

Comparison of the reaction outcome of the *N*,*N*-diethyl derivative **51** with the *N*,*N*-dipropyl derivative **50** (**Table 6.7** and **Table 6.4**) indicates that while the dipropyl leads exclusively to ɣ-lactam formation, for the diethyl derivative, β-lactam and sulfolane formation compete as minor reaction pathways. This can be rationalised on the basis of decreased efficiency of C–H insertion at the CH_3 relative to the CH_2 group.

All three isomers were successfully separated using careful column chromatography on silica gel. A gradient elution of ethyl acetate: hexane was found to be necessary to achieve the separation of the isomeric products. As none of the insertion products had previously been reported, full structural characterisation was obtained for all three. The ^{1}H NMR spectrum of the crude product mixture for reaction employing $Cu[CH_3CN)_4]PF_6$-NaBARF-(4*R*) Ph **20** and the purified products are presented in **Figure 6.13**.

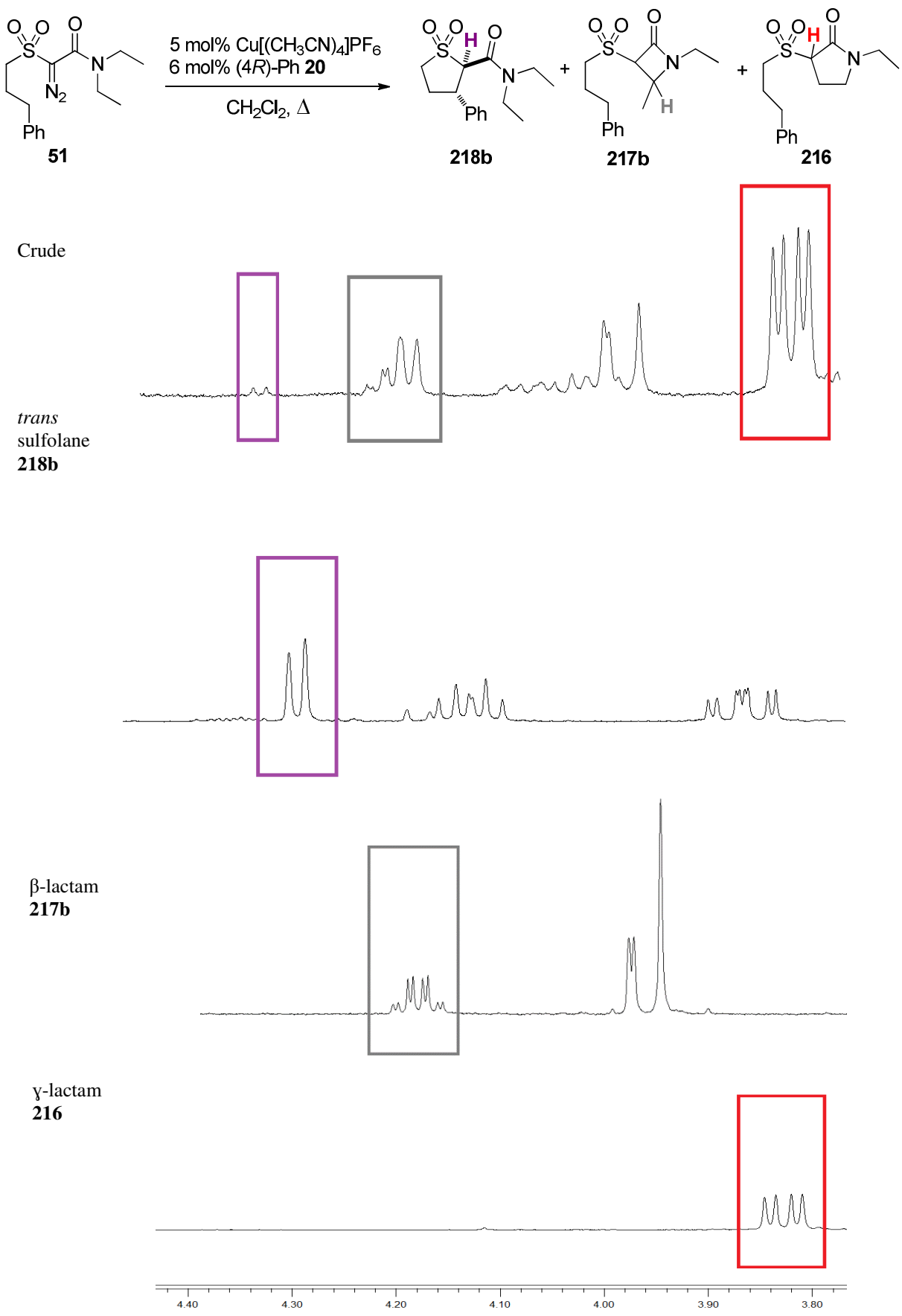


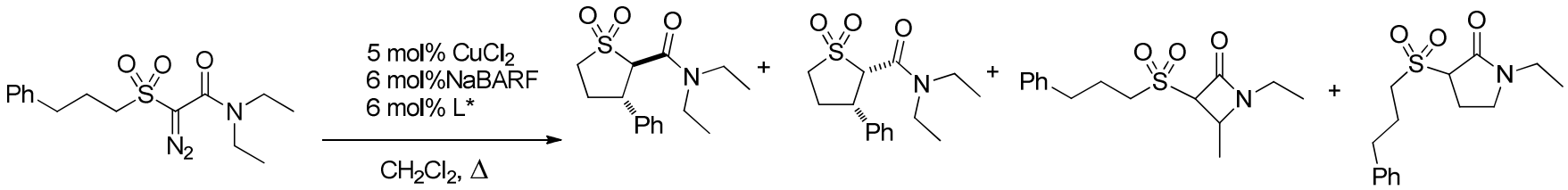
Figure 6.13 ^{1}H NMR ($CDCl_3$, 400 HHz)

The use of chiral copper catalysis was next employed. The $CuCl_2$-NaBARF-(4*R*)-Ph **20** ligand system was chosen as the initial catalyst conditions. The reaction efficiency of 80–90% achieved with this catalyst system (**Table 6.7**, entry 1) was the same as was achieved for rhodium acetate, however, there was a significant change in the proportion of reaction products observed. While the amount of sulfolane **218b** remained low (~2% of the insertion products), significantly more β-lactam **217b** was formed, moving from ~7% in the presence of rhodium acetate to ~37% when $CuCl_2$-NaBARF-(4*R*)-Ph **20** was used as a catalyst (**Table 6,7**, entries 1 and 3). Therefore, proportionately less ɣ-lactam **216** was formed as a result. It is important to note that the single stereocentre is labile and therefore may racemise leading to uncertainty regarding the enantioselectivity of the reaction. The chirality is solely due to the centre α- to the lactam, whereas with most other derivatives there is a stable stereocentre at the β-position to the carbonyl. Furthermore, the stereocentre in this compound is potentially labile *via* enolisation and therefore can potentially be altered through exposure to Lewis acids or bases including during chromatography. Measuring the enantiopurity of ɣ-lactam **216** was attempted but results have to be interpreted with some caution as the substrate contains one labile stereogenic centre, making racemisation possible. A moderate enantioselectivity of 46% ee was obtained with $CuCl_2$-NaBARF-(4*R*)-Ph **20**, showing that if racemisation is occurring, it had not happened completely. This reaction was repeated in order to see if the enantioselectivity could be reproduced (**Table 6.7**, entry 2). Enantiomeric disproportionation was also checked for at this stage, with the enantiopurity of three individual fractions of material from chromatography being measured individually (**Table 6.7**, entry 2). It was found that there was a slight change in enantiopurity of ɣ-lactam **216** from the three individual fractions with 32% ee being the lowest value recorded and 47% ee being the highest. (**Table 6.7**, entry 2). On average the enantioselectivity of 45% ee reproduces efficiently (**Table 6.7**, entry 1). The observation of determining some level of enantiopurity with samples which have been in contact with silica gel, and protic solvents such as IPA, is significant. It is also worth mentioning that as full separation of isomers was not achieved in all cases, trace amounts of other isomeric products could potentially affect the measured enantiopurities.

Lastly, changing the copper source/additive was explored, employing $Cu(CH_3CN)_4PF_6$-(4*R*)-Ph **20** as the catalyst system. While a decrease in reaction efficiency was observed (60–70%) (**Table 6.7**, entry 4) when compared to $CuCl_2$-NaBARF-(4*R*)-Ph **20** (80–90%)

(**Table 6.7**, entries 1 and 2) the relative amounts of the three isomeric products remained approximately the same. A decrease in reaction time from 21 to 2 h was also observed when $Cu(CH_3CN)_4PF_6$-(4*R*)-Ph **20** was employed as the catalyst system. Remarkably, the enantiopurity of the ɣ-lactam **216** was much higher, with a value of 69% ee being measured (**Table 6.7**, entry 4). The increase in enantiopurity has two possible explanations: firstly the use of different copper precursors results in intrinsically higher enantioselection or secondly the shorter reaction time in contact with the copper catalyst may result in less racemisation *via* enolisation. At this stage it is difficult to definitively confirm whether racemisation at the α-centre occurs in the reaction mixture (due to the presence of the copper catalyst as a Lewis acid) or on silica gel, but it is clear that if racemisation takes place it is a relatively slow process as the product has been recovered with moderate enantiopurity. The reproducibility of the enantiopurity seen in **Table 6.7** entries 1 and 2 offers evidence against epimerisation. Further investigation through exposure of the product to reaction conditions with monitoring of the enantiopurity would clarify this. Determination of enantiopurity of the minor products was not possible at this stage.

Table 6.7 *C–H insertion reactions of α-diazo-β-amido sulfone* **51** *catalysed by chiral copper catalysts; investigation into the diethyl amide.*



51 **218b** **218a** **217b** **216**

Entry	Method	M	Ligand	Time (h)	Crude Efficiency (%)[a]		Products		
						Crude Ratio **Purified Yield %** **Overall Yield (%)**	*trans* sulfolane[b] **218b** Least polar	β-lactam[b] **217b** Mid polarity	ɣ-lactam **216** Most polar
1	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	80–90[c]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	2 0.8%[d] 0.68%	37 -[e] -[e]	61 27%[f] (46% ee) 26%

2	**B**	$CuCl_2$/ Δ	(4*R*)-Ph **20**	21	80–90	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	2 0.7%[g] 0.65%	38 12%[h] 12%	60 9%[i] (47% ee) + 12%[j] (32% ee) + 5%[k] (39% ee) 21% (45% ee)
3	**E**	$Rh_2(OAc)_4$/Δ No NaBARF	-	4	80–90[l]	**Crude Ratio** **Purified Yield %** **Overall Yield (%)**	2 - 0.18%	7 3%[m] 2.6%	91 45% (0% ee) 45%
4	**B**	$Cu(CH_3CN)PF_6$/Δ No NaBARF	(4*R*)-Ph **20**	2	60–70[n]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	2 1.5%[o] 1.3%	23 8%[p] 4%	75 28% (69% ee) 28%

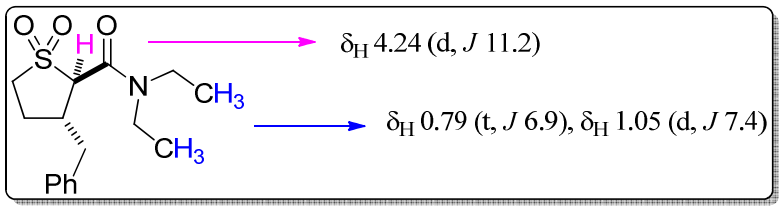
a. Efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *trans* sulfolane **218b**, δ_H 4.38 [1H, d, *J* 5.3, C(2)*H*]; β-lactam **217b**, δ_H 4.24 [1H, apparent qd, *J* 6.1, 1.6, C(4)*H*] and ɣ-lactam **216**, δ_H 3.83 [1H, dd, *J* 10.2, 4.2, C(3)*H*]. Yield (%) reported after purification using column chromatography on silica gel. Enantioselectivities measured for lactams only, the major enantiomer using (4*R*)-Ph **20** appeared at 30 mins and the minor at 28 mins, the details of which can be found in **Appendix I**.

b. Enantioselectivity was not measured due to impure samples.

c. Additional peaks may be present in the ^{1}H NMR spectra of the crude product in the region of 1.0–4.5 ppm but cannot be distinguished due to peak overlap. The following peaks were observed in the region of 4.5–10.0 ppm; δ_H 5.01–5.06 (m), 5.31 (br s), 6.13 (s), 6.19–6.32 (m), 6.45–6.59 (m), 7.97 (d, *J* 7.6), 8.28–8.36 (m).
d. Fraction contains 85% *trans* sulfolane **218b** and 15% *cis* sulfolane **218a**.
e. Product not isolated after purification by column chromatography
f. Fraction contains 96% γ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 1.71 (d, *J* 6.6), 3.11–3.18 (m), 4.12 (s), 7.45–7.50 (m), 7.56–7.58 (m), 7.95–7.99 (m).
g. Fraction contains 93% *trans* sulfolane **218b** and 7% *cis* sulfolane **218a**.
h. Fraction contains 97% β-lactam **217b**. Additional peaks present in the ^{1}H NMR spectra; δ_H 2.59–2.68 (m), 3.28–3.34 (m), 5.01–5.06 (m), 6.24–6.35 (m), 6.92 (d, *J* 16), 7.36–7.46 (m).
i. Fraction contains 90% γ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 1.72 (d, *J* 6.6), 3.09–3.29 (m), 4.64–4.72 (m), 5.20–5.28 (m).
j. Fraction contains 95% γ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.10–3.16 (m), 4.64–4.72 (m), 5.20–5.28 (m).
k. Fraction contains 94% γ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.07–3.14 (m), 4.64–4.72 (m), 5.21–5.28 (m).
l. Additional peaks may be present in the ^{1}H NMR spectra of the crude product in the region of 1.0-4.5 ppm but cannot be distinguished due to peak overlap. The following peaks were observed in the region of 4.5–10.0 ppm; δ_H 4.80–4.82 (m), 4.96–5.01 (m), 5.08 (s), 5.52 (s), 5.62 (s), 7.96–8.01 (m), 9.49 (s), 9.80 (s), 10.03 (s).
m. Fraction contains 88% β-lactam **217b** and 6% *trans* sulfolane **218b**. Additional peaks present in the ^{1}H NMR spectra; δ_H 4.67–4.75 (m), 6.99 (s), 7.47–7.54 (m), 7.60–7.64 (m).
n. Additional peaks may be present in the ^{1}H NMR spectra of the crude product in the region of 1.0–4.5 ppm but cannot be distinguished due to peak overlap. The following peaks were observed in the region of 4.5–10.0 ppm; δ_H 5.01–5.06 (m), 5.31 (br s), 6.13 (s), 6.19–6.32 (m), 6.45–6.59 (m), 7.97 (d, *J* 7.6), 8.28–8.36 (m).
o. Fraction contains 85% *trans* sulfolane **218b** and 7% *cis* sulfolane **218a**.
p. Fraction contains 50% β-lactam **217b** and 40% sulfone **125**, 3.97 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 6.01 (s), 9.49 (s).

Substrate **47** was next explored, which in contrast to α-sulfonyl diazoacetamide **51** had the potential to form thiopyran products, in addition to lactams. While rhodium acetate is an effective catalyst for the generation of racemic products of most compounds, it generally does not favour *cis* thiopyran formation. The generation of racemic products in this instance was therefore undertaken using $CuCl_2$-NaBARF with both (3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** in 1 : 1 ratio. The reason for making racemic samples in this way was that the product distribution should be similar to that obtained for the chiral ligand study, thus allowing the generation of several racemic products from one reaction. For this cyclisation up to five products have been detected; the presence of γ-lactam **219**, *cis* thiopyran **220a**, β-lactam **221b** and sulfone **118** (formed from reduction of the α-diazo-β-oxo sulfone **47**, see Chapter 4, **Section 4.1.3**) have been confirmed (in approximately equal amounts), and formation of a lesser amount of *trans* sulfolane **222** (**Figure 6.14**) is proposed due to the presence of two triplets at δ_H 0.79 (t, *J* 7.1), 1.01 (t, *J* 7.2) and a doublet at δ_H 4.24 (d, *J* 11.4) in the ^{1}H NMR spectrum of the purified γ-lactam **219** (**Table**

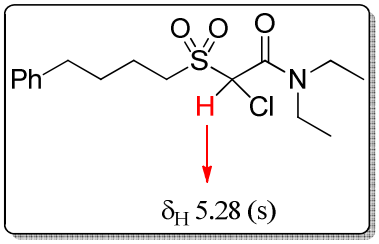
6.8, entry 3). A pure sample of *trans* sulfolane **222** was not isolated and characterised and therefore its formation is not confirmed.



222

Figure 6.14

The, crude product mixtures were very complex, with just three of the products detectable by ^{1}H NMR, namely; ɣ-lactam **219**, *cis* thiopyran **220a** and β-lactam **221b**, each of which are formed in approximately equal amounts (**Table 6.8** entries 1 and 3). In the purified fractions, minor amounts of the *trans* sulfolane **222** were seen in the ^{1}H NMR spectra of ɣ-lactam **219** (**Table 6.8**, entries 1 and 3). In addition there was evidence for the presence of the reduced sulfone **118**, which co-eluted with β-lactam **221b**. The presence of chloride abstraction product **223** (**Figure 6.15**) was also proposed in the crude reaction mixtures of **Table 6.8** (entries 1 and 2) due to the presence of a singlet at 5.28 ppm present in the ^{1}H NMR spectra of both mixtures. Other unidentified byproducts were also evident.

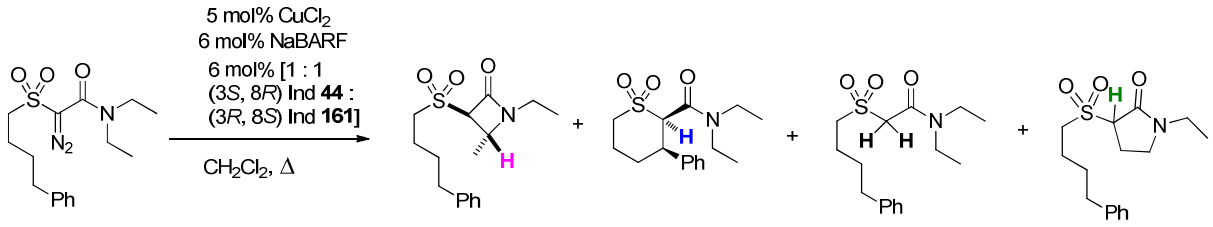


223

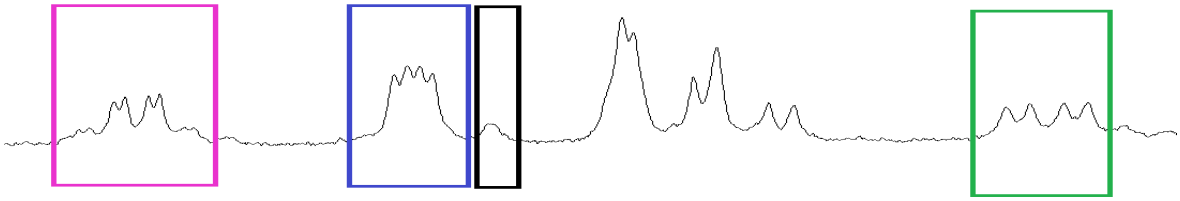
Figure 6.15

As all insertion products were novel, they were purified and fully characterised. Purification was carried out, using wet flash chromatography, using gradient ethyl acetate : hexane as a solvent system, and was an effective method, however, complete separation of isomers was challenging. A number of key characteristic signals in the ^{1}H NMR spectrum of the crude product mixtures allows the identification of a variety of isomers formed in these reactions. For example, the ^{1}H NMR spectrum for the reaction employing

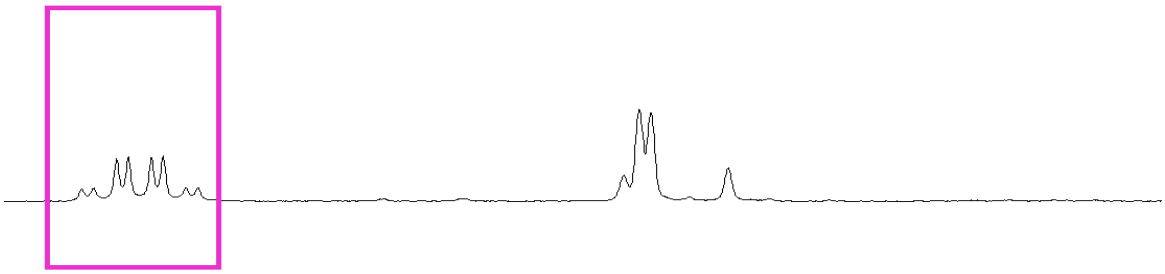
$CuCl_2$-NaBARF and (3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** in 1 : 1 ratio is shown in **Figure 6.16**, along with the purified products.



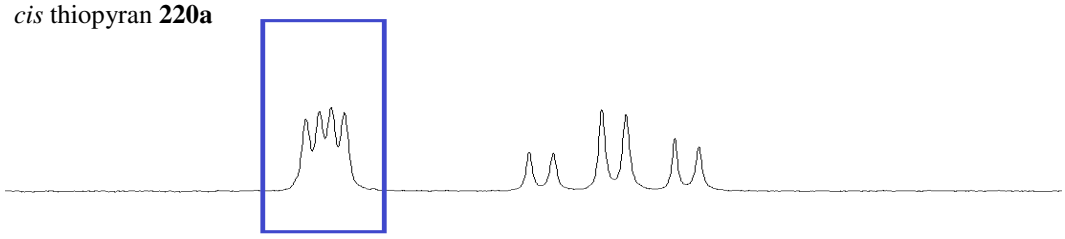
Crude



β-lactam **221b**



cis thiopyran **220a**



ɣ-lactam **219**

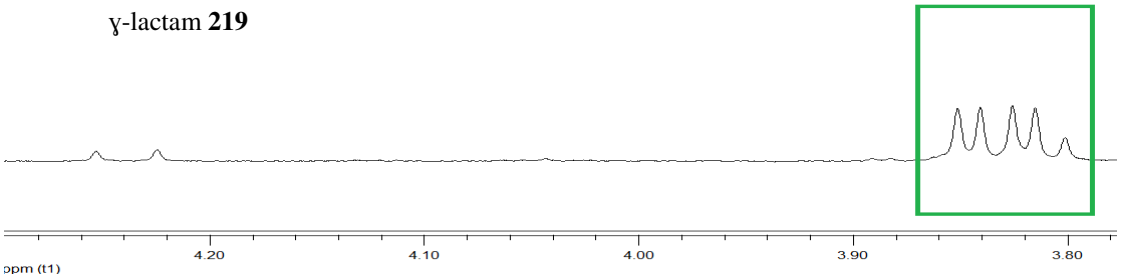
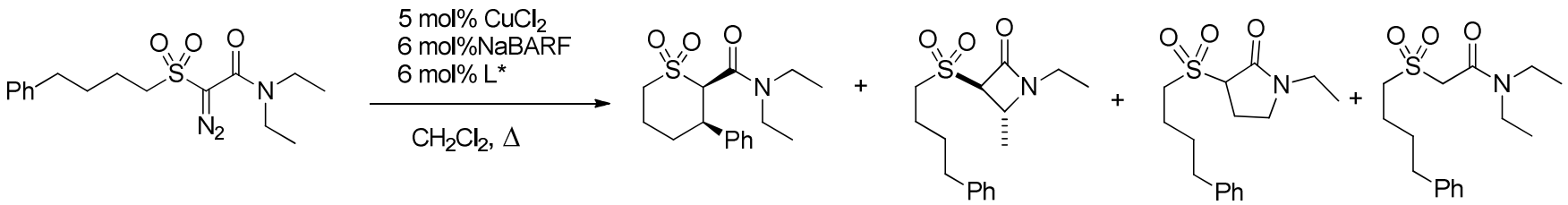


Figure 6.16-^{1}H NMR ($CDCl_3$, 400 MHz)

Table 6.8 *C–H insertion reactions of α-diazo-β-amido sulfone* ***47*** *catalysed by chiral copper catalysts; investigation into the* N,N*-diethyl amide.*



47 **220a** **221b** **219** **118**

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency (%)[a]	Crude Ratio[a] Purified Yield (%)[a] (% ee)[a]	Products		
							cis **thiopyran[a]** least polar	**β lactam[a,b]** more polar	**ɣ lactam[a]** most polar
1	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	48	70–80[c]	**Crude Ratio**	32	29	40
						Purified Yield (%)	10% (90% ee) (2*R*,3*R*) + 9% (94% ee) (2*R*, 3*R*)	8%[d] + 5%[e] + 6%[f]	4%[g] + 12%[h] + 5%[i]
						Overall Yield (%)	20% (92% ee)	11%	18%
							$[\alpha]_D^{20}$ -67.0 (*c* 0.05, CH_2Cl_2)	5.8% total estimated for sulfone **118**	

2	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	70–80[j]	**Crude Ratio** **Purified Yield (%)** **<u>Overall Yield (%)</u>**	17 4% (>99% ee) (2*S*,3*S*) + 6% (96% ee) (2*S*,3*S*) <u>10% (97% ee)</u> $[\alpha]_D^{20}$ +74.0 (*c* 0.05, CH_2Cl_2)	20 2% + 7%[k] + 3%[l] <u>10%</u> <u>0.77%</u> total estimated for sulfone **118**	63 12%[m] (54% ee) + 8%[n] (51% ee) + 6% (49% ee) <u>26% (52% ee)</u>
3	**D**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** (1:1)	21	70–80	**Crude Ratio** **Purified Yield (%)** **<u>Overall Yield (%)</u>**	38 15% (0% ee) <u>15% (0% ee)</u>	30 12%[o] (0%ee) <u>9% (0% ee)</u> <u>0.96%</u> total estimated for sulfone **118**	32 16%[p] (0% ee) <u>14% (0% ee)</u>

a. Efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **220a**, δ_H 4.12 [1H, dd, *J* 4.5, 2.4, C(2)*H*]; β-lactam **217b**, δ_H 4.25 [1H, q, *J* 6.1, C(4)*H*] and γ-lactam **219**, δ_H 3.83 [1H, dd, *J* 10.2, 4.2, C(3)*H*]. Reported yields (%) refer to purified material using column chromatography on silica gel. Enantioselectivities were measured using chiral HPLC, the details of which can be found in **Appendix I**. Where appropriate the absolute stereochemistry was assigned by analogy, details are included in **Appendix II**.

b. Measurement of the enantioselectivity of β-lactam **217b** by HPLC was attempted, however, results obtained were inconclusive.
Additional peaks may be present in the ^{1}H NMR spectra of the crude product but cannot be distinguished due to peak overlap.

c. Additional less polar fraction obtained (3 mg), δ_H 1.18 (3H, t, *J* 7.2), 1.29 (3H, t, *J* 7.2), 1.74–1.86 (2H, m), 1.89–1.99 (2H, m), 2.64–2.71 (2H, m), 3.31–3.50 (4H, m), 3.51–3.61 (4H, m), 5.28 (s), 7.14–7.21 (3H, m), 7.27–7.32 (2H, m). The presence of the following signals indicates the formation of chloride abstraction product **223**; δ_H 1.18 (3H, t, *J* 7.2), 1.29 (3H, t, *J* 7.2), 5.28 (s).

d. Fraction contains 70% β-lactam **217b**, 17% *cis* thiopyran **220a**, 11% sulfone **118** 3.98 (2H, s, SO_2CH_2CO). Additional peaks may be present in the ^{1}H NMR spectra of the crude product but cannot be distinguished due to peak overlap.

e. Fraction contains 65% β-lactam **217b** and 28% sulfone **118** 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.78–2.84 (m).

f. Fraction contains 30% β-lactam **217b** and 59% sulfone **118** 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.77–2.84 (m).

g. Fraction contains 85% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 3.05–3.19 (m), 3.80 (s), 4.24 (d, *J* 11.2). The presence of the following signals indicates the formation of *trans* sulfolane **222**; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 4.24 (d, *J* 11.2).

h. Fraction contains 86% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 3.03–3.20 (m), 3.80 (s), 4.24 (d, *J* 11.2). The presence of the following signals indicates the formation of *trans* sulfolane **222**; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 4.24 (d, *J* 11.2).

i. Fraction contains 83% ɣ- lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 3.03–3.20 (m), 3.80 (s), 4.04 (s), 4.24 (d, *J* 11.2), 7.42–7.49 (m), 7.51–7.60 (m), 7.93–7.97 (m). The presence of the following signals indicates the formation of *trans* sulfolane **222**; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 4.24 (d, *J* 11.2).

j. Additional peaks may be present in the ^{1}H NMR spectra of the crude product but cannot be distinguished due to peak overlap. Additional less polar fraction obtained (4 mg), δ_H 1.18 (3H, t, *J* 7.2), 1.29 (3H, t, *J* 7.2), 1.74–1.86 (2H, m), 1.89–1.99 (2H, m), 2.64–2.71 (2H, m), 3.31–3.50 (4H, m), 3.51–3.61 (4H, m), 5.28 (s), 7.14–7.21 (3H, m), 7.27–7.32 (2H, m). The presence of the following signals indicates the formation of chloride abstraction product **223**; δ_H 1.18 (3H, t, *J* 7.2), 1.29 (3H, t, *J* 7.2), 5.28 (s).

k. Fraction contains 85% β-lactam **217b** and 5% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.76–2.84 (m), 4.47 (d, *J* 6.8).

l. Fraction contains 62% β-lactam **217b** and 14% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.77–2.84 (m).

m. Fraction contains >99% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.19–3.34, 4.08–4.20 (m), 4.65–4.71 (m), 5.20–5.26 (m).

n. Fraction contains >99% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.20–3.25, 4.07–4.20 (m), 4.61–4.80 (m), 5.19–5.29 (m).

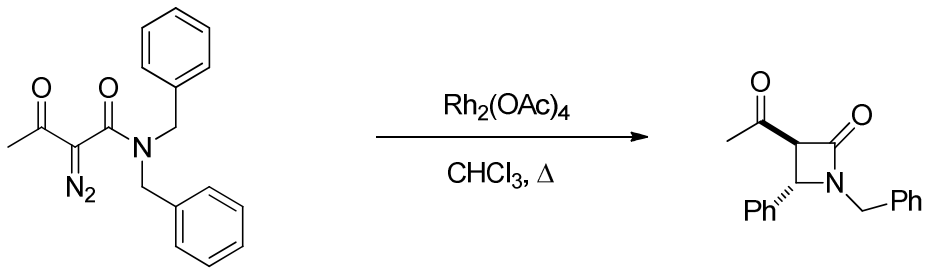
o. Fraction contains 76% β-lactam **217b**, 8% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.76–2.89 (m), 4.10 (s), 4.14 (s), 6.12–6.27 (m), 6.53 (d, *J* 16.2), 7.52 (s).

p. Fraction contains 90% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 7.1), 1.01 (t, *J* 7.2), 2.07–2.24 (m), 3.05–3.16 (m), 3.48–3.56 (m), 4.24 (d, *J* 11.4). The presence of the following signals indicates the formation of *trans* sulfolane **222**; δ_H 0.79 (t, *J* 7.1), 1.01 (t, *J* 7.2), 4.24 (d, *J* 11.4).

Two ligands were chosen for investigation: (3*S*,8*R*)-Ind **44** as it had previously given the best enantioselectivity for the ɣ-lactam series and (4*R*)-Ph **20** as it resulted in the best enantiocontrol for the *cis* thiopyran series. Reaction efficiencies observed for both ligands were good, with values of 70–80% being achieved in both cases (**Table 6.8**, entries 2 and 3). However, there is a marked difference in the relative amounts of each isomer formed. While the amount of β-lactam **221b** is approximately the same in both cases, proportionately less ɣ-lactam **219** and more *cis* thiopyran **220a** is seen for (3*S*,8*R*)-Ind **44** than for (4*R*)-Ph **20** (**Table 6.8**, entries 1 and 2), thus, indicating a ligand effect on product distribution. While minor effects had been seen to occur in other reactions, this is possibly the most significant ligand effect on regioselectivity of insertion seen in this programme of research. Enantioselectivities remained high for the *cis* thiopyran for both ligands, with 92% ee observed for (3*S*,8*R*)-Ind **44** and 97% ee observed for (4*R*)-Ph **20** (**Table 6.8**, entries 1 and 2). While the high enantioselectivity achieved using (4*R*)-Ph **20** is in agreement with previous trends, the high enantioselectivity achieved using (3*S*,8*R*)-Ind **44** was unexpected as it gave rise to moderate enantioselectivity for the ester series (**Chapter 4**). However, as will be discussed in **Section 6.3.4**, high enantioselectivities were also observed for both ligands for formation of *cis* thiopyran **224a**, a morpholine derivative (**Table 6.10**, entries 2 and 3)

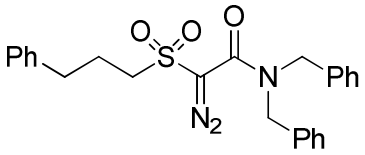
6.3.3 C–H insertion reactions of α-diazo-β-amido sulfone 53 containing *N*,*N*-dibenzyl amide

Having thoroughly investigated the C–H insertion reactions of α-diazo-β-amido sulfones **46**, **47**, **50**, **51**, **57** containing *N*,*N*-dialkyl amide groups, attention was next focused on exploring the impact of the electronic effect of an *N*,*N*-dibenzyl amide substituent on the outcome of C–H insertion. Exploration of C–H insertion at the benzylic position in the *N*,*N*-dibenzyl amide substituent was carried out to determine the impact of variation of the electronic properties at the site of insertion. The CH_2 in the *N*,*N*-dibenzyl substituent is doubly activated by the presence of an adjacent nitrogen atom and phenyl substituent; insertion into a benzylic CH_2 is known to be favourable electronically for C–H insertion processes[56] (**Scheme 6.16**).



Scheme 6.16[56]

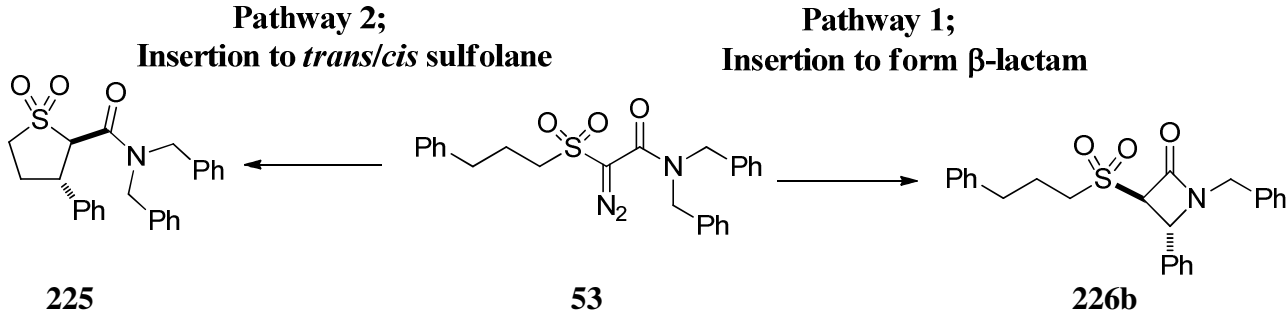
For these reasons, at the outset, C–H insertion to form a β-lactam product was envisaged. Substrate **53** was chosen for investigation as illustrated in **Figure 6.17**.



53

Figure 6.17

The two main potential reaction pathways, β-lactam and sulfolane formation are demonstrated in **Scheme 6.17**. C–H insertion to lead to ɣ-lactam and thiopyran are not possible for this substrate. As neither sulfolane nor β-lactam products have dominated the reaction pathway so far, with the *N*,*N*-dialkyl amides, this is an ideal substrate to probe these additional reaction pathways.



Scheme 6.17

$Rh_2(OAc)_4$ catalysed reaction of α-diazo-β-oxo sulfone substrate **53** was initially investigated with a view to generating a racemic sample of the reaction products. Subsequently, chiral copper catalysis was explored for substrate **53**, employing the

$CuCl_2$-NaBARF-L* catalyst system. Use of the five commercially available bisoxazoline ligands **20**, **43**, **44**, **137**, **138** were investigated in this study. The results of this study are presented in **Table 6.9**.

The sole intramolecular C–H insertion product observed in this study was *trans* β-lactam **226b**, with no evidence in the crude product mixture for sulfolane formation. The key characteristic signal observed for *trans* β-lactam **226b**, was the presence of a doublet at 4.96 ppm with a coupling constant of *J* 1.5, as shown in **Figure 6.18**; this coupling constant is consistent with literature values for *trans* β-lactam formation. Doyle and co-workers reported values of *J* 2.3 Hz for similar substrates (**Figure 6.18**).[56] In addition, a NOESY conducted on **221b**, which was obtained as a minor reaction product from the copper catalysed C–H insertion reactions of **47**, indicated that the most probable structure for **221b** is *trans*, as there is no interaction evident between C(3)*H* and C(4)*H*. However, there were interactions observed between both C(3)*H* and C(4)-CH_3 and C(4)*H* and C(4)-CH_3.

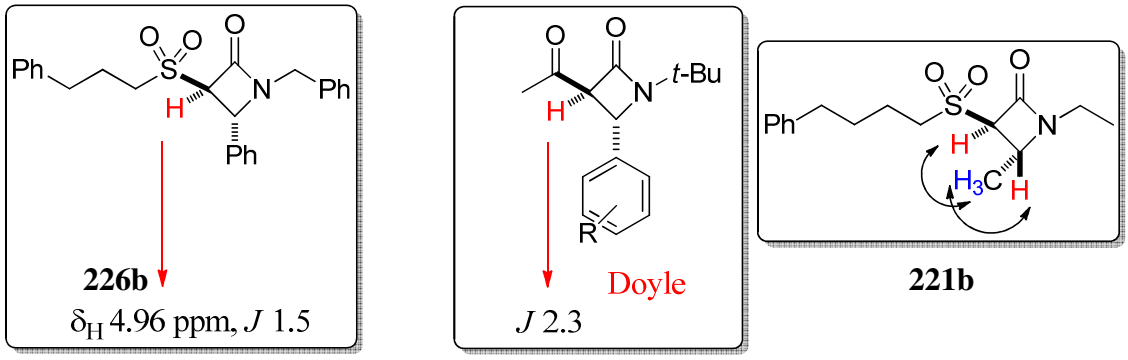
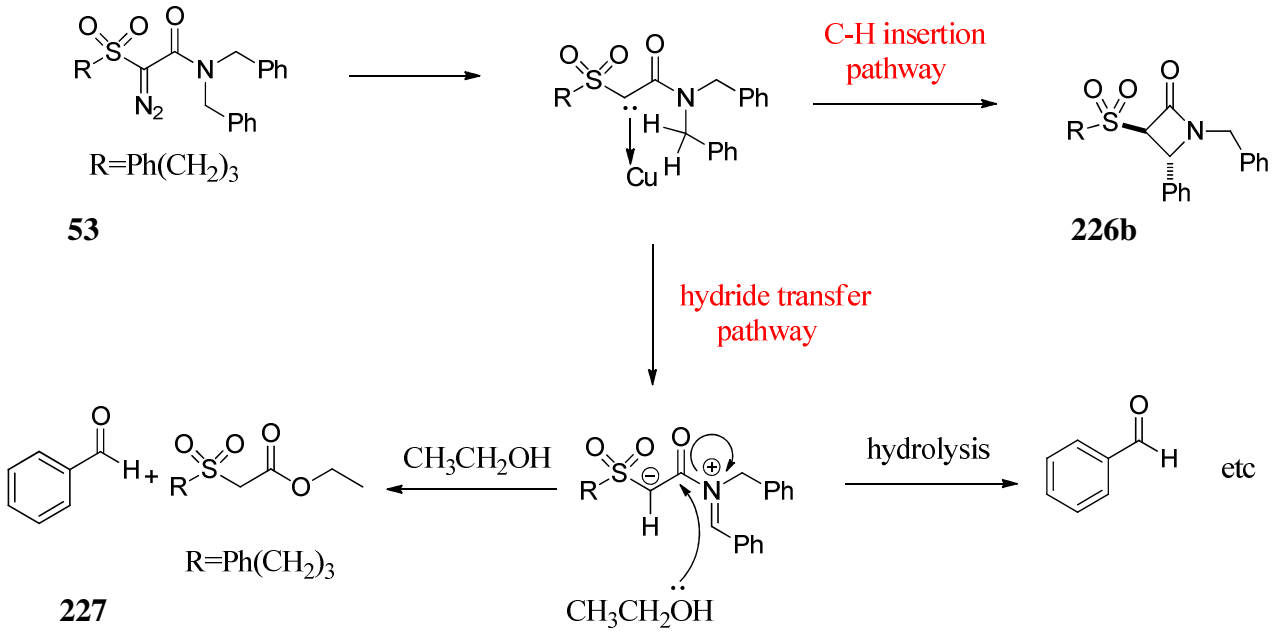


Figure 6.18[56]

Noticeably, however, an additional product, not due to intramolecular C–H insertion was observed in both the crude and purified spectra of *trans* β-lactam **226b** (**Table 6.9**, entries 2–6, 9). Closer inspection of this additional product revealed it to be β-oxo sulfone **227**, a compound previously prepared and fully characterised by Flynn.[48] The key signal that allowed identification of **227** was the CH_2 signal of the ethyl ester that appears at 4.24 ppm (2H, q, *J* 7.2). Identification of the ester side product was somewhat serendipitous. Thus, the $CuCl_2$-NaBARF-(4*R*)-Bn **43** catalysed reaction of α-sulfonyl diazoacetamide **53** was conducted on two occasions (**Table 6.9**, entries 1 and 3). The ^{1}H NMR spectra of the crude product mixtures indicated that efficiency of β-lactam formation was essentially

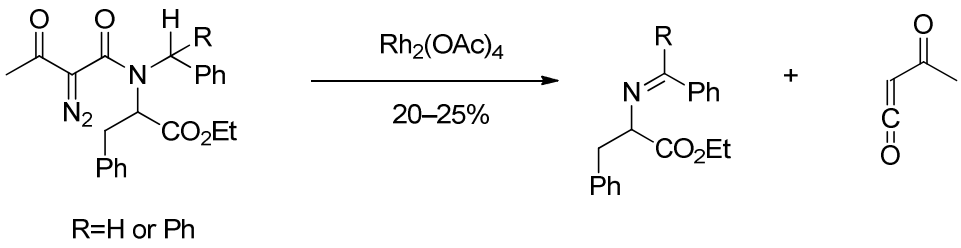
equivalent in both product mixtures; the key difference is that the ^{1}H NMR spectrum of the product of **Table 6.9**, entry 1, was much more complex than that seen for **Table 6.9**, entry 3. The identification of the sulfonyl ester **227** as a substantive component of the crude product mixture in **Table 6.9**, entry 3 provided insight into this behaviour. It is clear that the quality of the dichloromethane used in **Table 6.9** entries 1 and 3 is different, with a trace of ethanol present in the batch used for entry 3 but absent in the batch employed for **Table 6.9**, entry 1.

Examination of the ^{1}H NMR spectra of the crude product mixtures for **Table 6.9**, entries 2, 4-6, each showed the presence of the sulfonyl ester byproduct **227**; which was entirely consistent with use of the same batch of dichloromethane for these catalyst studies. Attempts to confirm the origin of the ester byproduct **227** (**Table 6.9**, entries 7 and 8) were undertaken where (**Table 6.9**, entry 8) HPLC grade dichloromethane was employed (*i.e*. in the absence of ethanol) while for **Table 6.9**, entry 7, the same HPLC grade dichloromethane was deliberately spiked with 1% of ethanol. The outcome of these two experiments clearly confirms that the presence of trace amounts of ethanol in the reaction solvent leads to trapping of a reaction intermediate as the ethyl ester. These observations can be rationalised as illustrated in **Scheme 6.18**, thus C–H insertion at the benzylic C–H bond to form the β-lactam is in competition with hydride transfer from this very activated position to yield a nitrogen stabilised carbocation. As summarised at the end of **Table 6.9**, it has been definitively confirmed that the origin of the sulfonyl ester is not simply by direct ethanolysis of the amide as exposure of sulfonyl amide to 5% ethanol in dichloromethane did not result in substitution of the dibenzyl amine moiety for ethanol. Products resulting from a hydride transfer pathway have been previously observed by Slattery and Flynn, in addition to being observed throughout this project.[48,49,57]



Scheme 6.18

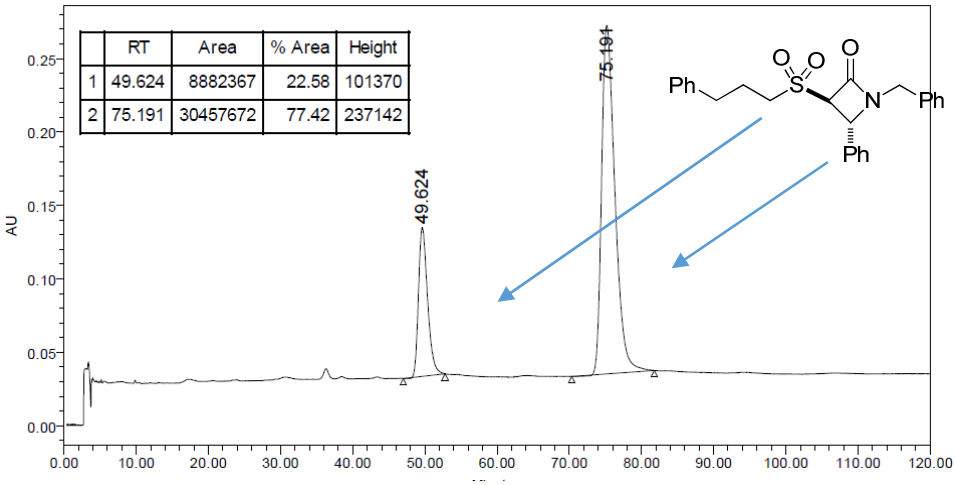
When ethanol is present, the highly reactive acyl iminium ion is very efficiently trapped with ethanol, leading to the ester byproduct **227**. In the absence of ethanol, hydrolysis of the intermediate to provide a number of byproducts (likely to be polar) occurs instead, resulting in the very complex ^{1}H NMR spectra of the crude products (**Table 6.9**, entries 1 and 3). Further evidence for this proposed pathway is that signals for benzaldehyde were observed in the crude product mixtures in most of the entries in **Table 6.9**. Interestingly, reaction efficiencies for β-lactam formation remain fairly constant whether or not ethanol is present. The competition between hydride transfer and C–H insertion is consistent with observations made by Flynn,[48] Slattery[48,49] and Ring.[51] Evidently, the hydride transfer competes effectively in this instance for two reasons: Firstly, the ring strain involved in the formation of the β-lactam ring, and secondly, the very high level of stabilisation of the carbocation by both the nitrogen and the benzene ring. There was no evidence for the comparable hydride transfer process in the *N*,*N*-dipropyl and *N*,*N*-diethyl analogues. Interestingly, Jung[38] has briefly mentioned hydride transfer in a *N*-benzyl amide substrate leading to a side reaction, which was rationalised on the basis of previous publications (**Scheme 6.19**).[58]



R=H or Ph

Scheme 6.19[58]

Attempts to fully separate β-lactam **226b** from sulfonyl ester byproduct **227** were unsuccessful using column chromatography. Different fractions of material contained differing relative amounts of the β-lactam **226b** and sulfonyl ester byproduct **227**. In the less polar fractions of the mixed material, greater amounts of sulfonyl ester byproduct **227** were present with greater quantities of β-lactam **226b** in the more polar fractions (**Table 6.9**, entries 2–6, 9). A pure sample of sulfonyl ester byproduct **227**, obtained from Flynn, allowed the development of HPLC conditions. Successful HPLC conditions were developed, separating the two enantiomers of β-lactam **226b** from each other and from sulfonyl ester byproduct **227**, thus allowing for successful measurements of enantiopurities of the *trans* β-lactams, as demonstrated in **Figure 6.19**.



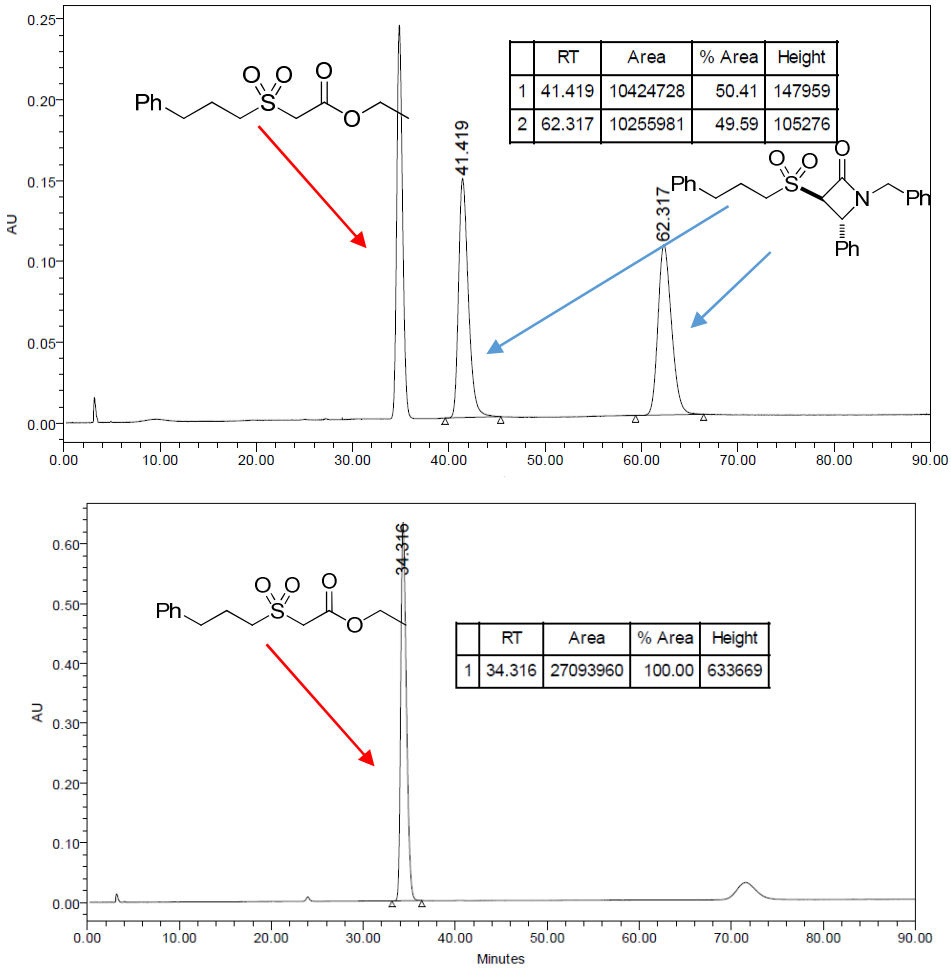


Figure 6.19

During chromatographic purification of **Table 6.9**, entry 7, the reaction mixture which was spiked with 1% ethanol, a fraction was recovered which has been tentatively assigned as the ethanol insertion product **228** (**Figure 6.20**).

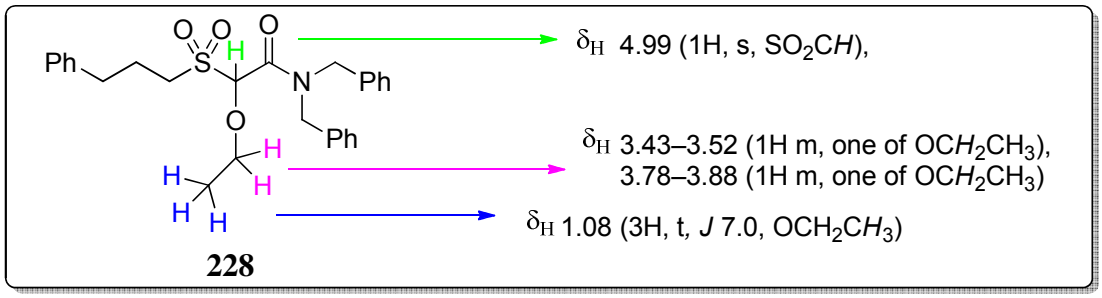
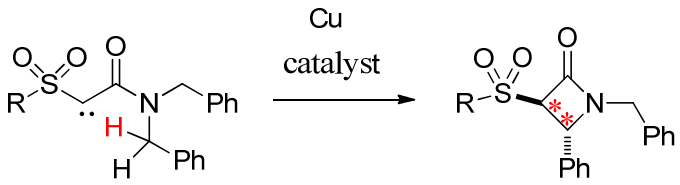


Figure 6.20

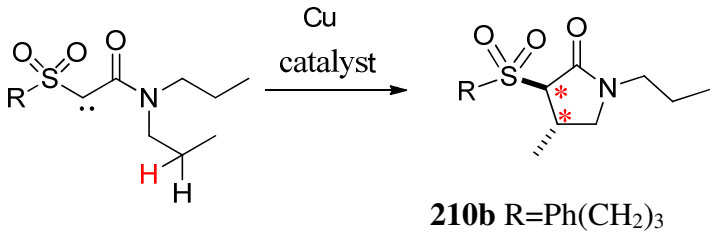
Having established the reaction pathways the next challenge was to explore enantiocontrol in the copper mediated transformations. The impact of the ligand on

enantiopurity displays similar trends to those discussed above for ɣ-lactam formation from *N*,*N* dipropyl substrates **208–210** discussed above. The ligand that gave rise to the best enantiocontrol was the (3*S*,8*R*)-Ind ligand **44**, giving β-lactam **226b** in 84% ee (**Table 6.9**, entry 5) with enantiocontrol for all other ligands decreasing in the order (3*S*,8*R*)-Ind **44** > (4*S*)-*t*-Bu **138** > (4*R*)-Bn **43** > (4*R*,5*S*) di-Ph **137** > (4*R*)-Ph **20**. The result obtained for (3*S*,8*R*)-Ind ligand **44** was repeated a number of times, both in the presence and the absence of ethanol. Interestingly, the enantioselectivities remained essentially the same on all occasions, thus showing that ethanol did not play a role in the high enantioselectivity achieved for β-lactam **226b** in the presence of (3*S*,8*R*)-Ind ligand **44** (**Table 6.9**, entries 6–8). A similar trend is seen in the presence of (4*R*)-Bn ligand **43**, with 55% ee being achieved for formation of β-lactam **226b** in the absence of ethanol and ~56% ee obtained when ethanol was present (**Table 6.9**, entries 1 and 3).

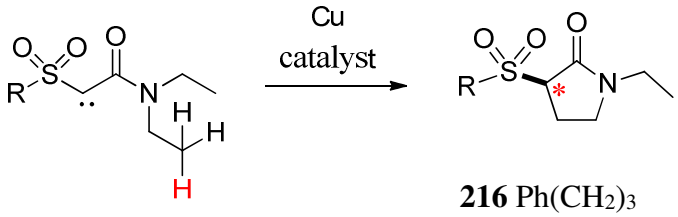
The ligand effect on enantiocontrol is particularly interesting as the same ligands lead to the highest enantioselectivity in both β- and ɣ-lactam formation, despite significant conformational and electronic differences in the pathway leading to four and five-membered ring formation. It is important to note since ɣ-lactams **216** and **219** possess only one stereocentre which is relatively labile the enantiopurity of the reaction product can be eroded after the product has been formed. This is not the case for lactams containing two stereocentres, since the second stereocentre cannot be altered after it has been formed. This indicates the potential for a generally effective enantioselective catalyst in the C–H insertion reactions of α-sulfonyl diazoacetamides (**Scheme 6.20**).



226b R=Ph$(CH_2)_3$



210b R=Ph$(CH_2)_3$
209b R=Ph$(CH_2)_4$
208b R= 2′ethylphenyl



216 Ph$(CH_2)_3$
219 R=Ph$(CH_2)_4$

Scheme 6.20

(3*S*,8*R*)-Ind 44
(4*S*)-*t*-Bu 138
(4*R*)-Ph 20

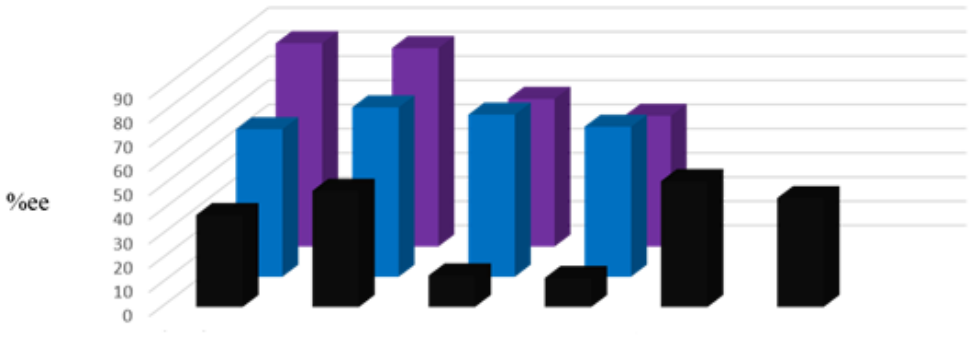
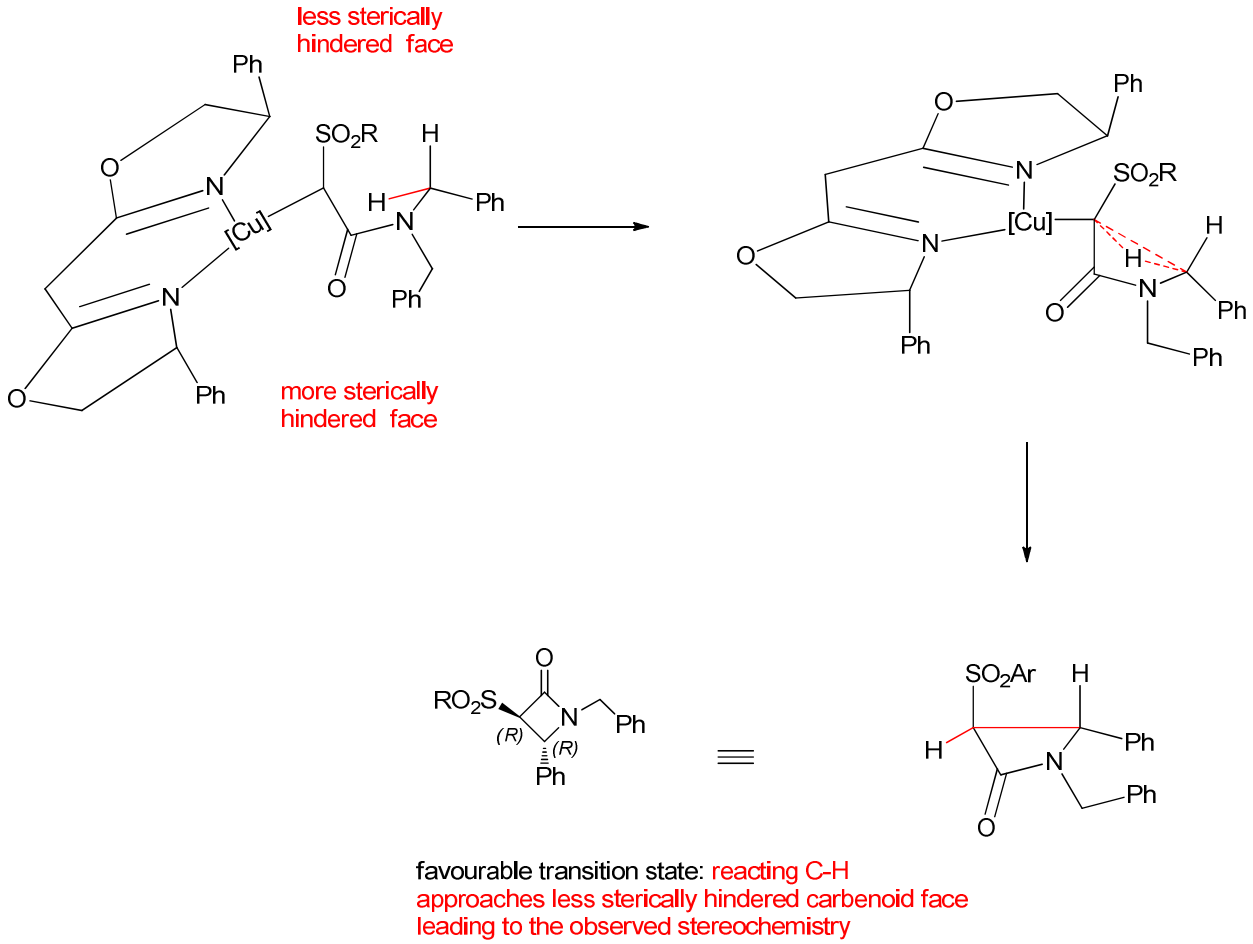


Figure 6.21

As the chromatographic separation of β-lactams was challenging, a number of fractions were isolated in most instances as illustrated in **Table 6.9**. As self-disproportionation of enantiomers was seen earlier in this work, and by other members of the team, the enantiopurities of the β-lactam portion of each fraction was determined individually. In most instances the enantiopurities were consistent across the chromatographic fractions. However, in one experiment (**Table 6.9**, entry 5) there was evidence of variation in enantiopurity across the fractions.

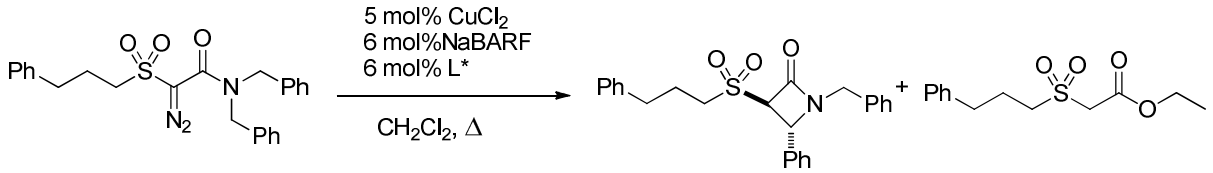
The β-lactam **226b** proved remarkably stable; ^{1}H NMR spectra recorded on a sample stored at room temperature in the dark after ~1 year indicated little or no deterioration. Recoveries of the β-lactam from chromatography were relatively low, as had been seen with earlier ɣ-lactams, and therefore the yields do not reflect the efficiency of the C–H insertion process.

In each case, the lactam-sulfone mixtures were isolated as oils, while the pure sample of the β-lactam **226b** isolated (**Table 6.9**, entry 1) was a low melting solid. Attempts to grow a single crystal proved unsuccessful. While the absolute stereochemistry could not be determined at this stage for compound **226b**, it is likely that the (3*R*,4*R*) enantiomer is the major enantiomer from a copper catalysed reaction employing the (4*R*)-Ph ligand **20** (**Scheme 6.21**), by analogy to the ɣ-lactam series. The transition state model drawn in **Scheme 6.21** is based on the same model leading to ɣ-lactam formation. As anticipated the same major enantiomer of **226b** formed using ligands (4*R*)-Bn **43**, (4*R*)-Ph **20** and (4*R*)-di-Ph **137**, while the other enantiomer predominated using the ligands (4*S*)-*t*-Bu **138** and (3*S*,8*R*)-Ind **44** with the opposite absolute stereochemistry.


less sterically
hindered face
more sterically
hindered face
favourable transition state: reacting C-H
approaches less sterically hindered carbenoid face
leading to the observed stereochemistry

Scheme 6.21

Table 6.9 *Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **53**



53 **226b** **227**

Entry	Method	Metal	Solvent	Purity of Solvent	Ligand	Time (h)	Crude Efficiency Lactam (%)[a]	Sulfone 227 (%) Crude[a]	Fraction	Purified ratios β-Lactam: Sulfone	Yield (%)[a] β-Lactam, Sulfone	β-Lactam % ee[a]
1	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, EtOH absent	(4*R*)-Bn **43**	30	50–60[b]	-	Fr1	13% **Lactam only**	13[c]	55 % ee[d]
2	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled,	(4*R*)-Ph **20**	21	30–40[e]	40–45	Fr 1 Fr 2 Fr 3	38 : 62 50 : 50 70 : 30[f]	8 6[g] 2[f]	39 % ee[d] 37 % ee[d] -

				trace EtOH					**Overall Yield**		(**7.44%, 8.56%**)	
3	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*R*)-Bn **43**	24	30–40[h]	40–45	Fr 1 Fr 2 Fr 3 Fr 4 **Overall Yield**	30 : 70 43 : 64 58 : 42[i] 69 : 31[i]	4 6 5 7 (**11.51%, 10.91%**)	59 % ee[d] 56 % ee[d] 56 % ee[d] 57 % ee[d]
4	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*R*,5*S*)-di-Ph **137**	30	10–20[j]	20–30	Fr1 Fr 2 **Overall Yield**	33 : 67 64 : 36	8 10[k] (**9.04%, 8.96%**)	52 % ee[d] 56 % ee[d]
5	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*S*)-*t*-Bu **138**	50	20–30[l]	35–45	Fr 1 [m,n] Fr 2[o] Fr 3[o] **Overall Yield**	42 : 58 35 : 65 58 : 42	5 10 9 (**10.82%, 13.18%**)	53 % ee[p] 78 % ee[p] 48 % ee[p]

6	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(3*S*,8*R*)-Ind **44**	21	30–40[q]	30–40	Fr 1 Fr 2 Fr 3 Fr 4 **Overall Yield**	33 : 67 48 : 52 61 : 39 68 : 32	2 9 6 4 (**11.36%, 9.64%**)	84 % ee[p] 82 % ee[p] 84 % ee[p] 84 % ee[p]
7	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, spiked with EtOH	(3*S*,8*R*)-Ind **44**	24	-[r]		Fr1 Fr 2 **Overall Yield**	38 : 62 50 : 50	5 9[s] (**6.4%, 7.6%**)	85 % ee[p] 81 % ee[p]
8	**B**	$CuCl_2/\Delta$	CH_2Cl_2	HPLC grade, no EtOH	(3*S*,8*R*)-Ind **44**	30	30–40[t]		Fr1 Fr2 **Overall Yield**	- -	9 12[u] **21% Lactam only**	89 % ee[p] 77 % ee[p,v]
9	**E**	$Rh_2(OAc)_4/\Delta$	CH_2Cl_2	Doubly distilled,	-	18	50–60[w]		Fr1 Fr2	37 : 63[x] 67 : 33[x]	6 10	0 % ee

				trace EtOH					**Overall Yield**		(**8.92%, 7.08%**)	

a. Crude Efficiencies and relative ratios were calculated approximately using C(3)*H* signal for β- lactam **226b**, δ_H 4.96 [1H, d, *J* 1.5, C(3)*H*] and OC*H*$_2$CH$_3$ for sulfone **227**, δ_H 4.24 (2H, q, *J* 7.2 OC*H*$_2$CH$_3$). Yields given are based on calculations, based on the molecular weight of β-lactam **226b** and have not been adjusted for the different molecular weights of the other products.

b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.96–3.13 (m), 3.28–3.40 (m), 3.49 (d, *J* 14.3), 3.52–3.63 (m), 3.64–3.74 (m), 3.84 (s), 4.07–4.15 (m), 4.43–4.49 (m), 4.51 (s), 4.75–4.79 (m), 4.82 (s), 4.90 (s), 5.12 (d, *J* 15.1), 5.22–5.40 (m), 5.57 (d, *J* 14.2), 6.62–6.67 (m), 6.68–6.73 (m), 6.78–6.84 (m), 6.86–6.90 (m), 6.91–6.97 (m), 7.03–7.11 (m), 7.61–7.67 (m), 7.71 (br s), 7.82 (br s), 7.86–7.90 (m), 8.25 (s), 8.41 (br s), 10.02 (s).

c. Baseline impurities were present in the ^{1}H NMR spectra of the pure product; δ_H 10.03 (s). Two additional fractions were obtained. A fraction (4 mg) that was less polar than *trans* **226b** was isolated with the following spectral characteristics; δ_H 2.16–2.35 (m), 2.76–2.88 (m), 3.08 (d, *J* 13.4), 3.26 (d, *J* 13.2), 3.49 (d, *J* 14.3), 3.53–3.74 (m), 4.47 (d, *J* 7.5), 4.52 (s), 4.91 (d, *J* 7.8), 4.94 (s), 5.57 (d, *J* 14.4),

d. The second eluting enantiomer of the *trans* isomer **226b** at 65-85 min is the major enantiomer, using 10% IPA/Hexane (Cell-2).

e. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.97–2.08 (m), 2.63–2.71 (m), 3.04–3.14 (m), 3.60–3.66 (m), 3.69 (m), 4.47 (d, *J* 5.8), 4.52 (s), 4.67 (s), 5.42 (s), 7.51 (br s), 7.54 (s), 7.56 (s), 7.61–7.67 (m), 7.71 (br s), 7.87–7.91 (m), 8.07–8.12 (m), 8.14–8.25 (m), 8.68–8.74 (m), 10.03 (s).

f. There were additional peaks present in the ^{1}H NMR spectra of Fr 3 (2 mg); δ_H 3.25–3.51 (m), 4.17 (s), 4.82 (d, *J* 5.3), 4.92 (s), 4.98–5.01 (m).

g. Two additional fractions were obtained. A fraction (1.5 mg) that was less polar than *trans* **226b** was isolated, containing majority sulfone **227**, that contained additional peaks in the ^{1}H NMR spectra; δ_H 3.02–3.08 (m), 3.47–3.49 (m), 3.81–3.87 (m), 5.20 (d, *J* 16.0), 6.76 (s), 6.80 (s), 7.57 (s), 7.61 (s). A fraction (6 mg) that was more polar than *trans* **226b** was isolated with the following spectral characteristics; δ_H (major signals) 0.82–0.91 (4H, m), 2.13–2.22 (2H, m), 2.75 (2H, t, *J* 7.5), 3.08–3.14 (2H, m), 3.85 (2H, s), 4.47 (d, *J* 5.80), 7.14–7.37 (15H, m). δ_H (minor signals) 4.64–4.71 (m), 5.19–5.26 (m).

h. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.06–3.03 (m), 3.86 (s), 4.48 (d, *J* 5.7), 4.68 (s), 7.49–7.54 (m), 7.71 (br s), 8.08 (s), 8.09 (s), 8.18–8.25 (m), 8.68–8.72 (m).

i. Contaminant present.

j. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.04–3.13 (m), 3.86 (s), 4.46–4.53 (m), 4.68 (s), 4.77–4.85 (m), 5.35 (s), 5.55–5.64 (m), 6.10 (s), 6.22–6.28 (s), 6.38 (s), 6.51 (s), 6.53 (s), 7.48–7.57 (m), 7.61–7.67 (m), 7.72 (br s), 7.77 (br s), 7.86–7.92 (br s), 8.08 (s), 8.09 (s), 8.20–8.23 (m), 10.03 (s).

k. Two additional fractions were obtained. A mixed fraction (1.3 mg) that was less polar than *trans* **226b** was isolated, that contained *trans* **226b** and sulfone **227** in a ratio of 33:67 (*approx* 50–60% combined of the mixture), in addition to another compound(s) that contained peaks in the ^{1}H NMR spectra; δ_H 3.02–3.07 (m), 3.54–3.68 (m), 4.02–4.16 (m), 4.47 (s), 4.50–4.53 (m), 4.77 (s), 4.81 (s), 6.10 (s), 6.76 (s), 6.80 (s), 7.49–7.53 (m). A fraction (0.5 mg) that was more polar than *trans* **226b** was isolated with the following spectral characteristics; δ_H series of overlapping signals 1.50–5.00 (m), 5.43 (s), 6.99–7.43 (m)

l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.04–3.15 (m), 4.47 (d, *J* 4.5), 4.51 (s), 4.52 (s), 4.68 (s), 4.76 (s), 4.81 (s), 5.35 (s), 8.08 (s).

m. After initial purification by column chromatography, an additional fraction was obtained. A fraction (2.1 mg) that was more polar than *trans* **226b** was isolated with the following spectral characteristics; δ_H 2.63–2.87(m), 2.19–3.50 (m), 3.82 (s), 3.84 (s), 3.85 (s), 3.87 (s), 3.93 (s), 3.94 (s), 3.98 (s), 4.04–4.19 (m), 4.20–4.28 (m), 4.30–4.38 (m), 4.66 (s), 4.69 (s), 4.81 (s), 4.82 (s), 4.89–4.99 (m), 7.14–7.43 (m).

n. After initial purification by column chromatography, two fractions containing *trans* **226b** were obtained. The first fraction obtained was of sufficient purity to undergo chiral HPLC analysis. The results reported for Fr 1, here, are for this initial pure fraction. The second fraction was not of sufficient purity to undergo HPLC analysis and therefore was purified a second time.

o. After initial purification by column chromatography two fractions containing *trans* **226b** were obtained. The second fraction contained additional peaks in the ^{1}H NMR spectra; δ_H 1.71–1.82 (m), 1.83–1.99 (m), 2.67 (t, *J* 7.4), 3.30–3.37 (m), 3.38–3.49 (m), 3.98 (s), 4.08–4.21 (m). The two compounds *trans* **226b** and sulfone **227** account for *approx* 90% of the mixture combined. The relative ratio of *trans* **226b** : sulfone **227** was 43:57. This fraction underwent a second purification using column chromatography on silica gel, using ethyl acetate-hexane as the eluent. Two additional fractions containing product were obtained and these are reported as Fr 2 and Fr 3.

p. The first eluting enantiomer of the *trans* isomer **226b** at 40-55 min is the major enantiomer, using 10% IPA/Hexane. (Cell-2)

q. Analysis of ^{1}H NMR spectra of the crude product showed that *approx* 5% of the starting material α-diazocarbonyl **53** was present. Additional signals observed in the ^{1}H NMR spectra of the crude product; δ_H 3.06–3.14 (m), 3.86 (s), 4.68 (s), 6.73 (br s).

r. ^{1}H NMR analysis of crude material not available.

s. Two additional fractions were obtained. The least polar fraction isolated was tentatively assigned as ethanol insertion product **228** (2 mg). A fraction that was more polar than β-lactam **226b** (1 mg) was isolated with the following spectral characteristics; δ_H 2.12–2.23 (2H, m), 2.75 (2H, t, *J* 7.4), 3.05–3.14 (2H, m), 3.85 (2H, s), 4.46 (1H, s), 4.48 (1H, s), 7.13–7.35 (15H m).

t. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.05–3.13(m), 3.53–3.59 (m), 3.85 (s), 4.46 (s), 4.47 (s), 4.76 (s), 4.81 (s), 5.35 (s), 7.50–7.56 (m), 7.61–7.66 (m), 7.72 (br s), 7.86–7.92 (m), 10.03 (s).

u. Additional less polar fraction obtained (2 mg), that contained peaks in the ^{1}H NMR spectra; δ_H 2.21–2.32 (m), 2.77–2.86 (m), 3.54–3.60 (m), 4.47 (s), 4.50 (s), 4.79 (d, *J* 17.6), 4.91 (d, *J* 14.7), 5.34 (s), 7.11–7.45 (m).

v. $[\alpha]_D^{20}$ +15.2(*c* 0.23, CH_2Cl_2).

w. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.59 (s), 4.67 (s), 4.85 (s), 7.44–7.66 (m), 7.77–7.82 (m), 7.87–7.92 (m), 8.09 (s), 8.41 (s), 10.03 (s).

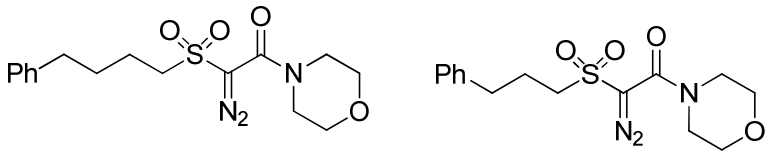
x. Results refer to data after a second purification. Both methods of purification were carried out using column chromatography on silica gel. A second purification was carried out in an attempt to separate sulfone **227** from lactam **226b**. Results after first purification; (50:50) lactam:sulfone.

Note: A solution of *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120** (100 mg) in dichloromethane (40 mL) and ethanol (2 mL) was stirred at reflux for 24 h. The solution was concentrated under reduced pressure and a ^{1}H NMR spectra of the resulting

compound was obtained. Only starting material *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120** was obtained.

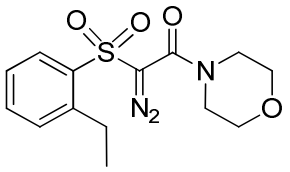
6.3.4 Asymmetric copper catalysed C–H insertion reactions of α-diazo-β-amido sulfones: investigation into the *N*-morpholine substituent.

Thus far, the investigation into C–H insertion reactions of α-diazo-β-amido sulfones has focused on the use of *N*,*N*-dialkyl substituents **46**, **47**, **50**, **51, 57**, as well as *N*,*N*-dibenzyl amide **53**. The results of this study have shown that in general, C–H insertion is favoured into an alkyl group on the amide substituent, rather than into the sulfonyl side chain. Our interests were subsequently directed to the use of the morpholine group, which has limited conformational freedom in comparison to previous substrates **46**, **47**, **50**, **51**, **53**, **57**. Four substrates were synthesised for this investigation **48**, **49**, **52**, **58**, all with differing sulfonyl groups to enable further exploration of the competition between insertion into the sulfone side chain and insertion at the amide functionality (**Figure 6.22**). Substrates **48**, **58** and **49** were chosen as they could potentially lead to lactams and thiopyran/sulfolane products, however, thiopyran synthesis is not expected with product **58**, due to results previously obtained in Chapter 5 with the comparable ester and ketone derivatives. Insertion to lead to thiopyran is impossible for α-diazo-β-amido sulfone **52**.

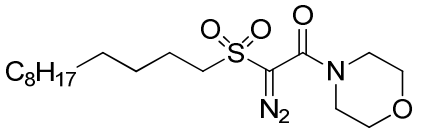


48

52



58



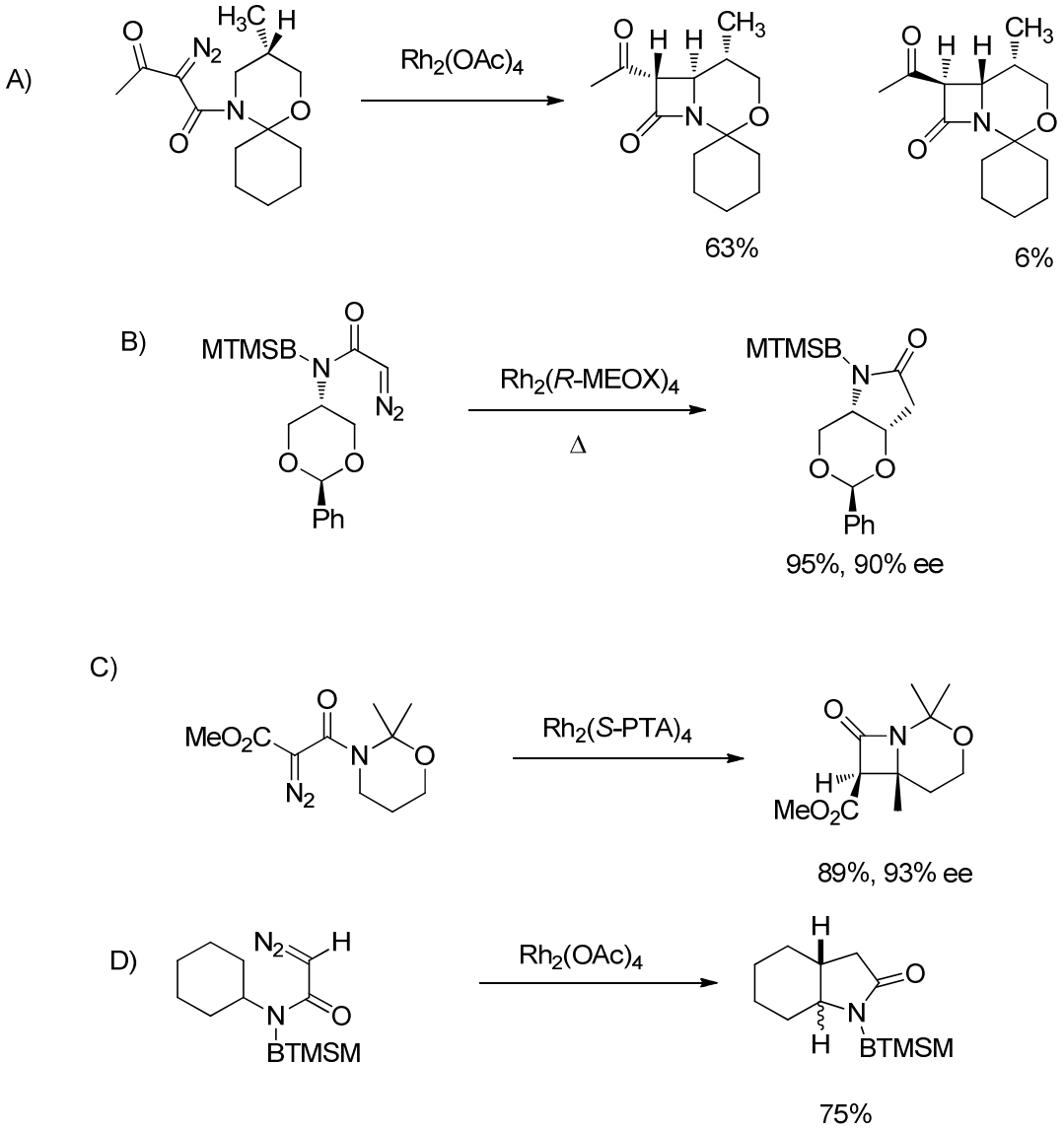
49

Figure 6.22

At the outset lactam formation *via* insertion into the morpholine moiety was envisaged to be less favourable than insertion into the freely rotating dialkyl or dibenzyl amides due to

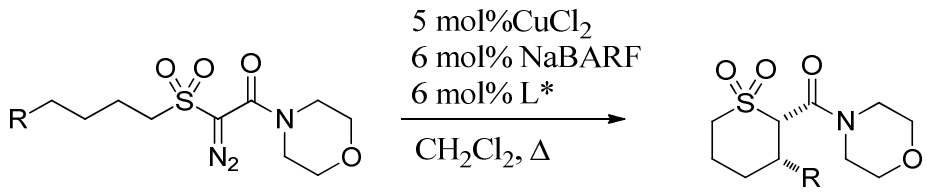
conformational constraints and ring strain in the fused lactams which would result. Accordingly it was envisaged that in this system insertion into the sulfone chain may compete to form thiopyrans and/or sulfolanes. Sulfonyl groups present in substrates **48**, **52** and **58** have previously been employed with the other amide groups **sections 6.3.1**, **6.3.2** and **6.3.3**) to allow direct comparisons of selectivity trends.

Southgate and co-workers [(**Scheme 6.22**, (**A**)], [59] Doyle and co-workers [(**Scheme 6.22**, (**B**)],[60] Hashimoto and co-workers [(**Scheme 6.22**, (**C**)] [61] and Wee and co-workers [(**Scheme 6.22**, (**D**)], [22] had demonstrated intramolecular C–H insertion to lead to fused β-lactams in a related system, which indicates that this reaction pathway is feasible with the morpholine amides (**Scheme 6.22**).



Scheme 6.22

Table 6.10 *Investigation into the copper catalysed C–H insertion reactions α-diazoacetamides* **48** *and* **49**



48 R= Ph
49 R= Oct

224a R= Ph
229a R= Oct

Entry	R	Ligand	Time (h)	Crude Efficiency (%)	Fraction after purification by chromatography	Yield (%)	% ee
1	Ph	(3*S*, 8*R*)-Ind **44** and (3*R*, 8*S*)-Ind **161** (1:1)	21	60–70[a]	Fraction 1	20	0
2	Ph	(4*R*)-Ph **20**	21	40–50[a]	Fraction 1 Fraction 2	4[b] 15	- 98 (2*S*,3*S*) $[\alpha]_D^{20}$ + 40.0 (*c* 0.05, CH_2Cl_2)
3	Ph	(3*S*,8*R*)-Ind **44**	21	40–50[a]	Fraction 1 Fraction 2	6[c] 7	 86 (2*R*,3*R*) $[\alpha]_D^{20}$ - 57.0 (*c* 0.1, CH_2Cl_2)

4	Oct	(3*S*, 8*R*)-Ind **44** and (3*R*, 8*S*)-Ind **161** (1:1)	75	10–20[d,e]	Not purified	-[f]	-[f]
5	Oct	(4*R*)-Ph **20**	96	10–20[d,g]	Not purified	-[f]	-[f]
6	Oct	(3*S*,8*R*)-Ind **44**	72	10–20[d,h]	Purified	*cis* thiopyran isolated as an impure fraction[i]	-[i]

a. Efficiency calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **224a** δ_H 4.22 [1H, dd, *J* 4.8, 2.3, C(2)*H*].
b. Two fractions of material were obtained, the first fraction contained impurities and therefore the % ee was not determined.
c. Two fractions of material were obtained, the first fraction contained impurities. Attempted HPLC analysis of the impure fraction (Fr 1) was unsuccessful due to peak overlap in the HPLC traces.
d. Efficiency calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **229a**, δ_H 4.10 [1H, dd, *J* 4.0, 2.1, C(2)*H*].
e. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.64–1.99 (m), 2.03–2.26 (m), 2.88–3.82 (series of multiplets), 4.68 (s), 5.44 (s), 5.95 (s), 9.48 (s).
f. Not purified.
g. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.64–1.99 (m), 2.03–2.26 (m), 3.15–3.82 (series of multiplets), 4.48 (s), 4.96 (s), 5.44 (s), 5.95 (s), 9.48 (s).
h. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.64–1.99 (m), 2.03–2.26 (m), 3.15–3.82 (series of multiplets), 4.96 (s), 5.44 (s), 5.95 (s), 9.48 (s).
i. Fraction contains *approx* 40–50% *cis* thiopyran **229a**, additional peaks were observed in the ^{1}H NMR spectra of the crude product and are listed above.

As has previously been established, *trans* thiopyrans are generally the preferred reaction product when rhodium catalysts are employed and *cis* thiopyrans are usually the major product arising from copper catalysed C–H insertion reactions, when ester and ketone diazocarbonyls are the substrates under investigation (Chapters 4 and 5). As α-diazoacetamides **48** and **49** have a number of potential C–H insertion sites and therefore could potentially lead to a number of different reaction products, a method for generating racemic samples of each of these potential products using one racemic catalyst was desirable. Therefore, $CuCl_2$ (5 mol%), NaBARF (6 mol%) and a 50 : 50 combination of

(3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** (6 mol% in total) was employed as a catalytic mixture. In general, the reactivity of α-diazoacetamide **48** is comparable with ester and ketone derivatives and reactions are essentially complete within 21 h at reflux in dichloromethane, while reactions of the alkyl derivative **49** were notably slower than reaction of α-diazoacetamide **48** or indeed with the analogous ester derivative **37** (**Section 4.3.2**, **Table 4.6**). The contrast in reaction rate between α-diazoacetamide **48** and α-diazoacetamide **49** presumably reflects the relative rate of C–H insertion at a benzylic C–H bond relative to an unactivated C–H bond on an alkyl chain. The only identifiable product in the crude product mixtures, and following chromatographic purification, is thiopyran. While the *cis* thiopyran **224a** was isolated as a pure compound and could be structurally characterised, the octyl substituted thiopyran **229a** was not recovered as a pure compound, however, it was identified by characteristic ^{1}H NMR signals in product mixtures. The structure of the products in terms of relative and absolute stereochemistry, was assigned as *cis* thiopyran by analogy to the corresponding ester and ketone series (**Figure 6.23**).

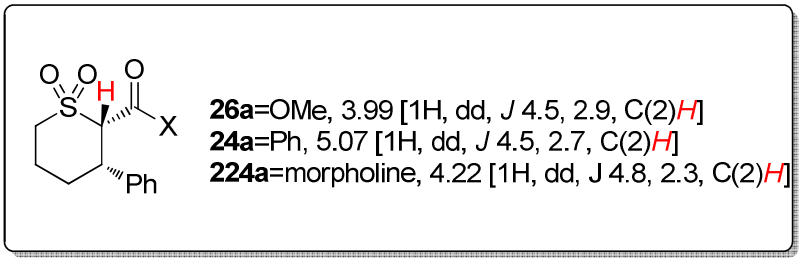
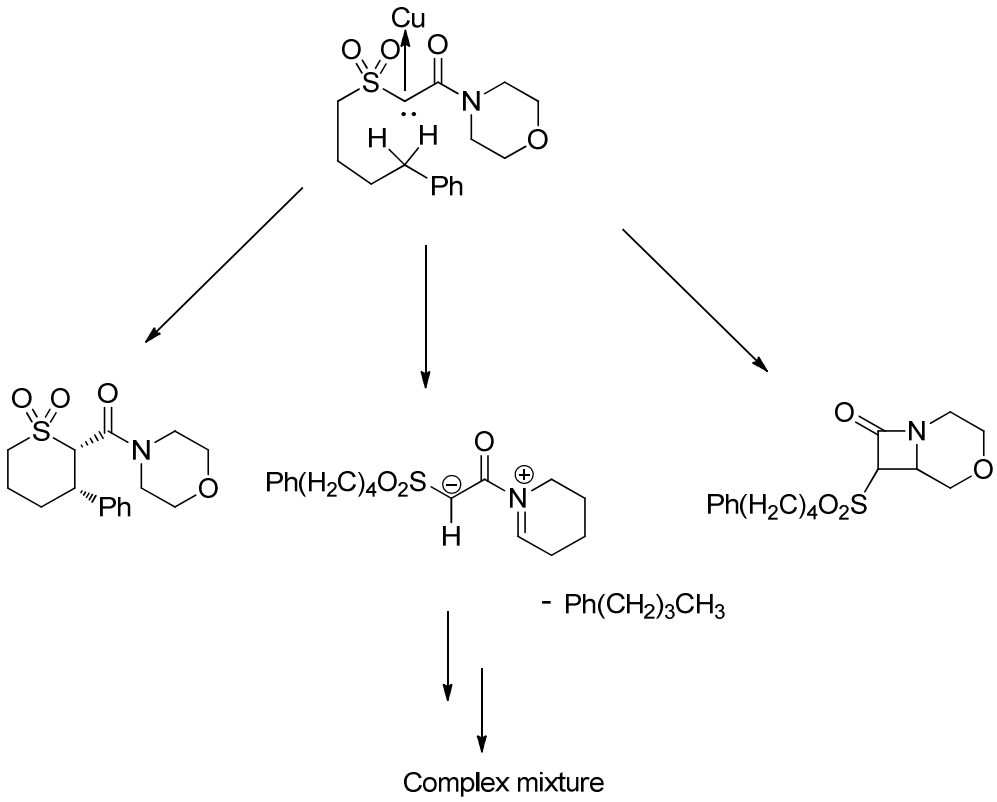


Figure 6.23

The longer reaction times with the α-diazoacetamides compared to α-diazo esters and ketones is consistent with literature reports, whereby α-diazoacetamides are considered less reactive than α-diazo esters and ketones.[2] Examination of the crude reaction mixtures reveal a striking difference for the α-diazo morpholine amides compared to the esters and ketones, whereby the efficiencies of C–H insertion to form the thiopyran estimated from the ^{1}H NMR spectra of the crude product mixtures is notably lower than that seen for ester and ketones and even more dramatically so for the octyl case. The decreased insertion efficiencies in **Table 6.10**, relative to those seen for the analogous esters and ketones, can be rationalised based on the results seen with the other α-diazoacetamides. While no evidence was seen for C–H insertion to form β-lactam, it is entirely feasible that hydride transfer from the carbon adjacent to the nitrogen competes with the C–H insertion

pathway to the thiopyran as illustrated in **Scheme 6.33**. This pattern of reactivity is entirely consistent with the competitive C–H insertion and hydride transfer pathways described for copper mediated C–H insertion in other aspects of programmes of research in our group.[48,49,57]

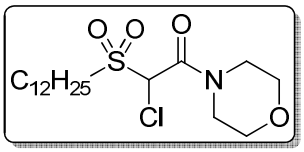


Scheme 6.33

cis Thiopyran **224a** was obtained in a relatively low yield of 20% after purification using column chromatography (**Table 6.10**, entry 1); optimisation of the purification of these compounds is recommended for future work in this area. As *cis* thiopyran **224a** is a novel compound, full characterisation of this compound obtained. Chiral HPLC analysis of *cis* thiopyran **224a** isolated from this reaction (**Table 6.10**, entry 1) proved successful with resolution of both enantiomers being achieved

Interestingly, the presence of additional C–H insertion products in the reaction of **49** was not detected in the crude reaction mixture, which is in direct contrast to copper-bisoxazoline catalysed reactions of dodecyl sulfonyl α-diazo-β-ester **37** (**Table 4.6**, entries 1–3, 11 and 16), where much higher reaction efficiencies were observed, in

addition to the formation of reasonable quantities of *trans* thiopyran **38b** and *trans* sulfolane **139b**. Examination of the ^{1}H NMR spectra of the crude reaction products revealed a complex mixture of largely unidentified material. Purification of the mixture was not attempted at this stage. The presence of two singlets in the ^{1}H NMR spectrum at 5.44 ppm and at 5.95 ppm was seen, one of which may be due to chloride abstraction product **230** (**Figure 6.24**), the formation of which was discussed in **Section 4.1.3**.



230

Figure 6.24

Two ligands were selected for investigation into the asymmetric copper-catalysed C–H insertion reactions of α-diazoacetamides **48** and **49**; (4*R*)-Ph **20**, as this ligand had resulted in the best enantioselectivities in *cis* thiopyran synthesis and (3*S*,8*R*)-Ind **44**, as this ligand gave rise to *N*,*N*-diethyl *cis* thiopyran **220a** with extremely high enantiopurity. Furthermore, the (3*S*,8*R*)-Ind **44** ligand was the most effective for enantioselective lactam formation. In the case of reactions employing 4-phenylbutyl α-diazoacetamide **48** (**Table 6.10**, entries 2 and 3), for both ligands **20** and **44**, the sole identifiable product observed in the crude mixture was *cis* thiopyran **224a**, with no evidence seen for insertion into the alkyl groups on the morpholine ring, which is consistent with the racemic $CuCl_2$-NaBARF-bisoxazoline reaction carried out using this compound (**Table 6.10**, entry 1). The activating effect of the nitrogen and oxygen atoms could potentially lead to β- or ɣ-lactam formation respectively. However, presumably due to conformational restraints, neither β- nor ɣ-lactam products were observed. Reaction efficiencies were moderate, with 40–50% efficiency being obtained in the presence of (4*R*)-Ph **20** and (3*S*,8*R*)-Ind **44** (**Table 6.10,** entries 2 and 3). The remaining reaction products were not identified, however, no characteristic signals were observed for any additional C–H insertion products. Purification of the crude reaction material proved to be moderately challenging, with two fractions of material being obtained in the purification of both reactions (**Table 6.10**, entries 2 and 3). In both cases, the first fraction containing *cis* thiopyran **224a** was impure, with additional signals observed in the corresponding ^{1}H NMR spectra. For this reason enantioselectivity could not be measured in either case. A second fraction of

material was isolated in both cases (**Table 6.10**, entries 2 and 3) as a pure compound in each case. Purified yields were low in both cases, with values of <20% obtained (**Table 6.10**, entries 2 and 3), reflecting challenges in chromatography rather than reaction efficiency. High enantioselectivies were obtained in both cases, with 98% ee being achieved for reaction with (4*R*)-Ph **20** (**Table 6.10**, **entry 2**) and 86% ee for (3*S*,8*R*)-Ind **44** (**Table 6.10**, entry 3). This trend in enantioselectivity for the two ligands is comparable to values achieved for *N*,*N*-diethyl substrate **220a**, however, contrasts to that seen for methyl ester substrate **26a**, where enantiocontrol was more sensitive to ligand variation. This trend is summarised in **Figure 6.24**.

The absolute stereochemistry of the ester derivative had been determined crystallographically as (2*S*,3*S*) when using the (4*R*)-Ph **20** ligand. During this work, the stereochemistry of the morpholine derivative **224a** is assigned as (2*S*,3*S*) when using the same ligand (4*R*)-Ph **20** ligand, by analogy, which is supported by the direction of the specific rotation (**Appendix II**). In line with the earlier *cis* thiopyran esters and ketones, *cis* thiopyran **224a** was a stable white solid with no evidence of degradation on storage.

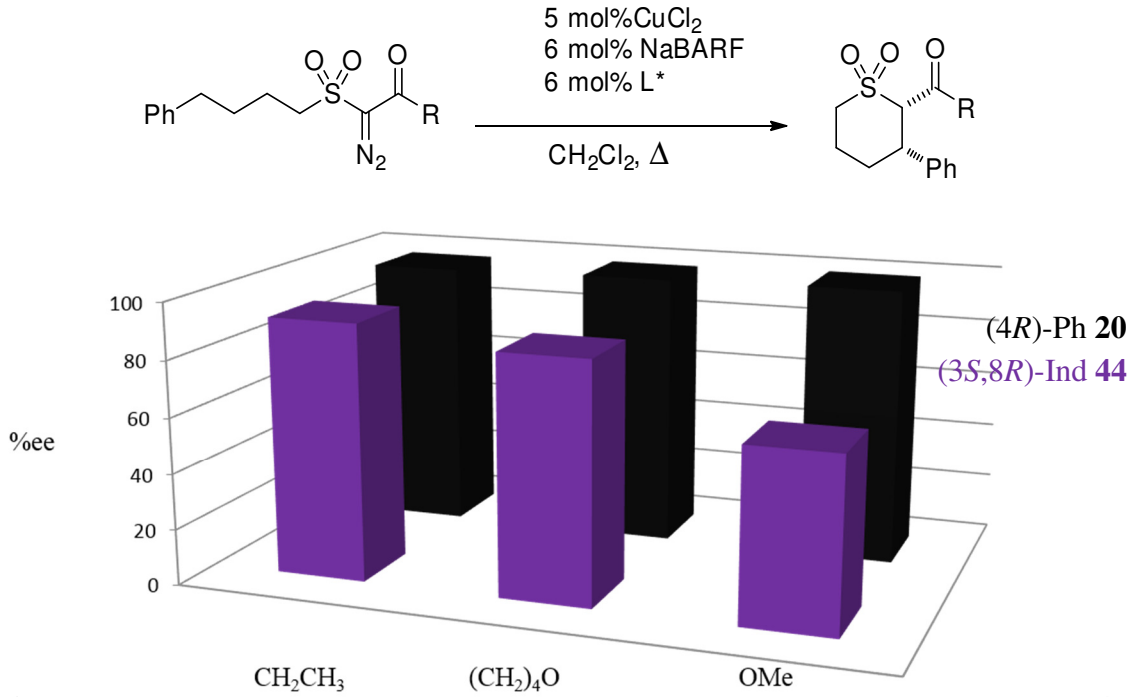


Figure 6.25 *Comparison of enantioselectivities achieved for* cis *thiopyrans* **220a**, **224a** *and* **26a** *with (4*R*)-Ph* **20** *and (3*S*,8*R*)-Ind* **44**. *Note: pre-formation the catalyst and slow addition of the* α*-diazocarbonyl compounds were carried out for the two amide compounds* **48** *and* **49**, *however, it was not carried out for the methyl ester* ***25***. *In a separate project, pre-formation of the catalyst for reaction of ester* ***25*** *was carried out with* $CuCl_2$, *NaBARF and (3S,8R)-Ind* **44** *which did result in a modest improvement of the enantioselectivity*.[62]

When dodecyl sulfonyl α-diazoacetamide **49** was exposed to asymmetric copper catalysts $CuCl_2$-NaBARF-(4*R*)-Ph **20** (**Table 6.10**, entry 5) and $CuCl_2$-NaBARF-(3*S*,8*R*)-Ind **44** (**Table 6.10**, entry 6), essentially the same reaction outcome was seen as was observed for the racemic reaction (**Table 6.10**, entry 4), with low reaction efficiencies calculated for *cis* thiopyran **229a** (~10–20%). *cis* Thiopyran **229a** was the only observable C–H insertion product, with byproduct **230** potentially being present (**Figure 6.24**). Purification of the crude reaction mixture for the reaction employing $CuCl_2$-NaBARF-(3*S*,8*R*)-Ind **44** (**Table 6.10**, entry 6), was attempted, however, low quantities of material were recovered which contained ~40–50% of *cis* thiopyran **229a**. No further attempts were made to purify this mixture.

Comparing the regioselectivity of the copper catalysed intramolecular C–H insertion reactions of *N*,*N*-dipropyl amide **46**, *N*,*N*-diethyl amide **47** and morpholino amide **48**,

some interesting facts emerge, as can be seen in **Figure 6.26**. When the amide group is *N*,*N*-dipropyl exclusively ɣ-lactam **209b** is observed, however, changing from *N*,*N*-dipropyl amide to *N*-morpholino essentially leads to a complete change in reaction pathway, from sole insertion into the alkyl groups on the amide functionality, to insertion into the sulfonyl chain, leading to *cis* thiopyran **224a** as the only C–H insertion product. In the case of *N*,*N*-diethyl amide substrate **47**, three intramolecular insertion products are seen; *cis* thiopyran **220a** and β-lactam **221b**, in addition to ɣ-lactam **219**. As has been discussed in **Section 6.3.2**, ɣ-lactam **219** is generally the major insertion product, with the other isomers observed as minor components of the reaction mixture, however, the exact ratios are dependent on the nature of the ligand involved. Minor amounts of the *trans* sulfolane isomer **222** are also detected in the purified products, but were not at a level which could be seen in the ^{1}H NMR spectrum of the crude mixture. Presumably, this isomer is formed in such small quantities that detection in the crude mixture is practically impossible due to peak overlap. Therefore, it appears that it is the amide group and not the sulfonyl group that dictates the regioselectivity of the insertion process.

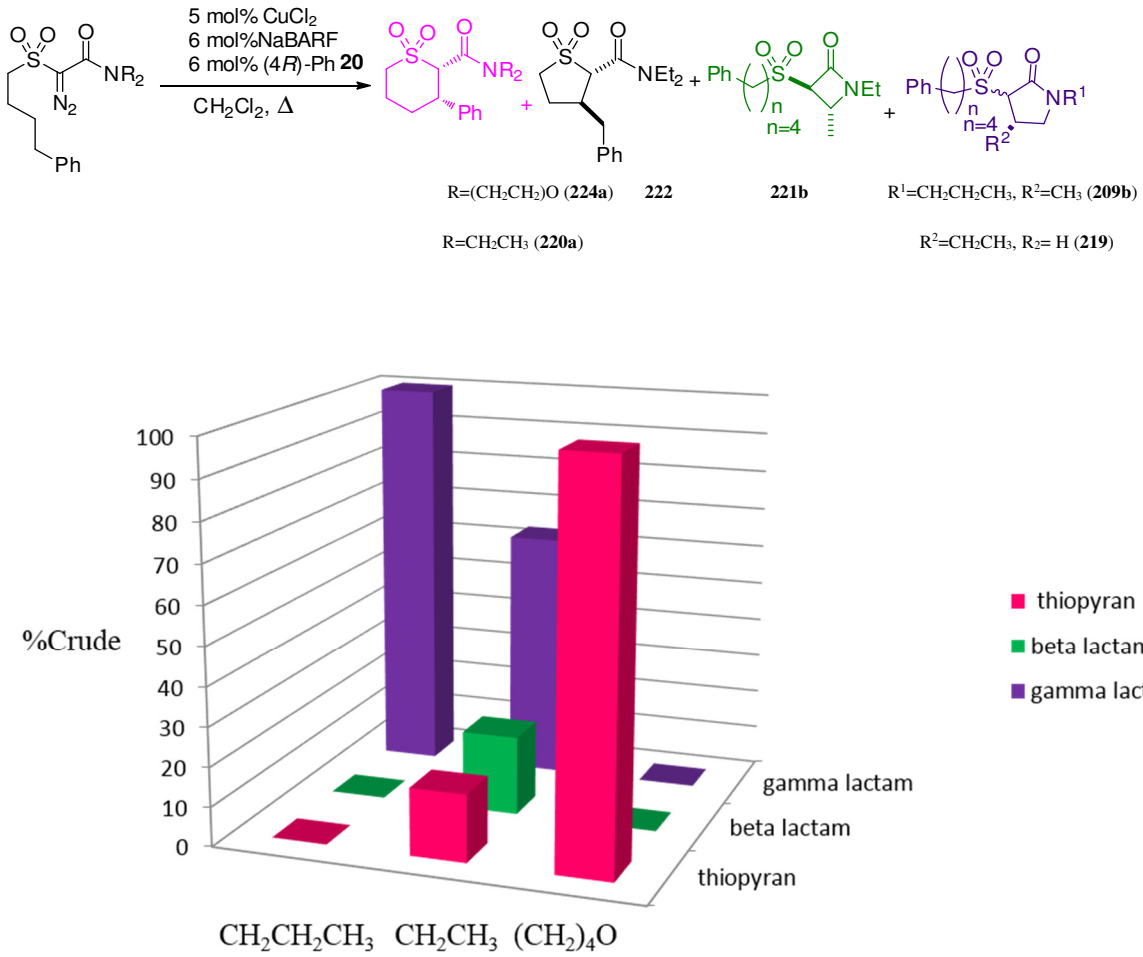
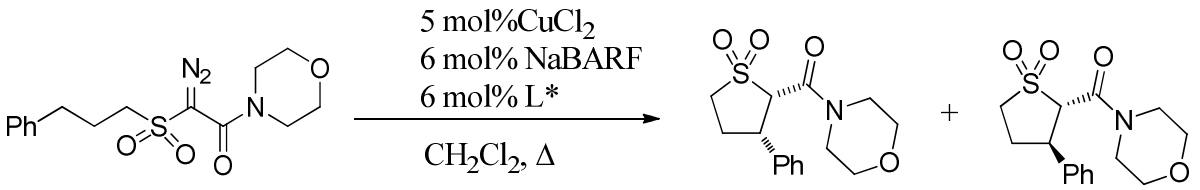


Figure 6.26 *Comparison of regioselectivity for copper catalysed C–H insertion reactions for compounds* **46**, **47** *and* **48**.

Minor amounts of hydride transfer at the benzylic position on the sulfonyl chain have been seen in the ester derivatives (**Section 4.2.1**, and **4.3.3**), however, there is no direct evidence for a comparable hydride transfer pathway in the amides. It is possible that alkene signals were not resolved in the complex ^{1}H NMR spectra of the crude products, although hydride transfer from the carbon adjacent to the nitrogen would seem more likely (**Scheme 6.33**).

Table 6.11 *Asymmetric copper catalysed C–H insertion reactions of 2- diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone* **52**



Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency (%)[a]	Crude Ratio[a] Purified Yield (%)[a] (% ee)[a]	Products *cis* sulfolane more polar **231a** : *trans* sulfolane less polar **231b**	
1	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	48	60–70[b]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	20 8%[c] 7	80 22%[d] (77% ee)[e] 23 $[\alpha]_D^{20}$ -22.78 (*c* 0.09, CH_2Cl_2)

2	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	60	60–70[f]	**Crude Ratio** **Purified Yield (%)** **<u>Overall Yield (%)</u>**	20 5% <u>5%</u>	80 8%[g] (45% ee)[h] $[\alpha]_D^{20}$ +1.961 (*c* 0.102, CH_2Cl_2) + 11 (43% ee)[h] $[\alpha]_D^{20}$ +7.692 (*c* 0.13, CH_2Cl_2) + 9% (9% ee)[h] <u>28% (42% ee)[i]</u>
3	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	21	60–70%[j]	**Crude Ratio** **Purified Yield (%)**	30 -	70 17%[k] (47% ee)[e] $[\alpha]_D^{20}$ -9.542 (*c* 0.105, CH_2Cl_2)
4	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	60–70%[l]	**Crude Ratio** **Purified Yield (%)**	70 18%[m]	30 6%[n]
5	**B**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	21	60–70%[o]	**Crude Ratio** **Purified Yield (%)**	60 15%[m]	40 8%[n]
6	**E**	$Rh_2(OAc)_4/\Delta$		6	50–60%[p]	**Crude Ratio** **Purified Yield (%)**	60 -	40 14%[q]

a. Efficiency and relative ratios were calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*; *cis* sulfolane **231a**, δ_H 4.04–4.12 [1H, m, C(3)*H*]; *trans* sulfolane **231b**, δ_H 4.12 [1H, d, *J* 9.6, C(2)*H*] and 4.32 [1H, ddd, *J* 12.6, 9.7, 6.0, C(3)*H*]. Relative ratios and crude efficiencies were estimated due to peak overlap. Yield (%) reported after purification using column chromatography on silica gel. Enantioselectivities were measured using chiral HPLC details of which can be found in **Appendix I**.

b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.40 (s), 5.92 (s), 6.19–6.34 (m), 6.90 (d, *J* 15.8), 9.48 (s). Additional peaks in the range of 2.0–4.5 ppm cannot be distinguished due to peak overlap.

c. Contains 86% *cis* sulfolane **231a**, 14% *trans* sulfolane **231b**.

d. An additional less polar fraction (3 mg) was obtained after purification using column chromatography on silica gel. This was the least polar fraction obtained. The following signals in the ^{1}H NMR spectra were observed; δ_H 2.15–2.29 (m), 2.74–2.83 (m), 2.86 (s), 2.95–3.02 (m), 3.19–3.27 (m), 3.28–3.35 (m), 3.36–3.50 (m), 3.51–3.64 (m), 3.65–3.86 (m), 5.40 (s), 5.91 (s), 7.14–7.37 (m).

e. The second eluting enantiomer of the *trans* isomer **231b** at ~45 min is the major enantiomer, using 30% IPA (Cell-4).

f. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.42 (s), 6.23–6.32 (m), 6.91 (d, *J* 15.6). Additional peaks in the range of 2.0–4.5 ppm cannot be distinguished due to peak overlap.

g. An additional less polar fraction (1.5 mg) was obtained after purification using column chromatography on silica gel. This was the least polar fraction obtained. The following signals in the ^{1}H NMR spectra were observed; δ_H 2.15–2.28 (m), 2.74–2.84 (m), 2.86 (s), 2.95–3.01 (m), 3.20–3.28 (m), 3.29–3.35 (m), 3.36–3.51 (m), 3.53–3.65 (m), 3.66–3.85 (m), 5.38 (s), 5.91 (s), 7.14–7.36 (m).

h. The first eluting enantiomer of the *trans* isomer **231b** at ~33 min is the major enantiomer, using 30% IPA/hexane (Cell-4).

i. Overall enantioselectivity calculated by weighted average.

j. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.71 (s), 5.42 (br s), 5.90–5.98 (m), 6.22–6.31 (m), 6.90 (d, *J* 15.8), 9.49 (s).

k. An additional fraction that was more polar than *cis* sulfolane **231a** was isolated. It has been tentatively assigned as hydride elimination product **232**, and its spectral characteristics are listed below.

l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.48 (s), 9.49 (s). Additional signals may be present in the region of 1.0–4.6 ppm but are not distinguished due to peak overlap.

m. Only one peak was detected during HPLC analysis of this compound.

n. % ee not determined.

o. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.71 (s), 5.42 (s). Additional signals may be present in the region of 1.0–4.6 ppm but are not distinguished due to peak overlap.

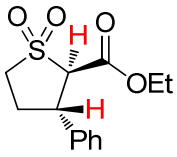
p. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.21–5.32 (m), 5.47–5.54 (m), 5.59–5.66 (m), 6.10 (s), 6.14 (s), 9.50 (s). Additional signals may be present in the region of 1.0–4.6 ppm but are not distinguished due to peak overlap.

q. Purified fraction contains an impurity with the following signals present in the ^{1}H NMR; δ_H 2.76–2.85 (m), 4.52 (s). HPLC trace is not clean.

With knowledge of the outcome of the C–H insertion reactions of α-diazoacetamides **48** and **49** in hand, attention was next turned to the reactions of 2-diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52**, which contained a 3-phenylpropyl chain, making insertion to form a *cis* thiopyran product impossible. As the synthesis of a *cis* thiopyran product could not occur, generation of a racemic sample was carried out in this instance using rhodium acetate. The outcome of this reaction is shown in **Table 6.11**, entry 6. As was the case with substrate **48**, insertion did not occur into the morpholine side chain, but rather into the sulfonyl chain. A moderate reaction efficiency was obtained (50–60%) for this cyclisation. C–H insertion proceeded to give the sulfolane as a mixture of *cis* and *trans* isomers (*cis* : *trans* 60 : 40) (**Table 6.11**, entry 6). The observation of both isomers in the ^{1}H NMR spectra is unusual for the sulfolane compounds and was rarely encountered in the cyclisations of the ester **39** and the ketone **41** analogues (Chapter 4, **Section 4.3.4**). However, identification of both *cis* and *trans* isomers for the fused sulfolanes in the ^{1}H NMR spectra of the crude mixture was not uncommon (Chapter 5). Purification of these compounds was carried out using column chromatography on silica gel. The recovered yield was quite poor, with only 14% obtained for *trans* **231b**, with *cis* **231a** not being isolated after purification. Initially it was thought that epimerisation of the *cis* isomer to the *trans* isomer was occurring on silica gel, as had been previously observed for the fused sulfolanes. However, when subsequent cyclisations were carried out, the *cis* isomer **231a** was isolated, as the more polar insertion product after purification using column chromatography. Therefore, in this instance failure to isolate the *cis* isomer is believed to be due to using an insufficiently polar eluent, rather than epimerisation of the compound.

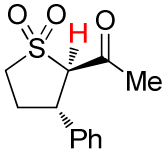
In some of the copper mediated C–H insertion processes with α-diazoacetamide **52**, pure samples of the *cis* and *trans* sulfolanes **231a** and **231b** were recovered, and while their stability was not exhaustively studied, we did not see any evidence for epimerisation of these compounds during the course of this investigation.

The structure and relative stereochemistry of the *cis* and *trans* sulfolanes **40b, 42b** and **231b** and **231a** were assigned based on ^{1}H NMR, including NOESY, with characteristics observed resembling those seen for the ester **40b** and ketone series **42b** (**Figure 6.27**).



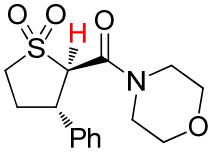
40b

δ_H ($CDCl_3$, 300 MHz)
4.89-4.08 [2H, m, C(2)*H* and C(3)*H*]



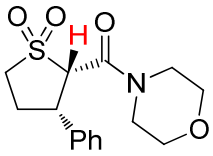
42b

δ_H ($CDCl_3$, 300 MHz)
4.17 [1H, d, *J* 9.8, C(2)*H*]



231b

δ_H ($CDCl_3$, 600 MHz)
4.12 [1H, d, *J* 9.6, C(2)*H*]

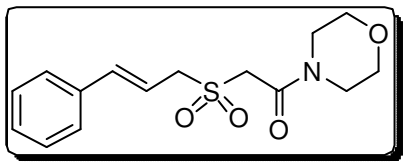


231a

δ_H ($CDCl_3$, 600 MHz)
4.28 [1H, d, *J* 6.9, C(2)*H*]

Figure 6.27

Subsequently asymmetric copper catalysed reactions were carried out on 2-diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52** using five commercially available bisoxazoline ligands (4*S*)-*t*-Bu **138**, (4*R*)-Bn **43**, (3*S*, 8*R*)-Ind **44**, (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** As has been the case with the cyclisations of all α-diazo-β-amido sulfones so far, pre-formation of the catalyst was carried out for ~2 h at reflux, prior to slow addition of the α-diazo-β-amido sulfone **52** in dichloromethane to the catalyst mixture. The results of this study are summarised in **Table 6.11**, entries 1-5. Moderate to good reaction efficiencies were obtained in all cases (60–70%) (**Table 6.11**, entries 1–5), slightly higher than those seen for the rhodium acetate catalysed reaction (50–60%) (**Table 6.11**, entry 6). Additional byproducts were formed during these reactions which remained largely unidentified, with the exception of hydride transfer product **232** (**Figure 6.28**), which was present in minor amounts in the crude reaction mixtures employing ligands (3*S*,8*R*)-Ind **44** and (4*S*)-*t*-Bu **138** (**Table 6.11**, entries 1 and 3), and was obtained in low quantities as the most polar fraction from cyclisation employing (3*S*,8*R*)-Ind **44**. Due to limited amounts of sample only a ^{1}H NMR analysis was obtained. However, the allylic sulfone signals are very characteristic enabling structure assignment.



232

Figure 6.28

While intramolecular C–H insertion proceeded to yield sulfolane products only, a result consistent with that seen for the rhodium acetate catalysed reaction, the ratio of *cis* : *trans* isomers in the crude reaction mixture varied greatly depending on the nature of the ligand involved. For both (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** ligands, the *cis* isomer was the major reaction product. For (4*R*)-Ph **20**, *cis* : *trans* sulfolane was formed in a ratio of 70 : 30, while for (4*R*,5*S*)-di-Ph **137** the ratio was 60:40 (**Table 6.11**, entries 4 and 5). The product ratios that were seen in the ^{1}H NMR spectra of the crude products were consistent with the relative amounts of material obtained after purification using column chromatography (18% *cis*, 6% *trans*) for use of the (4*R*)-Ph **20** ligand and (15% *cis*, 8% *trans*), with the *cis* isomer dominating in both cases. This suggests that epimerisation of the *cis* isomer to the *trans* isomer is not occurring on silica gel, in contrast to the fused systems seen in Chapter 5. For the three remaining ligands, (3*S*,8*R*)-Ind **44**, (4*S*)-*t*-Bu **138** and (4*R*)-Bn **43**, the *trans* isomer predominated, accounting for 80% of the insertion products for (4*S*)-*t*-Bu **138** and (4*R*)-Bn **43**, while constituting 70% of the insertion products for (3*S*,8*R*)-Ind **44** (**Table 6.11**, entries 1–3). In all cases the *cis* isomer **231a** made up the remaining insertion products. Once again, the isolated yields of the products obtained after purification reflected those seen in the crude reaction mixture. Enantiopurities were measured for the *trans* isomers, for (3*S*,8*R*)-Ind **44**, (4S)-*t*-Bu **138** and (4*R*)-Bn **43** ligands, with the highest enantioselectivity observed for the *t*-Bu **138** ligand (77% ee) (**Table 6.11**, entry 1). This is the highest enantioselectivity achieved to date for the synthesis of a *trans* sulfolane (not fused) using transition metal catalysed C–H insertion reactions. For the two remaining ligands (4*R*)-Bn **43** and (3*S*,8*R*)-Ind **44**, much lower enantioselectivities were achieved with 42% ee and 47% ee obtained respectively (**Table 6.11**, entries 2 and 3). Enantiopurities of the *trans* isomers isolated from reactions catalysed by (4*R*)-Ph **20** and (4*R*,5S)-di-Ph **137** ligands were not determined, mainly due to the small amounts of material recovered. Attempts were made to measure the enantiopurity of the *cis* isomers resulting from these two reactions. In both

cases only one peak was observed in the HPLC trace. However, in the absence of a racemic sample of the *cis* isomer, accurate enantiopurities for this compound cannot be reported (**Table 6.11**, entries 4 and 5).

Comparison of the enantioselectivities obtained for ethyl ester **40b**, methyl ketone **42b** and morpholine amide **231a** and **231b** for all five commercial ligands are presented in **Figure 6.29**. Interestingly each substrate behaves independently of one another, and no clear trend can be seen for correlating a relationship between a ligand and sulfolane enantioselectivity.

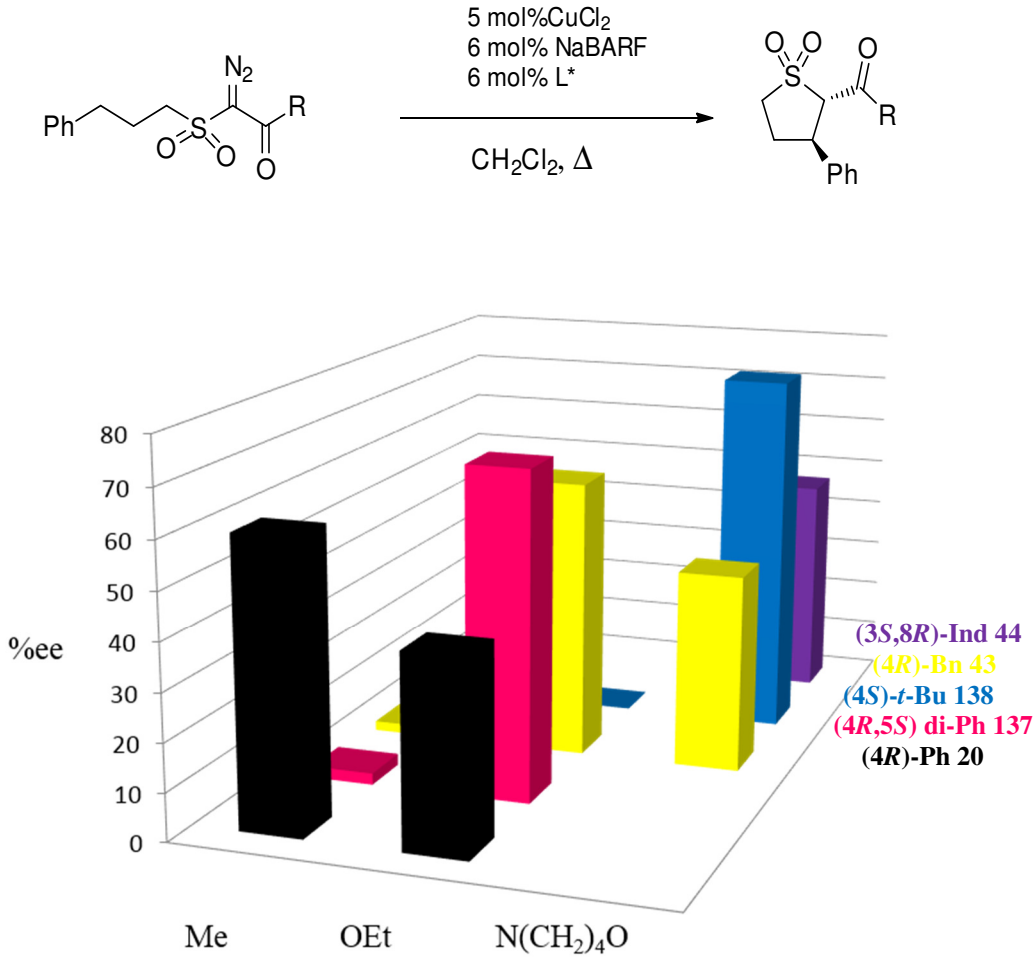
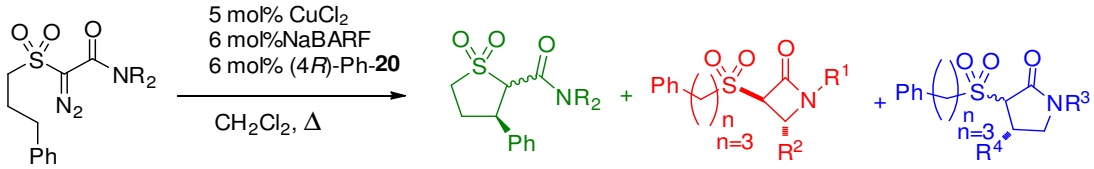


Figure 6.29 *Comparison of enantioselectivities achieved for copper catalysed C–H insertion reactions for substrates* **40b**, **42b** *and* **231b**.

Interpretation of the ligand trends for sulfolane formation from the morpholine derivative **231** is complicated by the fact that both *cis* and *trans* sulfolanes are formed, with significant differences in the isomer ratio depending on the ligand employed. As the mechanistic pathways for enantioselective C–H insertion to give *cis* and *trans* sulfolanes are different, this must be taken into consideration. In contrast, for the ethyl ester derivative, the *cis* isomer was only seen in one case when (4*R*,5*S*)-di-Ph **137** was used and this epimerised to *trans* on purification.

In summary, for the propylsulfonyl substrates **52**, **53**, **50** and **51** it is the nature of the amide and not the sulfone, that appears to dictate the regioselectivity of the reactions (**Figure 6.30**). This is in line with observations for the butyl sulfones (**Figure 6.26**). The presence of a *N*,*N*-dipropyl amide results in the formation of ɣ-lactam exclusively, while morpholine amide **52** gives rise to sulfolane products solely. In the case of *N*,*N*-dibenzyl amide **52**, no sulfolane is observed in the crude reaction mixture with β-lactam being the only observable product. *N*,*N*-diethyl amide results in the lowest regioselectivity with all three pathways being observed, however, ɣ-lactam is the major product formed.



231 R=(CH_2CH_2)O **226b** R^1=CH_2Ph, R^2=Ph **210a** R^3=$CH_2CH_2CH_3$, R^4=CH_3

218b R= CH_2CH_3 **217b** R^1=CH_2CH_3, R^2=CH_3 **216** R^3=CH_2CH_3, R^4=H

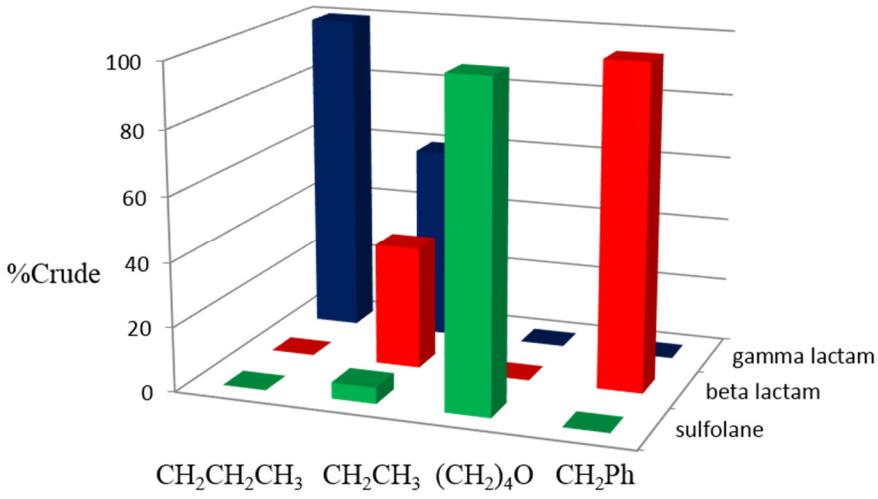
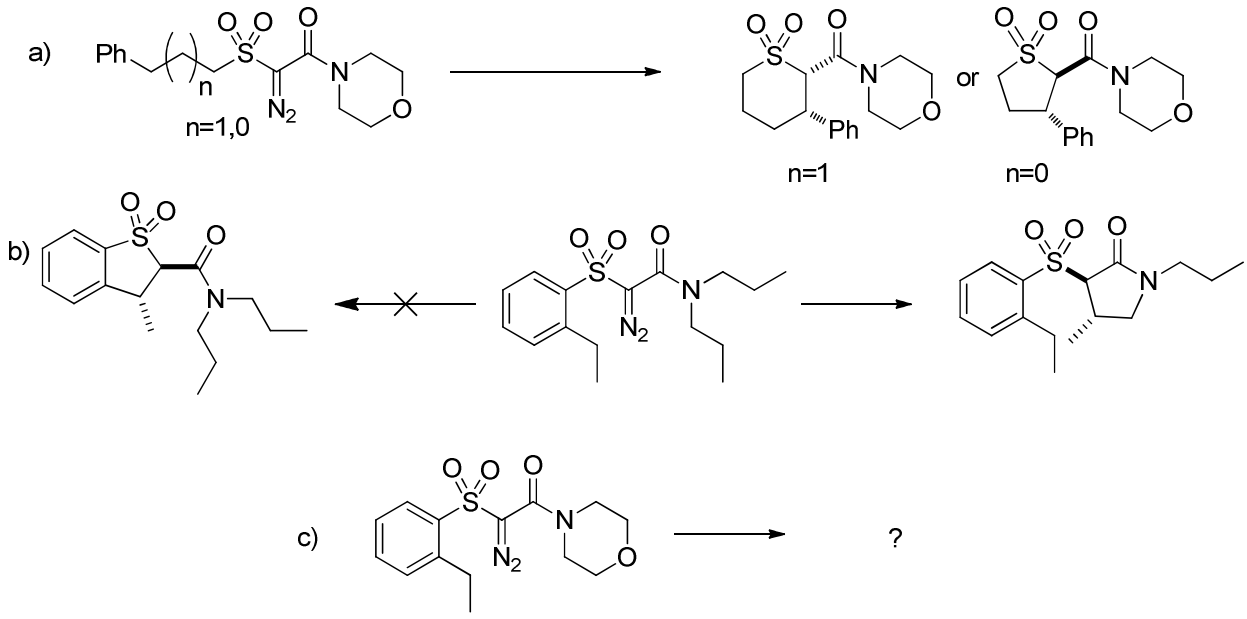


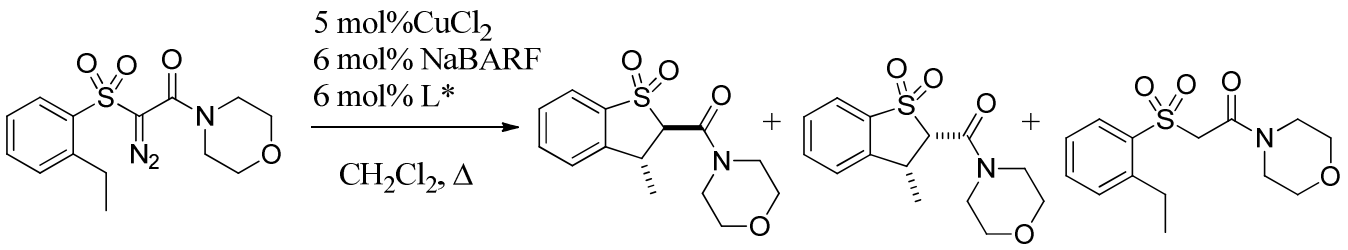
Figure 6.30 *Relative amounts of C–H insertion products formed for substrates* ***52****,* ***53****,* ***50*** *and* ***51****.*

Thus far in the study, it has been established that employing a morpholine amide functionality with a freely rotating sulfonyl chain results in insertion to yield sulfone containing rings, with no evidence for lactam products [**Scheme 6.34** (a)]. In contrast, investigation into the 2′-ethylphenylsulfonyl group resulted in complete ɣ-lactam formation, when using an *N*,*N*-dipropyl group, as shown in [**Scheme 6.34** (b)]. To further explore comparative reaction pathways, copper mediated C–H insertion of α-diazoacetamide (morpholine) **58** was explored [**Scheme 6.34** (c)], with the expectation on switching from *N*,*N*-dipropyl to morpholine that the insertion will switch from lactam formation to sulfolane formation. The results of this study are presented in **Table 6.12**.



Scheme 6.34

Table 6.12 *Rhodium acetate and asymmetric copper catalysed* C–*H insertion reactions of α-diazo-β-oxo sulfone* **58**



58 **233b** **233a** **117**

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency of C–H insertion (%)[a]	Sulfone 117 (%Crude)[b]	Yield (%)		Products ratios *trans* **233b**	*cis* **233a**	(S) **117**
1	**E**	$Rh_2(OAc)_4/\Delta$	-	21	>90%	-		**Crude ratio**	96	4	-
							46%	**Purified ratio**	99 (0% ee)	1	
2	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	24	50–60%[c]	10–15%		**Crude ratio**	44	44	12
								Purified ratio			
							Fr1 5%	**Fr1**	80 (10 % ee)[d,e]	10 (60% ee)[f]	10
							Fr2 8%	**Fr2**	66 (14% ee)[d,e]	12 (67% ee)[f]	22
							Total		**9.28%**	**1.46%**	**2.26%**

3	**B**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	21	50–60%[g]	10–15%		**Crude ratio**	36	52	12
								Purified ratio[i]		-	-
							Fr1 4%[h]		only (44% ee)[j]	-	-
							Fr2 3%		only (36% ee)[j]		
							Fr3 4%		62 (30% ee)[j,k]		38
							Total		**9.48%**		**1.52%**
4	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	6	50-55%[l]	~8%		**Crude ratio**	20	68	12
								Purified ratio[n]		-	-
							Fr1 1%[m]		only (90% ee)[j,o]	-	-
							Fr2 3%		only (70% ee)[j]		
							Fr3 2%		only (60% ee)[j]	-	-
							Total		**6%**		
5	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	21	50–60%[p]	~5%		**Crude ratio**	68	30	2
								Purified ratio			
							Fr1 4%[q]		78 (43% ee)[e,r]	$22^{s,t}$	-
							Fr2 6%[q]		73 (37% ee)[e,r]	$27^{s,t}$	-
							Fr3 4%[q]		74 (32% ee)[e,r]	$22^{s,t}$	2
							Total		**10.46%**	**3.38%**	**0.08%**
6	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	30	50–60	~5%		**Crude ratio**	74	22	4
								Purified ratio			-

							Fr1 2%[q]		77 (86% ee)[j,u]	23 (70% ee)[f]	-
							Fr2 4%[q]		81 (79% ee)[j,u]	19 (70% ee)[f]	-
							Fr3 3%[q]		82 (78% ee)[j,u]	8 (70% ee)[f]	10
							Total		**7.24%**	**1.76%**	
7	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	24	50–60	~1%		**Crude ratio**	72	27	1
								Purified ratio		-	-
							Fr1 5%		Only (37% ee)[e]	-	-
							Fr2 7%[v]		Only (33% ee)[e]		
							Total		**13%**		
8	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	48	50–60[w]	~1%		**Crude ratio**	80	19	1
								Purified ratio			
							Fr1 9%		only(60% ee)[j,x]		
							Fr2 6%		98 (50% ee)[j]	2[y]	
							Total		**14.88%**	**0.12%**	

a. Efficiency and relative ratios calculated using ^{1}H NMR using the following signals: δ_H 4.67 [1H, d, *J* 6.0, C(2)*H*] for *cis* sulfolane **233a**; δ_H 4.24 [1H, d, *J* 6.5, C(2)H] for *trans* sulfolane **233b**.

b. Amounts of sulfone **117** in both crude and purified samples are calculated using ^{1}H NMR using the following signals: δ_H 4.27 (2H, s, SO_2CH_2CO). Additional signals were observed for sulfone **117**; δ_H 1.35 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.10 (2H, q, *J* 7.5, $ArCH_2CH_3$).

c. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 5.60 (s), 7.00–7.17 (m), 9.40 (s).

d. Enantioselectivity estimated, unresolved peaks in HPLC analysis.

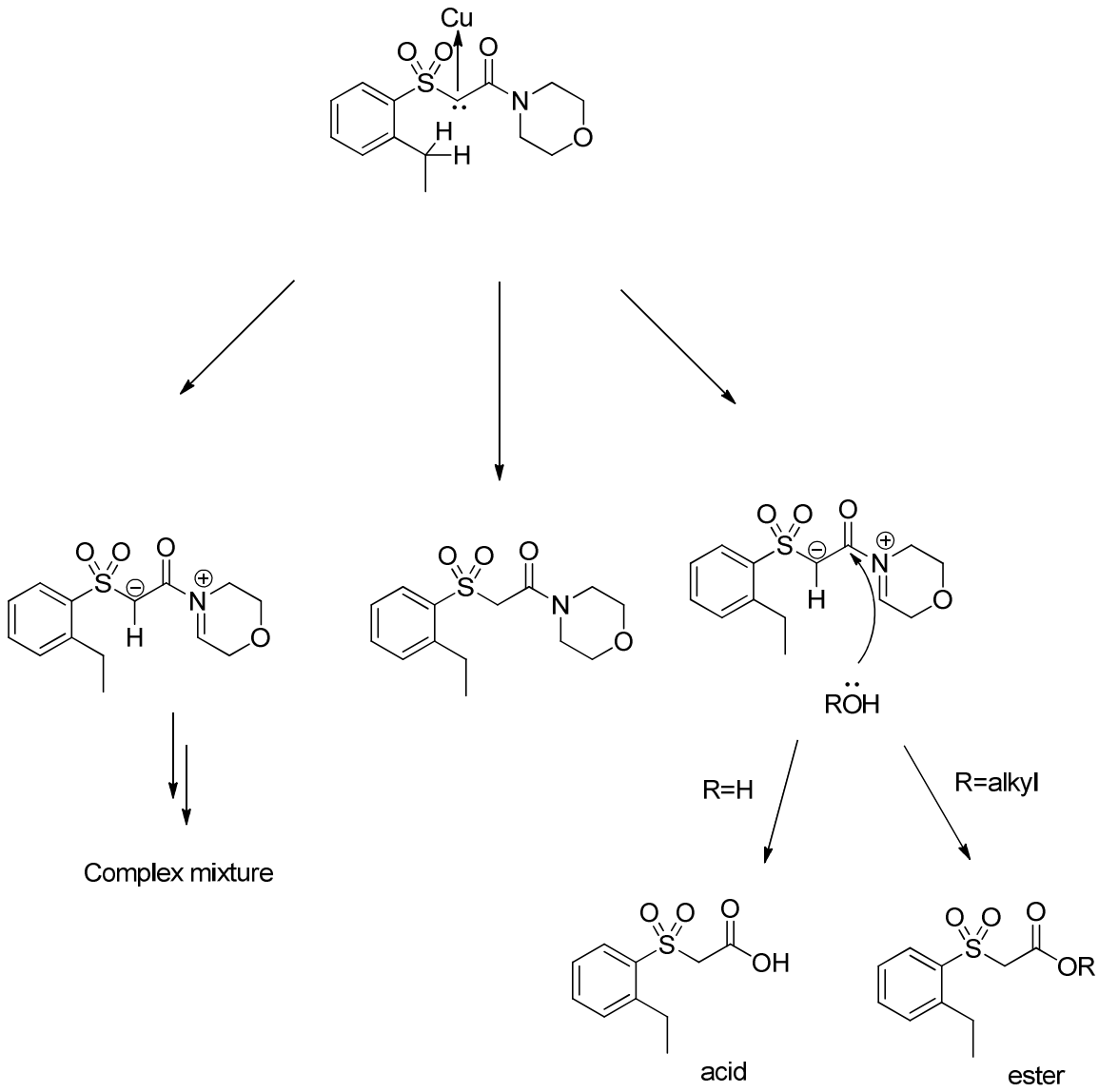
e. The first eluting enantiomer of the *trans* isomer **233b** at ~39 min is the major enantiomer, using 30% IPA/hexane (Cell-4).

f. The second eluting enantiomer of the *cis* isomer **233a** at ~62 min is the major enantiomer, using 30% IPA/hexane (Cell-4), values are estimated in all cases due to peak overlap.
g. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 5.59 (s).
h. Impure fraction. Additional peaks present in the ^{1}H NMR spectra of the purified product; δ_H 3.88–3.95 (m). Additional peaks were observed in aromatic region 7.30–8.0 ppm.
i. Compound was purified twice. The first purification used column chromatography on silica gel using gradient ethyl acetate-hexane (5:95–10:90–20:80–50:50–80:20) as eluent. The second purification used column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluent. The eluent contained 2% formic acid. Results in table are reported after a second purification.
j. The second eluting enantiomer of the *trans* isomer **233b** at ~45 min is the major enantiomer, using 30% IPA/hexane. (Cell-4)
k. Additional peak observed in HPLC trace for this fraction, tentatively assigned to sulfone **117.**
l. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 5.60 (s), 9.41 (s).
m. Impure fraction. Additional peaks present in the ^{1}H NMR spectra of the purified product; δ_H 3.77–3.99 (m), 4.59–4.70 (m), 5.17 (s). Additional peaks were observed in aromatic region 7.30–8.0 ppm.
n. Compound was purified four times. The first three purifications used column chromatography on silica gel using gradient ethyl acetate-hexane (5:95–10:90–20:80–50:50–80:20) as eluent, none of which were completely successful. The last purification used column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluent. The eluent contained 2% formic acid. Results in table are reported after the last purification.
o. Additional peaks present in HPLC.
p. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 6.11–6.24 (m), 6.44–6.52 (m).
q. Contains dioctyl phthalate (placticiser), detected by ^{1}H NMR.
r. Estimation due to peak overlap in HPLC analysis. Measurement of enantioselectivity was not perfect due to overlap with impurities; 43% ee is the most accurate value.
s. The first eluting enantiomer of the *cis* isomer **233a** at ~43 min is the major enantiomer, using 30% IPA/hexane. (Cell-4)-values are estimated in all cases due to peak overlap.
t. Could not be estimated due to peak overlap.
u. Estimation due to peak overlap in HPLC analysis.
v. Fraction contains ~15% additional compound that contains the following peaks in the ^{1}H NMR spectra of the purified product; δ_H 4.20–4.25 (m overlapping), 4.30 (d, *J* 5.4).
w. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 4.91 (s), 5.59 (s), 6.54–6.61 (m).
x. Contains ~5% additional compound that contains the following peaks in the ^{1}H NMR spectra of the purified product; δ_H 4.20–4.25 (m overlapping), 4.30 (d, *J* 5.4).
y. % ee of *cis* **233a** was not determined as peaks for this compound were not observed in the HPLC trace.

Note; In HPLC analysis additional peaks were observed which have been tentatively assigned to the *cis* isomer; peak at 43 min and 62 min. Reduction product seen at 48 min.

Note; All crude reaction mixtures were purified using column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluent. The eluent contained 2% formic acid, with the exception of reactions in Table 6.12, entries 1 and 2.

As summarised in **Table 6.12**, cyclisation of α-diazoacetamide **58** was undertaken with rhodium acetate and a series of copper catalysts with a range of bisoxazoline ligands. The reaction was cleanest with rhodium acetate, producing almost exclusively the novel sulfolane insertion products **233a** and **233b**, with a proton NMR spectrum of the crude product essentially consisting of just the signals for *cis* (**233a**) and *trans* (**233b**) sulfolanes (**Table 6.12**, entry 1). In contrast, the spectra of the crude products of each of the copper mediated insertions were much more complex, with signals clearly visible for both the *cis* and *trans* sulfolanes **233a** and **233b** as the most significant identifiable products, accounting 50–60% of the total reaction mixture (**Table 6.12**, entries 2-8). One further product identified in the crude product mixtures of the copper catalysed insertions was the sulfone reduction product **117**, identified through the characteristic CH_2 signal at 4.27 ppm (2H, s, $SO_2C\mathit{H}_2CO$). Apart from this, no other identifiable component was evident in the crude spectra or recovered following chromatography, indicating a diverse mix of byproducts. The observation of the sulfone product, presumably formed by reduction, was of particular interest. Considerable effort was invested in examination of the NMR spectra of fractions following chromatography to confirm the presence of the reduced sulfone amide **117**. Of course the CH_2 signal at 4.27 ppm could potentially indicate the presence of the sulfone acid or the sulfone ester rather than the sulfone amide: formation of either the acid or the ester could potentially indicate hydride transfer from the CH adjacent to the nitrogen to the carbene carbon, followed by hydrolysis as seen in the cyclisations of α-diazoacetamide **53** (di-benzyl) (**Scheme 6.18)**, and indeed this pathway may account for the complex unidentified mixture. However, we are confident that the reduced sulfone amide **117** is present at low levels in the reaction mixtures, which may be rationalised by intermolecular hydride transfer as illustrated below (**Scheme 6.35**). The results summarised in **Table 6.12** suggest that the extent of formation of the sulfone reduction product correlates to an extent with the proportion of *cis* sulfolane **233a** in the crude product mixture (**Table 6.12**, entries 2–4).



Scheme 6.35

Overall, as evidenced in **Table 6.12**, the principal reaction pathway, in both the rhodium and the copper mediated reactions of the α-diazoacetamide **58**, is insertion to form the sulfolane, as anticipated. With rhodium this is essentially the only transformation (**Table 6.12**, entry 1), while with copper there is some evidence for competing hydride transfer from the amide, in line with earlier observations (**Table 6.12**, entries 2-8). As anticipated, sulfolane formation through insertion at the benzylic C–H dominates, with no evidence for the formation of the thiopyran through competing C–H insertion at the primary C–H bond. Recovered yields were very low, principally due to challenging repeated chromatography in an attempt to recover pure compounds.

Both *cis* and *trans* sulfolanes **233a** and **233b** were clearly seen in both the ^{1}H NMR spectra of the crude and purified products, with different ratios depending on the nature of the bisoxazoline ligand on the copper catalyst with ligands (4*R*,5*S*)-di-Ph **137** and (4*R*)-Ph **20** (**Table 6.12**, entries 3–4) resulting in predominately *cis* **233a**, while ligands (4*R*)-Bn **43** and (4*S*)-*t*-Bu **138** (**Table 6.12**, entries 5–8) lead to predominately *trans* **233b** in the crude product mixtures, (3*S*,8*R*)-Ind ligand **44** gives equal amounts of both isomers (**Table 6.12**, entry 2). Following chromatography, there is evidence for partial epimerisation to the *trans* sulfolane, although this does not go to completion and alteration of the product ratio through fractionation cannot be definitively ruled out. Interestingly, earlier work with ester **54** showed that the *cis* isomer **165a** was the kinetic product, in general, and epimerised to the *trans* **165b** on chromatography, while in the ketone series for the methyl ketone **55**, the *trans* sulfolane **166b** is recovered, which is believed to indicate rapid epimerisation in the reaction mixture. In the case of phenyl ketone **56**, both *cis* **167a** and *trans* **167b** sulfolanes were evident. Thus, the amide series appears to be behaving somewhat differently in this regard, with two possible explanations: either the *cis* sulfolane **233a** is the kinetic product with partial epimerisation to the *trans* **233b**, or two parallel pathways are active; one leading to *cis* and the other leading to *trans*. The observation of different % ee values in some samples of *cis* and *trans* isomers points to the latter explanation, although further work would be required to definitively establish this.

The enantiopurity of the *trans* sulfolanes were determined by chiral HPLC, and in a few instances it was possible to determine the enantiopurity of the minor *cis* sulfolanes. The highest % ee was achieved with (4*S*)-*t*-Bu **138** and (4*R*)-Ph **20** ligands (Table 6.12, entries 4, 6 and 8), although direct interpretation of the trends is somewhat complicated by enantiomeric disproportionation during chromatography and *cis*/*trans* epimerisation, which may substantially alter kinetic enantiomer ratios as the *cis* and *trans* could be opposite at the site of insertion. By far the most interesting observation in this series is that the direction of enantioselection does not correlate cleanly with the enantiomeric series of the ligand employed. In the majority of other studies, one enantiomeric series of the insertion products is achieved when using the *R* ligands; (4*R*,5*S*)-di-Ph **137**, (4*R*)-Ph **20** and (4*R*)-Bn **43**, with the opposite enantiomeric series seen with *S* ligands; (4*S*)-*t*-Bu **138** and with (3*S*,8*R*)-Ind **44**. However, for the morpholine amide, the same enantiomeric series of the sulfolane product was obtained using ligands (4*R*,5*S*)-di-Ph **137**, (4*R*)-Ph **20**,

(4*S*)-*t*-Bu **138** and (3*S*,8*R*)-Ind **44** and the opposite series for reaction with (4*R*)-Bn **43**. Thus, it appears that in this specific transformation the (4*R*,5*S*)-di-Ph **137** and (4*R*)-Ph **20** ligands give the "wrong" enantiomeric series. This can be rationalised by specific ligand-substrate interactions in the transition state for the C–H insertion process. A number of specific interactions can be envisaged; firstly it is possible that there is a specific substrate ligand interaction occurring with the aromatic ring of the α-diazoacetamide **58** and the aromatic rings of the (4*R*,5*S*)-di-Ph **137** and (4*R*)-Ph **20** ligands. If this were the case, reactions catalysed by these ligands would potentially go through a transition state from the more hindered face, the same direction effected by (4*S*)-*t*-Bu **138** and (3*S*,8*R*)-Ind **44**. The reaction catalysed by the (4*R*)-Bn **43** ligand would thus proceed in the "correct direction", thus leading to the observed enantiomer forming. Another possibility is that the morpholine oxygen may co-ordinate to the copper, leading to an altered catalyst geometry and therefore different transition states, thus leading to more complex reaction pathways, which may account for a more complicated pattern of results.

Detailed interpretation of this behaviour will require exploration of the enantiomer ratio of both the *cis* and *trans* sulfolanes in the crude product mixtures and following chromatography to ensure the final enantiopurities genuinely reflect the enantiocontrol in individual insertion steps to form the *cis* or *trans* sulfolane, rather than a composite enantiopurity through epimerisation of *cis* and *trans* sulfolanes, with different enantiomer ratios and enantiomer direction of enantioselection. In addition, it is possible that the sense and extent of enantioselectivity in the insertion steps to yield the *cis* and *trans* isomers of the sulfolane differ which, in addition to epimerisation, leads to a very complex final picture.

At this stage in our research the absolute stereochemistry is unknown and given the unusual pattern of direction of enantioselection with ligand variation, it is not possible to draw a direct analogy with the ester and ketone series.

As anticipated at the outset, altering the amide from the *N*,*N*-dipropyl derivative to the morpholine amide resulted in a dramatic shift in the regiochemistry of the C–H insertion process, with morpholine derivatives leading to the sulfolane as the only isolated insertion product. Only ɣ-lactam formation was seen in reactions with dipropyl amide. The impact of conformational properties on reaction outcome is in line with observations by Doyle

and others. The absence of any lactam formation with the morpholine amide is interesting in the context of evidence for fused lactam formation in related systems (**Figure 6.31**)

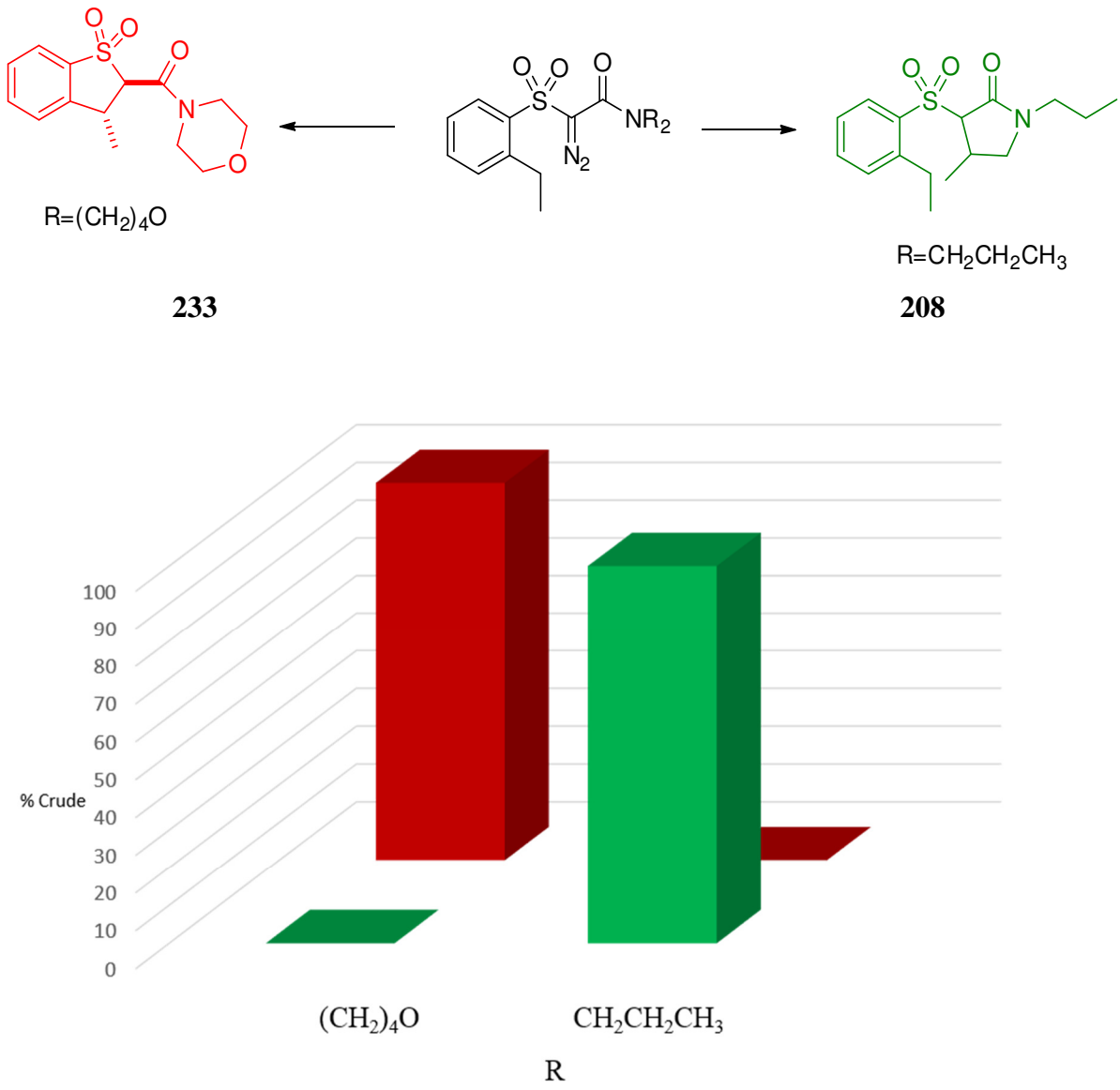


Figure 6.31

6.4 Conclusions

The work in this chapter describes an investigation into the asymmetric copper catalysed intramolecular C–H insertion reactions of ten novel α-diazo-β-oxo sulfone substrates. Each one of the α-diazo-β-oxo sulfone substrates was constructed in such a way that it allowed insertion to proceed to yield either lactams and/or sulfolanes/thiopyrans. One of the most interesting outcomes of this study was the effect that the amide functionality had on the regioselectivity of the reaction; use of an *N*,*N*-dipropyl amide led to exclusively ɣ-lactam products, the only intramolecular insertion pathway observed for the *N*,*N*-dibenzyl substrate was β-lactam formation and the use of the morpholine derivates resulted in only sulfolanes/thiopyrans being synthesised. However, while ɣ-lactam formation was favoured for the *N*,*N*-diethyl amide substrates, additional isomers did result, which was generally not the case for the other substrates. Presumably, a combination of electronic and steric effects may account for this.

In terms of enantioselectivities, 82% ee was the highest value achieved for ɣ-lactam synthesis; the highest reported value for ɣ-lactam formation using chiral copper catalysts to date. For comparative purposes, a study was conducted using chiral rhodium catalysts, which have been reported to give rise to enantioselectivities of up to 99% ee in related systems. However, in this project, products with much lower enantiopurities were obtained using these catalysts. Two of the ɣ-lactams in this chapter were formed *via* insertion into a tertiary C–H, leading to products that contained one chiral centre with an enolisable hydrogen. Despite this, it was still possible to measure the enantiopurities of these products, suggesting that if epimerisation is taking place it is a slow process.

In terms of β-lactam formation, values of up to 84% ee were attained, up to 98% ee for *cis* thiopyrans and up to 77% ee for *trans* sulfolanes. Interestingly, the values achieved for *cis* thiopyran synthesis are consistent with those reported for the ester and ketone series. However, for the *trans* sulfolane systems, a definite trend has not been established thus far, with not only differences in regioselectivities being observed across the series but also substantial differences seen for the enantiopurities of *trans* sulfolanes arising from reactions using different ligands.

Some unexpected results were achieved for synthesis of the morpholine fused sulfolane substrates; the direction of enantioselectivity did not appear to be dictated by the ligand. This was the first time in the project that we encountered a result of this nature. A similar

situation was seen for *trans* sulfolane synthesis in chapter seven. Presumably a specific substrate ligand interaction is at play, however, further work needs to be carried out to fully understand this process.

While this work was underway, Ring[51] in our research team was investigating rhodium and copper catalysed reactions of α-diazoacetamides **212, 234–236** (**Figure 6.34**) related to the compounds studied in this chapter, but with the key difference that the sulfonyl groups employed, phenyl and methyl sulfones, do not offer the possibility of C–H insertion into the sulfonyl substituent (**Figure 6.32**).

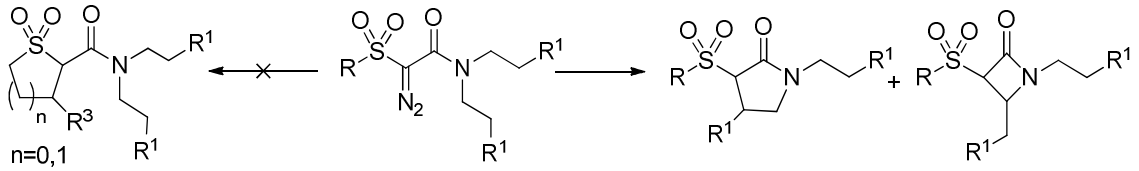


Figure 6.32

While ɣ-lactam formation is a significant reaction pathway seen with these compounds, there is evidence for competing hydride transfer, especially with the *N*,*N*-dibenzyl derivative, in line with the results seen in this study. Furthermore, C–H insertion to form β-lactams has been seen with the *N*,*N*-diethyl amide, especially with copper catalysts. Interestingly, the details of selectivity patterns, in terms of regioselectivity and enantioselectivity, while similar to the sulfones in this study, differ in certain aspects. This highlights the impact of variation of steric and electronic properties on reactions of α-sulfonyl carbenes. Furthermore, replacement of the sulfone by an alternative electron withdrawing group such as ester, ketone or phosphonate, result in subtle changes in the reaction pathways, as the behaviour of the carbene is modified by the nature of the substituent (**See Section 6.1**). Interestingly, when a mesityl sulfone is employed, insertion into the aryl methyl groups competes with lactam formation, reminiscent of the results seen for α-diazoacetamide **58** (**Figure 6.33**).

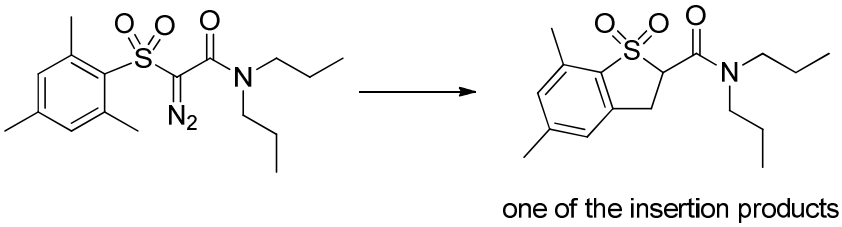


Figure 6.33

Comparing the regioselectivity observed in this project with that seen in Ring's work,[51] similar product distributions are observed for the *N*,*N*-dipropyl amide, however, the regioselectivity is essentially reversed for *N*,*N*-diethyl amide, with Ring obtaining mostly β-lactam for the copper catalysed reactions while ɣ-lactam predominates in this work. Ring did not observe insertion products for the *N*,*N*-di-benzyl amide and *N*-morpholine amide, which is in also contrast to the results seen in this work (**Figure 6.34**).

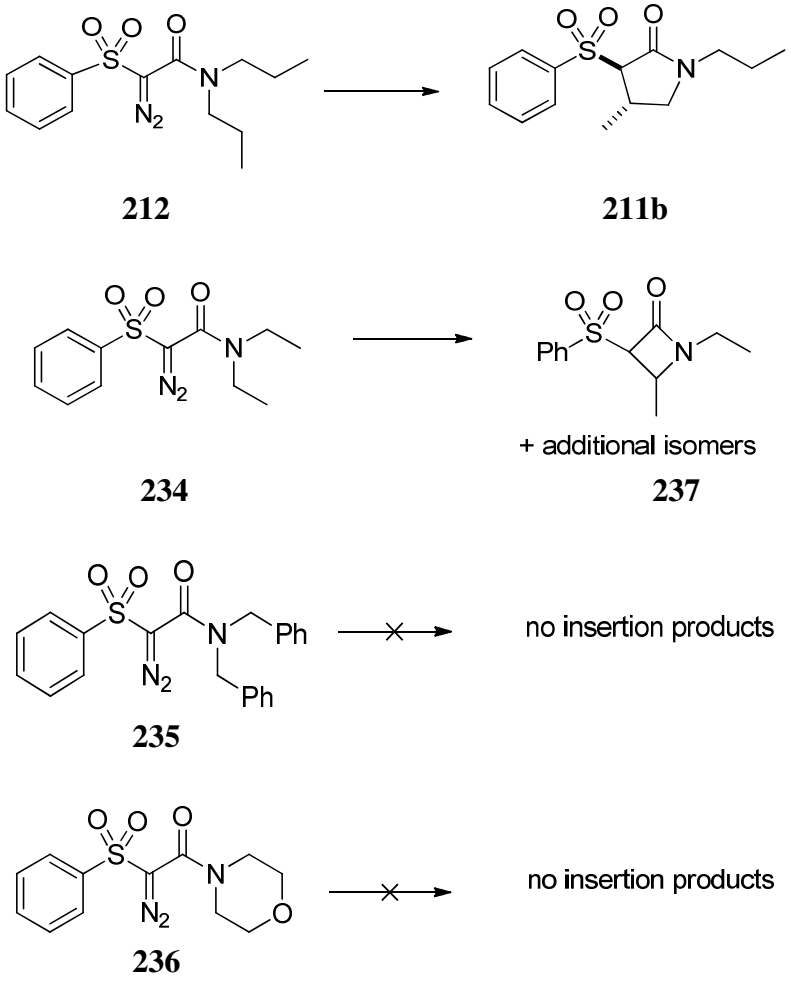
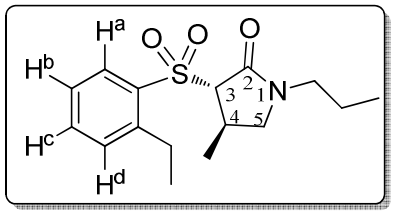


Figure 6.34[51]

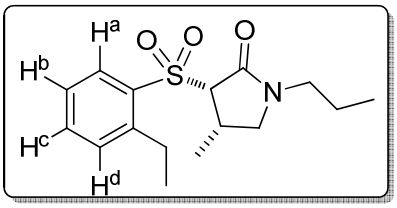
6.5 Experimental

(3*S*,4*R*) 3-[(2-Ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one 208b



$CuCl_2$ (2.0 mg, 14.8 μmol), (+)-2,2′-isopropylidenebis[(4*R*)-4-benzyl-2-oxazoline] **43** (6.4 mg, 17.8 μmol) and sodium tetrakis[3, 5-bis(trifluoromethyl)phenyl]borate (NaBARF) (15.8 mg, 17.8 μmol) were suspended/dissolved in doubly distilled dichloromethane (30 mL), heated while stirring under reflux for 2 h under an atmosphere of nitrogen, in accordance with Method **B**. A solution of 2-diazo-2-[(2-ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide **57** (100 mg**,** 0.29 mmol), in distilled dichloromethane (20 mL) was added dropwise to this over 15 min. The mixture was then stirred under reflux for 6 h and was subsequently cooled and concentrated under reduced pressure. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 80–90% efficient (12% *cis* **208a**: 88% *trans* **208b**). Following purification, by column chromatography on silica gel using gradient ethyl acetate-hexane (10:90–20:80–40:60) as eluent, 3-[(2-ethylphenyl)sulfony]-4-methyl-1-propylpyrrolidin-2-one (2% *cis* **208a**, 98% *trans* **208b**) [62.3 mg, 69%, 52% ee (*trans* **208b**) by chiral HPLC] was isolated as a colourless oil. Due to the presence of additional peaks [δ_H 4.21–4.32 (m)] in the ^{1}H NMR spectra of the purified product, a second purification was carried out using column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80–40:60) as eluent, (3*S*,4*R*) 3-[(2-ethylphenyl)sulfony]-4-methyl-1-propylpyrrolidin-2-one **208b** (100% *trans*) (52.9 mg, 59% overall, 52% ee by chiral HPLC) was isolated as a colourless oil; The following spectral characteristics are reported for *trans* **208b**; $[\alpha]_D^{20}$ −9.20 (*c* 0.103, CH_2Cl_2); ν_{max}/cm^{-1} (film): 2967, 2935, 2876 (CH), 1699 (CO), 1439, 1308, 1151, 1133 (SO_2); δ_H ($CDCl_3$, 600 MHz): 0.89 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.29 [3H, d, *J* 7.1, CH_3-C(4)], 1.33 (3H, t, *J* 7.5, $ArCH_2CH_3$), 1.47–1.60 (2H, m, $NCH_2CH_2CH_3$), 2.91 [1H, dd, *J* 9.6, 3.2, one of C(5)H_2], 2.94–3.31 (2H, m $ArCH_2CH_3$), 3.14–3.23 [2H, m, C(4)*H* and one of $NCH_2CH_2CH_3$], 3.24–3.33 (1H, m, one of $NCH_2CH_2CH_3$), 3.63 [1H, d, *J* 3.9, C(3)*H*], 3.79 [1H, dd, *J* 9.4, 7.8 one of C(5)H_2], 7.37 (1H, apparent t, *J* 7.7, ArH^c), 7.41 (1H, d, *J* 7.7, ArH^d), 7.58 (1H, apparent t, *J* 7.5 ArH^b), 7.96 (1H, d, *J* 8.0, ArH^a); δ_C ($CDCl_3$, 150.9 MHz): 11.1 (CH_3, $NCH_2CH_2CH_3$), 16.1 (CH_3, $ArCH_2CH_3$), 20.3 (CH_2, $NCH_2CH_2CH_3$), 20.9 [CH_3, CH_3-C(4)], 26.4 (CH_2, $ArCH_2CH_3$), 27.5 [CH, *C*(4)H], 44.7 (CH_2, $NCH_2CH_2CH_3$), 53.0 [CH_2, *C*(5)H_2], 73.1 [CH, *C*(3)H], 126.2 (CH, aromatic *C*H), 130.9 (CH, aromatic *C*H), 131.5 (CH, aromatic *C*H), 134.2 (CH, aromatic *C*H), 135.7 (C,

aromatic *C*), 144.8 (C, aromatic *C*), 164.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{24}NO_3S$ $[M+H]^+$, 310.1477. Found 310.1466. m/z (ESI+): 310.3 $[M+H]^+$.



Mixtures of *cis* **208a** and *trans* **208b** were observed in the ^{1}H NMR spectra of the majority of the crude products resulting from the cyclisations of 2-diazo-2-[(2-ethylphenyl)sulfonyl]-*N*,*N*-dipropylacetamide **43**. After purification using column chromatography on silica gel mixtures of these two products were also obtained on occasion. In all cases *trans* **208b** was the major compound. A pure sample of *cis* **208a** was not obtained during the course of this work. The compound tentatively assigned as *cis* **208a** has the following ^{1}H NMR spectral characteristics; δ_H ($CDCl_3$, 400 MHz): 1.65 [3H, d, *J* 7.2, C*H*$_3$-C(4)], 3.90 [1H, d, *J* 8.3, C(3)*H*], 7.89 (1H, dd, *J* 8.0, 1.4, Ar*H*^{a}).

Assignments were made with the aid of 2D experiments; namely HMBC, NOESY, HSQC.

Table 6.13 *Copper and rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***57***

Entry	**Method**	**Metal**	**Ligand**	**Time (h)**	**Crude Efficiency[a]**	**Yield (%)[a]**	**Crude Ratio[a]: Purified Ratio[a]:**	***cis* (% ee)[a]**	**:**	***trans* (% ee)[a]**
1	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	21	~80–90%	59	**Crude Ratio:** **Purified Ratio:**	12 -(-)[b]		88 100 (52% ee)[b] (3*S*,4*R*)
2	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	6	~80–90%	61	**Crude Ratio:** **Purified Ratio:**	4 1(-)[c]		96 99 (82% ee)[c] (3*R*,4*S*)
3	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	~75–85%[d]	48	**Crude Ratio:** **Purified Ratio:**	14 10 (43% ee)[e]		86 90 (48% ee)[f] (3*S*,4*R*)
4	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	48	~70–80%[g]	45	**Crude Ratio:** **Purified Ratio:**	8 6 (38% ee)[h,i]		92 94 (70% ee)[h] (3*R*,4*S*)
5	**B**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	21	~80–90%	53	**Crude Ratio:** **Purified Ratio:**	15 7 (53% ee)[e]		85 93 (34% ee)[j] (3*S*,4*R*)
6	**B**	$CuCl_2/\Delta$	CN-(4*S*)-Ph **158**	30	~70–80%[k]	32	**Crude Ratio:** **Purified Ratio:**	9 5 (6% ee)[i]		91 95 (4% ee) (3*R*,4*S*)
7	**B**	$CuCl_2/\Delta$	Py-(4*R*)-Ph **159**	21	~60–70%[l]	39	**Crude Ratio:** **Purified Ratio:**	20 15 (8% ee)[e]		80 85 (3% ee)[m] (3*S*,4*R*)

8	**B**	$CuCl_2/\Delta$	Py-(4*S*)-*i*-Pr **160**	72	~40–50%[n]	22	**Crude Ratio:** **Purified Ratio:**	26 26 (46% ee)[i]		74 74 (24% ee) (3*R*,4*S*)
9	**F**	Rh_2(*S*-PTTL)$_4$ 0 °C–rt	-	30	>90%	65	**Crude Ratio:** **Purified Ratio:**	11 11 (75% ee)[i]		89 89 (71% ee) (3*R*,4*S*)
10	**F**	Rh_2(*S*-PTPA)$_4$ 0 °C–rt	-	21	~80–90%[o]	59	**Crude Ratio:** **Purified Ratio:**	23 17 (60% ee)[i]		77 83 (41% ee) (3*R*,4*S*)
11	**G**	Rh_2(*S*-DOSP)$_4$ 0 °C–rt–Δ 30 h, 18 h	-	48	~80–90%[p]	62	**Crude Ratio:** **Purified Ratio:**	22 24 (20% ee)[i]		78 76 (6% ee) (3*R*,4*S*)
12	**G**	Rh_2(5*S*-MEPY)$_4$ 0 °C–rt–Δ 30 h, 42 h	-	72	~70–80%[q]	25[r]	**Crude Ratio:** **Purified Ratio:**	13 7 (-% ee)		87 93 (0% ee)
13	**F**	Rh_2(*S*-mand)$_4$ 0 °C–rt	-	7	~80–90%[s]	61	**Crude Ratio:** **Purified Ratio:**	18 9 (20% ee)[e]		82 91 (27% ee) (3*S*,4*R*)
14	**E**	$Rh_2(OAc)_4/\Delta$	-	18	~80–90%	52	**Crude Ratio:** **Purified Ratio:**	8 5 (0% ee)		92 95 (0% ee)
15[t]	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	21	~70–80%	64	**Crude Ratio:** **Purified Ratio:**	3 2 (-)		97 98 (78% ee) (3*R*,4*S*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product and ^{1}H NMR spectra of the purified product using, for example, signals for C(3)*H*, *cis* ɣ-lactam, **208a**, δ_H 3.90 [1H, d, *J* 8.3, C(3)*H*]; *trans* ɣ-lactam, **208b**, δ_H 3.63 [1H, d, *J* 3.9, C(3)*H*]. The yield (%) reported is after purification using

column chromatography on silica gel. Details of the HPLC conditions used to separate the enantiomers of **208a** and **208b** can be found in **Appendix 1**. The absolute stereochemistry was determined by analogy, details of which can be found in **Appendix II**.

b. Results refer to data after a second purification using column chromatography on silica gel. $[\alpha]_D^{20}$ -9.20 (*c* 0.1033 in CH_2Cl_2). A second purification using column chromatography on silica gel was carried out due to the presence of additional peaks in the ^{1}H NMR spectra of the purified product; δ_H 4.21–4.32 (m). These peaks were also observed on the ^{1}H NMR spectra of the crude product. Results obtained after the first purification were 68% yield (2% *cis* **208a**, 98% *trans* **208b**), 52% ee for *trans* **208b**. Due to overlapping peaks on HPLC, the enantioselectivity of the *cis* isomer **208** was not determined.

c. Results refer to data obtained after a second purification. Rotation measured on this sample was $[\alpha]_D^{20}$ +41.11(*c* 0.09, CH_2Cl_2). Both methods of purification were carried out using column chromatography on silica gel. Results obtained after the first purification were; 70% yield (3% *cis* **208a**, 97% *trans* **208b**). Additional peaks were observed in ^{1}H NMR spectra of the purified product; δ_H 4.22–4.34 (m). These peaks were also observed in the ^{1}H NMR spectra of the crude product. Enantioselectivity was not recorded after the first purification of the crude product. Enantioselectivity of *cis* **208a** was not determined due to peak overlap on the HPLC.

d. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.15 (s), 4.23 (s), 4.28 (s), 4.63 (d, *J* 6.1).

e. The second eluting enantiomer of the *cis* isomer at ~26–28 min is the major enantiomer, using 10% IPA/hexane, or at ~12 min if using 20% IPA/hexane (Cell-4)

f. Results refer to data after a second purification. Both methods of purification were carried out using column chromatography on silica gel. A second purification was carried out due to the presence of additional peaks in the ^{1}H NMR spectra of the purified product; δ_H 3.98–4.03 (m), 4.19–4.34 (m), 4.63 (d, *J* 6.2), 4.65–4.71 (m), 5.18–5.26 (m). Results obtained after the first purification were 55% yield (11% *cis* **208a**, 89% *trans* **208b**), 48% ee for *trans* **208b**. Due to overlapping peaks in the enantioselectivity of the *cis* isomer **208a** was not determined.

g. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.97–4.10 (m), 4.04 (s), 4.15 (s), 4.22–4.32 (m), 4.63 (d, *J* 6.2), 5.55 (s).

h. Enantioselectivity for *trans* **208b** is based on a weighted average. Two fractions of material obtained. The relative masses of each fraction are given as follows; first fraction (42% mass, contains *trans* **208b** only, 71% ee), second fraction (58% mass, 7% *cis* **208a**, 93% *trans* **208b**, 38% ee *cis* **208a**, 69% ee *trans* **208b**). Additional peaks were observed in the ^{1}H NMR spectra of fraction two; δ_H 4.04 (s), 4.06 (s), 4.12 (s), 4.14 (s), 4.20 (s). The rotation of each fraction was measured individually; Rotation measured on fraction one $[\alpha]_D^{20}$ +36.0 (*c* 0.1014 in CH_2Cl_2), Rotation measured on fraction two $[\alpha]_D^{20}$ +33.90 (*c* 0.103, CH_2Cl_2).

i. The first eluting enantiomer of the *cis* isomer **208a** at ~23–25 min is the major enantiomer, using 10% IPA/hexane, or at ~10 min if using 20% IPA/hexane (Cell-4).

j. Results refer to data after a second purification using column chromatography on silica gel. A second purification using column chromatography on silica gel was carried out due to the presence of additional peaks in the ^{1}H NMR spectra of the purified product; δ_H 4.21–4.30 (m). These peaks were also observed on the ^{1}H NMR spectra of the crude product. Results obtained after the first purification were 61% yield (12% *cis* **208a**, 88% *trans* **208b**), 57% ee for *cis* **208a**, 36% ee for *trans* **208b**.

k. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.95–3.99 (m), 4.15 (s), 4.15–4.29 (m), 4.63 (d, *J* 6.3), 5.54 (s).

l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.55 (q, *J* 7.5), 3.99-4.04 (m), 4.08 (s), 4.10 (s), 4.11 (s), 4.13 (s), 4.15 (s), 4.21–4.29 (m), 4.30–4.36 (m), 4.63 (d. *J* 6.7), 5.19 (s), 5.53 (s), 5.73 (s), 6.21 (d, *J* 6.5), 9.50 (s).

m. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.99–4.06 (m), 4.21–4.23 (m), 4.25 (s), 4.63 (d, *J* 6.2), 9.49 (s). Enantioselectivity of *trans* **208b** estimated due to peak overlap in HPLC trace.

n. Reaction gone to 50% completion after 72 h. ^{1}H NMR spectra of the crude product contains *approx* 50% of α-diazocarbonyl **57**. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.95–3.99 (m), 4.24 (s), 5.55 (s), 9.45 (s).

o. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.15 (s), 4.20–4.28 (m), 7.19–7.21 (m), 7.67–7.77 (m).

p. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.11 (s), 4.20–4.31 (m), 9.45 (s).

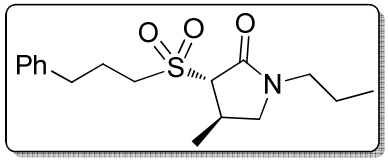
q. Analysis of the ^{1}H NMR spectra of the crude product showed that the reaction was ~90% complete, with *approx* 10% α-diazocarbonyl **57** remaining. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.14 (s), 4.20–4.31 (m), 5.56 (s), 6.10 (s), 6.99 (s).

r. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 3.50 (s), 3.53 (s), 3.67 (s), 4.15–4.29 (m), 5.18–5.23 (m), 5.89–5.96 (m), 7.61–7.77 (m), 7.80–7.91(m).

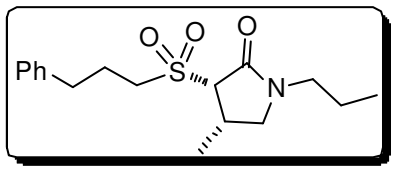
s. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.20–4.27 (m).

t. Reaction was carried out employing 300 mg of α-diazoacetamide **57**.

(3*S*,4*R*) 4-Methyl-3-[(3-phenylpropyl]sulfonyl)-1-propylpyrrolidin-2-one 210b



The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-2-[(3-phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide **50** (200 mg, 0.57 mmol), $CuCl_2$ (3.8 mg, 28.4 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (30.3 mg, 34.1 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (11.4 mg, 34.1 μmol) in dichloromethane (60 mL), stirred while heating under reflux for 18 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 80–90% efficient (5% *cis*: 95% *trans*). Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (3*S*,4*R*) 4-methyl-3-[(3-phenylpropyl]sulfonyl)-1-propylpyrrolidin-2-one (5% *cis* **210a**, 95% *trans* **210b**) (139 mg, 76%) was isolated as a colourless oil. The following spectral characteristics are reported for *trans* **210b**; 13% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (film): 2965, 2934, 2876 (CH), 1693 (CO), 1454, 1308, 1139, 1125 (SO_2), 701 (CS); δ_H ($CDCl_3$, 600 MHz): 0.92 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.29 [3H, d, *J* 7.0, CH_3-C(4)], 1.50–1.62 (2H, m, $NCH_2CH_2CH_3$), 2.16–2.27 [2H, m, C(2′)H_2], 2.74–2.84 [2H, m, C(3′)H_2], 2.94 [1H, dd, *J* 9.7, 3.9, one of C(5)H_2], 3.05–3.14 [1H, m, C(4)*H*], 3.19–3.28 (1H, m, one of $NCH_2CH_2CH_3$), 3.29–3.36 (1H, m, one of $NCH_2CH_2CH_3$), 3.37–3.43 [2H, m, C(1′)H_2], 3.45 [1H, d, *J* 4.7, C(3)*H*], 3.67–3.77 [1H, m, one of C(5)H_2], 7.16–7.24 (3H, m, Ar*H*), 7.25–7.33 (2H, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 11.1 (CH_3, $NCH_2CH_2CH_3$), 20.3 (CH_2, $NCH_2CH_2CH_3$), 20.9 [CH_3, CH_3-C(4)], 23.4 [CH_2, C(2′)H_2], 25.8 [CH, *C*(4)H], 34.4 [CH_2, C(3′)H_2], 44.8 (CH_2, $NCH_2CH_2CH_3$), 51.8 [CH_2, C(1′)H_2], 53.3 [CH, *C*(5)H], 69.8 [CH, *C*(3)H], 126.3 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.7 (CH, 2 × aromatic *C*H), 140.2 (C, aromatic *C*), 165.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{17}H_{26}NO_3S$ $[M+H]^+$, 324.1633. Found 324.1629. m/z (ESI+): 647.3 ($2M+H^+$).



Mixtures of *cis* **210a** and *trans* **210b** were observed in the ^{1}H NMR spectra of the majority of the crude products resulting from the cyclisations of 2-diazo-2-[(3-phenylpropyl)sulfonyl]-*N*,*N*-dipropylacetamide **50**.

After purification using column chromatography on silica gel mixtures of these two products were also obtained on occasion. In all cases *trans* **210b** was the major compound. A pure sample of *cis* **210a** was not obtained during the course of this work. No clear distinct signals were observed for *cis* **210a** in the ^{1}H NMR spectra. All signals for *cis* **210a** overlap to some extent with those of *trans* **210b**, two signals have been tentatively assigned to *cis* **210a**; δ_H ($CDCl_3$, 400 MHz): 0.95 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 3.73 [1H, d, *J* 8.6, C(3)*H*]. A second set of signals were observed in the ^{13}C NMR of *trans* **210b** and are tentatively assigned to *cis* **210a**; δ_C ($CDCl_3$, 150.9 MHz) 13.8 (CH or CH_3), 20.5 (CH_2), 23.4 (CH_2), 31.9 (CH or CH_3), 44.8 (CH_2), 53.3 (CH_2), 53.5 (CH_2), 65.7 (CH or CH_3), 126.3 (CH, aromatic *C*H), 128.5 (CH, aromatic *C*H), 140.2 (C, aromatic *C*), 166.7 (C, *C*O).

Assignments were made with the aid of 2D experiments; namely HMBC, NOESY, HSQC.

Table 6.14 *Copper and rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **50**

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency[a]	Yield (%)[a]	Crude Ratio[a] Purified Ratio[a]	*cis*[a,b]	:	*trans*(% ee)[a]
1	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	18	~80–90%	76	**Crude Ratio:** **Purified Ratio:**	5 3		95 97 (13% ee) (3*S*,4*R*)
2	**B**	$Cu(CH_3CN)_4PF_6/\Delta$	(4*R*)-Ph **20**	1	>90%	69	**Crude Ratio:** **Purified Ratio:**	15 12		85 88 (0% ee) (3*S*,4*R*)
3	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	16	>90%	58	**Crude Ratio:** **Purified Ratio:**	<10 1		>90 99 (61% ee) (3*R*,4*S*)
4	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	40	>90%	66	**Crude Ratio:** **Purified Ratio:**	<10 3		>90 97 (67% ee)[c,d] (3*R*,4*S*)
5	**B**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	30	>90%	67	**Crude Ratio:** **Purified Ratio:**	15 10		85 90 (4% ee) (3*S*,4*R*)
6	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	31	-[e]	65	**Crude Ratio:** **Purified Ratio:**	-[e] 1		-[e] 99 (48% ee)[f] (3*S*,4*R*)
7	**F**	Rh_2(*S*-PTTL)$_4$ 0 °C–rt	-	4	~80–90%[g]	74	**Crude Ratio:** **Purified Ratio:**	10 5		90 95 (51% ee)[h] (3*R*,4*S*)
8	**E**	$Rh_2(OAc)_4/\Delta$	-	2	~80–90%[i]	57	**Crude Ratio:** **Purified Ratio:**	12 10 (0% ee)		88 90 (0% ee)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for $NCH_2CH_2CH_3$, *cis* ɣ-lactam, **210a**, δ_H 0.95 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$); *trans* ɣ-lactam, **210b**, δ_H 0.92 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$). Relative ratios for *cis* and *trans* isomers are estimated due to peak overlap. The yield (%) reported is after purification using column chromatography on silica gel. Details of the HPLC conditions used to separate the enantiomers of **210b** and **210b** can be found **Appendix I**. The absolute stereochemistry was determined by analogy, details of which can be found in **Appendix II**.

b. % ee cannot be measured.

c. Additional peaks observed in the ^{1}H NMR spectra of the purified product, these signals were not observed in the ^{1}H NMR spectra of the crude product and may be due to external contamination; δ_H 3.79–3.81 (m), 4.15–4.22 (m).

d. Rotation value measured on this sample; $[\alpha]_D^{20}$ +47.27 (*c* 0.11, CH_2Cl_2).

e. Data not available

f. Rotation value measured on this sample; $[\alpha]_D^{20}$ -11.48 (*c* 0.0915, CH_2Cl_2).

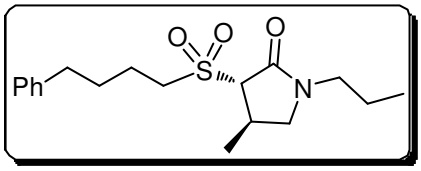
g. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.21 (s), 5.12 (s), 9.05 (s).

h. Additional peak observed in the ^{1}H NMR spectra of the crude product; δ_H 9.05 (s).

i. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.41 (s), 4.18 (s), 7.37–7.44 (m), 7.55–7.60 (m), 7.93–7.97 (m), 8.01–8.04 (m), 8.11–8.13 (m), 9.50 (s).

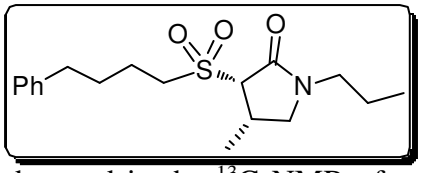
j. Additional peaks observed in the ^{1}H NMR spectra of the purified product; δ_H 2.41 (s), 4.18 (s), 7.37–7.60 (m), 7.94–7.97 (m), 8.01–8.04 (m), 9.50 (s).

4-Methyl-3-[(4-phenylbutyl)sulfonyl]-1-propylpyrrolidin-2-one 209b



2-Diazo-2-[(4-phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide **46** (100 mg, 0.27 mmol) in distilled dichloromethane was added dropwise over 5 min to a refluxing solution of $Rh_2(OAc)_4$ (~1 mg) in distilled dichloromethane (40 mL), stirred while heating under reflux for 6 h, in accordance to Method **E**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 90% efficient (8% *cis* **209a** : 92% *trans* **209a**). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–40:60) as eluent, 4-methyl-3-[(4-phenylbutyl)sulfonyl]-1-propylpyrrolidin-2-one (5% *cis* **209a**, 95% *trans* **209a**) (53 mg, 60%) was isolated as a colourless oil; 0 % ee (*trans* **209b**) (determined by chiral HPLC); The following spectral characteristics are reported for *trans* **209b**; ν_{max}/cm^{-1} (film): 2965, 2934, 2875 (CH), 1691 (CO), 1453, 1298, 1138 (SO_2), 748, 701 (CS); δ_H ($CDCl_3$, 400 MHz): 0.92 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.30 [3H, d, *J* 7.0, CH_3-C(4)], 1.49–1.63 (2H, m, $NCH_2CH_2CH_3$), 1.74–1.86 [2H, m, C(3′)H_2], 1.87–1.99 [2H, m, C(2′)H_2], 2.62–2.72 [2H, m, C(4′)H_2], 2.94 [1H, dd, *J* 9.6, 3.9, one of C(5)H_2], 3.03–3.17 [1H, m, C(4)*H*], 3.18-3.38 (2H, m, $NCH_2CH_2CH_3$), 3.39–3.47 [3H, m, contains C(1′)H_2, and C(3)*H*], 3.73 [1H, dd, *J* 9.6, 7.9, one of C(5)H_2], 7.13–7.23 (3H, m, Ar*H*), 7.24–7.33 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 11.1 (CH_3, $NCH_2CH_2CH_3$), 20.3 (CH_2, $NCH_2CH_2CH_3$), 20.8 [CH_3, CH_3-C(4)], 25.9 [CH_2, C(2′)H_2 or C(3′)H_2], 25.9 [CH, C(4)H], 30.2 [CH_2, C(2′)H_2 or C(3′)H_2], 35.3 [CH_2, C(4′)H_2], 44.8 (CH_2, $NCH_2CH_2CH_3$), 52.2 [CH_2, C(1′)H_2], 53.1 [CH_2, C(5)H_2], 69.8 [CH, C(3)H], 126.0 (CH, aromatic CH), 128.3 (CH, 2 × aromatic CH), 128.4 (CH, 2 × aromatic CH), 141.4 (C, aromatic C), 165.8 (C, CO); HRMS (ESI+): Exact mass calculated for $C_{18}H_{28}NO_3S$ $[M+H]^+$, 338.1790. Found 338.1779. m/z (ESI+): 338.3 $[M+H]^+$.

Mixtures of *cis* **209a** and *trans* **209b** were observed in the ^{1}H NMR spectra of the majority of the crude products resulting from the cyclisations of 2-diazo-2-[(4-phenylbutyl)sulfonyl]-*N*,*N*-dipropylacetamide **46**. After purification, using column chromatography on silica gel, mixtures of these two products were also obtained on occasion. In all cases *trans* **209b** was the major compound. A pure sample of *cis* **209a** was not obtained during the course of this work. No clear distinct signals were observed for *cis* **209a** in the ^{1}H NMR spectra. All signals for *cis* **209a** overlap to some extent with



those of *trans* **209b**, one signal has been tentatively assigned to *cis* **209a**; δ_H ($CDCl_3$, 400 MHz) 0.93 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$). A second set of signals were observed in the ^{13}C NMR of *trans* **209b** and are tentatively assigned to *cis* **209a**; δ_C ($CDCl_3$, 150.9 MHz): 13.8 (CH or CH_3), 20.5 (CH_2), 21.4 (CH_2), 31.9 (CH or CH_3), 53.3 (CH_2), 54.0 (CH_2), 65.6 (CH or CH_3), 125.9 (CH, aromatic *C*H), 141.5 (C, aromatic *C*), 166.8 (C, *C*O).

Table 6.15 *Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***46***

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency[a]	Yield (%)[a]	Crude Ratio[a] Purified Ratio[a]	*cis*[a,b]	:	*trans* (% ee)[a]
1	**E**	$Rh_2(OAc)_4$	-	6	>90%	60	**Crude Ratio:** **Purified Ratio:**	8 5		92 95 (0% ee)
2	**B**	$CuCl_2$	(4*R*)-Ph **20**	21	>90%	49	**Crude Ratio:** **Purified Ratio:**	3 3		97 97 (12% ee) (3*S*,4*R*)
3	**B**	$CuCl_2$	(3*S*,8*R*)-Ind **44**	21	>90%	61	**Crude Ratio:** **Purified Ratio:**	2 2		98 98 (54% ee) (3*R*,4*S*)
4	**B**	$CuCl_2$	(4*S*)-*t*-Bu **138**	50	>90%	60	**Crude Ratio:** **Purified Ratio:**	3 3		97 97 (62% ee) (3*R*,4*S*)
5	**B**	$CuCl_2$	(4*S*,5*R*)-di-Ph **137**	21	>90%	49	**Crude Ratio:** **Purified Ratio:**	5 5		95 95 (3% ee) (3*S*,4*R*)
6	**B**	$CuCl_2$	(4*R*)-Bn **43**	21	>90%	51	**Crude Ratio:** **Purified Ratio:**	5 0		95 100 (45% ee) $[\alpha]_D^{20}$ -11.36 (*c* 0.11 in CH_2Cl_2) (3*S*,4*R*)
7	**B**	$Cu(CH_3CN)_4PF_6$	(3*S*,8*R*)-Ind **44**	21	>90%	60	**Crude Ratio:** **Purified Ratio:**	5 2		95 98 (67% ee)

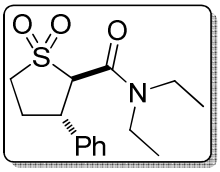
										(3*R*,4*S*)
8	**B**	$Cu(CH_3CN)_4PF_6$	(4*S*)-*t*-Bu **138**	21	>90%	52	**Crude Ratio:** **Purified Ratio:**	8 6		92 94 (72% ee) (3*R*,4*S*)

a. Efficiency and relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(3)*H*, *cis* γ-lactam **209a**, δ_H 0.93 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$); *trans* γ-lactam, **209b**, δ_H 0.92 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$). Relative ratios for *cis* and *trans* isomers are estimated due to peak overlap. The yield (%) reported is after purification using column chromatography on silica gel. Details of the HPLC conditions used to separate the enantiomers of **209b** can be found in **Appendix I**. The absolute stereochemistry was determined by analogy, details of which can be found in **Appendix II.**

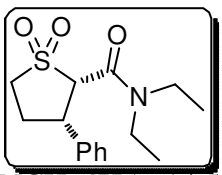
b. % ee cannot be measured.

Assignments were made with the aid of 2D experiments; namely COSY and HETCOR.

***N*,*N*-Diethyl-3-phenyltetrahydrothiophene-2-carboxamide 1,1-dioxide 218b**



The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-*N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **51** (200 mg, 0.61 mmol), $CuCl_2$ (4.1 mg, 30.5 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (32.0 mg, 36.6 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (12.2 mg, 36.6 μmol) in dichloromethane (60 mL), stirred while heating under reflux for 21 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 80–90% efficient. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–30:70–40:60–60:40) as eluent, *N*,*N*-diethyl-3-phenyltetrahydrothiophene-2-carboxamide 1,1-dioxide (1.4 mg, 0.8%) (15% *cis* **218a**, 85% *trans* **218b**) was isolated as a white solid. Spectral characteristics listed here are for *trans* **218b**; ν_{max}/cm^{-1} (neat, ATR) (for mixture of *cis* **218a** and *trans* **218b**): 2961, 2929 (CH), 1639 (CO), 1457, 1303, 1106 (SO_2), 764, 707 (CS); δ_H ($CDCl_3$, 600 MHz): 0.91 (3H, t, *J* 6.2, one of NCH_2CH_3), 0.95 (3H, t, *J* 6.2, one of NCH_2CH_3), 2.38–2.55 [1H, m, one of C(4)H_2], 2.95 (2H, q, *J* 7.2, one of NCH_2CH_3) 3.02–3.12 (1H, m, one of NCH_2CH_3), 3.13–3.26 [1H, m, one of C(4)H_2], 3.27–3.36 [1H, m, one of C(5)H_2], 3.37–3.51 (1H, m, one of NCH_2CH_3), 3.72–3.82 [1H, m, one of C(5)H_2], 3.95–4.07 [1H, m, C(3)*H*], 4.23 [1H, d, *J* 6.6, C(2)*H*], 7.23–7.36 (5H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 12.6 (CH_3, one of NCH_2CH_3), 14.4 (CH_3, one of NCH_2CH_3), 26.0 [CH_2, *C*(4)H_2], 41.0 (CH_2, one of NCH_2CH_3), 42.4 (CH_2, one of NCH_2CH_3), 45.1 [CH_2, *C*(3)H], 51.7 [CH_2, *C*(5)H_2], 65.2 [CH_2, *C*(2)H], 128.0 (CH, aromatic *C*H), 128.3 (CH, 2 × aromatic *C*H), 128.8 (CH, 2 × aromatic *C*H), 136.8 (C, aromatic *C*), 163.7 (C, *C*O).

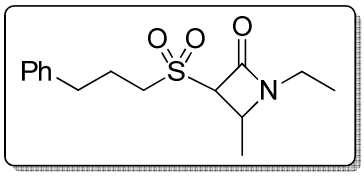


218a δ_H ($CDCl_3$, 600 MHz): 1.02 (3H, t, *J* 7.2, NCH_2CH_3), 1.14 (3H, t, *J* 7.1, NCH_2CH_3), 3.53–3.65 (m), 4.09 [1H, d, *J* 9.5, C(2)*H*], 4.24–4.35 [1H, m, C(3)*H*]; δ_C ($CDCl_3$, 150.9 MHz) 12.8 (CH_3, one of NCH_2CH_3), 14.5 (CH_3, one of NCH_2CH_3), 28.0 (CH_2), 41.5 (CH_2), 42.3 (CH_2), 45.7 (CH), 53.1 (CH_2), 69.0 (CH), 127.1 (CH), 127.8 (CH), 128.8 (CH), 140.0 (C), 162.7 (C, *C*O).

An additional more polar fraction was isolated, 1-ethyl-3-[(3-phenylpropyl)sulfonyl]pyrrolidin-2-one **216** (48.6 mg, 27%) as a colourless oil; 46% ee (determined by chiral HPLC); with spectral characteristics as identified below.

From the experiment reported in **Table 6.16**, entry 2, 2-diazo-*N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **51** (200 mg, 0.61 mmol), $CuCl_2$ (4.1 mg, 30.5 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (32.0 mg, 36.6 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (12.2 mg, 36.6 μmol) in dichloromethane (70 mL), stirred while heating under reflux for 21 h, in accordance with Method **B**; three compounds were isolated, the least polar compound (1.2 mg, 0.65%) was *trans* sulfolane **218b** with spectral characteristics as identified above, the most polar compound was ɣ-lactam product **216** [isolated as three fractions; fraction 1, (16.2 mg, 9%) (47% ee determined by chiral HPLC) (90% ɣ-lactam **216**, 10% unknown); fraction 2, (21.6 mg, 12%) (32% ee determined by chiral HPLC) (95% ɣ-lactam **216**, 5% unknown); fraction 3 (9.0 mg, 5%) (39% ee determined by chiral HPLC), (containing 94% ɣ-lactam **216**, 6% unknown), with spectral characteristics as identified below while the fraction of mid polarity (21.6 mg, 12%) was isolated as a colourless oil with the following spectral characteristics;

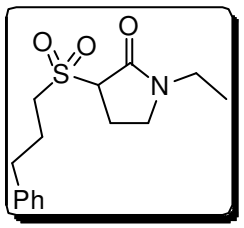
1-Ethyl-4-methyl-3-[(3-phenylpropyl)sulfonyl]azetidin-2-one 217b



ν_{max}/cm^{-1} (neat, ATR): 2975, 2932 (CH), 1754 (CO), 1454, 1408, 1308, 1139, 1124 (SO_2), 750, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 1.22 (3H, t, *J* 7.3 one of NCH_2CH_3), 1.48 [3H, d, *J* 6.2, CH_3-C(4)], 2.17–2.30 [2H, m, C(2′)H_2], 2.75–2.85 [2H, m, C(3′)H_2], 3.09–3.16 (1H, sym m, one of NCH_2CH_3), 3.17–3.25 [2H, m, C(1′)H_2], 3.39–3.48 (1H, m, one of NCH_2CH_3), 4.02 [1H, d, *J* 1.6, C(3)*H*], 4.24 [1H, apparent qd, *J* 6.1, 1.6, C(4)*H*], 7.18–7.24 (3H, m, Ar*H*), 7.28–7.33 (2H, m, Ar*H*); δ_c ($CDCl_3$, 150.9 MHz): 13.0 (CH_3, NCH_2CH_3), 18.0 [CH_3, CH_3-C(4)], 22.8 [CH_2, C(2′)H_2], 34.3 [CH_2, C(3′)H_2], 36.0 (CH_2, NCH_2CH_3), 47.7 [CH, C(4)H], 52.5 [CH_2, C(1′)H_2], 72.4 [CH, C(3)H], 126.5 (CH, aromatic CH), 128.5 (CH, 2 × aromatic CH), 128.6 (CH, 2 × aromatic CH), 139.9 (C, aromatic C), 158.0 (C, CO); HRMS (ESI+): Exact mass calculated for $C_{15}H_{22}NO_3S$ $[M+H]^+$ 296.1320. Found 296.1310. m/z (ESI+).

From the experiment reported in **Table 6.16**, entry 3, 2-diazo-*N*,*N*-diethyl-2-[(3-phenylpropyl)sulfonyl]acetamide **51** (200 mg, 0.61 mmol), $Rh_2(OAc)_4$ (2.6 mg, 6.1 μmol) in dichloromethane (60 mL), stirred while heating under reflux for 4 h, in accordance with Method **E**; three fractions were isolated, the least polar fraction (0.32 mg, 0.18%) was *trans* sulfolane **218b** with spectral characteristics as identified above, the fraction of mid polarity (5.4 mg, 3%) was β-lactam product **217b** with spectral characteristics as identified above while the most polar fraction (81 mg, 45%) (0% ee determined by chiral HPLC) was isolated as a colourless oil with the following spectral characteristics;

1-Ethyl-3-[(3-phenylpropyl)sulfonyl]pyrrolidin-2-one 216



ν_{max}/cm^{-1} (neat): 2936 (CH), 1683 (CO), 1455, 1435, 1305, 1281, 1122 (SO_2), 750, 700 (CS); δ_H ($CDCl_3$, 600 MHz) 1.16 (3H, t, *J* 7.3, NCH_2CH_3), 2.17–2.28 [2H, m, C(2′)H_2], 2.36–2.45 [1H, m, one of C(4)H_2], 2.71–2.78 [1H, m, one of C(4)H_2], 2.78–2.83 [2H, m, C(3′)H_2], 3.32–3.47 [5H, m, C(1′)H_2, NCH_2CH_3 and one of C(5)H_2], 3.58–3.64 [1H, m, overlapping dt, appears as quartet, *J* 16.1, 8.8, one of C(5)H_2], 3.83 [1H, dd, *J* 10.2, 4.2, C(3)*H*], 7.18–7.23 (3H, m, Ar*H*), 7.27–7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz) 12.2 (CH_3, NCH_2CH_3), 17.5 [CH_2, *C*(4)H_2], 23.3 [CH_2, *C*(2′)H_2], 34.4 [CH_2, *C*(3′)H_2], 38.0 [CH_2, NCH_2CH_3], 45.0 [CH_2, *C*(5)H_2], 51.5 [CH_2, *C*(1′)H_2], 62.9 [CH, *C*(3)H], 126.4 (CH, aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 128.6 (CH, 2 × aromatic *C*H), 140.1 (C, aromatic *C*), 165.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{22}NO_3S$ $[M+H]^+$, 296.1320. Found 296.1319. m/z (ESI+) 296.3 $[M+H]^+$.

*Assignments of the above compounds **216**, **217b** and **218b** were made with the aid of 2D experiments; namely HMBC, NOESY, HSQC.*

Table 6.16 *Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***51***

Entry	**Method**	**M**	**Ligand**	**Time (h)**	**Crude Efficiency (%)[a]**	**Crude Ratio** **Purified Yield %** **Overall Yield (%)**	**Products**		
							trans sulfolane[b] Least polar	β-lactam[b] Mid polarity	ɣ-lactam Most polar
1	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	80–90[c]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	2 0.8%[d] 0.68%	37 -[e] -[e]	61 27%[f] (46% ee) 26%
2	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	80–90	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	2 0.7%[g] 0.65%	38 12%[h] 12%	60 9%[i] (47% ee) + 12%[j] (32% ee) + 5%[k] (39% ee) 21% (45% ee)

3	**E**	$Rh_2(OAc)_4/\Delta$ No NaBARF	-	4	80–90[l]	**Crude Ratio** **Yield (purified)%** **Overall Yield (%)**	2 - 0.18%	7 3%[m] 2.6%	91 45% (0% ee) 45%
4	**B**	$Cu(CH_3CN)PF_6/\Delta$ No NaBARF	(4*R*)-Ph **20**	2	60–70[n]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	2 1.5%[o] 1.3%	23 8%[p] 4%	75 28% (69% ee) 28%

a. Efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *trans* sulfolane **218b**, δ_H 4.38 [1H, d, *J* 5.3, C(2)*H*]; β-lactam **217b**, δ_H 4.24 [1H, apparent qd, *J* 6.1, 1.6, C(4)*H*] and ɣ-lactam **216**, δ_H 3.83 [1H, dd, *J* 10.2, 4.2, C(3)*H*]. Yield (%) reported after purification using column chromatography on silica gel. Enantioselectivities measured for ɣ-lactam **216** only, the major enantiomer formed using (4*R*)-Ph **20** appeared at 30 min and the minor at 28 min, the details of which can be found in **Appendix I**.

b. Enantioselectivity was not measured due to impure samples.

c. Additional peaks may be present in the ^{1}H NMR spectra of the crude product in the region of 1.0–4.5 ppm but cannot be distinguished due to peak overlap. The following peaks were observed in the region of 4.5–10.0 ppm; δ_H 5.01–5.06 (m), 5.31 (br s), 6.13 (s), 6.19–6.32 (m), 6.45–6.59 (m), 7.97 (d, *J* 7.6), 8.28–8.36 (m).

d. Fraction contains 85% *trans* sulfolane **218b** and 15% *cis* sulfolane **218a**.

e. Product not isolated after purification by column chromatography

f. Fraction contains 96% ɣ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 1.71 (d, *J* 6.6), 3.11–3.18 (m), 4.12 (s), 7.45–7.50 (m), 7.56–7.58 (m), 7.95–7.99 (m).

g. Fraction contains 93% *trans* sulfolane **218b** and 7% *cis* sulfolane **218a**.

h. Fraction contains 97% β-lactam **217b**. Additional peaks present in the ^{1}H NMR spectra; δ_H 2.59–2.68 (m), 3.28–3.34 (m), 5.01–5.06 (m), 6.24–6.35 (m), 6.92 (d, *J* 16), 7.36–7.46 (m).

i. Fraction contains 90% ɣ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 1.72 (d, *J* 6.6), 3.09–3.29 (m), 4.64–4.72 (m), 5.20–5.28 (m).

j. Fraction contains 95% ɣ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.10–3.16 (m), 4.64–4.72 (m), 5.20–5.28 (m).

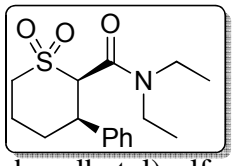
k. Fraction contains 94% ɣ-lactam **216**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.07–3.14 (m), 4.64–4.72 (m), 5.21–5.28 (m).

l. Additional peaks may be present in the ^{1}H NMR spectra of the crude product in the region of 1.0-4.5 ppm but cannot be distinguished due to peak overlap. The following peaks were observed in the region of 4.5–10.0 ppm; δ_H 4.80–4.82 (m), 4.96–5.01 (m), 5.08 (s), 5.52 (s), 5.62 (s), 7.96–8.01 (m), 9.49 (s), 9.80 (s), 10.03 (s).

m. Fraction contains 88% β-lactam **217b** and 6% *trans* sulfolane **218b**. Additional peaks present in the ^{1}H NMR spectra; δ_H 4.67–4.75 (m), 6.99 (s), 7.47–7.54 (m), 7.60–7.64 (m).

n. Additional peaks may be present in the ^{1}H NMR spectra of the crude product in the region of 1.0–4.5 ppm but cannot be distinguished due to peak overlap. The following peaks were observed in the region of 4.5–10.0 ppm; δ_H 5.01–5.06 (m), 5.31 (br s), 6.13 (s), 6.19–6.32 (m), 6.45–6.59 (m), 7.97 (d, *J* 7.6), 8.28–8.36 (m).
o. Fraction contains 85% *trans* sulfolane **218b** and 7% *cis* sulfolane **218a**.
p. Fraction contains 50% β-lactam **217b** and 40% sulfone **125** δ_H 3.97 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 6.01 (s), 9.49 (s).

(2*R*,3*R*)-*N*,*N*-diethyl-3-phenyltetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide 220a



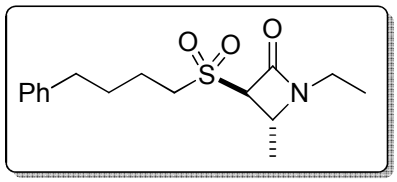
The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-*N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide **47** (90 mg, 0.26 mmol), $CuCl_2$ (1.8 mg, 13.3 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (14.2 mg, 16.0 μmol) and bisoxazoline ligand (3*S*,8*R*)-Ind **44** (5.3 mg, 8.5 μmol) in dichloromethane (40 mL), stirred while heating under reflux for 48 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 70–80% efficient. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80) as eluent, (2*R*,3*R*)-*N*,*N*-diethyl-3-phenyltetrahydro-2H-thiopyran-2-carboxamide 1,1-dioxide **220a** (15 mg, 19%) was isolated as a white solid; mp 118–119 °C; $[\alpha]_D^{20}$ -67.0 (*c* 0.05, CH_2Cl_2) 92% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (neat, ATR): 2971, 2918 (CH), 1631 (CO), 1443, 1309, 1294, 1145, 1116 (SO_2), 853, 763, 708 (CS); δ_H ($CDCl_3$, 600 MHz): 0.82 (3H, t, *J* 7.2 one of NCH_2CH_3), 0.99 (3H, t, *J* 7.2 one of NCH_2CH_3), 1.74 [1H, apparent dq, *J* 13.7, 3.2, one of C(4)H_2], 2.15–2.31 [2H, m, C(5)H_2], 2.59–2.67 (1H, m, one of NCH_2CH_3), 2.68–2.76 (1H, m, one of NCH_2CH_3), 2.88 [1H, apparent qd, *J* 13.4, 3.9 one of C(4)H_2], 2.94–3.06 [2H, m, one of C(6)H_2 and one of NCH_2CH_3], 3.53 (1H, sym m, one of NCH_2CH_3), 3.67 [1H apparent dt, *J* 14.1, 7.1, C(3)*H*], 3.99 [1H, apparent td, *J* 13.5, 4.2, one of C(6)H_2], 4.12 [1H, dd, *J* 4.5, 2.4, C(2)*H*], 7.23–7.33 (5H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 12.3 (CH_3, one of NCH_2CH_3), 13.8 (CH_3, one of NCH_2CH_3), 23.3 [CH_2, *C*(5)H_2], 24.2 [CH_2, *C*(4)H_2], 41.2 (CH_2, one of NCH_2CH_3), 42.3 (CH_2, one of NCH_2CH_3), 45.7 [CH, *C*(3)H], 48.3 [CH_2, *C*(6)H_2], 65.6 [CH, *C*(2)H], 127.77 (CH, 2 × aromatic *C*H), 127.84 (CH, aromatic *C*H), 128.9 (CH, 2 × aromatic *C*H), 140.0 (C, aromatic *C*), 164.3 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{24}NO_3S$ $[M+H]^+$, 310.1477. Found 310.1474. m/z (ESI+): 310.3 $[M+H]^+$.

Two additional more polar compounds were eluted, the fraction of mid polarity was identified as β-lactam **221b** recovered as three fractions; [fraction 1, (6.4 mg 8%), containing 70% β-lactam **221b**, 17% *cis* thiopyran **220a**, 11% sulfone **118** and 2 % unknown; fraction 2, (4 mg, 5%), containing 65% β-lactam **221b**, 28% sulfone **118** and

7 % unknown; fraction 3, (4.8 mg, 6%) containing 30% β-lactam **221b**, 59% sulfone **118** and 11 % unknown] all as colourless oils, with spectral characteristics as identified below. The most polar compound ɣ-lactam **219** [recovered as three fractions; [fraction 1, (3.2 mg, 4%), containing 85% ɣ-lactam **219**, 15% unknown; fraction 2, (9.6 mg, 12%), containing 86% ɣ-lactam **219**, 14 % unknown; fraction 3 (4 mg, 5%) containing 83% ɣ-lactam **219**, 17 % unknown], all as colourless oils with spectral characteristics as identified below.

From the experiment reported in **Table 6.17**, entry 2, 2-diazo-*N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide **47** (90 mg, 0.26 mmol), $CuCl_2$ (1.8 mg, 13.3 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (14.2 mg, 16.0 μmol) and bisoxazoline ligand (4*R*)-Ph **20** (2.8 mg, 8.5 μmol) in dichloromethane (40 mL), stirred while heating under reflux for 21 h, in accordance with Method **B**, three compounds were isolated, the least polar compound (8 mg, 10%) (97% ee, determined by chiral HPLC) was *cis* thiopyran **220a** with spectral characteristics as identified above, the compound of mid polarity was β-lactam product **221b** recovered as three fractions; [fraction 1, (1.6 mg, 2%) isolated pure and full analysis was carried out on this sample; fraction 2, (5.6 mg, 7%), containing 85% ɣ-lactam **219**, 5% sulfone **118**, 10 % unknown; fraction 3 (2.4 mg, 3%) containing 62% ɣ-lactam **219**, 14% sulfone **118**, 24 % unknown], all as colourless oils with the following spectral characteristics;

1-Ethyl-4-methyl-3-[(4-phenylbutyl)sulfonyl]azetidin-2-one 221b



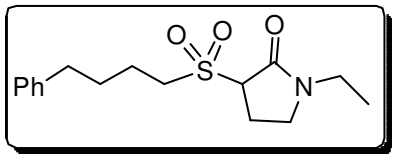
ν_{max}/cm^{-1} (neat): 2932 (CH), 1760 (CO), 1455, 1409, 1306, 1140 (SO_2), 748, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 1.23 (3H, t, *J* 7.3 one of NCH_2CH_3), 1.48 [3H, d, *J* 6.3, CH_3-C(4)], 1.76–1.85 [2H, m, C(2′)H_2 or C(3′)H_2], 1.86–1.99 [2H, m, C(2′)H_2 or C(3′)H_2], 2.68 [2H, t, *J* 7.5, C(4′)H_2], 3.10–3.17 (1H, sym m, one of NCH_2CH_3), 3.22 [2H, t, *J* 7.9, C(1′)H_2], 3.40–3.48 (1H, m, one of NCH_2CH_3), 4.02 [1H, br s, C(3)*H*], 4.25 [1H, q, *J* 6.1, C(4)*H*], 7.14–7.22 (3H, m, Ar*H*), 7.25–7.32 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 13.0 (CH_3, NCH_2CH_3), 18.0 [CH_3, CH_3-C(4)], 20.9 [CH_2, *C*(2′)H_2 or *C*(3′)H_2], 30.1 [CH_2, *C*(2′)H_2 or *C*(3′)H_2], 35.3 [CH_2, *C*(4′)H_2], 36.0 (CH_2, NCH_2CH_3), 47.7 [CH, *C*(4)H], 53.1 [CH_2, *C*(1′)H_2], 72.2 [CH, *C*(3)H], 126.1 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 141.2 (C,

aromatic *C*), 158.1 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{24}NO_3S$ $[M+H]^+$, 310.1477. Found 310.1466.

Note: Due to reduction of 2-diazo-*N*,*N*-diethyl-2-[(4-phenylbutyl)sulfonyl]acetamide **47**, sulfone **118** was formed. While it was not clearly distinguished in the ^{1}H NMR spectra of the crude product mixtures, it was isolated as mixtures with β-lactam **221b**. Full spectral characterisation of sulfone **118** can be found in **Section 3.7**, however the following key signals allow for its identification in the mixtures discussed here; δ_H 3.29–3.36 [2H, m, C(1′)H_2], 3.98 (2H, s, SO_2CH_2CO).

The most polar fraction recovered from **Table 6.17**, entry 2 was ɣ-lactam **219** isolated as three fractions; [fraction 1, (9.6 mg, 12%) (54% ee determined by chiral HPLC), containing >99% ɣ-lactam **219**; fraction 2, (6.4 mg, 8%), (51% ee determined by chiral HPLC), containing >99% ɣ-lactam **219**; fraction 3 (4.8 mg, 6%), (49% ee determined by chiral HPLC), isolated pure and full analysis was carried out on this sample], all as colourless oils with the following spectral characteristics;

1-Ethyl-3-[(4-phenylbutyl)sulfonyl]pyrrolidin-2-one 219



ν_{max}/cm^{-1} (neat): 2936, 2872 (CH), 1684 (CO), 1495, 1436, 1455, 1282, 1135 (SO_2), 748, 701 (CS) ; δ_H ($CDCl_3$, 600 MHz): 1.16 (3H, t, *J* 7.3, NCH_2CH_3), 1.77–1.84 [2H, m, C(3′)H_2], 1.90–1.98 [2H, m, C(2′)H_2], 2.26–2.45 [1H, m, one of C(4)H_2], 2.68 [2H, t, *J* 7.6, C(4′)H_2], 2.72–2.79 [1H, m, one of C(4)H_2], 3.32–3.49 [5H, m, C(1′)H_2, NCH_2CH_3 and one of C(5)H_2], 3.61 [1H, m, overlapping dt, appears as quartet, *J* 16.3, 8.6, one of C(5)H_2], 3.83 [1H, dd, *J* 10.2, 4.2, C(3)*H*], 7.15–7.22 (3H, m, Ar*H*), 7.25–7.31 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 12.2 (CH_3, NCH_2CH_3), 17.5 [CH_2, *C*(4)H_2], 21.3 [CH_2, *C*(2′)H_2], 30.2 [CH_2, *C*(3′)H_2], 35.4 [CH_2, *C*(4′)H_2], 38.0 [CH_2, NCH_2CH_3], 45.0 [CH_2, *C*(5)H_2], 52.0 [CH_2, *C*(1′)H_2], 62.8 [CH, *C*(3)H], 126.0 (CH, aromatic *C*H), 128.4 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 140.4 (C, aromatic *C*), 165.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{24}NO_3S$ $[M+H]^+$ 310.1477. Found 310.1462. m/z (ESI+): 310.3 $[M+H]^+$.

Note assignments of 2′ and 3′ on the chain in both ^{1}H and ^{13}C have been made by analogy as the HMBC was inconclusive; chain protons C(2)H, C(3)H and C(4)H all see each

other, so they cannot be distinguished. Assignment of ring protons are based on chemical shift as the HMBC is again inconclusive as all ring protons see each other.

Assignments of the above compounds were made with the aid of 2D experiments; namely HMBC, NOESY, HSQC.

Table 6.17 *Asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **47**

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency (%)[a]	Crude Ratio[a] Purified Yield (%)[a] (% ee)[a]	Products		
							cis **thiopyran**[a] least polar	**β lactam**[a,b] more polar	**ɣ lactam**[a] most polar
1	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	48	70–80[c]	**Crude Ratio**	32	29	40
						Purified Yield (%)	10% (90% ee) (2*R*,3*R*) + 9% (94% ee) (2*R*,3*R*)	8%[d] + 5%[e] + 6%[f]	4%[g] + 12%[h] + 5%[i]
						Overall Yield (%)	20% (92% ee) $[\alpha]_D^{20}$ -67.0 (*c* 0.05, CH_2Cl_2)	11% + 5.8% total estimated for sulfone **118**	18%

2	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	70–80[j]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	17 4% (>99% ee) (2*S*,3*S*) + 6% (96% ee) (2*S*,3*S*) 10% (97% ee) $[\alpha]_D^{20}$ +74.0 (*c* 0.05, CH_2Cl_2)	20 2% + 7%[k] + 3%[l] 10% 0.77% total estimated for sulfone **118**	63 12%[m] (54% ee) + 8%[n] (51% ee) + 6% (49% ee) 26% (52% ee)
3	**D**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** (1:1)	21	70–80	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	38 15% (0% ee) 15% (0 % ee)	30 12% (0% ee) 9% (0% ee) 0.96% total estimated for sulfone **118**	32 16%[p] (0% ee) 14% (0% ee)

a. Efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **220a**, δ_H 4.12 [1H, dd, *J* 4.5, 2.4, C(2)*H*]; β-lactam **221b**, δ_H 4.25 [1H, q, *J* 6.1, C(4)*H*] and ɣ-lactam **219**, δ_H 3.83 [1H, dd, *J* 10.2, 4.2, C(3)*H*]. Reported yields (%) refer to purified material using column chromatography on silica gel. Enantioselectivities were measured using chiral HPLC, the details of which can be found in **Appendix I**. Where appropriate the absolute stereochemistry was assigned by analogy, details of which are in **Appendix II**.

b. Measurement of the enantioselectivity of β-lactam **221b** by HPLC was attempted, however results obtained were inconclusive.

c. Additional peaks may be present in the ^{1}H NMR spectra of the crude product but cannot be distinguished due to peak overlap. Additional less polar fraction obtained (3 mg), 1.18 (3H, t, *J* 7.2), 1.29 (3H, t, *J* 7.2), 1.74–1.86 (2H, m), 1.89–1.99 (2H, m), 2.64–2.71 (2H, m), 3.31–3.50 (4H, m), 3.51–3.61 (4H, m), 5.28 (s), 7.14–7.21 (3H, m), 7.27–7.32 (2H, m). Some of these peaks may indicate chloride abstraction product **223**.

d. Fraction contains 70% β-lactam **221b**, 17% *cis* thiopyran **220a**, 11% sulfone δ_H **118** 3.98 (2H, s, SO_2CH_2CO). Additional peaks may be present in the ^{1}H NMR spectra of the crude product but cannot be distinguished due to peak overlap.

e. Fraction contains 65% β-lactam **221b** and 28% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.78–2.84 (m).

f. Fraction contains 30% β-lactam **221b** and 59% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.77–2.84 (m).

g. Fraction contains 85% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 3.05–3.19 (m), 3.80 (s), 4.24 (d, *J* 11.2) These peaks may indicate *trans* sulfolane **222b.**

h. Fraction contains 86% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 3.03–3.20 (m), 3.80 (s), 4.24 (d, *J* 11.2). These peaks may indicate *trans* sulfolane **222b.**

i. Fraction contains 83% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 3.03–3.20 (m), 3.80 (s), 4.04 (s), 4.24 (d, *J* 11.2), 7.42–7.49 (m), 7.51–7.60 (m), 7.93–7.97 (m). These peaks may indicate *trans* sulfolane.

j. Additional peaks may be present in the ^{1}H NMR spectra of the crude product but cannot be distinguished due to peak overlap. Additional less polar fraction obtained (4 mg), δ_H 1.18 (3H, t, *J* 7.2), 1.29 (3H, t, *J* 7.2), 1.74–1.86 (2H, m), 1.89–1.99 (2H, m), 2.64–2.71 (2H, m), 3.31–3.50 (4H, m), 3.51–3.61 (4H, m), 5.28 (s), 7.14–7.21 (3H, m), 7.27–7.32 (2H, m). Some of these peaks may indicate chloride abstraction product **223**

k. Fraction contains 85% β-lactam **221b** and 5% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.76–2.84 (m), 4.47 (d, *J* 6.8). These peaks may indicate *trans* sulfolane **222b.**

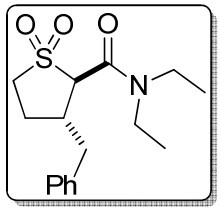
l. Fraction contains 62% β-lactam **221b** and 14% sulfone **118** δ_H 3.98 (2H, s, SO_2CH_2CO). Additional peaks present in the ^{1}H NMR spectra; δ_H 2.77–2.84 (m).

m. Fraction contains >99% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.19–3.34, 4.08–4.20 (m), 4.65–4.71 (m), 5.20–5.26 (m).

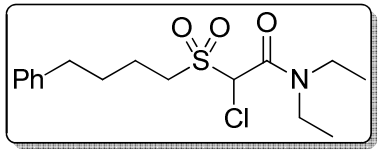
n. Fraction contains >99% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 3.20–3.25, 4.07–4.20 (m), 4.61–4.80 (m), 5.19–5.29 (m).

o. Fraction contains 76% β-lactam **221b**, 8% sulfone **118**. Additional peaks present in the ^{1}H NMR spectra; δ_H 2.76–2.89 (m), 4.10 (s), 4.14 (s), 6.12–6.27 (m), 6.53 (d, *J* 16.2), 7.52 (s).

p. Fraction contains 90% ɣ-lactam **219**. Additional peaks present in the ^{1}H NMR spectra; δ_H 0.79 (t, *J* 7.1), 1.01 (t, *J* 7.2), 2.07–2.24 (m), 3.05–3.16 (m), 3.48–3.56 (m), 4.24 (d, *J* 11.4). Some of these peaks may indicate *trans* sulfolane **222b.**



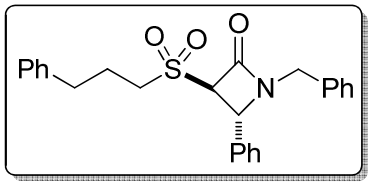
The presence of δ_H 0.79 (t, *J* 6.9), 1.18 (3H, t, *J* 7.4) and 4.47 (d, *J* 6.8) in the purified spectra of ɣ-lactam **219** and/or β-lactam **221b**, **Table 6.17**, entries 1-3 are indicative of *trans* sulfolane **222b** formation.



The presence of a singlet at 5.28 ppm is indicative of chloride abstraction **223** (**Table 6.17**, entries 1 and 2).

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1-Benzyl-4-phenyl-3-[(3-phenylpropyl)sulfonyl]azetidin-2-one 226b

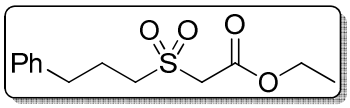


The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using *N*,*N*-dibenzyl-2-diazo-2-[(3-phenylpropyl)sulfonyl]acetamide **53** (100 mg, 0.22 mmol), $CuCl_2$ (1.5 mg, 11.2 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.9 mg, 13.4 μmol) and bisoxazoline ligand (4*R*)-Bn **43** (4.8 mg, 13.4 μmol) in dichloromethane (40 mL), stirred while heating under reflux for 30 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 50–60% efficient for C–H insertion, with evidence for benzaldehyde and complex mixture of impurities but no evidence for starting material. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80–40:60–50:50–80:20) as eluent, 1-benzyl-4-phenyl-3-[(3-phenylpropyl)sulfonyl]azetidin-2-one **226b** (12 mg, 13%) was isolated as a colourless oily solid; $[\alpha]_D^{20}$ -9.9 (*c* 0.05, CH_2Cl_2); 55% ee (determined by chiral-HPLC); ν_{max}/cm^{-1} (film): 2919 (CH), 1768 (CO), 1497, 1456, 1402, 1316, 1144 (SO_2), 699 (CS); δ_H ($CDCl_3$, 600 MHz): 2.16–2.29 [2H, m, C(2′)H_2], 2.74–2.85 [2H, m, C(3′)H_2], 3.16–3.27 [2H, m, C(1′)H_2], 3.92 (1H, d, *J* 15.3, one of NCH_2Ar), 4.32 [1H, d, *J* 1.6, C(3)*H*], 4.92 (1H, d, *J* 15.3, one of NCH_2Ar), 4.96 [1H, d, *J* 1.5, C(4)*H*], 7.15–7.35 (12H, m, Ar*H*), 7.36–7.40 (3H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 22.9 [CH_2, *C*(2′)H_2], 34.2 [CH_2, *C*(3′)H_2], 45.4 (CH_2, N*C*H_2Ar), 52.8 [CH_2, *C*(1′)H_2], 54.0 [CH, *C*(4)H], 74.6 [CH, *C*(3)H], 126.5 (CH, aromatic *C*H), 126.7 (CH, 2 × aromatic *C*H), 128.2 (CH, aromatic *C*H), 128.3 (CH, 2 × aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 128.7 (CH, 2 × aromatic *C*H), 128.9 (CH, 2 × aromatic *C*H), 129.4 (CH, 2 × aromatic *C*H), 129.5 (CH, aromatic *C*H), 133.6 (C, aromatic *C*), 134.5 (C, aromatic *C*), 139.7 (C, aromatic *C*), 159.2 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{25}H_{26}NO_3S$ $[M+H]^+$ 420.1633. Found 420.1624.

Several additional compounds were observed as a result of the catalysed reactions of *N*,*N*-dibenzyl-2-diazo-2-[(3-phenylpropyl)sulfonyl]acetamide **53**, most of which were unidentified. In cyclisations reported in **Table 6.18**, entries 2, 3-7, 9, the presence of ethanol led to sulfone byproduct **227**. This byproduct was isolated as a mixture with β-lactam **226b** in varying ratios presented on **Table 6.18**, but was never isolated

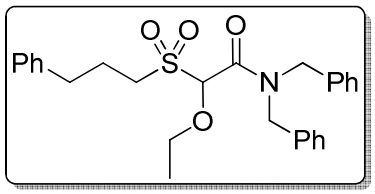
independently. Sulfone **227** is a known compound that was previously synthesised by Flynn, a sample of which was used for the development of chiral HPLC conditions. A ^{1}H NMR was obtained of this sample, the spectral characteristics remained unchanged and are given below;

Ethyl 2-[(3-phenylpropyl)sulfonyl]acetate[63] **227**



(oil) δ_H ($CDCl_3$, 400 MHz): 1.28 (3H, t, *J* 7.2 OCH_2CH_3), 2.17–2.26 [2H, m, C(2′)H_2], 2.80 [2H, t, *J* 7.4, C(3′)H_2], 3.21–3.28 [2H, m, C(1′)H_2], 3.92 (2H, s, SO_2CH_2CO), 4.24 (2H, q, *J* 7.2 OCH_2CH_3), 7.15–7.26 (3H, m, Ar*H*), 7.29–7.35 (2H, Ar*H*). HPLC analysis reveals a peak for this compound elutes at ~34 min, on chiral column Cell-4, using 10% IPA/hexane as eluent.

***N*,*N*-dibenzyl-2-ethoxy-2-[(3-phenylpropyl)sulfonyl]acetamide-assignment tentative 228**



From the experiment reported in **Table 6.18**, entry 7 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using *N*,*N*-dibenzyl-2-diazo-2-[(3-phenylpropyl)sulfonyl]acetamide **53** (100 mg, 0.22 mmol), $CuCl_2$ (1.5 mg, 11.2 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.9 mg, 13.4 μmol) and bisoxazoline ligand (3*S,8R*)-Ind **44** (4.4 mg, 13.4 μmol) in dichloromethane (40 mL) and ethanol (2 mL), stirred while heating under reflux for 24 h, in accordance with Method **B**, four fractions were recovered, the least polar compound (4 mg, 4%) was isolated as a colourless oil, *N*,*N*-dibenzyl-2-ethoxy-2-[(3-phenylpropyl)sulfonyl]acetamide **228** with the following spectral characteristics; δ_H ($CDCl_3$, 400 MHz)1.08 (3H, t, *J* 7.0, OCH_2CH_3), 2.17–2.27 [2H, m, C(2′)H_2 or C(3′)H_2], 2.74–2.82 [2H, m, C(2′)H_2 or C(3′)H_2], 3.20–3.31 [1H, m one of C(1′)H_2], 3.32–3.42 [1H, m one of C(1′)H_2], 3.43–3.52 (1H m, one of OCH_2CH_3), 3.78–3.88 (1H m, one of OCH_2CH_3), 4.30 (1H, d, *J* 15.0, one of NCH_2Ph), 4.53 (1H, d, *J* 17.7, one of NCH_2Ph), 4.88 (1H, d, *J* 17.8, one of NCH_2Ph), 4.99 (1H, s, SO_2CH), 5.17 (1H, d, *J* 15.0, one of NCH_2Ph), 7.11–7.41 (15H, Ar*H*). Three additional, more polar compounds were isolated; The next least polar fraction was recovered as a colourless oil (4.6 mg, 5%) and contained β-lactam **226b** and sulfone **227** in a ratio of 38 :62, spectral characteristics which are identified above. The compound of the next polarity was recovered as a colourless oil (8.3 mg, 9%) and contained β-lactam **226b** and sulfone

227 in a ratio of 50 :50. The most polar compound (1 mg) was an unidentified compound that had the following spectral characteristics; δ_H ($CDCl_3$, 400 MHz) 2.12–2.23 (2H, m), 2.75 (2H, t, *J* 7.4), 3.05–3.14 (2H, m), 3.85 (2H, s), 4.46 (1H, s), 4.48 (1H, s), 7.13–7.35 (15H m).

Table 6.18 *Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **53**

Entry	**Method**	**Metal**	**Solvent**	**Purity of Solvent**	**Ligand**	**T (h)**	**Crude Efficiency Lactam (%)[a]**	**Sulfone 227 (%) Crude[a]**	**Fraction**	**Purified Lactam: Sulfone**	**Yield (%)[a] Lactam, Sulfone**	**% ee[a] Lactam**
1	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, EtOH absent	(4*R*)-Bn **43**	30	50–60[b]	-	Fr1	13% Lactam only	13[c] Lactam only	55 % ee[d]
2	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*R*)-Ph **20**	21	30–40[e]	40–45	Fr 1 Fr 2 Fr 3 **Overall Yield**	(38 : 62) (50 : 50) (70 : 30)[f]	8 6[g] 2[f] (**7.44%**, **8.56%**)	39% ee[d] 37% ee[d] -

3	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*R*)-Bn **43**	24	30–40[h]	40–45	Fr 1 Fr 2 Fr 3 Fr 4 **Overall Yield**	(30 : 70) (34 : 64) (58 : 42)[i] (69 : 31)[i]	4 6 5 7 (**11.51%**, **10.91%**)	59% ee[d] 56% ee[d] 56% ee[d] 57% ee[d]
4	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*R*)-di-Ph **137**	30	10–20[j]	20–30	Fr1 Fr 2 **Overall Yield**	(33 : 67) (64 : 36)	8 10[k] (**9.04%, 8.96%**)	52% ee[d] 56% ee[d]
5	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	(4*S*)-*t*-Bu **138**	50	20–30[l]	35–45	Fr 1 [m,n] Fr 2[o] Fr 3[o] **Overall Yield**	(42 : 58) (35 : 65) (58 : 42)	5 10 9 (**10.82%**, **13.18%**)	53% ee[p] 78% ee[p] 48% ee[p]
6	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled,	(3*S*,8*R*)-Ind **44**	21	30–40[q]	30–40	Fr 1 Fr 2 Fr 3	(33 : 67) (48 : 52) (61 : 39)	2 9 6	84% ee[p] 82% ee[p] 84% ee[p]

				trace EtOH					Fr 4 **Overall Yield**	(68 : 32)	4 (**11.36%** , **9.64%**)	84% ee[p]
7	**B**	$CuCl_2/\Delta$	CH_2Cl_2	Doubly distilled, spiked with EtOH	(3*S*,8*R*)-Ind **44**	24	-[r]	-[r]	Fr1 Fr 2 **Overall Yield**	(38 : 62) (50 : 50)	5 9[s] (**6.4%, 7.6%**)	85% ee[p] 81% ee[p]
8	**B**	$CuCl_2/\Delta$	CH_2Cl_2	HPLC grade, no EtOH	(3*S*,8*R*)-Ind **44**	30	30–40[t]		Fr1 Fr2 **Overall Yield**	- -	9 12[u] **21%**	89% ee[p] 77% ee[p,v]
9	**E**	$Rh_2(OAc)_4/\Delta$	CH_2Cl_2	Doubly distilled, trace EtOH	-	18	50–60[w]		Fr1 Fr2 **Overall Yield**	(37 : 63)[x] (67 : 33)[x]	6 10 (**8.92%, 7..08%**)	0% ee

a. Crude Efficiencies and relative ratios were calculated approximately, using C(3)*H* signal for β-lactam **226b,** δ_H 4.96 [1H, d, *J* 1.5, C(3)*H*] and OCH_2CH_3 for sulfone **227** δ_H 4.24 (2H, q, *J* 7.2 OCH_2CH_3). Yields given are based on calculations, based on the molecular weight of β-lactam **226b** and have not been adjusted for the different molecular weights of the other products.

b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.96–3.13 (m), 3.28–3.40 (m), 3.49 (d, *J* 14.3), 3.52–3.63 (m), 3.64–3.74 (m), 3.84 (s), 4.07–4.15 (m), 4.43–4.49 (m), 4.51 (s), 4.75–4.79 (m), 4.82 (s), 4.90 (s), 5.12 (d, *J* 15.1), 5.22–5.40 (m), 5.57 (d, *J* 14.2), 6.62–6.67 (m), 6.68–6.73 (m), 6.78–6.84 (m), 6.86–6.90 (m), 6.91–6.97 (m), 7.03–7.11 (m), 7.61–7.67 (m), 7.71 (br s), 7.82 (br s), 7.86–7.90 (m), 8.25 (s), 8.41 (br s), 10.02 (s).

c. Baseline impurities were present in the ^{1}H NMR spectra of the pure product; δ_H 10.03 (s). Two additional fractions were obtained. A fraction (4 mg) that was less polar than *trans* **226b** was recovered with the following spectral characteristics; δ_H 2.16–2.35 (m), 2.76–2.88 (m), 3.08 (d, *J* 13.4), 3.26 (d, *J* 13.2), 3.49 (d, *J* 14.3), 3.53–3.74 (m), 4.47 (d, *J* 7.5), 4.52 (s), 4.91 (d, *J* 7.8), 4.94 (s), 5.57 (d, *J* 14.4), 6.69–6.74 (m), 6.92 (s), 7.02–7.09 (m), 7.11–7.45 (m), 7.50–7.54 (m). A fraction (3 mg) that was more polar than *trans* **226b** was recovered with the following spectral characteristics; δ_H (major signals) 2.13–2.23 (m), 2.75 (t, *J* 7.5), 3.04–3.14 (m), 3.85 (s), 4.47 (d, *J* 5.8). δ_H (minor signals) 2.56–2.61 (m), 2.86–3.03 (m), 3.29–3.35 (m), 3.61–3.72 (m), 3.89–4.17 (m), 4.50–4.62 (m), 4.83 (s), 4.84 (s), 4.95 (d, *J* 15.0), 5.13 (d, *J* 15.5), 5.23 (d, *J* 15.5), 6.22 (s), 6.72 (br s), 8.40 (s), 7.01–7.50 (m).

d. The second eluting enantiomer of the *trans* isomer **226b** at 65–85 min is the major enantiomer, using 10% IPA/Hexane (Cell-2).

e. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.97–2.08 (m), 2.63–2.71 (m), 3.04–3.14 (m), 3.60–3.66 (m), 3.69 (m), 4.47 (d, *J* 5.8), 4.52 (s), 4.67 (s), 5.42 (s), 7.51 (br s), 7.54 (s), 7.56 (s), 7.61–7.67 (m), 7.71 (br s), 7.87–7.91 (m), 8.07–8.12 (m), 8.14–8.25 (m), 8.68–8.74 (m), 10.03 (s).

f. There were additional peaks present in the ^{1}H NMR spectra of Fr 3 (2 mg); δ_H 3.25–3.51 (m), 4.17 (s), 4.82 (d, *J* 5.3), 4.92 (s), 4.98–5.01 (m).

g. Two additional fractions were obtained. A fraction (1.5 mg) that was less polar than *trans* **226b** was recovered, that contained majority sulfone **227**, that contained additional peaks in the ^{1}H NMR spectra; δ_H 3.02–3.08 (m), 3.47–3.49 (m), 3.81–3.87 (m), 5.20 (d, *J* 16.0), 6.76 (s), 6.80 (s), 7.57 (s), 7.61 (s). A fraction (6 mg) that was more polar than *trans* **226b** was recovered with the following spectral characteristics; δ_H (major signals) 0.82–0.91 (4H, m), 2.13–2.22 (2H, m), 2.75 (2H, t, *J* 7.5), 3.08–3.14 (2H, m), 3.85 (2H, s), 4.47 (d, *J* 5.80), 7.14–7.37 (15H, m). δ_H (minor signals) 4.64–4.71 (m), 5.19–5.26 (m).

h. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.06–3.03 (m), 3.86 (s), 4.48 (d, *J* 5.7), 4.68 (s), 7.49–7.54 (m), 7.71 (br s), 8.08 (s), 8.09 (s), 8.18–8.25 (m), 8.68–8.72 (m).

i. Contaminant present.

j. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.04–3.13 (m), 3.86 (s), 4.46–4.53 (m), 4.68 (s), 4.77–4.85 (m), 5.35 (s), 5.55–5.64 (m), 6.10 (s), 6.22–6.28 (s), 6.38 (s), 6.51 (s), 6.53 (s), 7.48–7.57 (m), 7.61–7.67 (m), 7.72 (br s), 7.77 (br s), 7.86–7.92 (br s), 8.08 (s), 8.09 (s), 8.20–8.23 (m), 10.03 (s).

k. Two additional fractions were obtained. A less polar mixed fraction (1.3 mg) that was less polar than *trans* **226b** was recovered, that contained *trans* **226b** and sulfone **227** in a ratio of 33:67 (*approx* 50–60% combined of the mixture), in addition to another compound(s) that contained peaks in the ^{1}H NMR spectra; δ_H 3.02–3.07 (m), 3.54–3.68 (m), 4.02–4.16 (m), 4.47 (s), 4.50–4.53 (m), 4.77 (s), 4.81 (s), 6.10 (s), 6.76 (s), 6.80 (s), 7.49–7.53 (m). A fraction (0.5 mg) that was more polar than *trans* **226b** was isolated with the following spectral characteristics; δ_H 1.50–5.00 (series of overlapping signals), 5.43 (s), 6.99–7.43 (m)

l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.04–3.15 (m), 4.47 (d, *J* 4.5), 4.51 (s), 4.52 (s), 4.68 (s), 4.76 (s), 4.81 (s), 5.35 (s), 8.08 (s).

m. After initial purification by column chromatography an additional fraction was obtained. A fraction (2.1 mg) that was more polar than *trans* **226b** was recovered with the following spectral characteristics; δ_H 2.63–2.87(m), 2.19–3.50 (m), 3.82 (s), 3.84 (s), 3.85 (s), 3.87 (s), 3.93 (s), 3.94 (s), 3.98 (s), 4.04–4.19 (m), 4.20–4.28 (m), 4.30–4.38 (m), 4.66 (s), 4.69 (s), 4.81 (s), 4.82 (s), 4.89–4.99 (m), 7.14–7.43 (m).

n. After initial purification by column chromatography two fractions containing *trans* **226b** were obtained. The first fraction obtained was of sufficient purity to undergo chiral HPLC analysis. The results reported for Fr 1 here, are for this initial pure fraction. The second fraction was not of sufficient purity to undergo HPLC analysis and therefore was purified a second time.

o. After initial purification by column chromatography two fractions containing *trans* **226b** were obtained. The second fraction contained additional peaks in the ^{1}H NMR spectra; δ_H 1.71–1.82 (m), 1.83–1.99 (m), 2.67 (t, *J* 7.4), 3.30–3.37 (m), 3.38–3.49 (m), 3.98 (s), 4.08–4.21 (m). The two compounds *trans* **226b** and sulfone **227** account for *approx* 90% of the mixture combined. The relative ratio of *trans* **226b** : sulfone **227** was 43:57. This fraction underwent a second purification using column chromatography on silica gel, using ethyl acetate-hexane as the eluent. Two additional fractions containing product were obtained and these are reported as Fr 2 and Fr 3.

p. The first eluting enantiomer of the *trans* isomer **226b** at 40-55 min is the major enantiomer, using 10% IPA/Hexane (Cell-2).

q. Analysis of ^{1}H NMR spectra of the crude product showed that *approx* 5% of the starting material α-diazocarbonyl **53** was present. Additional signals observed in the ^{1}H NMR spectra of the crude product; δ_H 3.06–3.14 (m), 3.86 (s), 4.68 (s), 6.73 (br s).

r. ^{1}H NMR analysis of crude material not available.

s. Two additional fractions were obtained. The least polar fraction isolated was tentatively assigned ethanol insertion product **228** (2 mg). A fraction that was more polar than β-lactam **226b** (1 mg) was isolated with the following spectral characteristics; δ_H 2.12–2.23 (2H, m), 2.75 (2H, t, *J* 7.4), 3.05–3.14 (2H, m), 3.85 (2H, s), 4.46 (1H, s), 4.48 (1H, s), 7.13–7.35 (15H m)

t. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 3.05–3.13(m), 3.53–3.59 (m), 3.85 (s), 4.46 (s), 4.47 (s), 4.76 (s), 4.81 (s), 5.35 (s), 7.50–7.56 (m), 7.61–7.66 (m), 7.72 (br s), 7.86–7.92 (m), 10.03 (s).

u. Additional less polar fraction obtained (2 mg), that contained peaks in the ^{1}H NMR spectra; δ_H 2.21–2.32 (m), 2.77–2.86 (m), 3.54–3.60 (m), 4.47 (s), 4.50 (s), 4.79 (d, *J* 17.6), 4.91 (d, *J* 14.7), 5.34 (s), 7.11–7.45 (m).

v. $[\alpha]_D^{20}$ +15.2 (*c* 0.23, CH_2Cl_2).

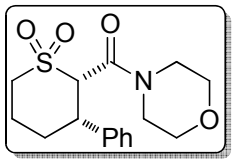
w. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.59 (s), 4.67 (s), 4.85 (s), 7.44–7.66 (m), 7.77–7.82 (m), 7.87–7.92 (m), 8.09 (s), 8.41 (s), 10.03 (s).

x. Results refer to data after a second purification. Both methods of purification were carried out using column chromatography on silica gel. A second purification was carried out in an attempt to separate sulfone **227** from lactam **226b**. Results after first purification; (50 : 50) **226b** lactam : sulfone **227**.

*Assignments of the above compound **226b** was made with the aid of 2D experiments; namely HMBC and HSQC.*

Note: A solution of *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120** (100 mg) in dichloromethane (40 mL) and ethanol (2 mL) was stirred at reflux for 24 h. The solution was concentrated under reduced pressure and a ^{1}H NMR spectra of the resulting compound was obtained. Only starting material, *N*,*N*-dibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide **120**, was recovered.

(1,1-Dioxido-3-phenyltetrahydro-2H-thiopyran-2-yl](morpholino)methanone 224a



The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-1-morpholino-2-[(4-phenylbutyl)sulfony])ethanone **48** (50 mg, 0.14 mmol), $CuCl_2$ (0.96 mg, 7.1 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (7.6 mg, 8.5 μmol) and bisoxazoline ligand (3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** (1: 1 ratio, 1.4 mg each, 2.8 mg total, 8.5 μmol) in dichloromethane (30 mL), stirred while heating under reflux for 21 h, in accordance with Method **D**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 60-70% efficient. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95-10:90-20:80) as eluent, 1,1-dioxido-3-phenyltetrahydro-2H-thiopyran-2-yl](morpholino)methanone **224a** (9 mg, 20 %) was isolated as white solid; mp 185–186° C; ν_{max}/cm^{-1} (neat, ATR): 2930, 2857 (CH), 1642 (CO), 1439, 1305, 1231, 1267, 1113 (SO_2), 762, 704 (CS); δ_H ($CDCl_3$, 600 MHz): 1.78 [1H, apparent dq, *J* 13.6, 3.2, one of C(4)H_2], 2.15–2.34 [2H, m, C(5)H_2], 2.47–2.56 (2H, sym m, morpholine NCH_2 and OCH_2), 2.77 [1H, apparent qd, *J* 13.5, 3.7 one of C(4)H_2], 3.02 [1H, apparent dq, *J* 13.4,

3.0, one of C(6)H_2], 3.08–3.14 (1H, sym m, morpholine NCH_2), 3.27–3.36 (2H, sym m, morpholine OCH_2), 3.37–3.44 (1H, sym m, morpholine NCH_2), 3.55–3.62 (2H, sym m, morpholine NCH_2 and OCH_2), 3.69–3.74 [1H, m, C(3)*H*], 3.98 [1H, apparent td, *J* 13.6, 4.2, one of C(6)H_2], 4.22 [1H, dd, *J* 4.8, 2.3, C(2)*H*], 7.23–7.27 (2H, m, Ar*H*), 7.28–7.37 (3H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 23.2 [CH_2, *C*(5)H_2], 23.9 [CH_2, *C*(4)H_2], 42.2 (CH_2, morpholine N*C*H_2), 45.3 [CH, *C*(3)H], 46.6 (CH_2, morpholine N*C*H_2), 48.6 [CH_2, *C*(6)H_2], 65.0 [CH, *C*(2)H], 65.6 (CH_2, morpholine O*C*H_2), 66.2 (CH_2, morpholine O*C*H_2), 127.6 (CH, 2 × aromatic *C*H), 128.1 (CH, aromatic *C*H), 129.1 (CH, 2 × aromatic *C*H), 139.9 (C, aromatic *C*), 163.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{22}NO_4S$ $[M+H]^+$, 324.1270. Found 324.1261. m/z (ESI+): 324.3 $[M+H]^+$.

Table 6.19 *Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **48**

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency (%)[a]	Fraction	Yield of 224a (%)	ee (%)
1	**D**	$CuCl_2$	(3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** (1:1)	21	60–70[b]	Fraction 1	20	0
2	**B**	$CuCl_2$	(4*R*)-Ph **20**	21	40–50[c]	Fraction 1 Fraction 2 **Overall yield (%)**	4[d] 15[d] **~19%**	- 98 (2S,3S) $[\alpha]_D^{20}$ + 40.0 (*c* 0.05, CH_2Cl_2)
3	**B**	$CuCl_2$	(3*S*,8*R*)-Ind **44**	21	40–50[e]	Fraction 1 Fraction 2 **Overall yield (%)**	6[f] 7 **~13%**	86 (2*R*,3*R*) $[\alpha]_D^{20}$ - 57.0 (*c* 0.1, CH_2Cl_2)

a. Efficiency calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **224a** δ_H 4.22 [1H, dd, *J* 4.8, 2.3, C(2)*H*]. Yield reported after purification using column chromatography on silica gel. Enantioselectivities were measured using chiral HPLC analysis, details of which are in **Appendix I**. Absolute stereochemistry was assigned by analogy, details of which are available in **Appendix II**.

b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.85–2.03 (m), 2.59–2.71 (m), 3.58 (d, *J* 9.7), 3.63–3.81 (m). The later signals overlap with signals for *cis* thiopyran **224a**.

c. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.58–2.71 (m), 3.58 (d, *J* 9.7), 3.63–3.82 (m). The later signals overlap with signals for *cis* thiopyran **224a**.

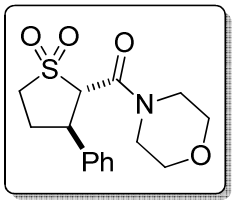
d. Fr 1 contained the following additional peaks in the ^{1}H NMR spectrum; δ_H 2.59–2.72 (m), 4.62–4.75 (m), 5.7–5.31 (m), 5.41 (s). A third fraction (2 mg) that was less polar than *cis* thiopyran **224a** was isolated, that contained *approx* 10% *cis* thiopyran **224a**, that contained additional peaks in the ^{1}H NMR spectra; δ_H 1.74–1.85 (m), 1.86–1.98 (m), 2.63–2.71 (m), 3.37–3.82 (m), 5.20 (s), 5.40 (s).

e. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 2.62–2.71 (m), 3.58 (d, *J* 9.7), 3.63–3.80 (m). The later signals overlap with signals for *cis* thiopyran **224a**.

f. Two fractions containing *cis* thiopyran **224a** were isolated. The ^{1}H NMR spectra of Fr 1 contained additional signals; δ_H 1.88–1.94 (m), 3.46–3.63 (m), 3.64–3.83. Attempted analysis of the enantiopurity of *cis* thiopyran **224a** in Fr1 was unsuccessful due to peak overlap during chiral HPLC.

Assignment of the above compound was made with the aid of 2D NMR experiments namely HSQC, HMBC and NOESY.

(1,1-Dioxido-3-phenyltetrahydrothiophen-2-yl)(morpholino)methanone 231b

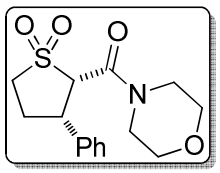


The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfony]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2- diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52** (70 mg, 0.21 mmol), $CuCl_2$ (1.4 mg, 10.4 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.0 mg, 12.4 μmol) and bisoxazoline ligand (*S*)-*t*-Bu **138** (3.7 mg, 12.4 μmol) in dichloromethane (40 mL), stirred while heating under reflux for 48 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 60–70% efficient (20% *cis* **231a**: 80% *trans* **231b**). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–30:70–40:60) as eluent, (1,1-dioxido-3-phenyltetrahydrothiophen-2-yl)(morpholino)methanone **231b** (11 mg, 17%) was isolated as a white solid; $[\alpha]_D^{20}$ -22.78 (*c* 0.09, CH_2Cl_2); 77% ee (determined by chiral-HPLC); mp 163–164 °C; ν_{max}/cm^{-1} (neat, ATR): 2963, 2872 (CH), 1651 (CO), 1449, 1300, 1260, 1114, 1032 (SO_2), 758, 701 (CS); δ_H ($CDCl_3$, 600 MHz): 2.37–2.46 [1H, m, one of C(4)H_2], 2.52–2.59 [1H, m, one of

C(4)H_2], 3.22 [1H, apparent dt, *J* 13.1, 6.7, one of C(5)H_2], 3.32–3.38 [1H, sym m, morpholine NCH_2], 3.42–3.48 [2H, m, one of C(5)H_2 and morpholine NCH_2], 3.63–3.79 (5H, m, morpholine CH_2), 3.97–4.03 (1H, sym m, morpholine NCH_2), 4.12 [1H, d, *J* 9.6, C(2)*H*], 4.32 [1H, ddd, *J* 12.6, 9.7, 6.0, C(3)*H*], 7.27–7.39 (5H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 28.2 [CH_2, *C*(4)H_2], 43.5 (CH_2, morpholine N*C*H_2), 45.0 [CH_2, *C*(3)H], 46.3 (CH_2, morpholine N*C*H_2), 53.2 [CH_2, *C*(5)H_2], 66.5 (CH_2, morpholine O*C*H_2), 66.6 (CH_2, morpholine O*C*H_2), 68.9 [CH_2, *C*(2)H], 127.3 (CH, 2 × aromatic *C*H), 127.9 (CH, aromatic *C*H), 129.2 (CH, 2 × aromatic *C*H), 139.6 (C, aromatic *C*), 161.6 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{20}NO_4S$ $[M+H]^+$, 310.1113. Found 310.1102. m/z (ESI+) 310.3 $[M+H]^+$.

A more polar fraction was isolated containing (5 mg, 8%) as a white solid, containing 86% *cis* sulfolane **231a** and 12% *trans* sulfolane **231b**. Spectroscopic characteristics of *cis* **231a** are consistent with those reported below.

(1,1-Dioxido-3-phenyltetrahydrothiophen-2-yl)(morpholino)methanone *cis* 231a



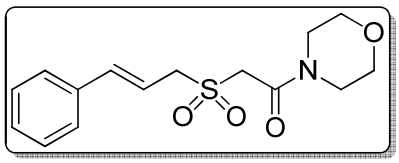
The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52** (70 mg, 0.21 mmol), $CuCl_2$ (1.4 mg, 10.4 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.0 mg, 12.4 μmol) and bisoxazoline ligand (4*R*)-Bn **43** (4.5 mg, 12.4 μmol) in dichloromethane (40 mL), stirred while heating under reflux for 60 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 60–70% efficient (20% *cis* **231a**: 80% *trans* **231b**). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–30:70–40:60) as eluent, [(2*S*,3*R*)-1,1-dioxido-3-phenyltetrahydrothiophen-2-yl](morpholino)methanone **231b** (18 mg, 28%) was isolated as a white solid; 42% ee (determined by chiral-HPLC); Full spectroscopic analysis of this compound was consistent with the data given above. A second more polar fraction was isolated (3 mg, 5%) as a white solid identified as the *cis* isomer **231a**; ν_{max}/cm^{-1} (neat, ATR): 2920, 2850 (CH), 1618 (CO), 1470, 1439, 1315, 1140, 1104, 1027 (SO_2), 757, 699 (CS); δ_H ($CDCl_3$, 600 MHz): 2.44–2.52 [1H, m, one of C(4)H_2], 2.53–2.59 (1H, sym m, morpholine OCH_2), 2.76–2.83 (1H, sym m, morpholine NCH_2), 3.12 [1H, apparent qd, *J* 12.2, 12.2, 12.2, 6.8 one of C(4)H_2], 3.28 (1H, ddd, *J* 13.0, 7.9, 3.1, morpholine NCH_2), 3.26–3.31 (1H, m,

morpholine OCH_2), 3.31–3.37 [2H, m, one of C(5)H_2 and morpholine NCH_2], 3.40–3.45 (1H, m, morpholine OCH_2), 3.57–3.62 (1H, sym m, morpholine OCH_2), 3.63–3.69 (1H, sym m, morpholine NCH_2), 3.75–3.81 [1H, m, one of C(5)H_2], 4.04–4.12 [1H, m, C(3)*H*], 4.28 [1H, d, *J* 6.9, C(2)*H*], 7.30–7.41 (5H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 25.7 [CH_2, *C*(4)H_2], 42.1 (CH_2, morpholine N*C*H_2), 45.0 [CH_2, *C*(3)H], 46.5 (CH_2, morpholine N*C*H_2), 51.8 [CH_2, *C*(5)H_2], 64.7 [CH_2, *C*(2)H], 65.8 (CH_2, morpholine O*C*H_2), 66.2 (CH_2, morpholine O*C*H_2), 128.3 (CH, 2 × aromatic *C*H), 128.5 (CH, aromatic *C*H), 129.1 (CH, 2 × aromatic *C*H), 136.5 (C, aromatic *C*), 163.0 (C, *C*O).

A second less polar compound, *trans* **231b**, with spectroscopic data consistent with that reported above was isolated and eluted over three fractions; Fraction 1 (5.19 mg, 8%), 45% ee, determined using chiral HPLC, Fraction 2 (7.14 mg, 11%), 43% ee determined using chiral HPLC and Fraction 3 (5.84 mg, 9%), 39% ee determined using chiral HPLC (**Table 6.20**, entry 2).

From the experiment reported in **Table 6.20**, entry 3, 2-diazo-1-morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52** (70 mg, 0.21 mmol), $CuCl_2$ (1.4 mg, 10.4 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.0 mg, 12.4 μmol) and bisoxazoline ligand (3*S*,8*R*)-Ind **44** (4.1 mg, 12.4 μmol) in dichloromethane (40 mL), stirred while heating under reflux for 21 h, in accordance with Method **B**, two fractions were isolated, the least polar compound (11 mg, 17%) (47% ee, determined by chiral HPLC) was *trans* sulfolane **231b** with spectral characteristics as identified above, the more polar fraction 2-(cinnamylsulfonyl)-1-morpholinoethanone **232** was isolated as a colourless oil (2 mg, 3%) with the following spectral characteristics;

2-(Cinnamylsulfonyl)-1-morpholinoethanone 232



δ_H ($CDCl_3$, 400 MHz): 3.57-3.63 (2H, m, CH_2 morpholine), 3.69 (4H, br s, CH_2 morpholine), 3.73–3.77 (2H, m, CH_2 morpholine), 4.06 (2H, s, SO_2CH_2CO), 4.13 [2H, d, *J* 7.6, C(1′)H_2], 6.21–6.32 [1H, m, C(2′)*H*], 6.90 [1H, d, *J* 15.9, C(3′)*H*], 7.27–7.38 (3H, m, Ar*H*), 7.40–7.46 (2H, m, Ar*H*).

*Assignment of the above compound **231a** and **231b** was made with the aid of 2D NMR experiments namely HSQC, HMBC and NOESY.*

Table 6.20 *Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***52***

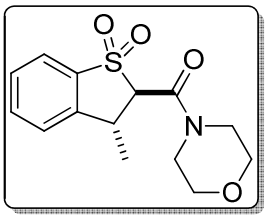
Entry	**Method**	**Metal**	**Ligand**	**Time (h)**	**Crude Efficiency (%)[a]**	**Crude Ratio[a]** **Purified Yield (%)[a]** **(% ee)[a]**	**Products** ***cis*** **sulfolane 231a more polar** :	***trans*** **sulfolane 231b less polar**
1	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	48	60–70[b]	**Crude Ratio** **Purified Yield (%)** **Overall Yield (%)**	20 8[c] 7	80 22[d] (77% ee)[e] 23 $[\alpha]_D^{20}$ -22.78 (*c* 0.09, CH_2Cl_2)
2	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	60	60–70[f]	**Crude Ratio** **Purified Yield (%)**	20 5%	80 8[g] (45% ee)[h] $[\alpha]_D^{20}$ +1.961 (*c* 0.102, CH_2Cl_2) + 11 (43% ee)[h] $[\alpha]_D^{20}$ +7.692 (*c* 0.13, CH_2Cl_2) + 9 (39% ee)[h]

						Overall Yield (%)	5%	28% (42% ee)[i]
3	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	21	60–70%[j]	**Crude Ratio** **Purified Yield (%)**	30 -	70 17%[k] (47% ee)[e] $[\alpha]_D^{20}$ -9.542 (*c* 0.105, CH_2Cl_2)
4	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	21	60–70%[l]	**Crude Ratio** **Purified Yield (%)**	70 18%[m]	30 6%[n]
5	**B**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	21	60–70%[o]	**Crude Ratio** **Purified Yield (%)**	60 15%[m]	40 8%[n]
6	**E**	$Rh_2(OAc)_4/\Delta$		6	50–60%[p]	**Crude Ratio** **Purified Yield (%)**	60 -	40 14%[q]

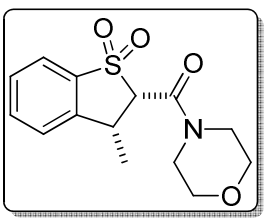
a. Efficiency and relative ratios were calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*; *cis* sulfolane **231a**, δ_H 4.04–4.12 [1H, m, C(3)*H*]; *trans* sulfolane **231b**, δ_H 4.12 [1H, d, *J* 9.6, C(2)*H*] and 4.32 [1H, ddd, *J* 12.6, 9.7, 6.0, C(3)*H*]. Relative ratios and crude efficiencies were estimated due to peak overlap. Yield (%) reported after purification using column chromatography on silica gel. Enantioselectivities were measured using chiral HPLC, details of which can be found in **Appendix I**.

b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.40 (s), 5.92 (s), 6.19–6.34 (m), 6.90 (d, *J* 15.8), 9.48 (s). Additional peaks in the range of 2.0–4.5 ppm cannot be distinguished due to peak overlap.
c. Contains 86% *cis* sulfolane **231a**, 14% *trans* sulfolane **231b**.
d. An additional less polar fraction (3 mg) was obtained after purification using column chromatography on silica gel. This was the least polar fraction obtained. The following signals in the ^{1}H NMR spectra were observed; δ_H 2.15–2.29 (m), 2.74–2.83 (m), 2.86 (s), 2.95–3.02 (m), 3.19–3.27 (m), 3.28–3.35 (m), 3.36–3.50 (m), 3.51–3.64 (m), 3.65–3.86 (m), 5.40 (s), 5.91 (s), 7.14–7.37 (m).
e. The second eluting enantiomer of the *trans* isomer **231b** at ~45 min is the major enantiomer, using 30% IPA (Cell-4).
f. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.42 (s), 6.23–6.32 (m), 6.91 (d, *J* 15.6). Additional peaks in the range of 2.0–4.5 ppm cannot be distinguished due to peak overlap.
g. An additional less polar fraction (1.5 mg) was obtained after purification using column chromatography on silica gel. This was the least polar fraction obtained. The following signals in the ^{1}H NMR spectra were observed; δ_H 2.15–2.28 (m), 2.74–2.84 (m), 2.86 (s), 2.95–3.01 (m), 3.20–3.28 (m), 3.29–3.35 (m), 3.36–3.51 (m), 3.53–3.65 (m), 3.66–3.85 (m), 5.38 (s), 5.91 (s), 7.14–7.36 (m).
h. The first eluting enantiomer of the *trans* isomer **231b** at ~33 min is the major enantiomer, using 30% IPA/hexane (Cell-4).
i. Overall enantioselectivity calculated by weighted average.
j. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.71 (s), 5.42 (br s), 5.90–5.98 (m), 6.22–6.31 (m), 6.90 (d, *J* 15.8), 9.49 (s).
k. An additional fraction that was more polar than *trans* sulfolane **231b** was isolated. It has been tentatively assigned as hydride elimination product **232**, and its spectral characteristics are listed above.
l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.48 (s), 9.49 (s). Additional signals may be present in the region of 1.0–4.6 ppm but are not distinguishable due to peak overlap.
m. Only one peak was detected during HPLC analysis of this compound.
n. % ee not determined.
o. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 4.71 (s), 5.42 (s). Additional signals may be present in the region of 1.0–4.6 ppm but are not distinguishable due to peak overlap.
p. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.21–5.32 (m), 5.47–5.54 (m), 5.59–5.66 (m), 6.10 (s), 6.14 (s), 9.50 (s). Additional signals may be present in the region of 1.0–4.6 ppm but are not distinguished due to peak overlap.
q. Purified fraction contains an impurity with the following signals present in the ^{1}H NMR; δ_H 2.76–2.85 (m), 4.52 (s). HPLC trace is not clean.

(3-Methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl)(morpholino)methanone 233b



2-Diazo-2-[(2-ethylphenyl)sulfonyl]-1-morpholinoethanone **58** (100 mg, 0.31 mmol) in distilled dichloromethane (15 mL) was added dropwise over 5 min to a refluxing solution of $Rh_2(OAc)_4$ (~1 mg) in distilled dichloromethane (20 mL), stirred while heating under reflux for 21 h, in accordance with Method **E**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* >90% efficient (4% *cis* **233a**: 96% *trans* **233b**). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80–50:50–80:20) as eluent, (3-methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl)(morpholino)methanone (1% *cis* **233a**, 99% *trans* **233b**) (42 mg, 46%) was isolated as a colourless oil; 0 % ee (*trans* **233b**) (determined by chiral HPLC); The following spectral characteristics are reported for *trans* **233b**; ν_{max}/cm^{-1} (film): 2971, 2930, 2862 (CH), 1652 (CO), 1447, 1305, 1278, 1248, 1175, 1156, 1133, 1114, 1065, 1037 (SO_2), 761 (CS); δ_H ($CDCl_3$, 400 MHz): 1.51 [3H, d, *J* 7.0, C(1′)*H*$_3$], 3.41 (1H, ddd, *J* 13.1, 8.6, 3.4, morpholine C*H*$_2$), 3.56–3.65 (1H, m, morpholine C*H*$_2$), 3.66–3.74 (1H, m, morpholine C*H*$_2$), 3.77–3.81 (1H, m, morpholine C*H*$_2$), 3.82–3.88 (2H, m, morpholine C*H*$_2$), 3.95–4.05 (1H, sym m, morpholine C*H*$_2$), 4.07–4.14 (1H, sym m, morpholine C*H*$_2$), 4.24 [1H, d, *J* 6.5, C(2)*H*], 4.36 [1H, apparent quint, *J* 6.9, C(3)*H*], 7.43–7.52 (2H, Ar*H*), 7.61–7.71 (2H, m, Ar*H*); δ_C ($CDCl_3$, 75.5 MHz): 18.9 [CH_3, *C*(1′)H$_3$], 36.6 [CH, *C*(3)H], 43.6 (CH_2, morpholine N*C*H$_2$), 46.7 (CH_2, morpholine N*C*H$_2$), 66.7 (CH_2, morpholine O*C*H$_2$), 66.9 (CH_2, morpholine O*C*H$_2$), 69.7 [CH, *C*(2)H], 121.5 (CH, aromatic *C*H), 125.5 (CH, aromatic *C*H), 128.9 (CH, aromatic *C*H), 134.2 (CH, aromatic *C*H), 136.9 (C, aromatic *C*), 141.5 (C, aromatic *C*), 160.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{14}H_{18}NO_4S$ $[M+H]^+$, 296.0957. Found 296.0950. m/z (ESI+): 296.2 $[M+H]^+$.



^{1}H NMR spectral characteristics of *cis* were determined from the spectra of the crude product **233a**; δ_H ($CDCl_3$, 400 MHz): 1.59 [3H, d, *J* 7.0, C(1')*H*$_3$], 4.67 [1H, d, *J* 6.0, C(2)*H*].

*Assignment of **233b** was made with the aid of 2D NMR experiments, namely HETCOR and COSY.*

Table 6.21 *Rhodium acetate and Asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **58**

Entry	**Method**	**M**	**Ligand**	**Time (h)**	**Crude Efficiency of C–H insertion (%)[a]**	**Sulfone 117 (%Crude)[b]**	**Yield (%)**		**Products ratios** *trans* **233b**	*cis* **233a**	(**S**) **117**
1	**E**	$Rh_2(OAc)_4/\Delta$	-	21	>90%	-	46%	**Crude ratio** **Purified ratio**	96 99 (0% ee)	4 1	-
2	**B**	$CuCl_2/\Delta$	(3*S*,8*R*)-Ind **44**	24	50–60%[c]	10–15%	Fr1 5% Fr2 8% **Total**	**Crude ratio** **Purified ratio** **Fr1** **Fr2**	44 80 (10% ee)[d,e] 66 (14% ee)[d,e] **9.28%**	44 10 (60% ee)[f] 12 (67% ee)[f] **1.46%**	12 10 22 **2.26%**
3	**B**	$CuCl_2/\Delta$	(4*R*,5*S*)-di-Ph **137**	21	50–60%[g]	10–15%	Fr1 4%[h] Fr2 3% Fr3 4%	**Crude ratio** **Purified ratio**[i]	36 only (44% ee)[j] only (36% ee)[j] 62 (30% ee)[j,k]	52 - -	12 - - 38

							Total		**9.48%**		**1.52%**
4	**B**	$CuCl_2/\Delta$	(4*R*)-Ph **20**	6	50–55%[l]	~8%		**Crude ratio**	20	68	12
								Purified ratio[n]			
							Fr1 1%[m]		only (90% ee)[j,o]	-	-
										-	-
							Fr2 3%		only (70% ee)[j]		
										-	-
							Fr3 2%		only (60% ee)[j]		
							Total		**6%**		
5	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	21	50–60%[p]	~5%		**Crude ratio**	68	30	2
								Purified ratio			
							Fr1 4%[q]		78 (43% ee)[e,r]	22[s,t] 27[s,t]	- -
							Fr2 6%[q]		73 (37% ee)[e,r]	22[s,t]	2
							Fr3 4%[q]		74 (32% ee)[e,r]		
							Total		**10.46%**	**3.38%**	**0.08%**
6	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	30	50–60	~5%		**Crude ratio**	74	22	4
								Purified ratio			-
							Fr1 2%[q]		77 (86% ee)[j,u]	23 (70% ee)[f]	- -
							Fr2 4%[q]		81 (79% ee)[j,u]	19 (70% ee)[f]	

							Fr3 3%[q] **Total**		82 (78% ee)[j,u] **7.24%**	8 (70% ee)[f] **1.76%**	
7	**B**	$CuCl_2/\Delta$	(4*R*)-Bn **43**	24	50–60	~1%	 Fr1 5% Fr2 7%[v] **Total**	**Crude ratio** **Purified ratio**	72 only (37% ee)[e] only (33% ee)[e] **13%**	27 - - **1.76%**	1 - -
8	**B**	$CuCl_2/\Delta$	(4*S*)-*t*-Bu **138**	48	50–60[w]	~1%	 Fr1 9% Fr2 6% **Total**	**Crude ratio** **Purified ratio**	80 only (60% ee)[j,x] 98 (50% ee)[j] **14.88%**	19 2[y] **0.12%**	1

a. Efficiency and relative ratios calculated using ^{1}H NMR using the following signals: δ_H 4.67 [1H, d, *J* 6.0, C(2)*H*] for *cis* sulfolane **233a**; δ_H 4.24 [1H, d, *J* 6.5, C(2)*H*] for *trans* sulfolane **233b**.

b. Amounts of sulfone **117** in both crude and purified samples are calculated using ^{1}H NMR using the following signals: δ_H 4.27 (2H, s, SO_2CH_2CO). Additional signals were observed for sulfone **117**; δ_H 1.35 (3H, t, *J* 7.5, $ArCH_2CH_3$), 3.10 (2H, q, *J* 7.5, $ArCH_2CH_3$).

c. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 5.60 (s), 7.00–7.17 (m), 9.40 (s).

d. Enantioselectivity estimated, unresolved peaks in HPLC analysis.

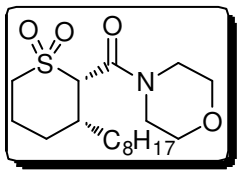
e. The first eluting enantiomer of the *trans* isomer **233b** at ~39 min is the major enantiomer, using 30% IPA/hexane (Cell-4).

f. The second eluting enantiomer of the *cis* isomer **233a** at ~62 min is the major enantiomer, using 30% IPA/hexane (Cell-4), values are estimated in all cases due to peak overlap.
g. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 5.59 (s).
h. Impure fraction. Additional peaks present in the ^{1}H NMR spectra of the purified product; δ_H 3.88–3.95 (m). Additional peaks were observed in aromatic region 7.30–8.0 ppm.
i. Compound was purified twice. The first purification used column chromatography on silica gel using gradient ethyl acetate-hexane (5:95–10:90–20:80–50:50–80:20) as eluent. The second purification used column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluent. The eluent contained 2% formic acid. Results in table are reported after a second purification.
j. The second eluting enantiomer of the *trans* isomer **233b** at ~45 min is the major enantiomer, using 30% IPA/hexane (Cell-4).
k. Additional peak observed in HPLC trace for this fraction, tentatively assigned to sulfone **117**.
l. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 5.60 (s), 9.41 (s).
m. Impure fraction. Additional peaks present in the ^{1}H NMR spectra of the purified product; δ_H 3.77–3.99 (m), 4.59–4.70 (m), 5.17 (s). Additional peaks were observed in aromatic region 7.30–8.0 ppm.
n. Compound was purified four times. The first three purifications used column chromatography on silica gel using gradient ethyl acetate-hexane (5:95–10:90–20:80–50:50–80:20) as eluent, none of which were completely successful. The last purification used column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluent. The eluent contained 2% formic acid. Results in table are reported after the last purification.
o. Additional peaks present in HPLC.
p. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 5.17 (s), 6.11–6.24 (m), 6.44–6.52 (m).
q. Contains dioctyl phthalate (placticiser).
r. Estimation due to peak overlap in HPLC analysis. Measurement of enantioselectivity was not perfect due to overlap with impurities; 43% ee is the most accurate value due to the best separation being achieved in this instance.
s. The first eluting enantiomer of the *cis* isomer **233a** at ~43 min is the major enantiomer, using 30% IPA/hexane. (Cell-4)-values are estimated in all cases due to peak overlap.
t. Could not be estimated due to peak overlap.
u. Estimation due to peak overlap in HPLC analysis.
v. Fraction contains ~15% additional compound that contains the following peaks in the ^{1}H NMR spectra of the purified product; δ_H 4.20–4.25 (m overlapping), 4.30 (d, *J* 5.4).
w. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 4.91 (s), 5.59 (s), 6.54–6.61 (m).
x. Contains ~5% additional compound that contains the following peaks in the ^{1}H NMR spectra of the purified product; δ_H 4.20–4.25 (m overlapping), 4.30 (d, *J* 5.4).
y. % ee of *cis* **233a** was not determined as peaks for this compound were not observed in the HPLC trace.

Note; In HPLC analysis additional peaks were observed which have been tentatively assigned to the *cis* isomer **233a**; peak at 43 min and 62 min. Reduction product **117** was seen at 48 min (**Appendix I**)

Note; All crude reaction mixtures were purified using column chromatography on silica gel using ethyl acetate-hexane (80:20) as eluent. In all cases the eluent contained 2% formic acid, with the exception of reactions in Table 6.21, entries 1 and 2.

Morpholino[(2*S*,3*R*)-3-octyl-1,1-dioxidotetrahydro-2H-thiopyran-2-yl]methanone 229a



The title compound was prepared according to the procedure described for 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b**, using 2-diazo-2-(dodecylsulfonyl)-1-morpholinoethanone **49** (80 mg, 0.22 mmol), $CuCl_2$ (1.4 mg, 10.8 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (10.1 mg, 12.4 μmol) and bisoxazoline ligand (3*S*,8*R*)-Ind **44** (4.1 mg, 12.4 μmol) in dichloromethane (60 mL), stirred while heating under reflux for 72 h, in accordance with Method **B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 10–20% efficient, with a complex mixture of products. Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, morpholino[(2*S*,3*R*)-3-octyl-1,1-dioxidotetrahydro-2H-thiopyran-2-yl]methanone **229a** (35 mg) was obtained as an impure fraction that contained *approx* 40–50% *cis* thiopyran **229a** as a colourless oil; ν_{max}/cm^{-1} (film): 2923, 2854 (CH), 1644 (CO), 1315, 1115 (SO_2); Characteristic signals are seen at δ_H ($CDCl_3$, 400 MHz): 0.88 [3H, t, *J* 6.6, C(8′)H_3], 1.18–1.40 [14H, m, C(7′)H_2, C(6′)H_2, C(5′)H_2, C(4′)H_2, C(3′)H_2, C(2′)H_2, C(1′)H_2], 2.89 [~0.4H, apparent dq, *J* 13.5, 3.0 one of C(6)H_2], 4.10 [~0.7H, dd, *J* 4.0, 2.1, C(2)*H*]; δ_C ($CDCl_3$, 100.6 MHz): 164.2 (C, *C*O) HRMS (ESI+): Exact mass calculated for $C_{18}H_{34}NO_4S$ $[M+H]^+$, 360.2209. Found 360.2211. m/z (ESI+): 360.3 $[M+H]^+$.

Additional signals observed in the ^{1}H NMR spectra of the purified spectra δ_H ($CDCl_3$, 400 MHz): 1.39–1.49 (0.97H, m), 1.75–1.95 (0.92H, m), 2.19–2.30 (0.46H, sym m), 2.33–2.55 (0.72H, m), 2.64–2.76 (0.13H, m), 3.01–3.16 (0.41H, m), 3.17–3.33 (0.52H, m), 3.34–3.68 (3.3H, m), 3.69–3.81 (5.1H, m), 3.85–3.94 (0.46H, m), 3.97–4.06 (0.25H, m), 4.07 (0.05H, s), 5.41 (0.26H, s).

The only confirmed C–H insertion product from the copper catalysed reactions of 2-diazo-2-(dodecylsulfonyl)-1-morpholinoethanone **49** is *cis* thiopyran **229a**. However the presence of additional isomers cannot be ruled out due to a complex mixtures of products being obtained.

^{13}C NMR analysis of the mixed fraction obtained contained multiple peaks in the r,egion of 10–70 ppm. The only distinguishable signal observed in this case is the presence of a peak at 164.2 ppm, which has tentatively been assigned to *cis* thiopyran **229a**. The

presence of signals in the alkene region >80 ppm were not observed, and for this reason the presence of dimer is ruled out at present.

Table 6.22 *Asymmetric copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* **49**

Entry	Method	M	Ligand	Time (h)	Crude Efficiency (%)[a]	Yield (%)
1	**B**	$CuCl_2$	(3*S*,8*R*)-Ind **44**	72	10–20[b]	[c]
2	**B**	$CuCl_2$	(4*R*)-Ph **20**	96	10–20[d]	-[e]
3	**D**	$CuCl_2$	(3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** (1:1)	75	10–20[f]	-[e]

a. Efficiency calculated using ^{1}H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **229a** δ_H 4.10 [1H, dd, *J* 4.0, 2.1, C(2)*H*].

b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.64–1.99 (m), 2.03–2.26 (m), 3.15–3.82 (series of multiplets), 4.96 (s), 5.44 (s), 5.95 (s), 9.48 (s).

c. Fraction contains *approx* 40–50% *cis* thiopyran **229a**, additional peaks were observed in the ^{1}H NMR spectra of the crude product and are listed above.

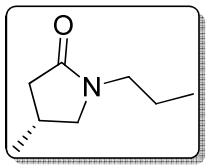
d. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.64–1.99 (m), 2.03–2.26 (m), 3.15–3.82 (series of multiplets), 4.48 (s), 4.96 (s), 5.44 (s), 5.95 (s), 9.48 (s). Note: there are comparatively smaller amounts of unidentified compound **238** with δ_H 5.95 (s) signal in the ^{1}H NMR spectra when compared to reactions reported in entries 1 and 3.

e. Not purified.

f. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 1.64–1.99 (m), 2.03–2.26 (m), 2.88–3.82 (series of multiplets), 4.68 (s), 5.44 (s), 5.95 (s), 9.48 (s).

Note: Two singlets are present in the ^{1}H NMR of crude products at 5.44 ppm and at 5.95 ppm, either one of which may be due to chlorine abstraction product. Relatively larger integrations are observed for these signals in the spectra of the crude products for **Table 6.22**, entries 1 and 3 than for entry 2.

***R*-4-Methyl-1-propylpyrrolidin-2-one 213**



Magnesium turnings (0.31 g, 12.5 mmol) were added to a stirred solution of 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** (150 mg, 0.48 mmol) (78% ee, 3*R*,4*S*) (sample isolated from **Table 6.13**, entry 15) in methanol (20 mL) under an atmosphere of nitrogen and the mixture was stirred for 20 h. The reaction mixture was then carefully poured onto a mixture of hydrochloric acid (10%, w/w aqueous solution, ~30 mL) and ice (~50 g). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate (3 × 20 mL), brine (50 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure to yield *R*-4-methyl-1-propylpyrrolidin-2-one **213** (43 mg, 64%) as a colourless oil; $[\alpha]_D^{20}$ +5.66 (*c* 0.38, CH_2Cl_2); ν_{max}/cm^{-1} (neat): 2962, 2930 (CH), 1682 (CO), 1267; δ_H ($CDCl_3$, 600 MHz): 0.90 (3H, t, *J* 7.4, $NCH_2CH_2CH_3$), 1.12 [3H, d, *J* 6.8, CH_3-C(4)], 1.54 (2H, apparent sextet, *J* 7.4, $NCH_2CH_2CH_3$), 2.05 [1H, dd, *J* 16.4, 6.6, one of C(3)H_2], 2.38–2.48 [1H, m, C(4)*H*], 2.57 [1H, dd, *J* 16.5, 8.6, one of C(3)H_2], 2.95 [1H, dd, *J* 9.6, 5.8 one of C(5)H_2], 3.14–3.31 (2H, sym m, $NCH_2CH_2CH_3$), 3.49 [1H, dd, *J* 9.6, 7.7, one of C(5)H_2]; δ_C ($CDCl_3$, 150.9 MHz): 11.3 (CH_3, $NCH_2CH_2CH_3$), 19.9 [CH_3, CH_3-C(4)], 20.5 (CH_2, $NCH_2CH_2CH_3$), 26.4 [CH, *C*(4)H], 39.5 [CH_2, *C*(3)H_2], 44.1 (CH_2, $NCH_2CH_2CH_3$), 54.5 [CH_2, *C*(5)H_2], 174.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_8H_{16}NO$ ($M+H^+$) 142.1232. Found 142.1227 ($M+H^+$); m/z (ESI+) 142.4 ($M+H^+$).

Assignment of the above compound was made using 2D NMR experiments namely HMBC and HSQC.

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Chapter Seven
Cyclopropanation and C–H insertion reactions of α-diazo-β-oxo sulfones

"If all men count with you, but none too much; If you can fill the unforgiving minute With sixty seconds' worth of distance run, Yours is the Earth and everything that's in it, And—which is more—you'll be a Man, my son" Rudyard Kipling

7.1 Background

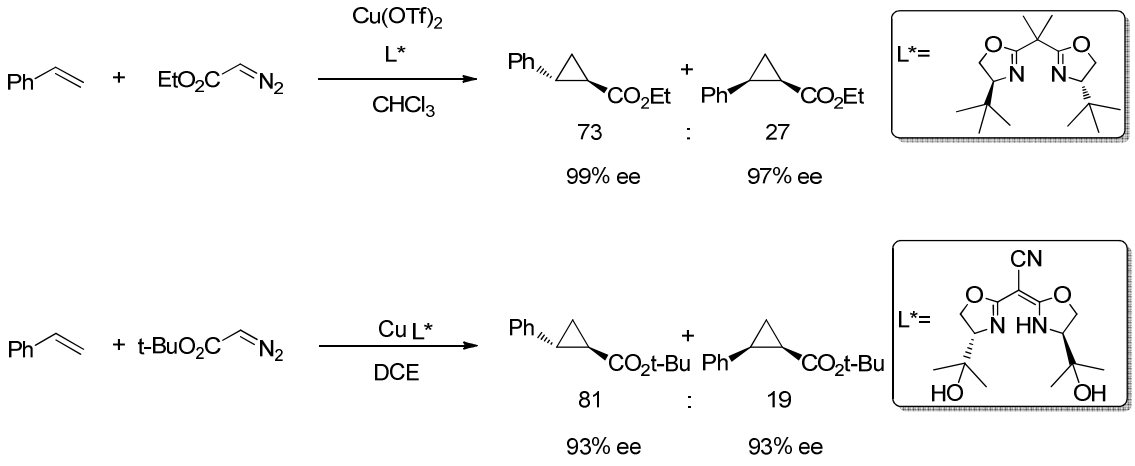
There are many synthetic strategies available for the synthesis of cyclopropane derivatives;[1] of these the transition metal catalysed cyclopropanation of alkenes employing diazo compounds as a carbene source is one of the most efficient methods.[1–7] Cyclopropanation reactions of this type are proposed to occur *via* the simultaneous formation of two new carbon carbon bonds to the "carbene" carbon by means of a concerted process (**Scheme 7.1**).



Scheme 7.1

Both inter- and intramolecular cyclopropanation reactions of diazo compounds have produced cyclopropanes in a highly diastereo- and enantiocontrolled manner.[2,3] The nature of the catalyst and diazo compound are important factors in determining the successful outcome of both inter- and intramolecular cyclopropanation reactions. A number of transition metals have successfully catalysed cyclopropanation reactions, for example copper, rhodium, iridium, iron, cobalt, palladium and ruthenium, to mention a few.[8–21]

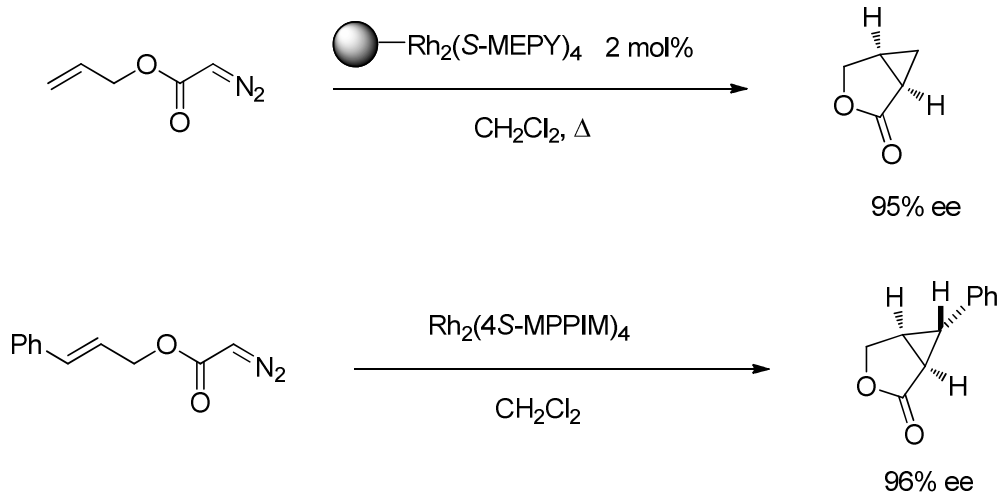
The intermolecular variant of this reaction is a very well-studied transformation and has been enormously successful; copper-bisoxazoline catalysed reactions have proved to be particularly effective, in terms of both diastereo- and enantioselection,[22–26] with values of up to 99% ee recorded (**Scheme 7.2**).[24] The use of copper-semicorrin catalysts have also proved useful with enantioselectivities of up to 93% ee being recorded.[27]



Scheme 7.2[24,27]

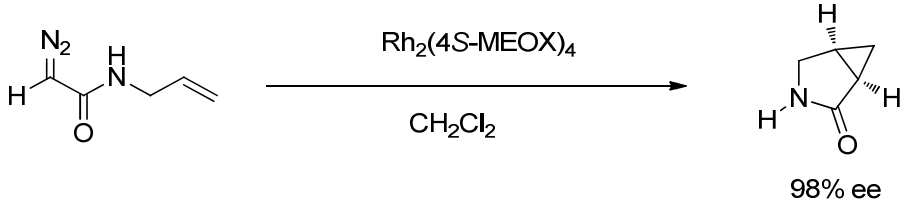
Other catalysts such as complexes of rhodium, cobalt, ruthenium and iridium have also successfully catalysed this process.[12,28–32] As the transition state for the intramolecular reaction is more constrained than that for the intermolecular reaction, catalysts leading to a highly enantioselective reaction for the intermolecular reaction may not necessarily have the same effect for the intramolecular version and *vice versa*.

Since the first intramolecular cyclopropanation reaction was reported in 1961,[33] substantial efforts have been invested into the development of chiral metal catalysts capable of synthesising cyclopropanes in an enantiopure form. A great deal of advancement has been made in this area. The use of chiral rhodium carboxamidates have been shown to be extremely effective in the intramolecular cyclopropanation of α-diazoesters(**Scheme 7.3**)[34–36]



Scheme 7.3[34,36]

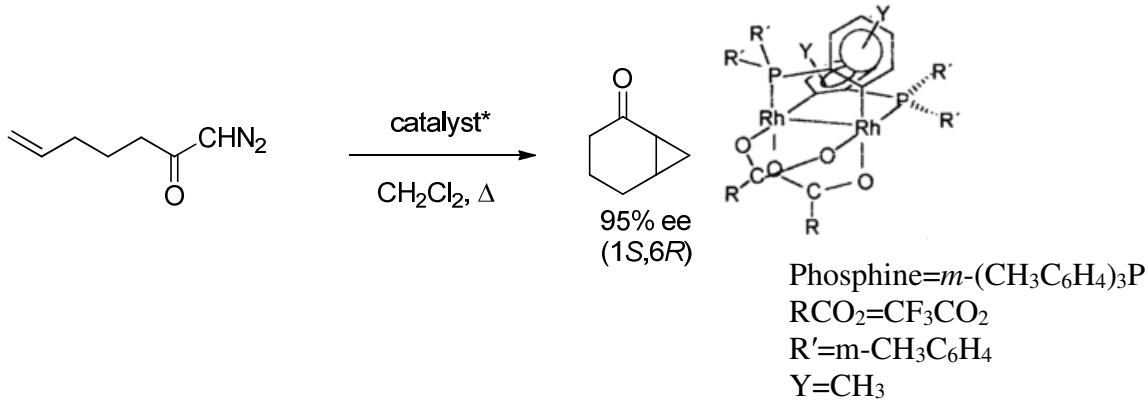
Chiral rhodium carboxamidates have also been successfully applied in the cyclopropanation reactions of α-diazoacetamides, with enantioselectivities of greater than 90% ee being achieved (**Scheme 7.4**).[35,37,38]



Scheme 7.4[35]

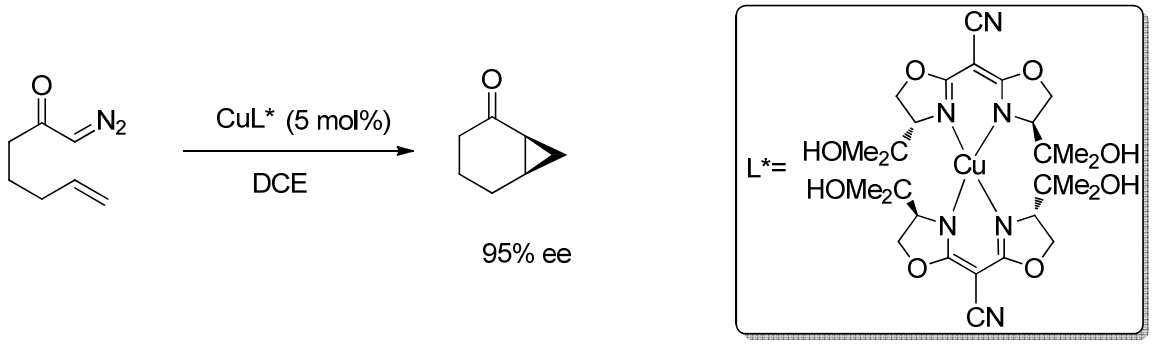
Chiral rhodium complexes that contain aryl orthometalated aryl phosphine ligands were claimed by Lahuerta and co-workers to be the most useful chiral rhodium catalyst series

for the cyclopropanation of α-diazoketones, with enantioselectivities of up to 95% ee being reported (**Scheme 7.5**).[39,40]



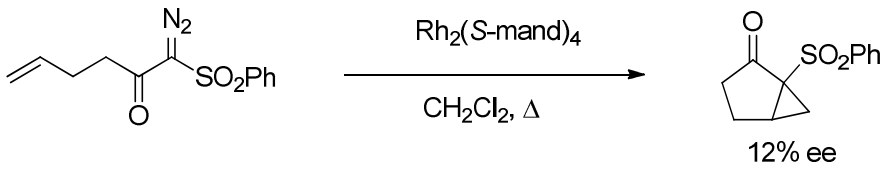
Scheme 7.5[39]

Chiral semicorrin-copper catalysts have been demonstrated to efficiently catalyse intramolecular cyclopropanation reactions of α-diazoketones with enantioselectivities of up to 95% ee being achieved (**Scheme 7.6**).[41]



Scheme 7.6

While asymmetric cyclopropanation has been very well studied, and has enjoyed a great deal of success in recent years, there is still a need to expand both the range of catalysts capable of successful cyclopropanation as well as broadening the range of substrate classes, so that different structural motifs can be synthesised. There have been, to date, a limited number of reports in the literature on the use of α-diazosulfone substrates for inter- and intramolecular cyclopropanation reactions.[42–48] Monteiro and McKervey were the first to report the use of these substrates for this transformation, with McKervey and co-workers achieving 12% ee for the rhodium mandelate catalysed cyclopropanation reaction of an α-diazosulfone substrate, as illustrated in **Scheme 7.7**.[49,50]

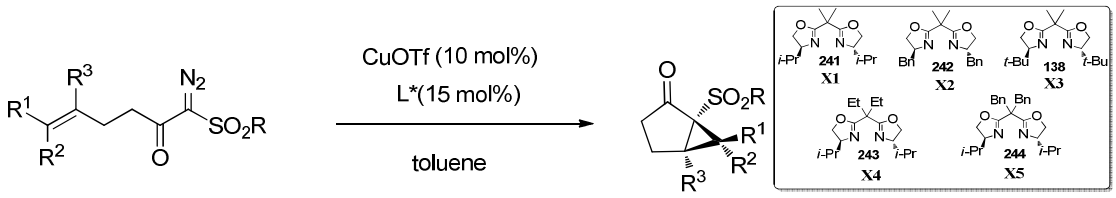


239 **240**

Scheme 7.7

Nakada and co-workers made a breakthrough in the asymmetric copper catalysed cyclopropanation reactions of α-diazo-β-keto sulfones achieving enantioselectivities of up to 98% ee. A summary of their results are presented in **Table 7.1**.[45]

Table 7.1 *Asymmetric copper catalysed cyclopropanation reactions of α-diazo-β-oxo sulfones*[45]



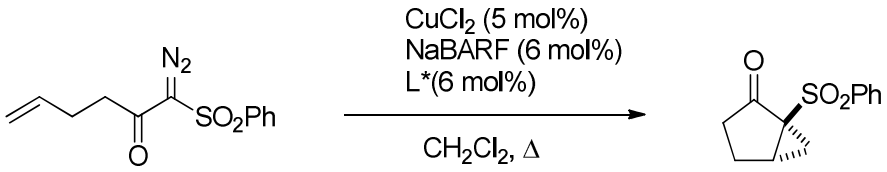
Entry	R	R^1	R^2	R^3	Starting Material	Product Material	L^*	Temp.	Time (h)	Yield (%)	ee (%)
1	Ph	H	H	H	**239**	**240**	**241 (X1)**	rt	2	91	65 (1*R*,5*R*)
2	Ph	H	H	H	**239**	**240**	**242 (X2)**	rt	2	67	75 (1*R*,5*R*)
3	Ph	H	H	H	**239**	**240**	**243 (X4)**	rt	2	67	72 (1*R*,5*R*)
4	Ph	H	H	H	**239**	**240**	**244 (X5)**	rt	5.5	61	73 (1*R*,5*R*)
5	Ph	H	H	H	**239**	**240**	**138 (X3)**	50 °C	5.5	61	32 (1*R*,5*R*)
6	Mes	H	H	H	**245**	**246**	**241 (X1)**	50 °C	1.5	93	83 (1*R*,5*R*)
7	Mes	H	H	H	**245**	**246**	**243 (X4)**	rt, 50 °C	2,2	89	90 (1*R*,5*R*)
8	Mes	H	H	H	**245**	**246**	**244 (X5)**	rt, 50 °C	2,2.5	87	93 (1*R*,5*R*)

9	Mes	H	H	Me	**247**	**248**	**244 (X5)**	50 °C	2	90	98 (1*R*,5*R*)
10	Mes	Me	Me	H	**249**	**250**	**244 (X5)**	rt	5	84	92 (1*R*,5*R*)
11	Mes	H	H	Br	**251**	**252**	**244 (X5)**	50 °C	2.5	63	98 (1*S*,5*S*)

The study focused on variation of both the bisoxazoline ligand and the α-diazo-β-keto sulfone. The use of five bisoxazoline ligands was initially explored; phenylsulfonyl substrate **239**, with (4*S*)-Bn ligand **242** giving the best enantioselectivity of 75% ee (**Table 7.1**, entry 2). Enantioselectivities remained high for the (4*S*)-*i*-Pr **243** and (4*S*)-*i*-Pr **244** ligands with values of 72% ee and 73% ee achieved respectively (**Table 7.1**, entries 3 and 4). The lowest level of enantiocontrol obtained in the study was 32% ee, which was obtained with (4*S*)-*t*-Bu ligand **138**. Modification of the substrate structure was then examined. Variation of the sulfone group from a phenylsulfone to a bulkier mesityl sulfone caused a modest increase in enantioselectivity, with 93% ee attained for reaction with (4*S*)-*i*-Pr ligand **244** (**Table 7.1**, entry 8). The substrates that gave the highest enantioselectivities were those where a methyl or bromo substituent was introduced on the internal alkene carbon **247** and **251**, giving rise to enantioslectivities of 98% ee in both cases (**Table 7.1**, entries 9 and 11). Interestingly, substituting the terminal end of the alkene with a *gem*-dimethyl group resulted in a slight decrease in enantioselectivity when compared to the unsubstituted compound, and the internally methyl substituted compound, for the same ligand (92, 93 and 98% ee respectively) (**Table 7.1**, entries 8, 9 and 10).

Given the success of the CuCl-NaBARF-bisoxazoline ligand system for C–H insertion reactions of α-diazosulfones, with enantioselectivities of up to 98% ee being achieved in *cis* thiopyran synthesis and values of up to 89% ee obtained in cyclopentanone synthesis,[51–55] Slattery applied this catalytic system to cyclopropanation reactions of α-diazo-β-keto sulfone **239**. The result of this study is presented in **Table 7.2**.[56]

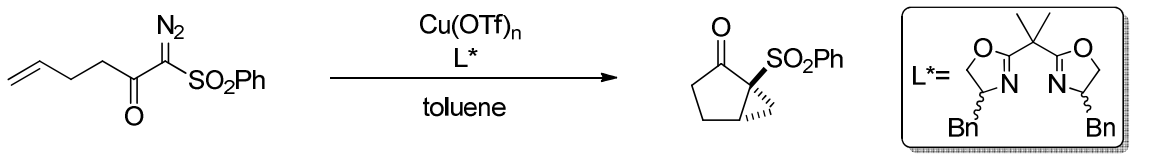
Table 7.2 *Asymmetric copper catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* ***239****, investigation of the additive NaBARF*[56]



239 **240**

Entry	L*	Time (h)	Yield (%)	ee (%)
1	(4*R*)-Bn **43**	2	81	7 (1*S*,5*S*)
2	(4*R*)-Ph **20**	4	93	8 (1*R*,5*R*)
3	(4*R*,5*S*)-di-Ph **137**	2	93	17 (1*R*,5*R*)
4	(4*S*)-*t*-Bu **138**	4	87	26 (1*S*,5*S*)
5	(3*S*,8*R*)-Ind **44**	2	82	9 (1*S*,5*S*)

To ensure reproducibility, Slattery initially attempted to replicate the results obtained by Nakada. The enantioselectivity obtained for $Cu(OTf)_2$-(4*R*)-Bn **43** in this study (61% ee) (**Scheme 7.8**) is broadly comparable to that achieved by Nakada for reaction of the same α-diazosulfone **239** with Cu(OTf)-(4*S*)-Bn **43** (75% ee) (**Scheme 7.8**) (**Table 7.1**, entry 2); the difference may be rationalised by the fact that while Nakada's reactions were complete in 2 h at room temperature, Slattery had to heat the reaction to 35 °C for 1 h as the reaction was not complete following 4 h at room temperature. In addition, Nakada used a different copper precursor, Cu(I)OTf, which may have had an impact.



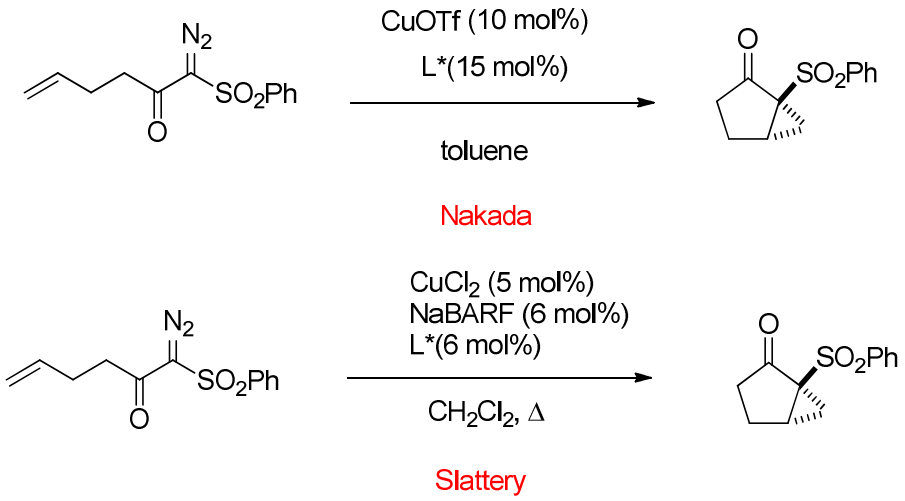
Nakada, Cu(OTf), (4*S*)-Bn **242**, rt, 75% ee
Slattery, $Cu(OTf)_2$, (4*R*)-Bn **43** rt 4h, 35 °C 1h, 61% ee

Scheme 7.8[45,56]

Interestingly, a significant decrease in enantioselectivity was observed for reaction of $CuCl_2$-NaBARF-(4*R*)-Bn **43** with α-diazosulfone **239**, when compared to reaction with

$Cu(OTf)_2$-(4*R*)-Bn **43** (7% ee and 61 % ee respectively) (**Table 7.2**, entry 1, **Scheme 7.8**). The enantioslectivities obtained using $CuCl_2$-NaBARF-L* catalyst system for all five commercially available ligands, were low (**Table 7.2**, entries 1–5) with the highest value of 26% ee attained for reaction with (4*S*)-*t*-Bu **138** (**Table 7.2**, entry 4). The lower enantioselectivities achieved with $CuCl_2$-NaBARF-L* catalyst system when compared to Cu(OTf)-L*system (**Table 7.1** *cf.* **Table 7.2**) highlight the importance of counterion effects, which is consistent with previous reports by Evans of intermolecular cyclopropanation.[24] A direct comparison of the difference in the reported enantioselectivities by Slattery and Nakada is shown in **Table 7.3**, for benzyl substituted ligands **242** and **43** and for (4*S*)-*t*-Bu ligand **138**. In **Table 7.3**, entry 3, the difference in enantioselectivity achieved is relatively modest compared to entry 4, presumably as Nakada heated this reaction to 50 °C.

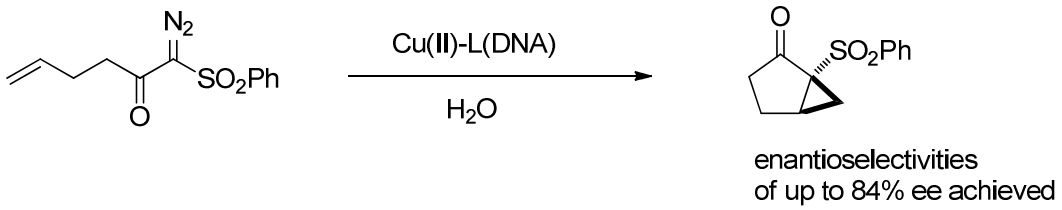
Table 7.3 *Comparison of results achieved by Slattery and Nakada for the intramolecular cyclopropanation reactions of α-diazosulfone* ***239***



Entry	Procedure	Ligand	Yield (%)	ee (%)
1	Nakada, rt	(4*S*)-Bn **242**	67	75
2	Slattery, Δ	(4*R*)-Bn **43**	81	7
3[a]	Nakada, 50 °C	(4*S*)-*t*-Bu **138**	61	32
4	Slattery, Δ	(4*S*)-*t*-Bu **138**	87	26

a. Reaction was heated to 50 °C.

Recently, enantioselectivities of up to 84% ee were achieved in the DNA-based organometallic catalysed cyclopropanation reaction of α-diazosulfone **239** (**Scheme 7.9**).[57]

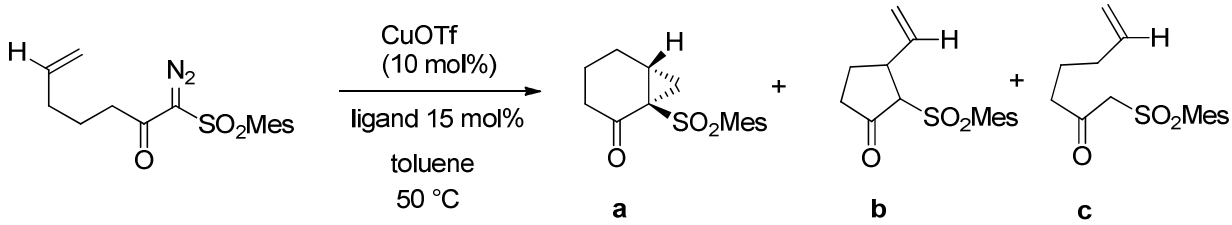


239 **240**

Scheme 7.9

Nakada and co-workers also investigated the synthesis of bicyclo[4.1.0]heptanes using asymmetric copper catalysed intramolecular cyclopropanation reactions of α-diazo-β-oxo sulfones.[58] It was demonstrated that high enantioselectivities (up to 94% ee, **Table 7.4**, entry 2) could be obtained for the six-membered ring-fused cyclopropane products, using similar catalytic conditions reported for the synthesis of five-membered ring products. For example, when α-diazo-β-oxo sulfone substrate **253** underwent reaction in the presence of copper-bisoxazoline catalysts cyclopropanation product **254** was the major reaction product. However, one notable difference was that additional products formed during the reaction with the longer chained substrates **253**, not previously observed for the shorter chained starting materials; included a reduction product **255** and a C–H insertion product **256**; the exact amounts formed varied depending on the nature of the ligand employed (**Table 7.4**).

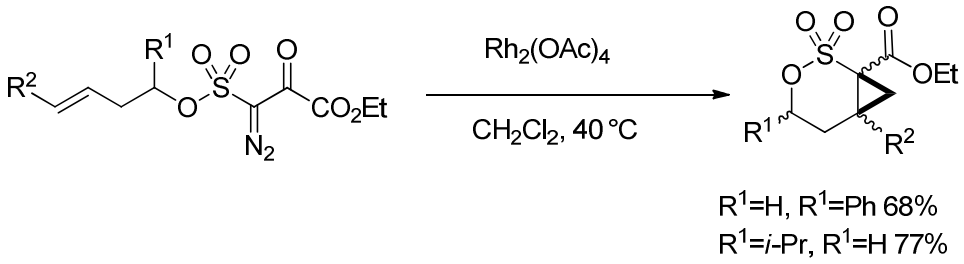
Table 7.4 *Asymmetric copper catalysed cyclopropanation reactions of α-diazo-β-oxo sulfones*[58]



253 **a** **254** **b** **256** **c** **255**

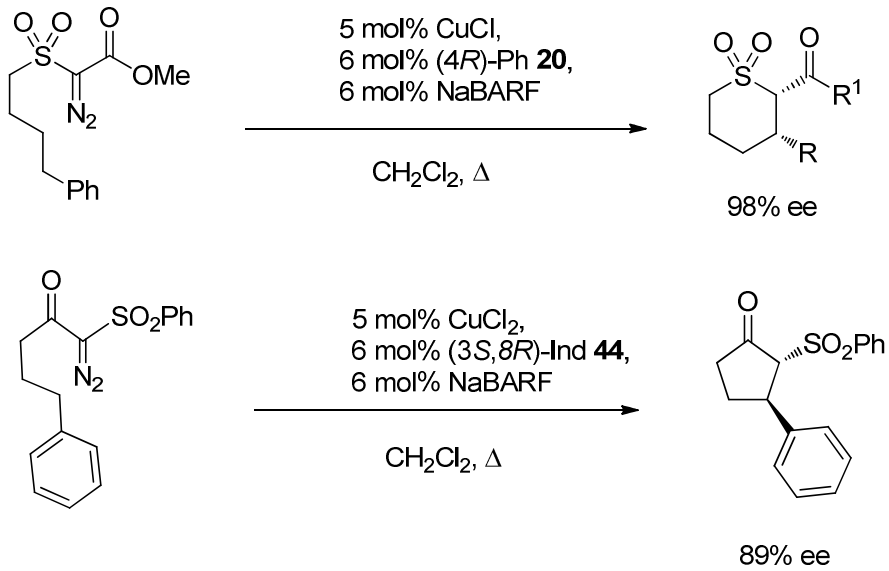
Entry	Ligand	Time (h)	Yield (%) b and c	Yield (%) a	%ee a
1	**243**	2	8	23	94
2	**244**	16	17	31	98
3	**242**	3.5	14	16	67

Successful cyclopropanation reactions were reported for the rhodium acetate catalysed reactions of α-diazosulfonates, bearing some resemblance to the compounds targeted in this project. (**Scheme 7.10**).[59]



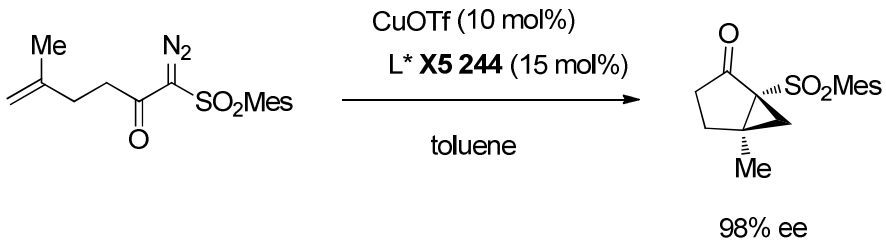
Scheme 7.10

Good to excellent enantioselectivities were achieved in the copper-bisoxazoline catalysed reactions of α-diazosulfones to yield either thiopyrans[53] or cyclopentanones,[55] depending on the structure of the starting α-diazosulfones. Good enantioselectivities are achieved in the synthesis of α-sulfonyl cyclopentanones, with values of up to 89% ee reported. However, when the starting material is constructed such that the sulfone is contained in the ring structure, enantioselectivities of up to 98% ee have been obtained. (**Scheme 7.11**).



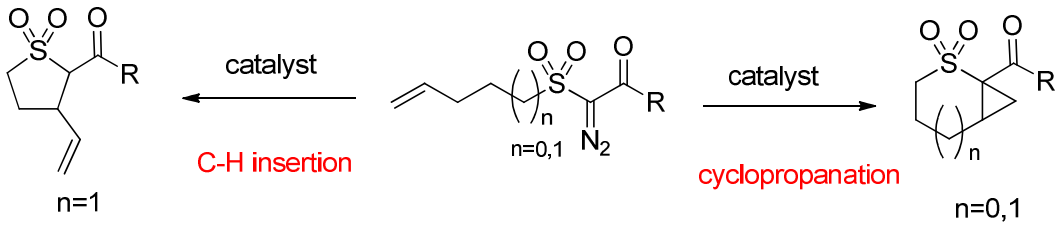
Scheme 7.11

As discussed above (**Table 7.1**), enantioselectivities of up to 98% ee were achieved by Nakada and co-workers in the cyclopropanation of α-diazosulfones (**Scheme 7.12**).



Scheme 7.12

With these facts in mind, the next logical step was to explore asymmetric cyclopropanation reactions of α-diazo-β-oxo sulfones, where the product would contain the sulfone in the ring structure. To the best of our knowledge reactions of this type have not been previously reported. For α-diazosulfonyl substrates **59-61**, where n=1, there is a potential competing C–H insertion reaction to yield sulfolanes. One of the key aims of the study was to explore the selectivity between C–H insertion and cyclopropanation in these systems (**Scheme 7.13**)



Scheme 7.13

For this investigation, four substrates were selected for study, the syntheses of which are described in Chapter 3. The substrates were selected to enable investigation of the impact of the linker chain length and variation of an ester to a ketone substituent, in addition to the impact of the terminal substituent (**Figure 7.1**).

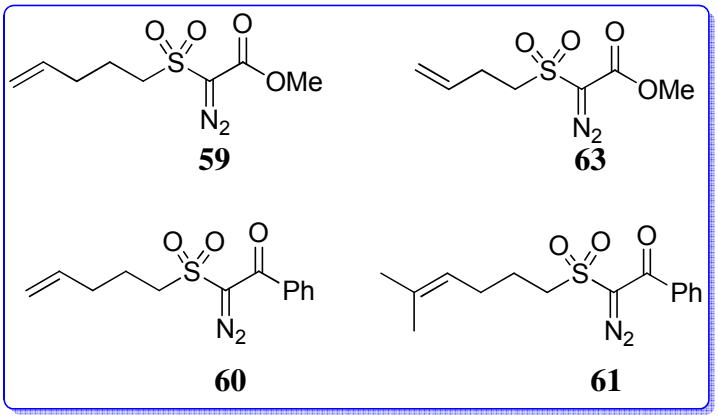
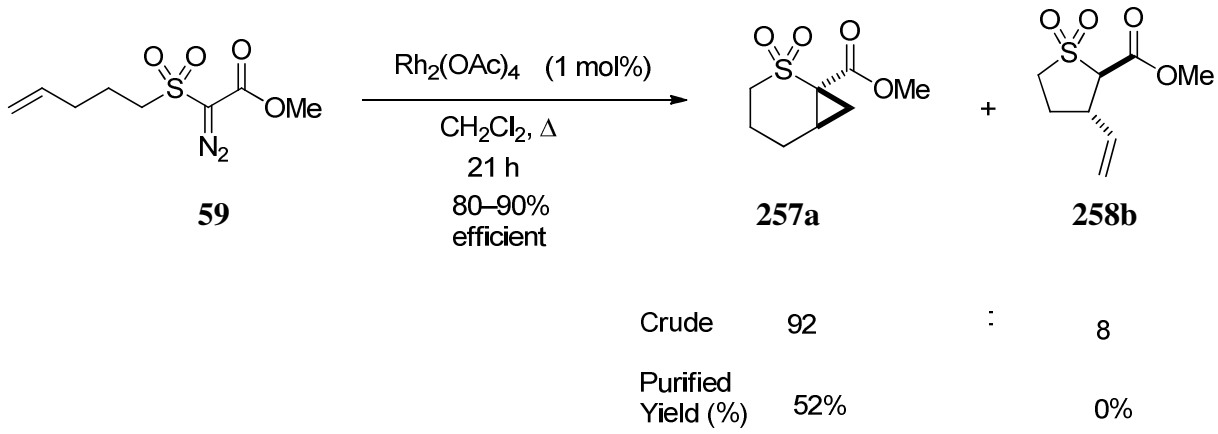


Figure 7.1

7.2 Results and Discussion

7.2.1 Investigation into the transition metal catalysed reactions of 59

Initially, the rhodium acetate catalysed reaction of novel α-diazo-β-oxo sulfone **59** was investigated, the results of which are shown in **Scheme 7.14**. As has been previously discussed, in Chapters 4–6, ~1 mol% of rhodium acetate is employed in refluxing dichloromethane, with reaction monitoring being carried out using IR spectroscopy. In this instance disappearance of the diazo stretch at ν_{max} 2126 cm^{-1} ($C{=}N_2$) had occurred within 21 hours, at which time the reaction was deemed complete.



Scheme 7.14

Examination of the ^{1}H NMR spectrum of the crude reaction mixture revealed that the major reaction product was cyclopropane product **257a** with minor amounts of C–H insertion product **258b** also present (cyclopropane **257a**: C–H insertion product **258b**, 92:8) (**Scheme 7.14**). The overall reaction efficiency for both cyclopropanation and C–H insertion was very high with a value of ~80–90% calculated from the ^{1}H NMR spectrum of the crude mixture and with no other identifiable products present. Purification was carried out on neutral alumina, to separate the cyclopropanation product **257a** from the C–H insertion product **258b**. However, while novel thiopyran **257a** was isolated in a yield of 52%, in its pure form, novel sulfone **258b** was not obtained after chromatography, in this case. Chromatographic purification on silica is also possible although resolution of the compounds proved easier on alumina. In later rhodium catalysed cyclisations of α-diazo-β-oxo sulfone **59** (**Table 7.7**), sulfolane **258b** was isolated as a pure compound after chromatography; it was a less polar fraction than thiopyran **257a**.

Thiopyran **257a** was fully characterised using ^{1}H NMR, ^{13}C NMR and IR spectroscopy and high resolution mass spectrometry. There are a number of key distinctive signals

present in the ^{1}H NMR spectra of thiopyran **257a**; of these those signals, assigned to C(7)H_2 are the most immediately identifiable. As the cyclopropane ring is sterically constrained, the presence of isomers in this instance is not possible.

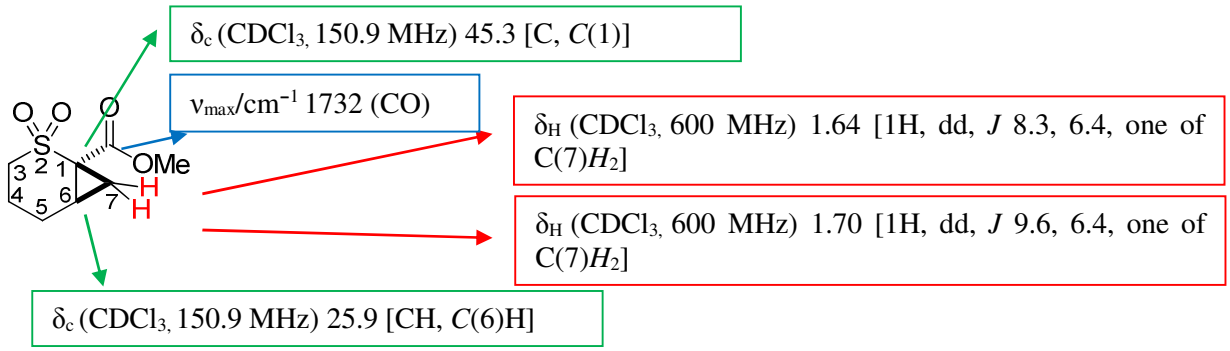


Figure 7.2

The most characteristic feature of the ^{1}H NMR spectrum is the presence of two distinct signals for the inequivalent protons at C(7)H_2 at δ_H 1.64 [1H, dd, *J* 8.3, 6.4, one of C(7)H_2] and at δ_H 1.70 [1H, dd, *J* 9.6, 6.4, one of C(7)H_2] (**Figure 7.2**). There is also a characteristic absorbance present in the IR spectrum for the carbonyl functionality, at ν_{max}/cm^{-1} 1732 (CO). These characteristic spectroscopic features allow the identification of cyclopropanation product **257a** in the crude reaction mixtures of cyclisations of α-diazo-β-oxo sulfone **59**.

One of the main purposes of carrying out a racemic cyclisation, using rhodium acetate as a catalyst, prior to carrying out an asymmetric catalytic study, is to obtain racemic cyclisation products so that they can be used for chiral stationary phase HPLC analysis. In the case of cyclopropanation product **257a**, attempts to develop suitable conditions for such analysis were only mildly successful. While separation of the two enantiomers of **257a** was achieved, poor absorbance was picked up by the UV detector, presumably due to the lack of a chromophore in product **257a**. For this reason separation of the enantiomers was attempted using chiral shift ^{1}H NMR, employing [(+)-Eu(hfc)$_3$] as a chiral shift reagent, which proved successful as can be seen in **Figure 7.3**.

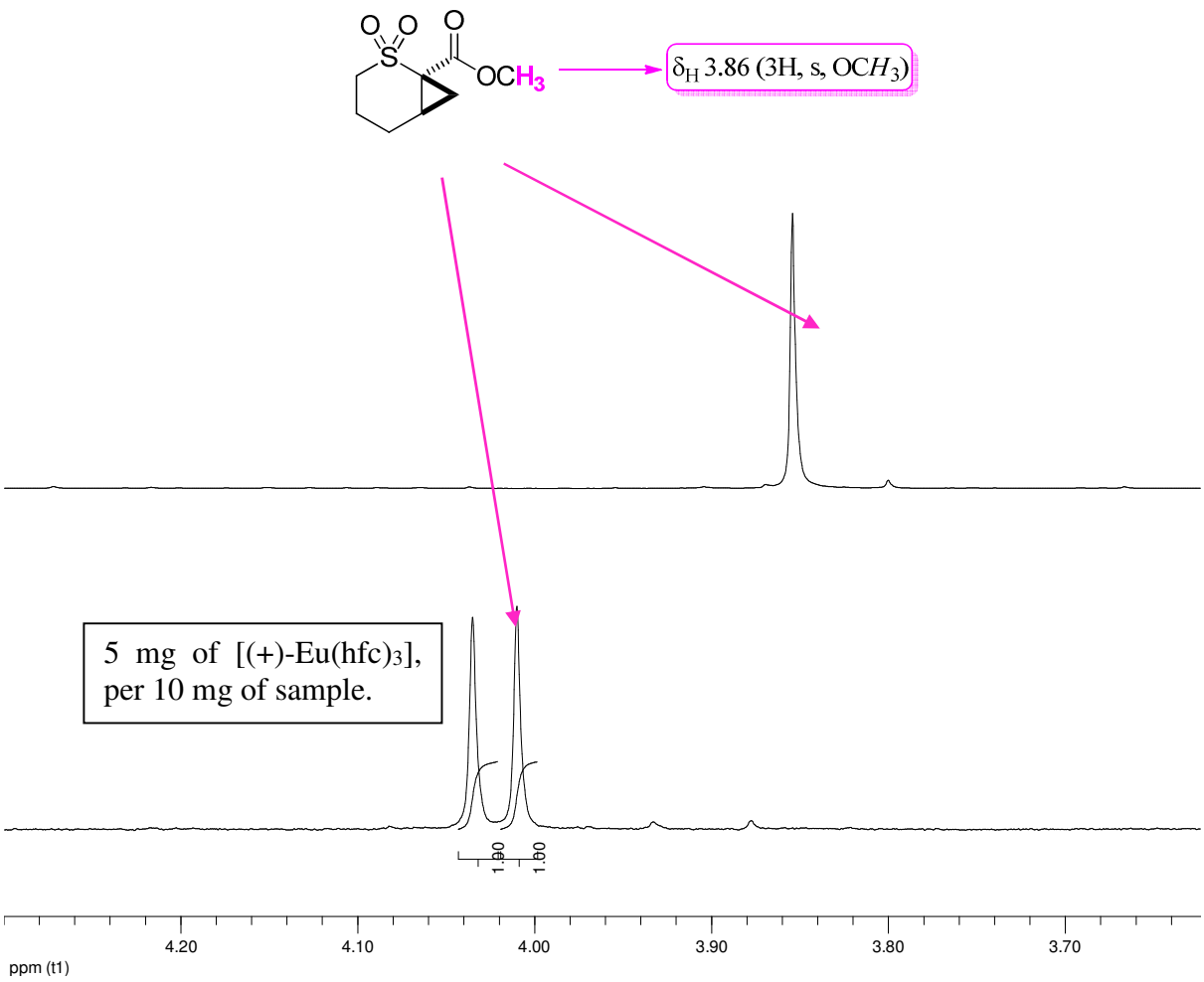


Figure 7.3 *^{1}H NMR spectra recorded in ($CDCl_3$, 400 MHz)*

The identification of C–H insertion product **258b** is most readily made by the presence of unchanged alkene protons; thus a 2H multiplet at δ_H 5.16–5.85 for the terminal alkene protons and a 1H multiplet at δ_H 5.69–5.85 for the internal alkene proton are characteristic of the sulfolane **258b**. In addition to the alkene protons, the presence of a doublet for C(2)*H* proton δ_H 3.74 (1H, d, *J* 10.2) is also indicative of a C–H insertion product. In contrast, no such signal is present at this position for the cyclopropane product, as a quaternary carbon is present at this position (**Figure 7.4**).

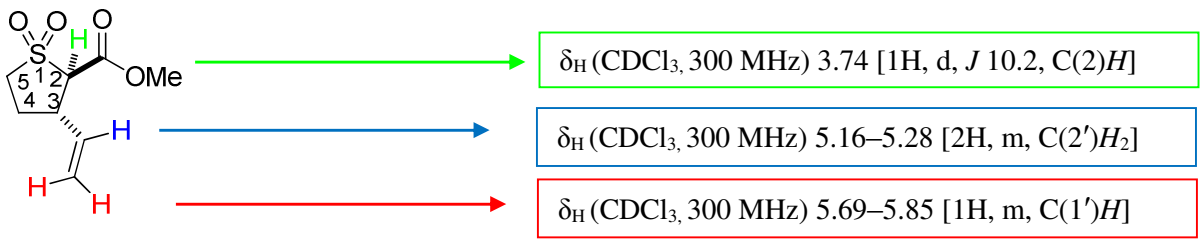
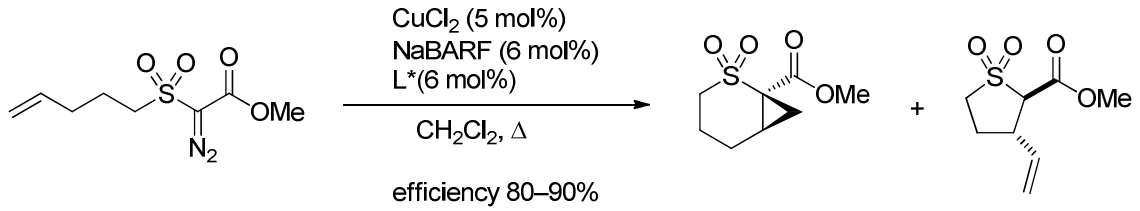


Figure 7.4

Using these characteristic signals product ratios in both the crude and pure product mixtures were readily ascertained as summarised in subsequent **Tables 7.5** and **7.7**.

Copper-bisoxazoline catalysed cyclisations of α-diazo-β-oxo sulfone **59** were next conducted. The catalyst, which consisted of 5 mol% $CuCl_2$, 6 mol% NaBARF and 6 mol% bisoxazoline ligand, was pre-formed for ~2 h before slow addition of the α-diazo-β-oxo sulfone **59** in dichloromethane. Five commercially available bisoxazoline ligands **20**, **44**, **137**, **138** were used, and the reactions were monitored using IR spectroscopy as discussed earlier in this section. Reactions employing ligands (4*R*)-Ph **20**, (4*R*,5*S*)-di-Ph **137**, (3*S*,8*R*)-Ind **44** and (4*R*)-Bn **43** were all complete within 21 h (**Table 7.5**, entries 1–4), while use of ligand (4*S*)-*t*-Bu **138** required a longer reaction time of 48 h (**Table 7.5**, entry 5).

Table 7.5 *Asymmetric chiral copper bisoxazoline catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* **59**



59 **257a** **258b**

Entry	L	Time (h)	Crude ratios[a] Purified Yields (%)[a] ee (%)[a]	Products	
				thiopyran (cyclopropanation) More polar **257a**	*trans* sulfolane (C–H insertion) Less polar **258b**
1	(4*R*)-Ph **20**	21	**Crude ratio** **Purified Yield (%)** **ee (%)**	90 70% 67% ee (1*S*,6*R*) (72%ee)[b]	10 -
2	(4*R*,5*S*)-di-Ph **137**	21	**Crude ratio** **Purified Yield (%)** **ee (%)**	90 66% 61% ee (1*S*,6*R*)	10 - -
3	(3*S*,8*R*)-Ind **44**	21	**Crude ratio** **Purified Yield (%)** **ee (%)**	92 59% 68% ee (1*R*,6*S*)	8 -

4	(4*R*)-Bn **43**	21	**Crude ratio** **Purified Yield (%)** **ee (%)**	95 63% 38% ee[c] (1*S*,6*R*)	5 -
5	(4*S*)-*t*-Bu **138**	48	**Crude ratio** **Purified Yield (%)** **ee (%)**	98 61% 61% ee (1*R*,6*S*)	2 - -

a. Crude efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **257a**; δ_H 1.64 (1H, dd, *J* 8.3, 6.4, one of methylene C*H*$_2$), 1.70 (1H, dd, *J* 9.6, 6.4, one of methylene C*H*$_2$) and signals for *trans* sulfolane **258b**; δ_H 3.39–3.51 [1H, m, C(3)*H*]. Yield (%) refers to material purified by column chromatography on silica gel. In general all enantioselectivities were measured using chiral shift ^{1}H NMR, employing [(+)-Eu(hfc)$_3$] as a chiral shift reagent. In one case chiral HPLC with a UV detector was also used (b), and will be noted where relevant. The absolute stereochemistry was assigned by analogy and will be discussed in **Appendix II**.

b. Measurement of enantioselectivity using chiral HPLC was also attempted using a UV detector. Although poor detection of compound **257a** was observed, a value of 72% ee was measured.

c. The experiment reported here was carried out once and was not repeated.

Reaction efficiencies for cyclopropanation and C–H insertion were high in all cases, with values of ~80–90% measured using the ^{1}H NMR spectra of the crude products (**Table 7.5**), a similar value to that observed for the rhodium acetate catalysed reaction (**Scheme 7.14**). Once again it was the cyclopropanation product **257a** that predominated, with minor amounts of C–H insertion product **258b** observed in all cases (it typically accounted for less than 10% of the crude product mixture) (**Table 7.5**). The largest amounts of C–H insertion product **258b** were observed for reactions with ligands (4*R*)-Ph **20**, (4*R*,5*S*)-di-Ph **137** (cyclopropane **257a** : C–H insertion product **258b**, 90 : 10) (**Table 7.5**, entries 1 and 2) and (3*S*,8*R*)-Ind **44** (cyclopropane **257a**: C–H insertion product **258b**, 92 : 8). Slightly lower amounts were observed for use of (4*R*)-Bn **43** (cyclopropane **257a**: C–H insertion product **258b**, 95 : 5) (**Table 7.5**, entry 4) and (4*S*)-*t*-Bu **138** (cyclopropane **257a**: C–H insertion product **258b**, 98 : 2) (**Table 7.5**, entry 5), suggesting the presence of an aryl ring adjacent to the coordinating nitrogen on the bisoxazoline ligand enhances the extent of C–H insertion. The crude product mixtures were purified using column chromatography on neutral alumina, with cyclopropanation product **257a** being isolated in moderate to good yields (59–70%) (**Table 7.5**). C–H insertion product **258b** was not isolated after purification in any of the cases presented in **Table 7.5**, although it was recovered in later studies using rhodium (**Table 7.7**).

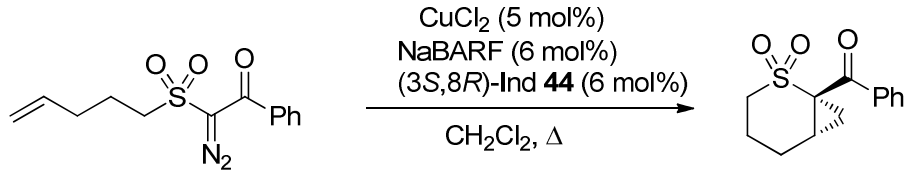
Moderate to good enantioselectivities were achieved for the $CuCl_2$-NaBARF-bisoxazoline catalyst system, with 68% ee being the highest value attained in this study for reaction with (3*S*,8*R*)-Ind ligand **44** (**Table 7.5,** entry 3). Similar enantioselectivities

were obtained for the use of (4*R*)-Ph ligand **20** (67% ee, **Table 7.5**, entry 1) with slightly lower values observed for (4*R*,5*S*)-di-Ph ligand **137** (61% ee, **Table 7.5**, entry 2) and (4*S*)-*t*-Bu **138** (61% ee, **Table 7.5**, entry 5), suggesting that enantioinduction in this reaction has little sensitivity to the nature of the substituents on the ligand. The only exception to this trend is seen for (4*R*)-Bn **43**, where a much lower value of 38% ee was measured (**Table 7.5**, entry 4).

The highest value obtained in this study for the synthesis of sulfone containing rings (68% ee, **Table 7.5** entry 3) was significantly lower than the highest value reported by Nakada and co-workers for α-sulfonyl cyclopentanones (98% ee, **Table 7.1**, entries 9 and 11). However, the high enantioselectivities reported by Nakada were achieved for reaction of the bulkier mesityl sulfone with a substituted alkene bond, as seen in **Table 7.1**. When Nakada used unsubstituted terminal alkenes and phenyl sulfones, the highest enantioselectivity achieved was 75% ee, comparable to the results in this work. For this reason, substrate modification will be discussed later in this chapter, in **Section 7.2.2**. Nakada also obtained high enantioselectivities for cyclopropanation reactions involving six-membered systems, with values of up to 98% ee being reported (**Table 7.4,** entry 2), demonstrating that it is possible to attain an excellent level of enantiocontrol for these systems. However, with (4*S*)-Bn **242** ligand, the enantioselectivity was somewhat lower at 67% ee (**Table 7.4**, entry 3). This is interesting as in this work use of (4*R*)-Bn **43** resulted in the lowest enantioselectivity (**Table 7.5**, entry 4), while all other ligands gave 60–70% ee. In contrast Nakada showed that the (4*S*)-Bn **242** gave some of the highest enantioselectivities for cyclopropanation yielding cyclopentanones (75% ee, **Table 7.1**, entry 2).

The absolute stereochemistry of **257a** was assigned by analogy for this series. The absolute stereochemistry of phenyl ketone cyclopropane **259a** (see **Section 7.2.2.1**) was determined using X-ray crystallography. To ensure the correct assignment, the single crystal was dissolved in IPA and injected onto a chiral HPLC column. The absolute stereochemistry for this compound, generated using (3*S*,8*R*)-Ind **44** as a ligand, was determined to be (1*R*,6S) and the rotation of this sample was positive $[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH_2Cl_2) (**Figure 7.15**). In comparison with the methyl ester series **257a**, a positive rotation was also obtained when (4*S*)-*t*-Bu **138** was employed as a ligand and a negative rotation was obtained through use of (4*R*)-Bn **43**. This was the basis of the assignment of

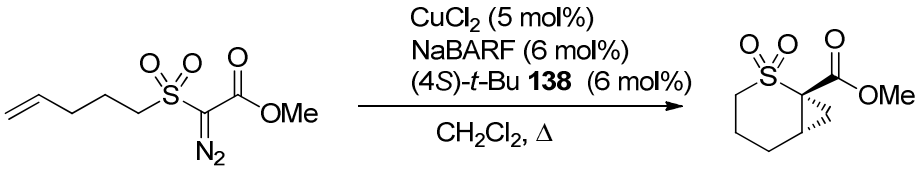
the absolute stereochemistry of **257a** and will be further discussed **Section 7.2.2.1** and **Appendix II**.



60 **259a**

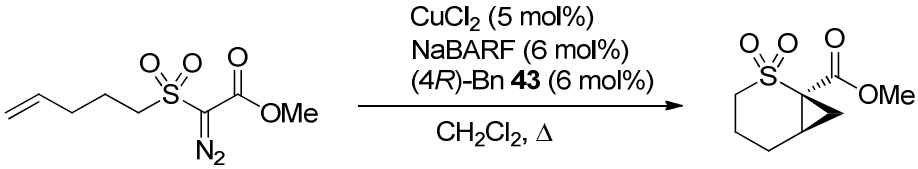
Determined using X-ray crystallography

$[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH_2Cl_2).



59 **257a**

$[\alpha]_D^{20}$ +15.7 (*c* 0.15, CH_2Cl_2).



59 **257a**

$[\alpha]_D^{20}$ -13.0 (*c* 0.1, CH_2Cl_2).

Scheme 7.15

As illustrated in **Figure 7.5**, the effect of ligand variation on enantioselectivity in C–H insertion and cyclopropanation with very similar substrates show quite different trends. In general, higher enantioselectivities are seen in the C–H insertion processes [up to 98% ee for (4*R*)-Ph **20**] and furthermore, the sensitivity to the nature of the ligand variation is higher in the C–H insertion processes than in cyclopropanation. While (3*S*,8*R*)-Ind **44** gave the highest enantiocontrol in cyclopropanation, in contrast, it resulted in the lowest

enantioselectivity in the C–H insertion process, highlighting the impact of differences in the transition states of the two reaction pathways.

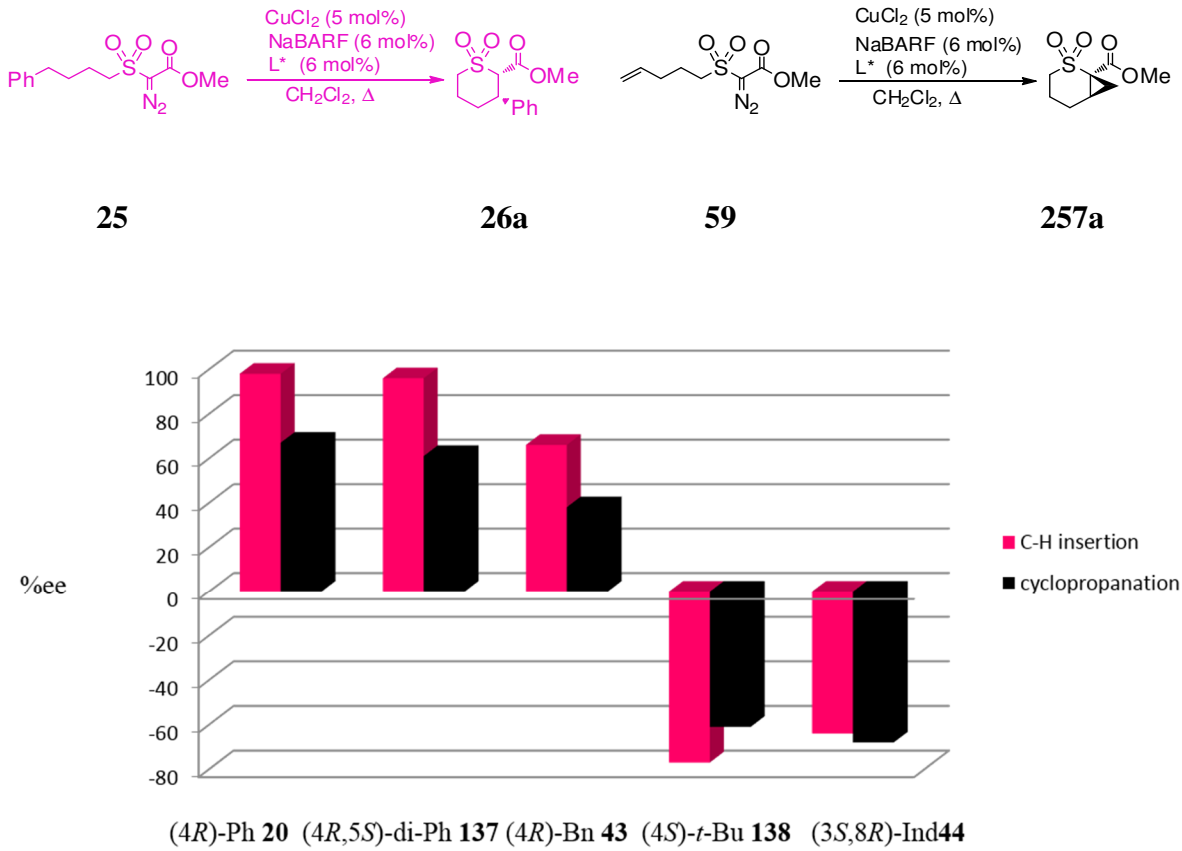
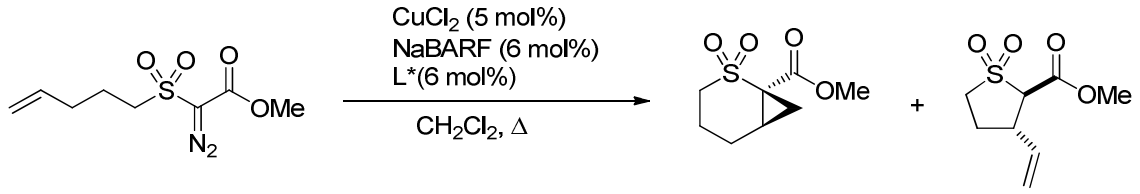


Figure 7.5 *Comparison of enantioselectivities in cyclopropanation and C–H insertion with bisoxazoline ligand variation.*

Having examined the effects of variation of the copper-bisoxazoline catalysts on the outcome of the cyclopropanation reaction of α-diazo-β-oxo sulfone **59**, attention was next focused on the copper-semicorrin and copper-pybox catalysed reactions. One commercially available semicorrin ligand CN-(4*S*)-Ph **158** and two commercially available pybox ligands Py-(4*R*)-Ph **159** and Py-(4*S*)-*i*-Pr **160** were selected for investigation. The results of this study are presented in **Table 7.6**. After prolonged stirring under reflux in dichloromethane (150 hours), no reaction was observed using either semicorrin ligand **158** or pybox ligands **159** and **160** (**Table 7.6**, entries 1–3). Examination of ^{1}H NMR spectra of the reaction mixture after 150 hours showed that only starting material α-diazo-β-oxo sulfone **59** was present, with no evidence of degradation or byproduct formation (**Table 7.6**, entries 1–3).

Table 7.6 *Asymmetric chiral copper semicorrin and pybox catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* ***59***



59 **257a** **258b**

Entry	L[a]	Time (h)	Crude Efficiency (%)
1	CN-(4*S*)-Ph **158**	150	Starting material only recovered
2	Py-(4*R*)-Ph **159**	150	Starting material only recovered
3	Py-(4*S*)-*i*-Pr **160**	150	Starting material only recovered

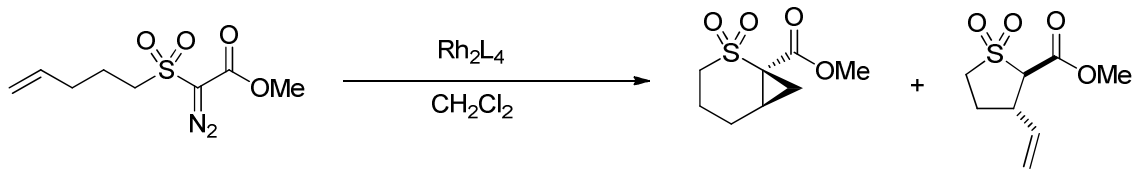
a. Structures of ligands are shown in **Chapter 4**, **Section 4.6.2**, **Figure 4.31**

7.2.1.1 Asymmetric rhodium catalysed cyclopropanation reactions of 59

The use of five chiral rhodium catalysts for the cyclopropanation of α-diazo-β-oxo sulfone **59** was investigated for comparison with the chiral copper-bisoxazoline catalysed reactions of the same substrate **59** (**Table 7.7**). Four rhodium carboxylates [Rh_2(*S*-PTTL)$_4$, Rh_2(*S*-PTPA)$_4$, Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-mand)$_4$] and one rhodium carboxamidate [Rh_2(*S*-MEPY)$_4$] were examined. The chiral rhodium reactions were carried out with 1 mol% of chiral rhodium catalyst. Addition of the α-diazo-β-oxo sulfone **59** in dichloromethane to the rhodium catalyst in dichloromethane was carried out 0 °C, and the reaction mixture was then allowed to slowly return to room temperature. The results of this study are presented in **Table 7.7**. For the rhodium carboxylate catalysts [Rh_2(*S*-PTTL)$_4$, Rh_2(*S*-PTPA)$_4$ and Rh_2(*S*-mand)$_4$], each of the reactions was complete within 30 h at room temperature (**Table 7.7**, entries 1,3,5). With Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-MEPY)$_4$ IR monitoring after 24 h indicated no reaction of the α-diazosulfone **59** and an additional 24 h at reflux was required for complete reaction (**Table 7.7**, entry 2) while with Rh_2(*S*-

MEPY)$_4$ even following heating for 120 h only unreacted starting material was recovered (**Table 7.7**, entry 4).

Table 7.7 *Asymmetric chiral rhodium catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* ***59***



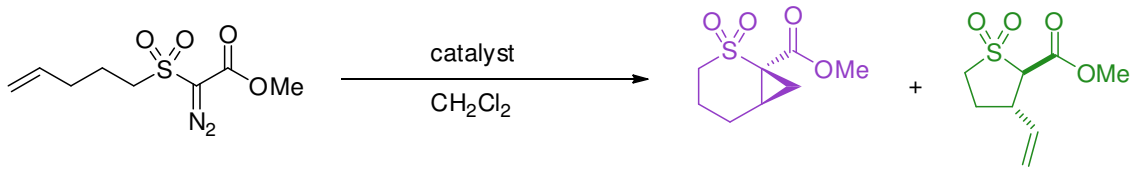
59 **257a** **258b**

Entry	Metal	Time (h)	Crude Efficiency (%)[a]	Crude ratio[a] Purified Yield (%)[a] % ee[a]	Products	
					thiopyran (cyclopropanation) More polar **257a**	*trans* sulfolane (C–H insertion) Less polar **258b**
1	Rh_2(*S*-PTTL)$_4$ 0 °C-rt	6 rt	80–90%	**Crude ratio** **Purified Yield (%)** **% ee**	88 67% 34% ee (1*R*,6S)	12 3% -
2	Rh_2(*S*-DOSP)$_4$ 0 °C-rt-Δ	24 rt + 24Δ	80–90%	**Crude ratio** **Purified Yield (%)** **% ee**	82 58% 11% ee	18 4%
3	Rh_2(*S*-PTPA)$_4$ 0 °C-rt	8 rt	80–90%	**Crude ratio** **Purified Yield (%)** **% ee**	83 67% 8% ee (1*R*,6*S*)	17 4%
4	Rh_2(*S*-MEPY)$_4$ 0 °C-rt-Δ	30 rt +120Δ	-	-	Starting material only recovered	-
5	Rh_2(*S*-mand)$_4$ 0 °C-rt	21 rt	80–90%	**Crude ratio** **Purified Yield (%)** **% ee** **Total**	91 54% (contains ~10% *trans* sulfolane **258b**) ~12% ee[b] (1*S*,6*R*) **49%**	9 **5%**

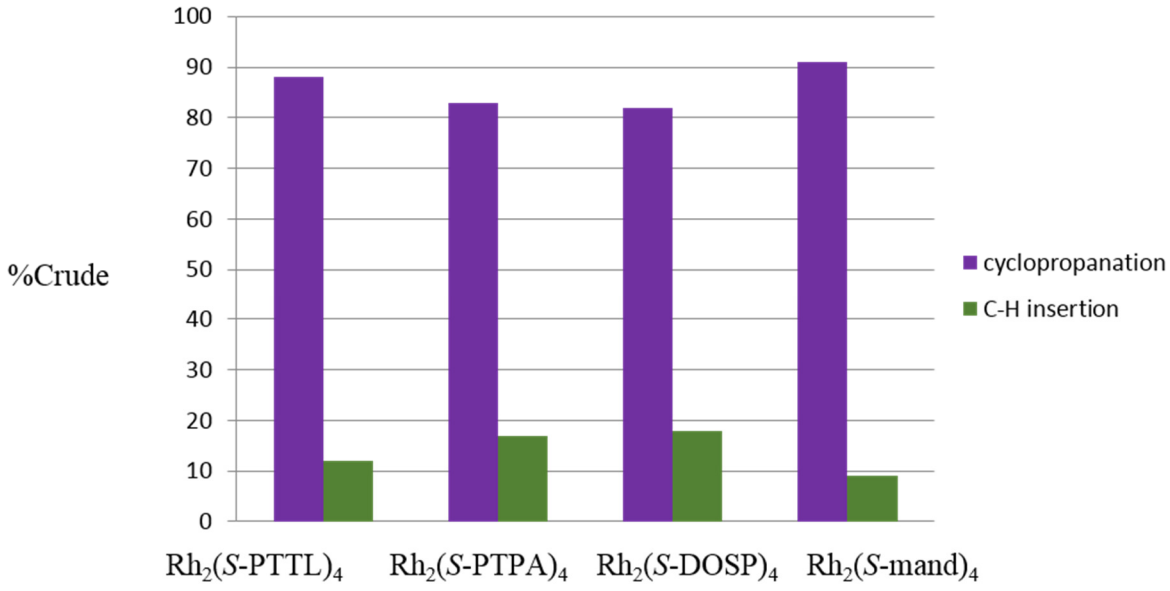
a. Crude efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **257a**; δ_H 1.64 (1H, dd, *J* 8.3, 6.4, one of methylene C*H*$_2$), 1.70 (1H, dd, *J* 9.6, 6.4, one of methylene C*H*$_2$) and signals for *trans* sulfolane **258b**; δ_H 3.39–3.51 [1H, m, C(3)*H*]. Yield (%) refers to material purified by column chromatography on silica gel. In general all enantioselectivities were measured using chiral ^{1}H NMR, employing [(+)-Eu(hfc)$_3$] as a chiral shift reagent., details of which can be found in **Appendix I**.

b. Estimated due to presence of C–H insertion product **258b** in purified product.

Reaction efficiencies are high for all reactions catalysed by chiral rhodium carboxylates (80–90% efficient) (**Table 7.7**, entries 1-3, 5), and are comparable to those achieved for the copper-bisoxazoline catalysed reactions (**Table 7.5**). While cyclopropanation is still the major reaction pathway observed for the rhodium catalysed reactions, there is a notable change in the ratio of cyclopropanation : C–H insertion when compared to the copper catalysed reactions (**Table 7.5** *cf* **Table 7.7**), with slightly larger amounts of C–H insertion product **257a** present in the crude reaction mixtures of the rhodium catalysed reactions. This effect is most notable for reactions with Rh_2(*S*-DOSP)$_4$ (cyclopropanation : C–H insertion, 82 : 18) (**Table 7.7**, entry 2) and Rh_2(*S*-PTPA)$_4$ (cyclopropanation : C–H insertion, 83 : 17) (**Table 7.7**, entry 3). In addition to the alteration of the metal catalyst, the increased proportion of the C–H insertion may be associated with the lower reaction temperatures of the rhodium catalysed processes, compared to the copper catalysed transformations. This effect is summarised in **Figure 7.6**.



59 **257a** **258b**



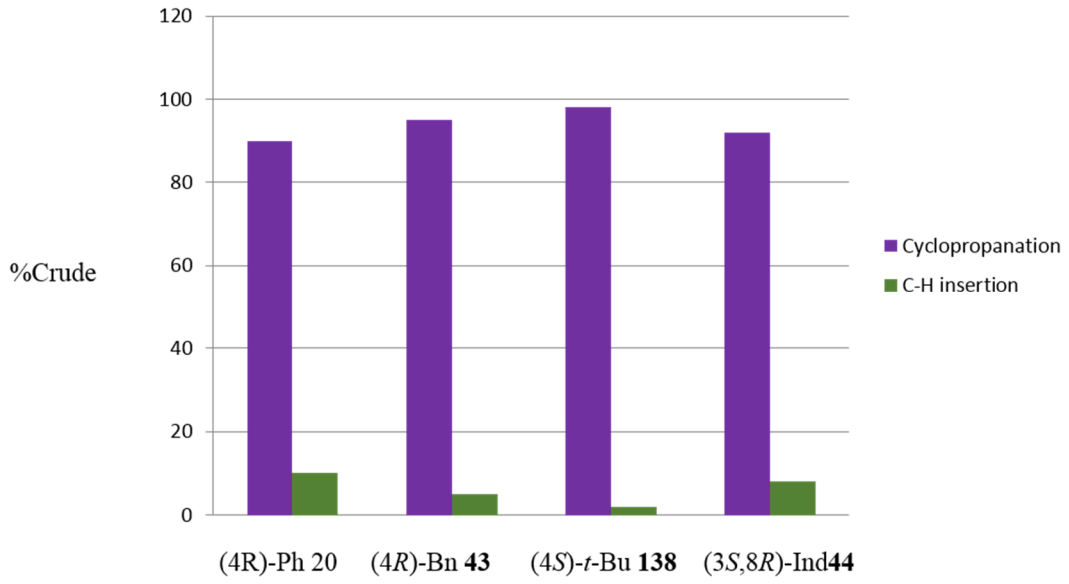


Figure 7.6 *Relative amounts of cyclopropanation product **257a** and C–H insertion product **258b**, estimated from the ^{1}H NMR spectra of the crude product mixture*

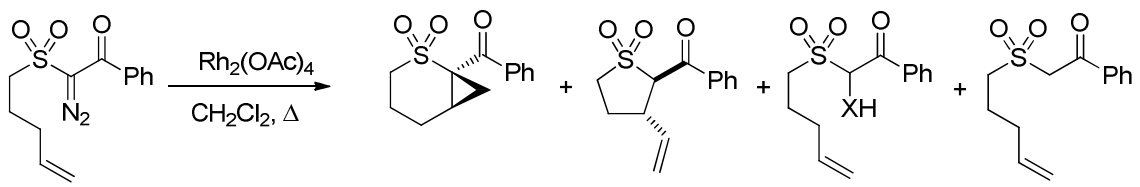
In this instance both cyclopropanation and C–H insertion products were isolated after purification using column chromatography on alumina, in relatively good yields (**Table 7.7**, entry 1–3). Separation of the two products was achieved in all but one instance; for reaction with Rh_2(*S*-mand)$_4$, where the two isomers were isolated as a mixed fraction in 54% combined yield (**Table 7.7**, entry 5). As limited amounts of sulfolane **258b** were isolated, and in the absence of a racemic sample of **258b**, determination of the enantiopurities of this product arising from reactions with Rh_2(*S*-DOSP)$_4$, Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-PTPA)$_4$ (**Table 7.7**, entries 1–3) was not attempted.

Much lower enantioselectivities were achieved for the cyclisations of α-diazo-β-oxo sufone **59** with the rhodium carboxylate catalysts (**Table 7.7**, entries 1–3, 5) than for reactions with the copper bisoxazoline catalysed reactions (**Table 7.5**). Rh_2(*S*-PTTL)$_4$ gave the highest enantioselectivity of all the chiral rhodium catalysed reactions with a value of 34% ee measured for cyclopropanation product **257a** (**Table 7.7**, entry 1). Much lower values were obtained in all other cases 8–12% (**Table 7.7**, entries 2–3, 5). The low enantioselectivities achieved with the chiral rhodium catalysed reactions are comparable to the enantioselectivity of 12% ee achieved for the Rh_2(*S*-mand)$_4$ cyclopropanation reaction to produce α-sulfonyl cyclopentanone product **240**, reported by McKervey (**Scheme 7.7**).[50]

7.2.2 Investigation into the effects of substrate modification

7.2.2.1 Rhodium acetate and chiral copper-bisoxazoline catalysed reactions of 60

Having thoroughly investigated the asymmetric copper and rhodium catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone **59**, our attention was next focused on changing the nature of the diazocarbonyl group from a methyl ester **59** to a phenyl ketone **60**. Initially, the rhodium acetate catalysed reaction of the novel α-diazo-β-oxo sulfone **60** was carried out to generate racemic cyclisation products for the development of chiral HPLC conditions. The outcome of this reaction is presented in **Scheme 7.16**.

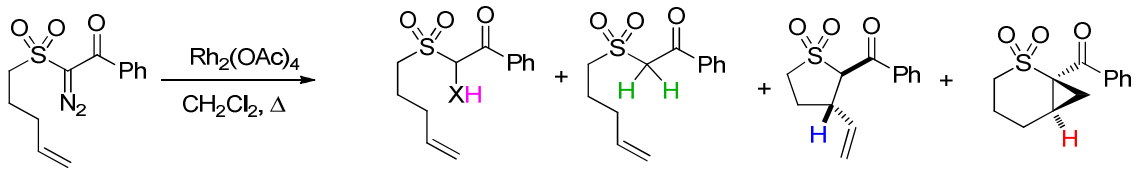


Crude (%)	60%	6%	1%	2%
Purified (%)	41%	3%		
% ee	0% ee	0% ee		
60	**259a**	**260b**	**261**	**131**

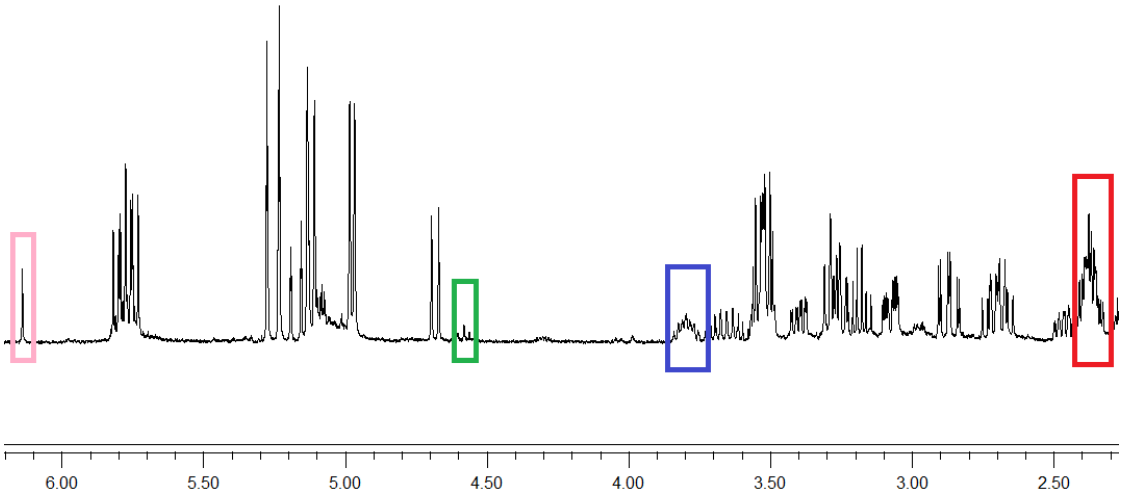
Scheme 7.16

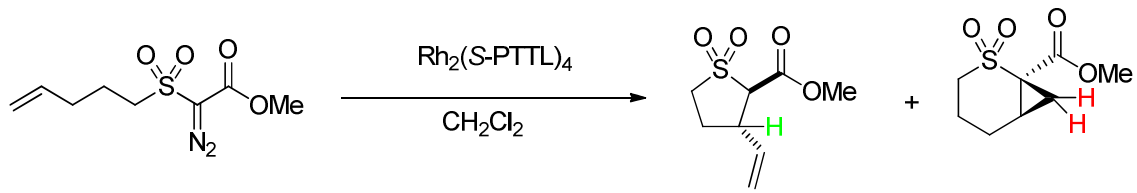
The first notable feature of this reaction is a slight decrease in reaction efficiency for cyclopropanation and C–H insertion (60–70%) (**Scheme 7.16**), when compared to the rhodium acetate catalysed reaction of the analogous methyl ester substrate **59** (80–90%) (**Scheme 7.14**). Cyclopropanation is still the favoured reaction pathway with thiopyran **259a** constituting 60% of the crude reaction products, while there were minor amounts of C–H insertion product **260b** present (6%) **Scheme 7.16**. The relative product distribution is similar to that seen for methyl ester product **59** (**Table 7.5** and **7.7**). Two additional byproducts were also in the ^{1}H NMR spectra of the crude reaction mixture; sulfone **131** formed by reduction of the parent α-diazo-β-oxo sulfone **60** accounts for 2% and X–H insertion product **261** is also present at low levels (1%). (The formation of these byproducts has been previously discussed in greater detail in **Chapter 4**, **Section 4.1.3**).

All four reaction products are observed in the ^{1}H NMR spectrum of the crude mixture, and can be quantified using the integration of a number of key signals as indicated in **Figure 7.7**. The signals used in each case must be carefully selected as the occurrence of peak overlap is quite high due to the number of products present. Interestingly the presence of the analogous byproducts were not observed in either the copper or rhodium catalysed reactions of the methyl ester substrate **59** (**Table 7.5** and **7.7**). Both thiopyran **259a** and sulfolane **260b** were isolated in respectable yields, after purification using column chromatography, which reflected the amounts present of each in the crude reaction material (**Figure 7.7**). For comparison purposes the ^{1}H NMR spectra of the crude reaction material of the cyclisation of methyl ester **59** using Rh_2(*S*-PTTL)$_4$ as a catalyst is included in **Figure 7.7**.



60 **261** **131** **260b** **259a**





59 **258b** **257a**

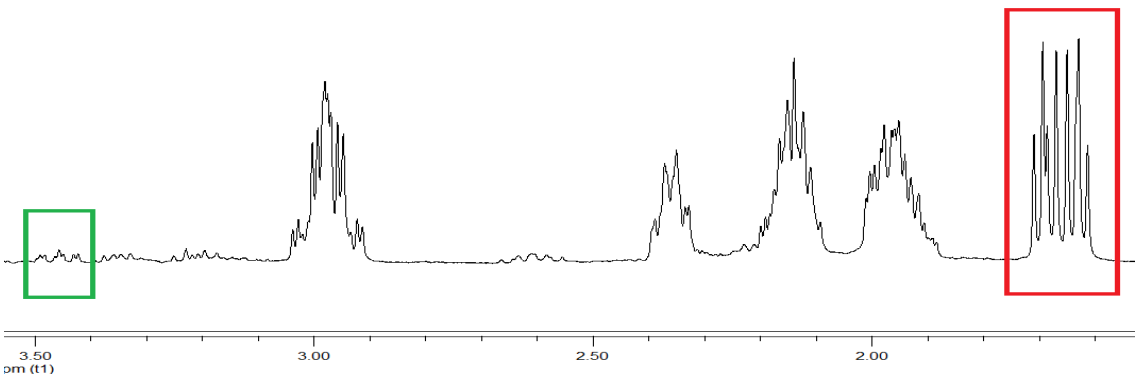
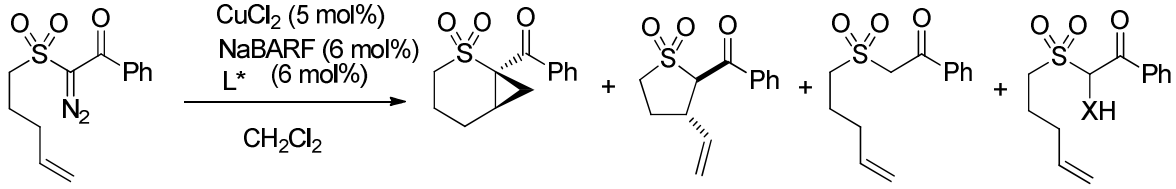


Figure 7.7 *^{1}H NMR spectra recorded in ($CDCl_3$, 400 MHz)*

Unlike methyl ester thiopyran **257a**, phenyl ketone thiopyran **259a** and phenyl ketone sulfolane **260b** possessed a sufficiently strong chromophore to enable the successful development of chiral HPLC conditions for both cyclisation products **259a** and **260b** (**Scheme 7.16**). As both of these reaction products **259a** and **260b** were novel, they were fully characterised using ^{1}H NMR, ^{13}C NMR and IR spectroscopy, as well as with high resolution mass spectrometry.

In terms of enantioselectivity, the copper-bisoxazoline catalysts were the most successful for the cyclopropanation of α-diazo-β-oxo sulfone **59**, therefore, this catalyst system was also utilised for the cyclisation of α-diazo-β-oxo sulfone **60**. Pre-formation of the catalyst was carried out by mixing 5 mol% $CuCl_2$, 6 mol% NABARF and 6 mol% bisoxazoline ligand before the slow addition of the α-diazo-β-oxo sulfone **60** in dichloromethane was carried out. The results of this study are presented in **Table 7.8**.

Table 7.8 *Asymmetric chiral copper bisoxazoline catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone **60***



60 **259a** **260b** **131** **261**

Entry	L*	Crude Ratio[a-d] Purified Yield (%)[e] % ee [f]	Products			
			cis thiopyran **259a** [a]	*trans* sulfolane **260b** [b]	sulfone **131**[c]	X–H Insertion **261**[d]
1	(3*S*,8*R*)-Ind **44**	**Crude (%)** **Purified Yield (%)** **% ee**	72% 56 % 80% ee (1*R*,6*S*)	4% 1%[g] (50 : 50) -[h]	3%	5% 0.6%
2	(4*R*,5*S*)-di-Ph **137**	**Crude (%)** **Purified Yield (%)** **% ee**	84% 45% 73% ee (1*S*,6*R*)	2% 1% 0 %ee	0% -	2%
3		**Crude (%)**	70%	2%	2%	1%

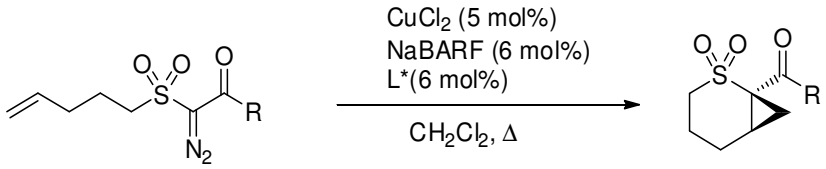
	(4*R*)-Ph **20**	**Purified Yield (%)**	49%	2%[g] 83:17		
		% ee	75% ee (1*S*,6*R*)	-[h]		
4	(4*R*)-Bn **43**	**Crude (%)**	70%	1%	2%	3%
		Purified Yield (%)	52%	1%[g] 93:7		
		% ee	75% ee (1*S*,6*R*)	-[h]		
5	(4*S*)-*t*-Bu **138**	**Crude (%)**	83%	6%	0%	0%
		Purified Yield (%)	58	2		
		% ee	80% ee (1*R*,6*S*)	-[h]		

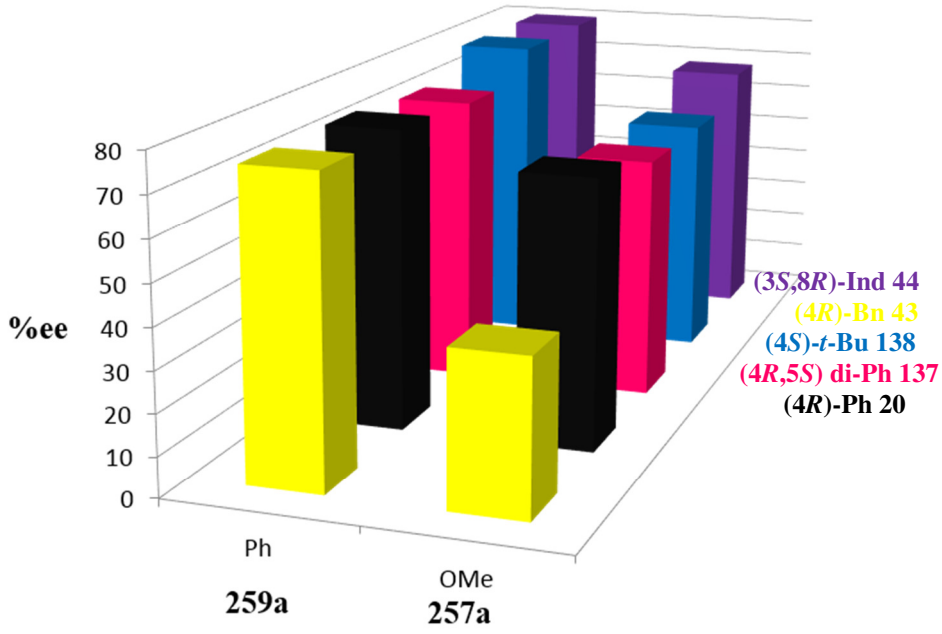
a. Relative ratios of reaction products calculated using ^{1}H NMR spectra of the crude product using signals for C(6)*H*; δ_H 2.36–2.42 [1H, m, C(6)*H*] for *cis* thiopyran **259a**
b. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(3)*H*; δ_H 3.70–3.78 [1H, m, C(3)*H*] for *trans* sulfolane **260b**
c. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for reduction product **131**; δ_H 4.57 (2H, s, SO_2CH_2CO).
d. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for X–H insertion product **261**; δ_H 6.02 (2H, s, SO_2CHXCO).
e. Yields are reported after purification using column chromatography on silica gel.
f. Enantioselectivities were measured using chiral HPLC, see **Appendix I** for details.
g. *Trans* sulfolane **260b** and sulfone **131** were isolated as a mixed fraction. The yield (%) reported is for both compounds. The ratio of the two compounds in the purified product was calculated from ^{1}H NMR spectra of the purified product, using signals indicated in footnotes (b) and (c) above.
h. Enantioselectivity could not be accurately determined due to multiple peaks being present in the HPLC trace.

Reaction efficiencies remained high for C–H insertion and cyclopropantion with values ranging between ~70–90% (**Table 7.8**), which is comparable to the copper-bisoxazoline catalysed reactions of methyl ester substrate **59** (**Table 7.5**). Thiopyran **259a** typically accounted for 70–84% of the crude reaction mixture, with sulfolane **260b** accounting for up to 6% of the crude reaction products, clearly demonstrating that the cyclopropanation pathway is once again favoured for the copper catalysed reaction. (**Table 7.8**). The sulfone reduction product **131** was present at low levels (<5%) for reactions with (3*S*,8*R*)-Ind **44**, (4*R*)-Ph **20** and (4*R*)-Bn **43** ligands (**Table 7.8**, entries 1, 3–4). An additional byproduct, X–H insertion product **261**, constituted between 1–5% of the crude reaction mixture for ligands (3*S*,8*R*)-Ind **44**, (4*R*)-di-Ph **137**, (4*R*)-Ph **20** and (4*R*)-Bn **43** (**Table 7.8**, entries 1–4). Interestingly, neither byproduct **131** nor **261** was observed in the crude reaction mixture for the reaction catalysed by $CuCl_2$-NaBARF-(4*S*)-*t*-Bu **138** (**Table 7.8**,

entry 5), demonstrating the effect of the sterically demanding ligand on the chemoselectivity/efficiency of the reaction.

After purification using column chromatography, thiopyran **259a** was isolated in moderate quantities in all cases (49–58%) (**Table 7.8**, entries 1–5), and successful separation was achieved from sulfolane **260b** and byproducts **131** and **261**. The highest enantioselectivity was 80% ee which was achieved when either the (3*S*,8*R*)-Ind **44** or the (4*S*)-*t*-Bu **138** ligand was employed (**Table 7.8**, entries 1 and 5). The enantioselectivity of the reaction did not appear to be largely impacted on by the nature of the bisoxazoline ligand, with 75% ee attained for cyclisations employing (4*R*)-Ph **20** and (4*R*)-Bn **43** (**Table 7.8**, entries 3 and 4) with 73% ee being the lowest enantioselectivity obtained in this study, for the use of (4*R*)-di-Ph **137** (**Table 7.8**, entry 2). This trend is similar to the one observed for the copper-bisoxazoline catalysed reactions of the methyl ester α-diazo-β-oxo sulfone **59**, where only the (4*R*)-Bn **43** ligand had a significant impact on the enantioselectivty of the reaction. Therefore, it appears that the nature of the starting α-diazo-β-oxo sulfone has a greater impact on the enantiopurity of the cyclopropanation products than the nature of the bisoxazoline ligand. The use of the phenyl ketone α-diazo-β-oxo sulfone **60** gave rise to thiopyran **259a** with enantiopurities between 70–80% ee (**Table 7.8**), while the methyl ester α-diazo-β-oxo sulfone **59** produced products with enantiopurities typically in the range of 60–70% ee, [with the exception of (4*R*)-Bn **43** which gave 38% ee, **Table 7.5,** entry 4], suggesting that the nature of the carbonyl substituent is critical in achieving cyclopropane products with high enantiopurities. This trend can be visualised in **Figure 7.8**.


CuCl2 (5 mol%)
NaBARF (6 mol%)
L*(6 mol%)
CH2Cl2, Δ
O
O
S
O
R
N2


%ee
80
70
60
50
40
30
20
10
0
Ph
OMe
259a
257a
R
(3S,8R)-Ind 44
(4R)-Bn 43
(4S)-t-Bu 138
(4R,5S) di-Ph 137
(4R)-Ph 20

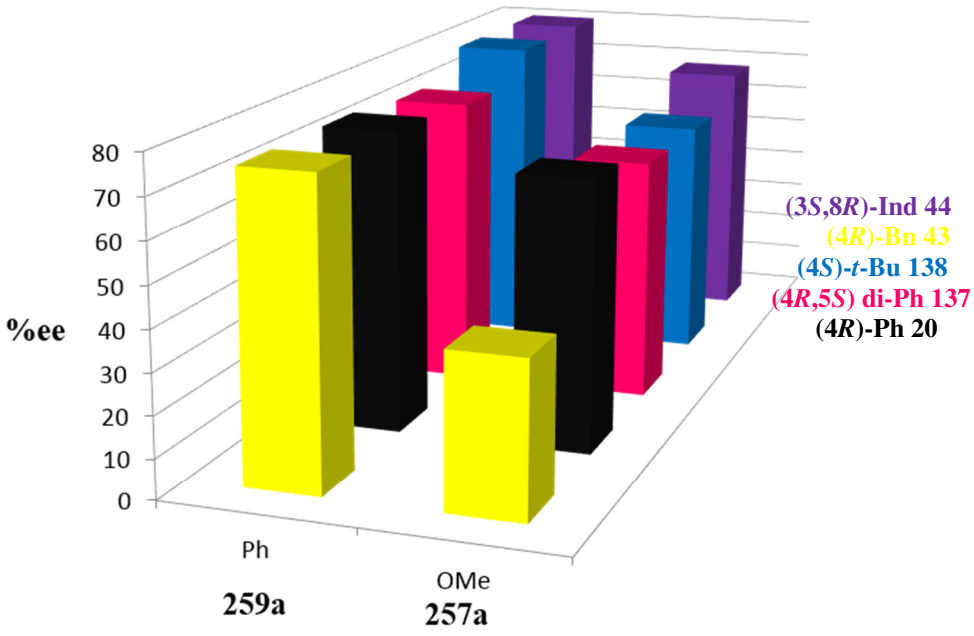
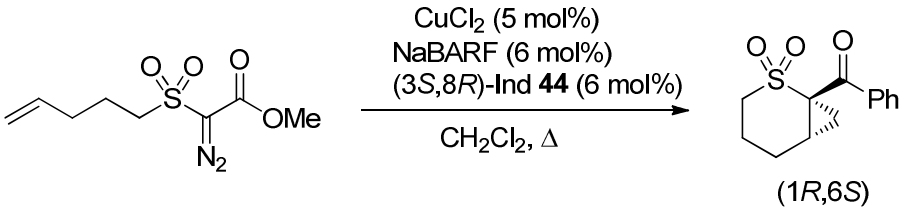

%ee
80
70
60
50
40
30
20
10
0
Ph
OMe
259a
257a
R
(3S,8R)-Ind 44
(4R)-Bn 43
(4S)-t-Bu 138
(4R,5S) di-Ph 137
(4R)-Ph 20

Figure 7.8

The absolute stereochemistry of the cyclopropane products was determined from a crystal structure obtained from a reaction employing $CuCl_2$-NaBARF-(3*S*,8*R*)-Ind **44** as catalyst system (**Table 7.8**, entry 1) (**Figure 7.9**).



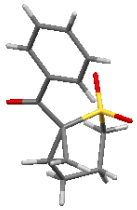


Figure 7.9 *A view of **259a** showing the structure and relative stereochemistry. Anisotropic displacement parameters are drawn at the 30% probability level.*

The absolute stereochemistry of the single crystal was determined to be (1*R*,6*S*), and this was confirmed as the major enantiomer by injection of a solution of the single crystal into the chiral column (further discussion can be found in **Appendix II**). Knowing the absolute stereochemistry then allowed a transition state model to be constructed. As can be seen in **Figure 7.10**, the favoured transition state for cyclopropanation is one where the double bond is orientated in a position where there is minimal steric hindrance.

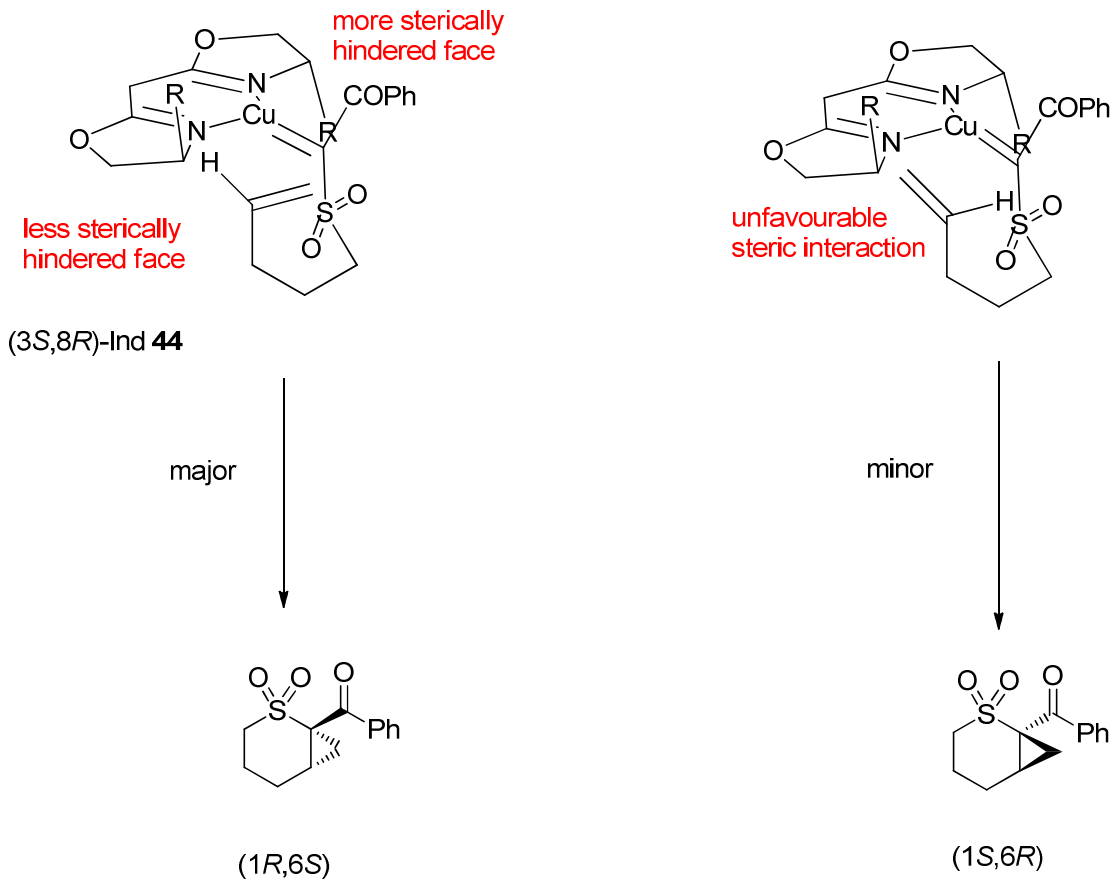
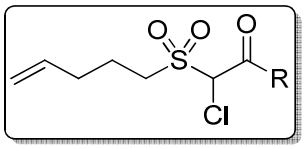


Figure 7.10

C–H insertion product **260b** was isolated in minor quantities, which typically reflects the proportion of this product in the crude reaction mixtures. In certain cases, it was isolated cleanly (**Table 7.8**, entries 2 and 5), while in all other instances it was isolated as a mixture which also contained the reduced sulfone **131** (**Table 7.8**, entries 1, 3–4). While low quantities of *trans* sulfolane were isolated and there were challenges in obtaining the sulfolanes in a pure form, enantioselectivity was measured in one instance, for reaction with (4*R*)-di-Ph **44**, where a racemic sample was obtained (**Table 7.8**, entry 2). Obtaining a low enantioselectivity for *trans* sulfolanes is not unusual, as was observed in Chapter 4, **Section 4.34**. A clean sample of X–H insertion product **261** was isolated in one instance, in a yield of 0.6%, for reaction in the presence of (3*S*,8*R*)-Ind **44** (**Table 7.8**, entry 1). It is envisaged that this compound is due to chloride abstraction from dichloromethane (**Figure 7.11**), but this has not been confirmed (this has been previously discussed in **Chapter 4**, **Section 4.1.3**).



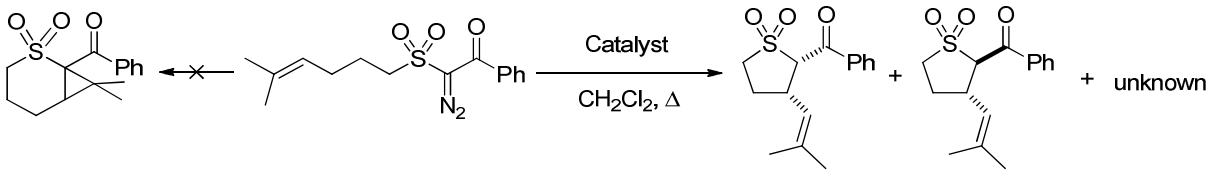
262

Figure 7.11

7.2.2.2 Investigation of the C–H insertion reaction of α-diazo-β-oxo sulfone 61

A further substrate modification was investigated; in this instance alteration of the double bond, was explored. An α-diazo-β-oxo sulfone **61** was synthesised with two methyl groups on the terminal end of the alkene, to examine the impact of increased steric effects on the outcome of the reaction. The results of this study are presented in **Table 7.9**.

Table 7.9 *Rhodium acetate and chiral copper bisoxazoline catalysed reactions of α-diazo-β-oxo sulfone* ***61***



61 **263a** **263b** **264**

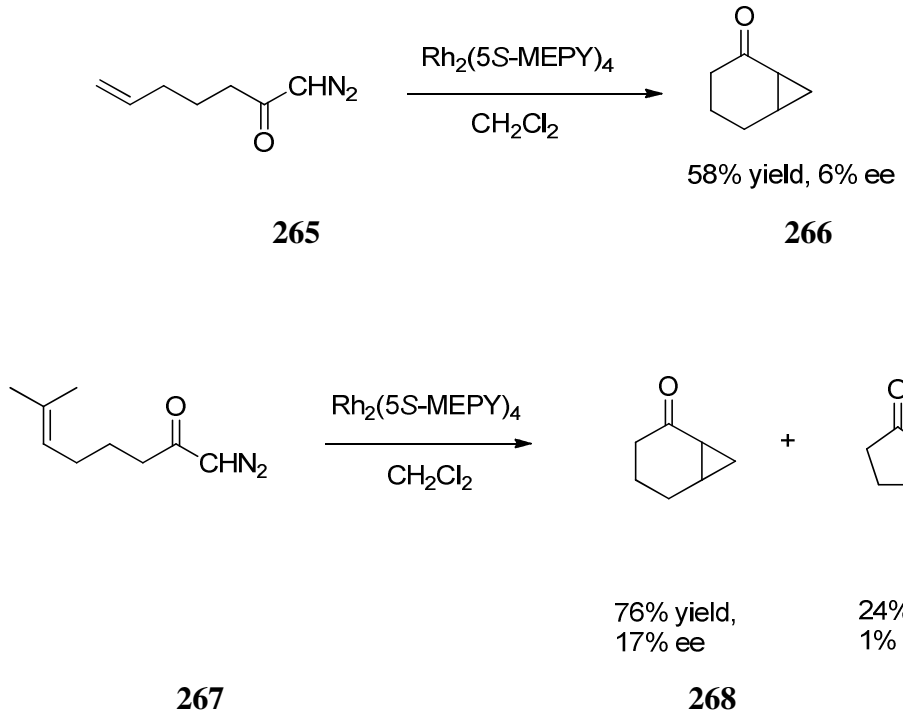
Entry	Catalyst	Time (h)	Crude (%) Purified Yield (%) %ee	*cis* [a] 263a	*trans*[a] 263b	*unknown*[a] 264
1	$Rh_2(OAc)_4$ (1 mol%)	24	**Crude (%)**[b] **Purified Yield (%)** **% ee**	60% - -	20% 43% 6% ee[c]	-
2	$CuCl_2$ (5 mol%) (3*S*,8*R*)-Ind **44** (6 mol%) NaBARF (6 mol%)	24	**Crude (%)**[d] **Purified Yield (%)**[b] **% ee** **Fr 1**[e] **Fr 2**[g] **Fr 3** **Total**	8% - 	72% 12 (47% ee)[c,f] 20 (47% ee)[c,f] 7 (47% ee)[c,f] **39% (47% ee)**	12%

3	$CuCl_2$ (5 mol%) (4*R*)-Bn **43** (6 mol%) NaBARF (6 mol%)	24	**Crude (%)**[h] **Purified Yield(%)** **%ee** **Fr 1**[i] **Fr 2** **Total**	4% - - 	79% 16% (44% ee)[j] 21% (41% ee)[j] **37% (42% ee)**	12%
4	$CuCl_2$ (5 mol%) (4*S*)-*t*-Bu **138** (6 mol%) NaBARF (6 mol%)	48	**Crude (%)**[k] **Purified Yield(%)** **% ee**	2% - -	78% 37%[l] 53% ee[f]	20%
5	$CuCl_2$ (5 mol%) (4*R*,5*S*)-di-Ph **137** (6 mol%) NaBARF (6 mol%)	21	**Crude(%)** **Purified Yield(%)** **% ee**	36% - -	54% 32% 38% ee[f]	-
6	$CuCl_2$ (5 mol%) (4*R*)-Ph **20** (6 mol%) NaBARF	21	**Crude (%)** **Purified Yield (%)** **% ee**	26% - -	61% 40% 43% ee[f]	2%

	(6 mol%)					

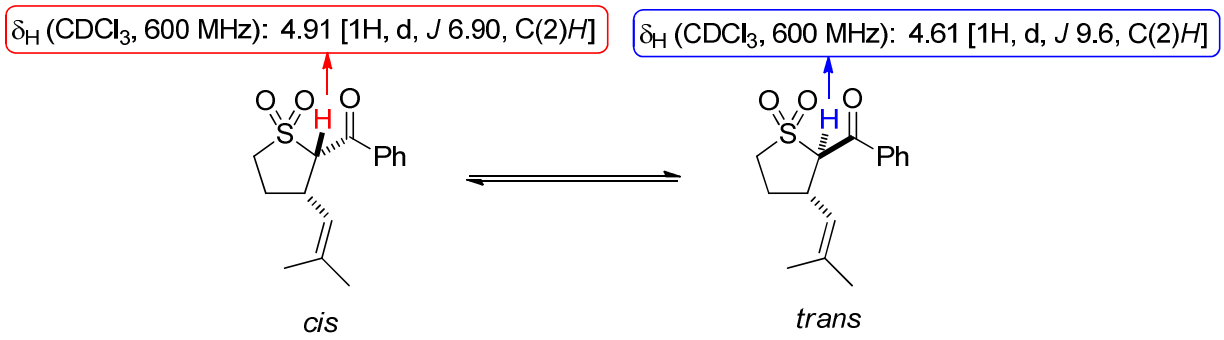
a. Quantities of products in crude mixtures are calculated from the ^{1}H NMR spectra using the following signals; δ_H 3.96–4.04 [1H, m, C(3)*H*] for *trans* sulfolane **263b** and δ_H 4.91 (d, *J* 6.90) for *cis* sulfolane **263b**; δ_H 6.16 (1H, d, *J* 2.6) for unknown **264**.
b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 9.67 (s).
c. HPLC trace not clean.
d. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 6.01 (s), 6.19 (s).
e. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~5%
f. The first eluting enantiomer at ~36 min is the major enantiomer. (Amylose 2)
g. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~10%
h. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 6.01 (s), 6.19 (s).
i. Contains impurity ~15%; δ_H 5.49–5.51 (m), 5.52–5.75 (m), 6.19 (s).
j. The second eluting enantiomer at ~75 min is the major enantiomer. (Amylose 2)
k. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.49–5.51 (m), 5.52–5.75 (m), 6.19 (s)
l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~5%

Surprisingly, when novel α-diazo-β-oxo sulfone **61** was exposed to rhodium acetate, there was no evidence of any cyclopropanation product in the ^{1}H NMR spectrum of the crude reaction product. The only observable intramolecular cyclisation product was a C–H insertion product yielding both *cis* and *trans* sulfolane in 75 : 25 ratio (**Table 7.9**, entry 1). The reaction proceeded with relatively good efficiency with both *cis* and *trans* sulfolane **263a** and **263b** accounting for ~80% of the crude reaction mixture. There is literature precedent for increasing the amount of C–H insertion product obtained relative to the amount of cyclopropanation product through increased substitution on the double bond. Lahuerta reported that for the Rh_2(5*S*-MEPY)$_4$ catalysed reaction of **265**, only cyclopropanation product **266** was observed. However, when α-diazoketone **267**, containing two methyl groups on the terminal end of the alkene bond, underwent reaction in the presence Rh_2(5*S*-MEPY)$_4$, a notable difference in product distribution was seen; while cyclopropanation product **268** was still the main reaction product, C–H insertion product **269** was isolated in 24% yield.[39] Therefore, while the cyclopropanation pathway was not completely switched off when the alkene bond was substituted, as was the seen in this work, there was a notable difference in product distribution.



Scheme 7.17

After purification using column chromatography on silica gel, the *trans* isomer **263b** was the only product isolated, in a 43% yield, suggesting that epimerisation had taken place (**Scheme 7.18**). Resolution of the two enantiomers of the *trans* sulfolane **263b** by chiral HPLC was achieved, however, an enantiopurity of 6% ee was measured, which was unexpected (**Table 7.9**, entry 1), as an achiral catalyst was employed. This may be accounted for by the fact that the HPLC trace was not entirely clean.



263a **263b**

Scheme 7.18

Work subsequently began on the asymmetric copper-bisoxazoline catalysed reactions of α-diazo-β-oxo sulfone **61**. Examination of the ^{1}H NMR spectra of the crude reaction mixtures of each of the copper-bisoxazoline catalysed reactions revealed that only *cis* and *trans* sulfolane cyclisation products were present, and once again there was no evidence for cyclopropanation having occurred (**Table 7.9**, entries 2–5). Therefore, it can be concluded that modification of the terminal end of the alkene alters the reaction pathway significantly; when the terminus is unsubstituted the cyclopropanation pathway is favoured and when it is substituted with two methyl groups no cyclopropanation product is detected, with C–H insertion preferred. While this alteration may be rationalised due to steric and/or electronic effects, examining a model indicates that steric congestion in the transition state for cyclopropanation is the key factor. As can be seen in **Figure 7.12**, the presence of the two methyl groups may have proved too bulky for cyclopropanation to occur.

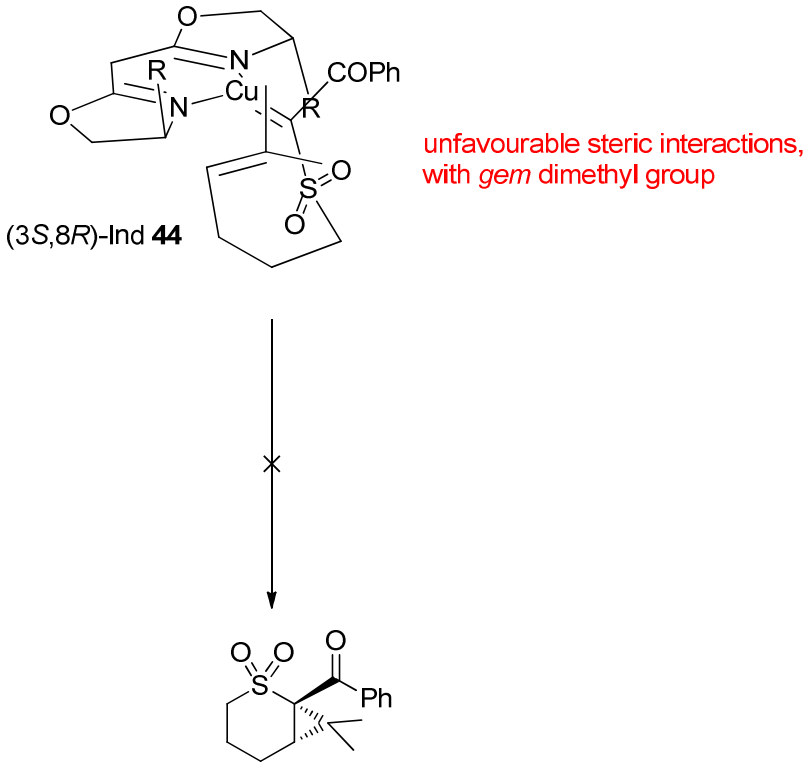


Figure 7.12

In general, reaction efficiencies for the C–H insertion reaction were high with *cis* and *trans* sulfolanes **263a** and **263b** typically accounting for 70–80% of the crude reaction mixtures in each case (**Table 7.9**, entries 2–6). The amounts of *cis* and *trans* isomers varies depending on the ligand employed; larger amounts of the *cis* isomer were seen with (4*R*,5*S*)-di-Ph **137** and (4*R*)-Ph **20** ligands, accounting for 26% and 36% of the crude reaction mixtures respectively, with the *trans* isomers being present at 54% and 61% (**Table 7.9**, entries 5 and 6). For the remaining three ligands used; (3*S*,8*R*)-Ind **44**, (4*R*)-Bn **43** and (4*S*)-*t*-Bu **138**, far smaller amounts of the *cis* isomer were observed in the ^{1}H NMR spectra of the crude reaction mixture, with values ranging from 2 to 8% (**Table 7.9**, entries 2–4). This would suggest that the presence of a freely rotating phenyl group adjacent to the coordinating nitrogen atom favours the formation of the *cis* isomer **263a**. In each of the reactions, full epimerisation of the *cis* to the *trans* isomer occurred after purification on silica gel, with moderate isolated yields ranging from 32 to 40% in all cases (**Table 7.9**, entries 2–6). The enantioselectivities of *trans* sulfolanes were generally modest, 53% ee being the highest value attained in this study, when (4*S*)-*t*-Bu ligand **138** was utilised (**Table 7.9**, entry 4). The enantiopurity of *trans* sulfolane **263b** was relatively insensitive to variation of the bisoxazoline ligand. The lowest value of 38% ee was obtained when (4*R*,5*S*)-di-Ph **137** was employed (**Table 7.9**, entry 5). The remaining

ligands (3*S*,8*R*)-Ind **44**, (4*R*)-Bn **43**, and (4*R*)-Ph **20** all gave rise to *trans* sulfolane **263b** in enantiopurities between 42 and 47% ee (**Table 7.9**, entries 2, 3 and 6). Enantiomeric disproportionation was also checked through collection of fractions and independent measurement of enantiopurities of each fraction by HPLC, for reactions employing (3*R*,8*S*)-Ind **44** and (4*R*)-Bn **43** ligands (**Table 7.9**, entries 2 and 3), there was no evidence for significant alteration in enantioselectivity in individual fractions in this instance.

Significantly, while in most cases throughout this work there is a direct correlation between the enantiomeric series of the ligand employed and the direction of the enantioinduction in C–H insertion and/or cyclopropanation processes, this study provides one of the clearest examples where this correlation breaks down. Thus, while use of (4*R*)-Ph **20**, (4*R*,5*S*)-di-Ph **137** and (4*R*)-Bn **43** ligands, are expected to lead to the opposite enantiomeric outcome to the use of (3*S*,8*R*)-Ind **44** and (4*S*)-*t*-Bu **138** ligand, in this instance (4*R*)-Bn **43** ligand gave the opposite enantiomeric series of *trans* sulfolanes to that of the other four ligands (4*R*)-Ph **20**, (4*R*,5*S*)-di-Ph **137** (3*S*,8*R*)-Ind **44** and (4*S*)-*t*-Bu **138**. This is reminiscent for the behaviour described for substrate **58** (**Chapter 6**, **Section 6.3.4**). In rationalising this unexpected outcome, it is significant that the ratio of *cis* and *trans* sulfolanes in the crude product mixtures vary substantially with the ligand used. It is possible that the preferred enantiomer of the *cis* sulfolane is opposite to that of the *trans* sulfolane, due to different transition states, and therefore on epimerisation of the *cis* to the *trans* during chromatography, the ultimate enantiomeric series observed is a balance of two competing processes. In particular, the results of **Table 7.9**, entries 5 and 6, the reactions which appear to give the "wrong" enantiomeric series, are precisely the experiments where the proportion of the *cis* sulfolane in the crude is relatively high.

The presence of an unidentified byproduct **264** was also detected in the crude reaction mixtures. It was present at relatively high levels in the cyclisations employing (3*S*,8*R*)-Ind **44**, (4*R*)-Bn **43** and (4*S*)-*t*-Bu **138** ligands, ranging from 12 to 20% (**Table 7.9**, entries 2, 3 and 4), while its presence was not detected for the rhodium acetate catalysed reaction or when (4*R*,5*S*)-di-Ph **137** was used. It was also only present at 2% in the reaction employing (4*R*)-Ph **20** (**Table 7.9**, entries 1, 5-6). While the exact structure was not elucidated, it may be occurring *via* a hydride abstraction or a chloride abstraction pathway or a combination of both (**Figure 7.13**). The compound possesses a number of key characteristic signals in the ^{1}H NMR spectrum. The presence of signals at δ_H 1.72 (3H, d,

J 1.1) and 1.83 (3H, d, *J* 1.1) with long range coupling suggest that the two methyl groups are still intact and possibly couple to the vinyl proton. The presence of signals in the alkene region at δ_H 5.41–5.48 (1H, m) and 5.53–5.61 (1H, m) indicate that a double bond is present, possibly indicating migration as illustrated below (**Figure 7.13**). An additional signal at [δ_H 6.16 (1H, d, *J* 2.6), may also be two singlets δ_H 6.1 and 6.2 ppm] and implies that there may be a third alkene proton in the structure.

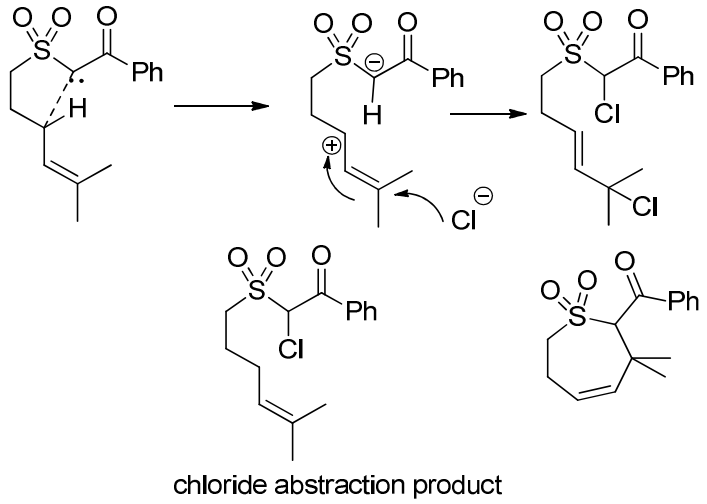


Figure 7.13

Interestingly, there is a correlation between the amount of the *cis* isomer **263a** and the amount of the byproduct **264**, believed to be formed through hydride transfer, present in the crude material. In cases where there is a substantial amount of the *cis* isomer **263a** present, byproduct **264** is not present or occurs at very low levels, this is the case for reaction with rhodium acetate and for reactions with $CuCl_2$-NaBARF-(4*R*)-Ph **20** and $CuCl_2$-NaBARF-(4*R*,5*S*)-di-Ph **137** (**Table 7.9**, entries 1, 5 and 6). Therefore, it appears that the hydride transfer competes more effectively with the C–H insertion pathway to form *trans* sulfolane, than with the diastereomeric pathway to form the *cis* sulfolane (**Figure 7.14**). Thus, subtle steric and/or conformational differences effect the balance of the various pathways. Interestingly, increased *cis* sulfolane formation is seen with use of the (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** ligands, which may indicate a pi stacking interaction between the double bonds and the aryl ring of the ligand. It is likely that this interaction is also responsible for the alteration in the sense of enantioselection resulting from (4*R*)-Ph **20** and (4*R*,5*S*)-di-Ph **137** ligands.

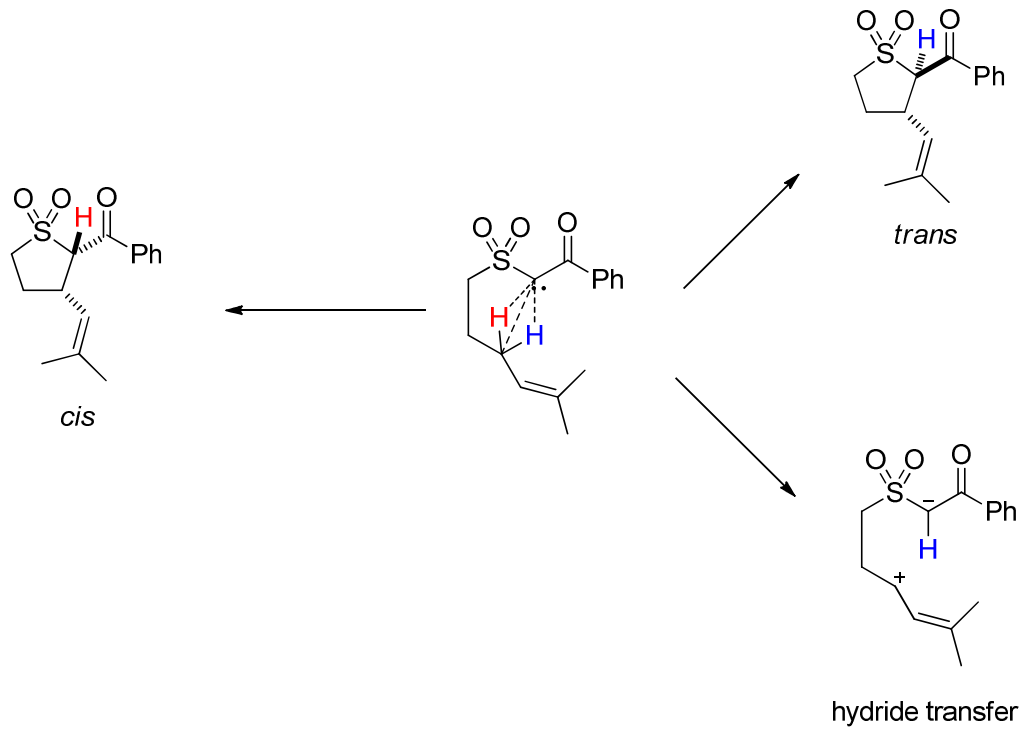
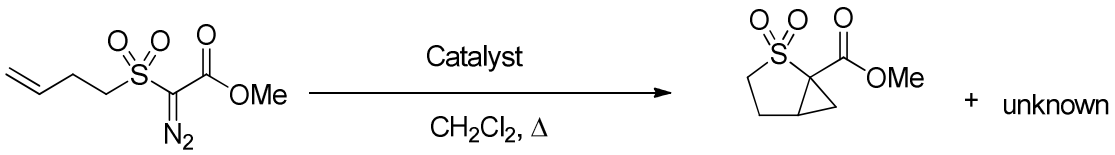


Figure 7.14

7.2.2.3 Investigation into the synthesis of five-membered ring

A further substrate modification was investigated, where the length of the alkyl chain was shortened such that six-membered ring formation was no longer possible *via* a cyclopropanation reaction. The initial part of this investigation aimed to probe whether or not cyclopropanation would proceed, resulting in a sterically constrained system: a sulfolane fused to a cyclopropane ring, methyl 2-thiabicyclo[3.1.0]hexane-1-carboxylate 2,2-dioxide **270a**. α-Diazo-β-oxo sulfone **63** was cyclised in the presence of rhodium acetate and with several copper-bisoxazoline catalysts. The results of this study are presented in **Table 7.10**. There are stability concerns about α-diazo-β-oxo sulfone **63**, which were previously discussed in Chapter 3, therefore α-diazo-β-oxo sulfone **63** was prepared freshly before use and was used in the catalytic reactions on the same day, which it was prepared.

Table 7.10 *Asymmetric rhodium acetate and chiral copper bisoxazoline catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* ***63***



63 **270a** **271**

Entry	Catalyst	T (h)	Purified Yield[a] (%)	Crude ratio Purified yield (%)	Sulfolane 270a[b]	Byproduct[b] 271	%ee Sulfolane 270a[c]	
							%ee[c] (UV detector)	%ee[c] (LSD detector)
1	$Rh_2(OAc)_4$ (1 mol%)	18	41%	**Crude ratio** **Purified yield (%)**	95 96	5 4	0	8[d]
2	$CuCl_2$ (5 mol%) (4*R*)-Bn **43** (6 mol%) NaBARF (6 mol%)	18	33%	**Crude ratio** **Purified yield (%)**	77 77	23 23	-[f]	71[e]

3	$CuCl_2$ (5 mol%) (4*S*)-*t*-Bu **138** (6 mol%) NaBARF (6 mol%)	50	43%	**Crude ratio** **Purified yield (%)**	53 48	47 52	98[d]	90[d]
4	$CuCl_2$ (5 mol%) (4*R*,5S)-di-Ph **137** (6 mol%) NaBARF (6 mol%)	18	39%	**Crude ratio** **Purified yield (%)**	83 85	17 15	37[e]	57[e]
5	$CuCl_2$ (5 mol%) (3*S*,8*R*)-Ind **44** (6 mol%) NaBARF (6 mol%)	18	40%	**Crude ratio** **Purified Yield (%)**	90 90	10 10	58[d]	87[d]
6	$CuCl_2$ (5 mol%) (4*R*)-Ph **20** (6 mol%) NaBARF	30	25%	**Crude ratio** **Purified Yield (%)**	60 64	40 36	-[f]	-[f]

	(6 mol%)							

a. The yield (%) is a combined yield of sulfolane **270a** and byproduct **271**, recorded as an inseparable mixture calculated based on the molecular weight of sulfolane **270a**
b. Relative amounts of *trans* sulfolane **270a** and byproduct **271** in both the crude and purified spectra were calculated using ^{1}H NMR spectra of the crude product using signals for OCH_3; δ_H 3.88 (3H, s, OCH_3) for *trans* sulfolane **270a**, and δ_H 3.90 (3H, s, OCH_3) for byproduct **271**.
c. Several attempts were made to calculate the enantiopurity of *trans* sulfolane **270a**. The use of a chiral shift reagent in ^{1}H NMR was explored, but due to impurities in the purified products, this method was not deemed suitable. The use of chiral HPLC was employed with the use of a UV detector, however due to a lack of a strong chromophore this method had limited use. The method that gave the most promising results was the use of chiral HPLC in conjugation with a light scattering detector. However as there was an impurity present in all measured samples, three peaks were seen in the HPLC traces. The first two eluting enantiomers were tentatively assigned to *trans* sulfolane **270a**, and the last one was assigned to the uncharacterised impurity **271**. Therefore the calculated values for enantioselectivity in **Table 7.10** should be viewed with caution and further work is needed to confirm these results.
d. The first eluting enantiomer at ~33 min is the major enantiomer (Amylose 2).
e. The second eluting enantiomer at ~36 min is the major enantiomer (Amylose 2).
f. Signal too weak to be calculated.

Initially examining the reaction of novel α-diazo-β-oxo sulfone **63** in the presence of rhodium acetate, it can be clearly seen that cyclopropanation is the major reaction pathway occurring (**Table 7.10**, entry 1). Visual inspection of the ^{1}H NMR spectrum of the crude reaction mixture suggests that cyclopropanation proceeded with relatively good efficiency, with only minor byproduct formation apparent. One of these, byproduct **271**, could not be separated from cyclopropanation product **270a**. Following purification using column chromatography on silica gel, they were isolated in a moderate yield of 41%, 5% of which was the byproduct (**Table 7.10**, entry 1). In the case of the rhodium acetate catalysed reaction it was a minor component; its precise identity was not confirmed, however, it has the following spectral characteristics; δ_H 2.33 (3H, br s), 3.31-3.36 (2H, m), 3.91 (3H, s, OC*H*$_3$). The presence of a singlet at 3.91 ppm would suggest that the methoxy group is present in the structure. It is possible that this byproduct formed as a result of the degradation of the parent α-diazo-β-oxo sulfone **63**, as previously discussed α-diazo-β-oxo sulfone **63** was unstable at room temperature and the formation of **271** may be independent of the impact of the catalyst. Having obtained a racemic sample of cyclopropanation product **270a**, a method for separating the enantiomers was now required. As **270a** does not possess a strong chromophore, the use of chiral HPLC with a UV detector was not ideal. The use of a chiral ^{1}H NMR shift reagent was also not possible due to the presence of byproduct **271** in the purified ^{1}H NMR spectra. For these reasons, chiral HPLC analysis was attempted with both an LSD detector and a UV detector. Promising results were obtained with both of these methods; three peaks were observed in both cases, two of these were assigned to the enantiomers of sulfolane **270a** and the third to the byproduct **271**. A value of 0% ee was measured using the UV detector with slightly enhanced enantioselectivity being picked up on the LSD detector, with 8% ee observed, however, the strength of the signals was much stronger on the LSD detector compared to the peaks measured in the UV spectrum. It was decided that this was a suitable method for the separation of byproduct **270a** from the enantiomers of sulfolane **270a**, and that both the UV and LSD measurements would be used in conjunction with one another to obtain reasonable estimates of enantioselectivities.

The use of asymmetric copper-bisoxazoline catalysed reactions was then commenced employing $CuCl_2$ (5 mol%), NaBARF (6 mol%) and bisoxazoline ligand (6 mol%). The

catalytic components were stirred together at reflux for 2 h before slow addition of α-diazo-β-oxo sulfone **63** took place, in dichloromethane, with reaction monitoring being carried out by IR spectroscopy. Five commercially bisoxazoline ligands were employed in this study; (4*R*)-Ph **20**, (4*R*,5*S*)-di-Ph **137**, (4*R*)-Bn **43**, (4*S*)-*t*-Bu **138** and (3*S*,8*R*)-Ind **44** (**Table 7.10**, entries 2-6). Two major reaction products were observed in all cases; cyclopropanation product **270a** and byproduct **271**. The relative amounts of these varied greatly depending on the ligand used. For both (4*S*)-*t*-Bu **138** and (4*R*)-Ph **20** ligands, nearly equal amounts of both products were seen in the ^{1}H NMR spectra of the crude mixtures (**Table 7.10**, entries 3 and 6). The use of (4*R*,5*S*)-di-Ph **137** and (3*S*,8*R*)-Ind **44** ligands appear to favour cyclopropanation **270a**, with byproduct **271** accounting for 17% and 10% of the mixture respectively (**Table 7.10**, entries 4 and 5) and with (4*R*)-Bn **43** resulting in slightly higher amounts of the byproduct **271** (23%) (**Table 7.10**, entry 2). Once again it should be stated that these different product ratios are not necessarily reflective of the bisoxazoline catalyst employed and instead maybe due to the independent decomposition of the α-diazo-β-oxo sulfone **63**. Despite the relatively larger proportion of byproduct **271** present in the copper catalysed reactions, compared to the rhodium acetate catalysed reaction, there was no observable change in the cyclopropanation product : byproduct ratio in the purified spectra of the copper catalysed reactions (**Table 7.10**, entries 1-6), suggesting that little or no separation of the two components occurred (^{1}H NMR spectrum of sample containing byproduct included in **Appendix III**, for information).The measurement of the enantiopurities of sulfolane **270a** was subsequently attempted on the mixtures, which led to mixed success. A result could not be obtained for (4*R*)-Ph **20**, as the absorbance recorded on this sample was too low to produce a reliable result. For the remaining four ligands, results obtained using UV detection differed from that using the LSD detector. The most promising result achieved was for (4*S*)-*t*-Bu **138**, with very high enantioselectivities being recorded in both cases; 98% ee for the UV detector and 90% ee for the LSD detector. As signals measured by the LSD were stronger, these results are probably more accurate. Examining values obtained by this method suggest that enantiopurity remains high at 71% ee and 87% ee when (4*R*)-Bn **43** and (3*S*,8*R*)-Ind **44** ligands are employed (**Table 7.10**, entries 2 and 5), with (4*R*,5*S*)-di-Ph **137** ligand resulting in the lowest enantioselectivity of 57% ee (**Table 7.10**, entry 4). Where available, a comparison of results obtained taking measurements from both detectors is present in **Figure 7.15**. Due to the differences in the values obtained, results

obtained in this study need to be interpreted with caution. This study warrants further investigation.

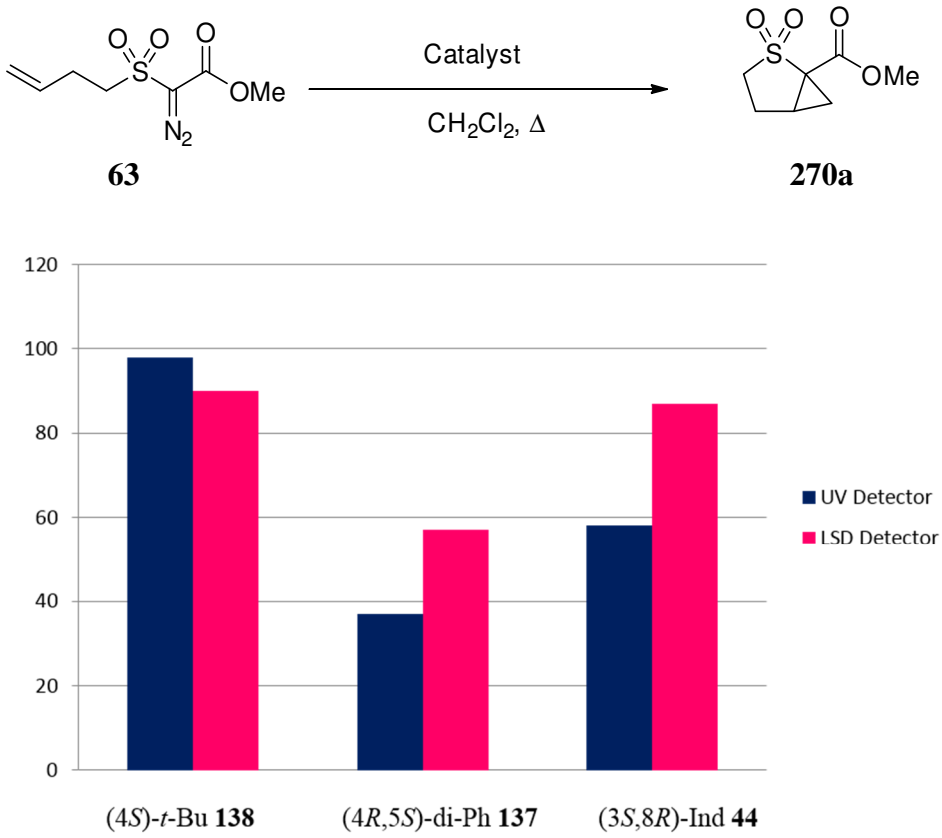


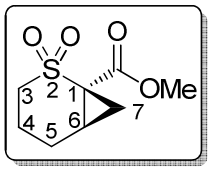
Figure 7.15

7.3 Conclusions

In conclusion, it is clear that intramolecular cyclopropanation to generate thiopyrans and sulfolanes bearing fused cyclopropanes is feasible starting from appropriately substituted α-diazo-β-oxo sulfone precursors. Cyclopropanation is possible for both ester and ketone derivatives. C–H insertion competes as a pathway when sulfolane formation through insertion at an allylic C–H bond is possible. Interestingly, the enantioselectivity in the cyclopropanation process is relatively insensitive to variation of the bisoxazoline ligand, but instead is dependent on the nature of the ester/ketone substrate. The ligand trends in terms of enantioselectivity are quite different to those for C–H insertion pathways, reflecting the different transition states for the cyclopropanation and C–H insertion pathways. The highest enantioselectivity obtained to date for cyclopropanation was 80% ee (**Table 7.8**, entries 1 and 5) and the absolute stereochemistry is established. Most significantly, use of a $CuCl_2$-NaBARF-bisoxazoline system, which had been developed for C–H insertion processes, can be generalised to enantioselective cyclopropanation.

7.4 Experimental

(1*S*,6*R*)-Methyl 2-thiabicyclo[4.1.0]heptane-1-carboxylate 2,2-dioxide 257a



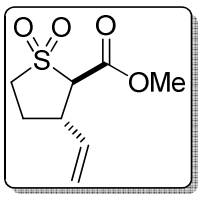
The title compound was prepared according to the procedure described for (3*S*,4*R*) 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using methyl 2-diazo-2-(pent-4-en-1-ylsulfonyl)acetate **59** (100 mg, 0.43 mmol), $CuCl_2$ (2.8 mg, 21.2 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (22.5 mg, 25.5 μmol) and bisoxazoline ligand (4*R*)-Ph **20** in dichloromethane (50 mL) for 21 h, in accordance with **Method B**. ^{1}H NMR spectroscopy of the crude product shouwed that the reaction was *approx* 80–90% efficient (90% *cis* thiopyran **257a** : 10% *trans* sulfolane **258b**). Following purification by column chromatography on neutral alumina, using gradient ethyl acetate-hexane (10:90–20:80–30:70) as eluent, (1*S*,6*R*)-methyl 2-thiabicyclo[4.1.0]heptane-1-carboxylate 2,2-dioxide **257a** (61 mg, 70%) was isolated as a colourless oil, the most polar fraction eluted. Addition of [(+)-Eu(hfc)$_3$] to the ^{1}H NMR sample of the purified product indicated that the product had 67% ee; ν_{max}/cm^{-1} (film): 2955 (CH), 1732 (CO), 1438, 1315, 1298, 1274, 1162, 1120 (SO_2); δ_H ($CDCl_3$, 600 MHz): 1.64 [1H, dd, *J* 8.3, 6.4, one of C(7)H_2)], 1.70 [1H, dd, *J* 9.6, 6.4, one of C(7)H_2)], 1.90–2.01 [2H, m, one of C(4)H_2 and one of C(5)H_2], 2.11–2.19 [2H, m, one of C(4)H_2 and one of C(5)H_2], 2.34–2.41 [1H, m, C(6)*H*], 2.92–3.04 [2H, m, C(3)H_2], 3.86 (3H, s, OCH_3); δ_C ($CDCl_3$, 150.9 MHz): 19.6 [CH_2, *C*(4)H_2 or *C*(5)H_2], 20.1 [CH_2, *C*(7)H_2], 20.8 [CH_2, *C*(4)H_2 or *C*(5)H_2], 25.9 [CH, *C*(6)H], 45.3 [C, *C*(1)], 51.2 [CH_2, *C*(3)H_2], 53.5 (CH_3, O*C*H_3) 167.0 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_8H_{13}O_4S$ [M+H]$^+$, 205.0535. Found 205.0531.

Note: The absolute stereochemistry was assigned by analogy, the details of which are in **Appendix II**.

Assignments made with the aid of 2D NMR experiments, namely HSQC and HMBC.

From the experiment reported in **Table 7.11**, entry 8, using methyl 2-diazo-2-(pent-4-en-1-ylsulfonyl)acetate **59** (100 mg, 0.43 mmol) and Rh_2(*S*-PTPA)$_4$ (6.3 mg, 4.3 μmol) in dichloromethane (50 mL), in accordance with Method **F**. Two fractions were isolated, the more polar fraction (59 mg, 67%) was cyclopropanation product **257a** with spectral characteristics as identified above, while the less polar fraction (3.5 mg, 4%) was the C–

H insertion product **258b** which was isolated as a colourless oily solid with the following spectral characteristics;



Colourless oily solid; δ_H ($CDCl_3$, 300 MHz): 1.93–2.13 [1H, m, one of C(4)H_2], 2.29–2.46 [1H, m, one of C(4)H_2], 3.06–3.21 [1H, m, one of C(5)H_2], 3.28–3.38 [1H, m, one of C(5)H_2], 3.39–3.51 [1H, m, C(3)*H*], 3.74 [1H, d, *J* 10.2, C(2)*H*], 3.85 (3H, s, OCH_3), 5.16–5.28 [2H, m, C(2′)H_2], 5.69–5.85 [1H, sym m, C(1′)*H*], δ_C ($CDCl_3$, 150.9 MHz): 26.5 [*C*(4)H_2], 43.2 [CH, *C*(3)H], 52.6, 53.5 [*C*(5)H_2 and O*C*H_3], 69.8 [CH, *C*(2)H], 118.1 [*C*(2′)H_2], 135.5 [CH, *C*(1′)H], 175.3 (*C*O).

Note: DEPT 90 was the only DEPT experiment run for this sample, so assignment of CH_2 and CH_3 peaks not confirmed by DEPT 90.

Table 7.11 *Copper and rhodium catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* **59**

Entry	Method	Metal	L	Time (h)	Crude Efficiency (%)[a]	Crude ratio[a] Purified yield(%)[a] % ee[a]	Products	
							cis thiopyran (cyclopropanation) More polar **257a**	*trans* sulfolane (C–H insertion) Less polar **258b**
1	**B**	$CuCl_2$/ Δ	(4*R*)-Ph **20**	21	80–90	**Crude ratio** **Purified yield (%)** **% ee**	90 70% 67% ee (1*S*,6*R*) (72% ee)[b]	10 -
2	**B**	$CuCl_2$/ Δ	(4*R*,5*S*)-di-Ph **137**	21	80–90	**Crude ratio** **Purified yield (%)** **% ee**	90 66% 61% ee (1*S*,6*R*)	10 - -
3	**B**	$CuCl_2$/ Δ	(3*S*,8*R*)-Ind **44**	21	80–90	**Crude ratio**	92	8

						Purified yield (%) **% ee**	59% 68% ee (1*R*,6*S*)	-
4	**B**	$CuCl_2$/ Δ	(4*R*)-Bn **43**	21	80–90	**Crude ratio** **Purified yield (%)** **% ee**	95 63% 38% ee (1*S*,6*R*) $[\alpha]_D^{20}$ −13.0 (*c* 0.1, CH_2Cl_2)	5 -
5	**B**	$CuCl_2$/Δ	(4*S*)-*t*-Bu **138**	48	80–90	**Crude ratio** **Purified yield (%)** **% ee**	98 61% 61% ee (1*R*,6*S*) $[\alpha]_D^{20}$ +15.7 (*c* 0.1, CH_2Cl_2)	2 - -
6	**F**	Rh_2(*S*-PTTL)$_4$ 0 °C-rt	-	6	80–90	**Crude ratio** **Purified yield (%)** **% ee**	88 67% 34% ee (1*R*,6S)	12 3% -
7	**G**	Rh_2(*S*-DOSP)$_4$ 0 °C-rt- Δ 24h, 24h	-	48	80–90	**Crude ratio** **Purified yield (%)**	82 58%	18 4%

						% ee	11% ee	
8	**F**	Rh_2(*S*-PTPA)$_4$ 0 °C-rt	-	8	80–90	**Crude ratio** **Purified yield (%)** **% ee**	83 67% 8% ee (1*R*,6*S*)	17 4%
9	**G**	Rh_2(*S*-MEPY)$_4$ 0 °C-rt- Δ 30 h ,120[c]	-	150	-	-	Starting material only recovered	-
10	**F**	Rh_2(*S*-mand)$_4$ 0 °C-rt	-	21	80–90	**Crude ratio** **Purified yield (%)** **% ee**	91 54% (contains ~10% *trans* sulfolane **258b**) ~12% ee[d] (1*S*,6*R*)	9
11	**B**	$CuCl_2$/ Δ[c]	CN-(4*S*)-Ph **158**	-	-	-	Starting material only recovered	-
12	**B**	$CuCl_2$/ Δ[c]	Py-(4*R*)-Ph **159**	-	-	-	Starting material only recovered	-
13	**B**	$CuCl_2$/ Δ[c]	Py-(4*S*)-*i*-Pr **160**		-	-	Mainly starting material ~10% cyclopropanation	-
14	**E**	$Rh_2(OAc)_4$/ Δ	-	21	80–90	**Crude ratio** **Purified yield (%)** **% ee**	92 52% 0% ee (0%)[e]	8 - -

a. Crude efficiency and relative ratios calculated using ^{1}H NMR spectra of the crude product using signals for *cis* thiopyran **257a**; δ_H 1.64 (1H, dd, *J* 8.3, 6.4, one of methylene C*H*$_2$), 1.70 (1H, dd, *J* 9.6, 6.4, one of methylene C*H*$_2$) and signals for *trans* sulfolane **258b**; δ_H 3.39–3.51 [1H, m, C(3)*H*]. Yield (%) refers to material purified by column chromatography on neutral alumina. In general all enantioselectivities were measured using chiral ^{1}H NMR, employing [(+)-Eu(hfc)$_3$] as a chiral shift reagent. In two cases UV data was also used, and will be noted where relevant. Details of the determination of the enantiopurity of **257a** can be found in **Appendix I**. The absolute stereochemistry was assigned by analogy and will be discussed in **Appendix II.**

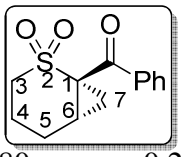
b. Measurement of enantioselectivity using chiral HPLC was also attempted using a UV detector. Although poor detection of compound **257a** was observed, a value of 72% ee was measured.

c. After one week of stirring at reflux the reaction was stopped. Analysis of the ^{1}H NMR spectra of the crude mixture revealed only α-diazocarbonyl **59** was present.

d. Estimated due to presence of C-H insertion product **258b** in purified product.

e. Measurement of enantioselectivity using chiral HPLC was also attempted using a UV detector. Although poor detection of compound **257a** was observed, a value of 0% ee was measured.

[(1*R*,6*S*)-2,2-dioxido-2-thiabicyclo[4.1.0]heptan-1-yl](phenyl)methanone 259a



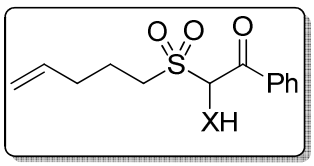
The title compound was prepared according to the procedure described for (3*S*,4*R*) 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **60** (80 mg, 0.29 mmol), $CuCl_2$ (1.9 mg, 14.3 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (15.2 mg, 17.2 μmol) and bisoxazoline ligand (3*S*,8*R*)-Ind **44** (5.9 mg, 17.2 μmol) in dichloromethane (50 mL), stirred while heating under reflux for 22 h, in accordance with **Method B**. ^{1}H NMR spectroscopy of the crude product showed that the reaction contained 72% *cis* thiopyran **259a** and 4% *trans* sulfolane **260b**. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–40:60–60:40) as eluent, [(1*R*,6*S*)-2,2-dioxido-2-thiabicyclo[4.1.0]heptan-1-yl](phenyl)methanone **259a** (41 mg, 56%) was isolated as a white solid, the most polar fraction eluted; $[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH_2Cl_2); 80% ee (determined by chiral-HPLC); mp 128–130 ºC ν_{max}/cm^{-1} (neat): 2950, 2927 (CH), 1677 (CO), 1598 (C=C), 1450, 1308, 1294, 1274, 1123, (SO_2), 766, 686, 658 (CS); δ_H ($CDCl_3$, 600 MHz): 1.57 [1H, dd, *J* 9.6, 6.4, one of C(7)H_2], 1.90 [1H, dd, *J* 8.4, 6.5, one of C(7)H_2], 1.93–2.02 [1H, m, one of C(4)H_2], 2.06–2.13 [1H, m, one of C(4)H_2], 2.14–2.18 [1H, m, one of C(5)H_2], 2.19–2.26 [1H, m, one of C(5)H_2], 2.36–2.42 [1H, m, C(6)*H*], 2.87 [1H, apparent td, *J* 13.3, 2.8, one of C(3)H_2], 3.09 [1H, ddd, *J* 13.6, 5.2, 2.4, one of C(3)H_2], 7.48–7.54 (2H, m, ArH_{meta}), 7.58–7.63 (1H, m, ArH_{para}), 8.16–8.20 (2H, m, ArH_{ortho}); δ_C ($CDCl_3$, 150.9 MHz): 18.1 [CH_2, *C*(7)H_2], 18.2 [CH_2, *C*(4)H_2], 21.5 [CH_2, *C*(5)H_2], 22.1 [CH, *C*(6)H], 50.7 [C, *C*(1)], 53.0 [CH_2, *C*(3)H_2], 128.7 (2 × CH, aromatic *C*H_{meta}), 129.7 (2 × CH, aromatic *C*H_{ortho}), 134.0 (CH, aromatic *C*H_{para}), 136.1 (C, aromatic *C*), 190.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{15}O_3S$ $[M+H]^+$, 251.0742. Found 251.0733. m/z (ESI+): 251.3 $[M+H]^+$.

The relative stereochemistry was determined by single crystal X-ray diffraction on a crystalline sample of **259a,** recrystallised from IPA.[60] Full Structural details are contained on the accompanying CD.

Crystals of **259a** are orthorhombic, space group $P2_12_12_1$, formula $C_{13}H_{14}O_3S$, M = 250.30, *a* = 7.1141(3) Å, *b* = 9.0186(4) Å, *c* = 18.8063(9) Å, *U* = 1206.60(9) Å^3, *F(000)* = 528, μ(Cu Kα) = 2.340 mm^{-1}, *R*(F_o) = 0.032, for 1845 observed reflections with I > 2σ(I), $wR_2(F^2)$ = 0.082 for all 2006 unique reflections. Data in the θ range 5.44 – 65.93° were

collected on a Bruker APEX DUO diffractometer using Cu Kα radiation, λ = 1.54178 Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom. Full details are given on the accompanying CD.

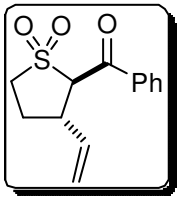
Assignments made with the aid of 2D NMR experiments, namely HSQC and HMBC.



Two additional less polar fractions were isolated, a fraction of mid polarity (0.72 mg, 1%) which consisted of 50% C–H insertion product **260b**, with spectral characteristics as identified below, and 50% sulfone **131**, while the least polar fraction (0.44 mg, 0.6%) was the X–H insertion product **261** which was isolated as a colourless oil with the following spectral characteristics;

The least polar fraction was obtained as a colourless oil, tentatively assigned as X–H insertion product **261**. δ_H ($CDCl_3$, 400 MHz): 1.97–2.08 [2H, m, C(2′)H_2 or C(3′)H_2], 2.20–2.31 [2H, m, C(2′)H_2 or C(3′)H_2], 3.27–3.39 [1H, m, one of C(1′)H_2], 3.45–3.56 [1H, m, one of C(1′)H_2], 5.05–5.16 [2H, m, C(5′)H_2], 5.70–5.84 [1H, m, C(4′)*H*], 6.02 (2H, s, SO_2C*H*XHCO), 7.50–7.58 (2H, m, Ar*H*), 7.65–7.72 (1H, m, Ar*H*), 7.98–8.05 (2H, m, Ar*H*).

From the experiment reported in **Table 7.12**, entry 2, using 2-diazo-2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **60** (80 mg, 0.29 mmol), $CuCl_2$ (1.9 mg, 14.3 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (15.2 mg, 17.2 μmol) and bisoxazoline ligand (4*R*,5*S*)-di-Ph **137** (7.8 mg, 17.2 μmol) in dichloromethane (50 mL), stirred while heating under reflux for 22 h, in accordance with Method B. Two fractions were isolated, the more polar fraction (32.6 mg, 45%) was cyclopropanation product **259a**, with spectral characteristics as identified above, while the less polar fraction (0.73 mg, 1%) was the C–H insertion product **260b** which was isolated as a colourless oily solid with the following spectral characteristics;



260b Colourless oily solid ν_{max}/cm^{-1} (neat, ATR): 2954 (CH), 1683 (CO), 1597 (C=C), 1449, 1312, 1273, 1122, (SO_2), 753 (CS); δ_H ($CDCl_3$, 600 MHz): 2.09 [1H, apparent qd, *J* 12.8, 7.1, one of C(4)H_2], 2.37–2.44 [1H, m, one of C(4)H_2], 3.13 [1H, apparent td, *J* 12.8, 7.1 one of C(5)H_2], 3.35 [1H, ddd, *J* 12.9, 7.1, 1.8, one of C(5)H_2], 3.70–3.78 [1H, m, C(3)*H*], 4.61 [1H, d, *J* 10.0, C(2)*H*], 5.14 [1H, apparent dt, J_{cis} 10, 1.0, one of C(2′)H_2], 5.21 [1H, apparent dt, J_{trans} 17, 1.0, C(2′)H_2], 5.66–5.74 [1H, sym m, C(1′)*H*], 7.42–7.51 (2H, m, Ar*H*), 7.54–7.61 (1H, m, Ar*H*), 8.01–8.06 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 25.4 [CH_2, *C*(4)H_2], 41.9 [CH_2, *C*(3)H], 52.4 [CH_2, *C*(5)H_2], 69.7 [CH_2, *C*(2)H], 116.9 [CH_2, *C*(2′)H_2], 129.1 (CH, 2 × aromatic *C*H), 129.8 (CH, 2 × aromatic *C*H), 134.5 [CH, aromatic *C*H or *C*(1′)H], 136.0 [CH, aromatic *C*H or *C*(1′)H], 164.4 (C, aromatic *C*), 187.9 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{15}O_3S$ $[M+H]^+$, 251.0742. Found 251.0755. m/z (ESI+): 251.3 $[M+H]^+$.

Assignments made with the aid of 2D NMR experiments, namely HSQC and HMBC.

Table 7.12 *Copper and rhodium catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* **60**

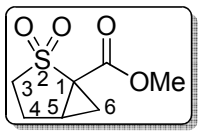
Entry	**Method**	**Method**	**L***	**Time (h)**		**Products**			
					Crude (%)[a-d] **Purified yields (%)**[e] **% ee**[f]	*cis* thiopyran[a] **259a** Most polar	*trans* sulfolane[b] **260b** Mid polarity	sulfolane[c] **131**	X–H insertion[d] **261** Least polar
1	**B**	$CuCl_2$	(3*S*,8*R*)-Ind **44**	22	**Crude (%)**	72%	4%	3%	5%
					Purified yield (%)	56 %	1%[g] 50:50		0.6%
					% ee	80% ee (1*R*,6*S*)	-[h]		
2	**B**	$CuCl_2$	(4*R*,5*S*)-di-Ph **137**	22	**Crude (%)**	84%	2%	0%	2%
					Purified yield (%)	45%	1%	-	
					% ee	73% ee (1*S*,6*R*)	0% ee		

						$[\alpha]_D^{20}$ −101.7 (*c* 0.12, CH_2Cl_2)			
3	**B**	$CuCl_2$	(4*R*)-Ph **20**	22	**Crude (%)**	70%	2%	2%	1%
					Purified yield (%)	49%	2%[g] 83:17		
					% ee	75% ee (1*S*,6*R*)	-[h]		
4	**B**	$CuCl_2$	(4*R*)-Bn **43**	22	**Crude[i] (%)**	70%	1%	2%	3%
					Purified yield (%)	52%	1%[g,j] 93:7		
					% ee	75%ee (1*S*,6*R*)	-[h]		
5	**B**	$CuCl_2$	(4*S*)-*t*-Bu **138**	48	**Crude (%)**	83%	6%	0%	0%

					Purified yield (%)	58	2[k]		
					% ee	80% ee (1*R*,6*S*) $[\alpha]_D^{20}$ +133.3 (*c* 0.21, CH_2Cl_2)	-[h]		
6	**E**	$Rh_2(OAc)_4$	-	22	**Crude[l] (%)**	60%	6%	1%	2%
					Purified yield (%)	41[m]	3[n]		
					% ee	3% ee[h]	0%ee		

a. Relative ratios of reaction products calculated using ^{1}H NMR spectra of the crude product using signals for C(6)*H*; δ_H 2.36–2.42 [1H, m, C(6)*H*] for *cis* thiopyran **259a**.
b. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for C(3)*H*; δ_H 3.70–3.78 [1H, m, C(3)*H*] for *trans* sulfolane **260b**.
c. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for reduction product **131**; δ_H 4.57 (2H, s, SO_2CH_2CO).
d. Relative ratios of isomers calculated using ^{1}H NMR spectra of the crude product using signals for X–H insertion product **261** δ_H 6.02 (2H, s, SO_2CHXCO).
e. Yields are reported after purification using column chromatography on silica gel.
f. Enantioselectivities were measured using chiral HPLC, see **Appendix I** for details.
g. *trans* Sulfolane **260b** and sulfone **131** were isolated as a mixed fraction. The yield (%) reported is for both compounds. The ratio of the two compounds in the purified product was calculated from ^{1}H NMR spectra of the purified product, using signals indicated in footnotes b and c above.
h. Enantioselectivity could not be accurately determined due to multiple peaks being present in the HPLC trace.
i. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 6.53 (s), 6.99 (s).
j. Additional peaks present in the ^{1}H NMR spectra of the purified product; δ_H 6.34–6.41 (m), 7.02 (s), 9.69 (s).
k. Impure fraction. Additional peaks present in the ^{1}H NMR spectra of the purified product; δ_H 2.79–3.98 (m), 4.03–4.29 (m).
l. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 9.69 (s). Additional peaks were present in the region of 1.47-3.90 ppm but were not distinguished due to peak overlap.
m. Impure fraction. Additional peaks present in the ^{1}H NMR spectra of the crude product; δ_H 3.51–3.79 (m), 5.05–5.18 (m), 5.68–5.91 (m), 6.12 (s), 7.91–8.02 (m).
n. Impure fraction. Contained *approx* 5% additional material; the following peaks were observed in the ^{1}H NMR spectra of the purified product; δ_H 3.47–3.78 (m), 3.99–4.20 (m), 4.90–5.12 (m), 6.13 (s), 2.21–2.32 (m).

Methyl 2-thiabicyclo[3.1.0]hexane-1-carboxylate 2,2-dioxide 270a



Methyl 2-(but-3-en-1-ylsulfonyl)-2-diazoacetate **63** (50 mg, 0.23 mmol), in distilled dichloromethane (20 mL) was added dropwise over 5 min to a refluxing solution of $Rh_2(OAc)_4$ (~1 mg) in distilled dichloromethane (10 mL), stirred while heating under reflux for 18 h, in accordance with Method **E**. ^{1}H NMR spectroscopy of the crude product showed that the reaction contained cyclopropanation product **270a** and unknown **271** in a 95 : 5 ratio. Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (10:90–20:80–30:70) as eluent, methyl 2-thiabicyclo[3.1.0]hexane-1-carboxylate 2,2-dioxide **270a** (18 mg, 41%) was isolated as a colourless oil; 8% ee (determined by chiral HPLC with light scattering detector), 0% ee (determined by chiral HPLC with light UV detector); ν_{max}/cm^{-1} (neat, ATR): 2958 (CH), 1724 (CO), 1439, 1309, 1291, 1119 (SO_2); δ_H ($CDCl_3$, 600 MHz): 1.69 [1H, apparent t, *J* 6.6, one of C(6)H_2], 1.83 [1H, dd, *J* 8.6, 6.9, one of C(6)H_2], 2.29 [1H, dd, *J* 13.6, 7.6, one of C(4)H_2], 2.44–2.52 [1H, m, one of C(4)H_2], 2.54–2.58 [1H, m, C(5)*H*], 2.92 [1H, ddd, *J* 13.9, 12.6, 7.6, one of C(3)H_2], 3.08 [1H, dd, *J* 13.9, 8.3, one of C(3)H_2], 3.88 (3H, s, OCH_3), δ_C ($CDCl_3$, 150.9 MHz): 18.4 [CH_2, *C*(6)H_2], 19.9 [CH_2, *C*(4)H_2], 27.0 [CH, *C*(5)H], 43.9[C, *C*(1)], 46.1 [CH_2, *C*(3)H_2], 53.5 (CH_3, O*C*H_3) 166.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_7H_{11}O_4S$ $[M+H]^+$, 191.0378. Found 191.0372.

Assignments made with the aid of 2D NMR experiments, namely HSQC and HMBC.

Additional unknown byproduct (BP) **271** was observed in both the crude and purified ^{1}H NMR spectra, with the following characteristic signals; δ_H ($CDCl_3$, 400 MHz) 2.33 (3H, br s), 3.31-3.36 (2H, m), 3.91 (3H, s, OCH_3).

Table 7.13 *Copper and rhodium catalysed cyclopropanation reactions of α-diazo-β-oxo sulfone* **63**

Entry	Method	Metal	Ligand	Time (h)	Yield[a] (%)	Product Ratio[b]	sulfolane 270a [b]	BP[b] 271	% ee Sulfolane 270a [c]	
									ee (%)[c] (UV detector)	ee (%)[c] (LSD detector)
1	**E**	$Rh_2(OAc)_4$	-	18	41%	**Crude ratio**[d] **Purified ratio**	95 96	5 4	0	8[e]
2	**B**	$CuCl_2$	(4*R*)-Bn **43**	18	33%	**Crude ratio** **Purified ratio**	77 77	23 23	-[1]	71[f]
3	**B**	$CuCl_2$	(4*S*)-*t*-Bu **138**	50	43%	**Crude ratio** **Purified ratio**	53 48	47 52	98[e]	90[e]

4	**B**	$CuCl_2$	(4*R*,5S)-di-Ph **137**	18	39%	**Crude ratio** **Purified ratio**	83 85	17 15	37[f]	57[f]
5	**B**	$CuCl_2$	(3*S*,8*R*)-Ind **44**	18	40%	**Crude ratio**[g] **Purified ratio**	90 90	10 10	58[e]	87[e]
6	**B**	$CuCl_2$	(4*R*)-Ph **20**	30	25%	**Crude ratio**[h] **Purified ratio**[i]	60 64	40 36	[j]	[j]

a. The yield (%) is a combined yield of sulfolane **270a** and byproduct **271**, which are inseparable by chromatography.

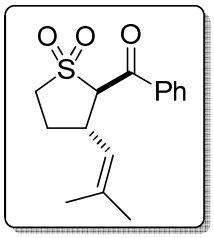
b. Relative amounts of sulfolane **270a** and byproduct **271** in both the crude and purified spectra were calculated using ^{1}H NMR spectra of the crude product using signals for OCH_3; δ_H 3.88 (3H, s, OCH_3) for sulfolane **270a**, and δ_H 3.90 (3H, s, OCH_3) for byproduct **271**.

c. Several attempts were made to calculate the enantiopurity of sulfolane **270a**. The use of a chiral shift reagent was explored, but due to impurities in the purified products, this method was deemed not suitable. The use of chiral HPLC was employed with the use of a UV detector, however due to a lack of a strong chromophore this method had limited use. The method that gave the most promising results was the use of chiral HPLC in conjugation with a light scattering detector. However, as there was an impurity present in all measured samples, three peaks were seen in the HPLC traces. The first two eluting enantiomers were tentatively assigned to sulfolane **270a**, and the last one was assigned to the uncharacterised impurity **271**. Therefore, the calculated values for enantioselectivity in **Table 7.13** should be viewed with caution and further work is needed to confirm these results.

d. Additional peaks present in the ^{1}H NMR of the spectra of the crude product; δ_H 2.75–2.85 (m), 3.16–3.27 (m), 3.31–3.37, 3.41–3.52 (m), 4.02 (s), 4.76 (dd, *J* 19.3, 3.9), 5.24 (dd, *J* 19.4, 9.1).
e. The first eluting enantiomer at ~33 min is the major enantiomer (Amylose 2).
f. The second eluting enantiomer at ~36 min is the major enantiomer (Amylose 2).
g. Additional peaks present in the ^{1}H NMR of the spectra of the crude product; δ_H 2.61–2.80 (m), 3.15-3.20 (m), 3.37–3.45.
h. Additional peaks present in the ^{1}H NMR of the spectra of the crude product; δ_H 3.15–3.25 (m), 3.30–3.36 (m), 3.37–3.43 (m), 4.59–4.76 (m), 4.96–5.25 (m).
i. Additional peaks present in the ^{1}H NMR of the spectra of the purified product; δ_H 4.67 (dd, *J* 10.1, 8.4), 5.23 (dd, *J* 10.1, 7.7).
j. Signal too weak to be calculated.

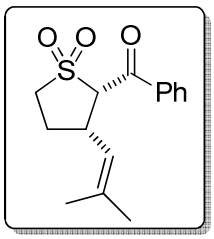
Note: Signals detected using the LSD detector are stronger than those obtained from the UV detector, making these values more potentially accurate.

3-(2-Methylprop-1-en-1-yl)-1,1-dioxidotetrahydrothiophen-2yl)(phenyl)methanone 263b



2-Diazo-2-[(5-methylhex-4-en-1-yl)sulfonyl]-1-phenylethanone **61** (50 mg, 0.16 mmol), in distilled dichloromethane was added dropwise over 5 min to a refluxing solution of $Rh_2(OAc)_4$ (~1 mg) in distilled dichloromethane (20 mL), stirred while heating under reflux for 24 h, in accordance with Method **E**. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 80–90% efficient, (75% *cis* **263a**, 25% *trans* **263b**); Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80–40:60–80:20) as eluent, 3-(2-methylprop-1-en-1-yl)-1,1-dioxidotetrahydrothiophen-2-yl)(phenyl)methanone **263b** (19 mg, 43%) was isolated as a colourless oily solid; 6% ee (*trans* **263b**) (determined by chiral HPLC); The following spectral characteristics are reported for *trans* **263b**; ν_{max}/cm^{-1} (neat, ATR): 2927, 2854 (CH), 1684 (CO), 1597 (C=C), 1449, 1312, 1279, 1126 (SO_2), 749 (CS); δ_H ($CDCl_3$, 600 MHz): 1.66 (3H, d, *J* 1.3, one of C*H*$_3$), 1.74 (3H, d, *J* 1.3, one of C*H*$_3$), 1.98–2.08 [1H, m, one of C(4)*H*$_2$], 2.31–2.38 [1H, m, one of C(4)*H*$_2$], 3.19 [1H, apparent td, *J* 12.9, 7.0 one of C(5)*H*$_2$], 3.38 [1H, ddd, *J* 12.8, 7.0, 1.5, one of C(5)*H*$_2$], 3.96–4.04 [1H, m, C(3)*H*], 4.61 [1H, d, *J* 9.6, C(2)*H*], 4.96–5.01 [1H, m, C(1′)*H*], 7.51–7.56 (2H, m, Ar*H*), 7.61–7.66 (1H, m, Ar*H*), 8.06–8.11 (2H, m, Ar*H*); δ_C ($CDCl_3$, 150.9 MHz): 18.3 (CH_3, one of C*H*$_3$), 25.8 (CH_3, one of C*H*$_3$), 27.6 [CH_2, *C*(4)H_2], 39.0 [CH, *C*(3)H], 53.6 [CH_2, *C*(5)H_2], 71.4 [CH, *C*(2)H], 123.1 [CH, *C*(1′)H], 128.99 (CH, 2 × aromatic *C*H), 129.0 (CH, 2 × aromatic *C*H), 134.5 (CH, aromatic *C*H), 136.6 [C, aromatic *C* or C(2′)], 137.0 [C, aromatic *C* or C(2′)], 189.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{15}H_{19}O_3S$ $[M+H]^+$, 279.1055. Found 279.1041. m/z (ESI+): 279.3 $[M+H]^+$.

Assignments made with the aid of 2D NMR experiments, namely HSQC and HMBC.



263a Characteristic signals seen in ^{1}H NMR of the crude products: δ_H ($CDCl_3$, 600 MHz): 1.59 (3H, d, *J* 1.3, one of C*H*$_3$), 1.70 (3H, d, *J* 1.3, one of C*H*$_3$), 2.44–2.65 (m), 3.46–3.56 [1H m, one of C(5)*H*$_2$], 3.66–3.77 [1H, m, C(3)*H*], 4.51–4.62 (overlapping m), 4.91 [1H, d, *J* 6.90, C(2)*H*], 5.03–5.06 [1H, m, C(1′)*H*], 7.82–7.93 (m, Ar*H*). Assignment is partial and tentative (made from spectra of crude product)

A third, unidentified compound **264** appeared in the ^{1}H NMR spectra of a number of reactions. It was not obtained as a pure compound after chromatography (possible structures in results and discussion) but occasionally co-eluted with *trans* sulfolane **263b**. The compound was not characterised but has the following characteristic peaks in the ^{1}H NMR of the crude products; δ_H ($CDCl_3$, 400 MHz) 1.72 (3H, d, *J* 1.1), 1.83 (3H, d, *J* 1.1), 3.47–3.58 (1H, m), 5.41–5.48 (1H, m), 5.53–5.61 (1H, m), 6.16 (1H, d, *J* 2.6) [or 6.1 (s) and 6.2 (s)].

.

Table 7.14 *Copper and rhodium catalysed C–H insertion reactions of α-diazo-β-oxo sulfone* ***61***

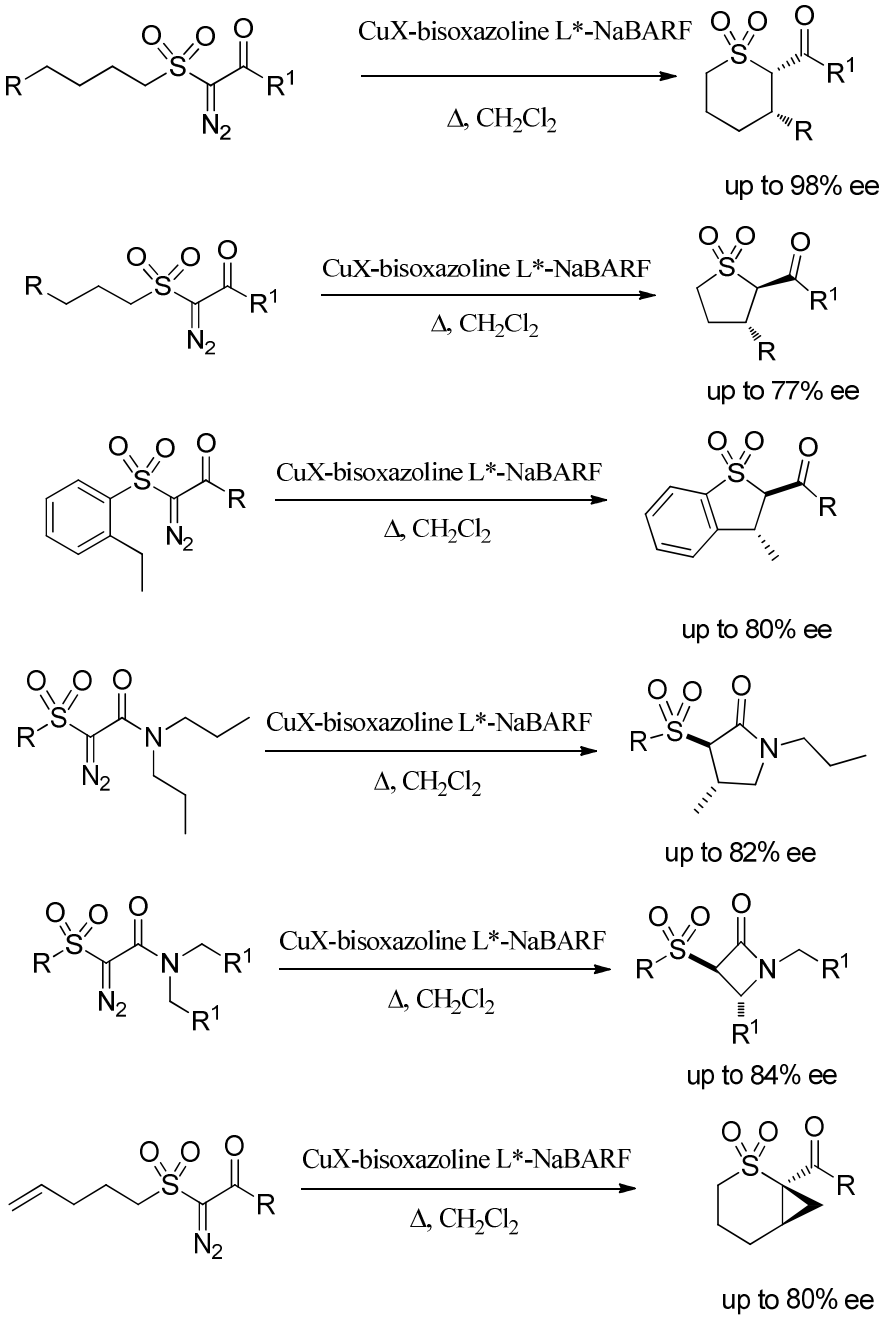
Entry	Method	Metal	L	Time (h)		*cis* [a]	*trans*[a]	*unknown*[a]
1	**E**	$Rh_2(OAc)_4$	-	24	**Crude ratio (%)**[b]	60	20	-
					Purified yield (%)	-	43%	
					% ee	-	(6% ee)[c]	
2	**B**	$CuCl_2$	(3*S*,8*R*)-Ind **44**	24	**Crude ratio (%)**[d]	8	72	12
					Purified yield (%)	-		
					% ee			
					Fr 1[e]		12 (47% ee)[c,f]	
					Fr 2[g]		20 (47% ee)[c,f]	
					Fr 3		7 (47% ee)[c,f]	
					Total		**39% (47% ee)**	
3	**B**	$CuCl_2$	(4*R*)-Bn **43**	24	**Crude ratio** [h]	4	79	12
					Purified yield (%)			
					% ee			

					Fr 1[i] **Fr 2** **Total**	- - 	16% (44% ee)[j] 21% (41% ee)[j] **37% (42% ee)**	
4	**B**	$CuCl_2$	(4*S*)-*t*-Bu **138**	48	**Crude ratio**[k] **Purified yield (%)** **% ee**	2 - 	78 37%[l] 53% ee[f]	20
5	**B**	$CuCl_2$	(4*R*,5*S*)-di-Ph **137**	21	**Crude ratio** **Purified yield (%)** **% ee**	36 - 	54 32% 38% ee[f]	-
6	**B**	$CuCl_2$	(4*R*)-Ph **20**	21	**Crude ratio** **Purified yield (%)** **% ee**	26 - 	61 40% 43% ee[f]	2

a. Quantities of products in crude mixtures are calculated from the ^{1}H NMR spectra using the following signals; δ_H 3.96–4.04 [1H, m, C(3)*H*] for *trans* sulfolane **263b** and δ_H 4.91 (d, *J* 6.90) for *cis* sulfolane **263b** and δ_H 6.16 (1H, d, *J* 2.6) for unknown **264**.
b. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 9.67 (s).
c. HPLC trace not clean.
d. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 6.01 (s), 6.19 (s).
e. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~5%
f. The first eluting enantiomer at ~36 min is the major enantiomer (Amylose 2).
g. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~10%
h. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 6.01 (s), 6.19 (s).
i. Contains impurity; δ_H 5.49–5.51 (m), 5.52–5.75 (m), 6.19 (s). ~15%
j. The second eluting enantiomer at ~75 min is the major enantiomer (Amylose 2).
k. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.49–5.51 (m), 5.52–5.75 (m), 6.19 (s)
l. Additional peaks observed in the ^{1}H NMR spectra of the crude product; δ_H 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~5

7.5 Overall Conclusions

The work in this thesis demonstrates that intramolecular C–H insertion and cyclopropanation reactions of α-diazo-β-oxo-sulfones are synthetically powerful transformations which can be affected with excellent enantioselectivity through use of copper-bisoxazoline catalysts, enabling access to a range of structurally diverse heterocycles and fused carbocycles as summarised in **Scheme 7.19**.



Scheme 7.19

Through a detailed, systematic study of the influence of variation of the substrate structure and the nature of the catalyst, including the metal ion, counterions, ligand and additive, it has proved possible to gain insight into the steric and/or electronic factors which influence reaction efficiency, choice of reaction pathway, regioselectivity, diastereoselectivity and enantioselectivity. Clearly, the ultimate goal is design of an enantioselective catalyst which can be employed across a diverse range of α-diazo-β-oxo-sulfones and reaction transformations; this requires a detailed understanding of the nature of the catalyst substrate interactions in the transition states. Indeed considerable progress has been made in this work as the highest enantioselectivities are in general obtained using either the (4*R*)-Ph **20** or (3*S*,8*R*)-Ind **44** ligand, although individual substrate effects cannot be overlooked. Significantly, the optimum ligand trends are consistent across both C–H insertion and cyclopropanation, providing optimism for a generally enantioselective catalyst across a wide range of transformations.

One of the most important aspects of this study was the exploration of the reactions with α-diazo-β-amido-sulfones. In these systems two distinct C–H insertion pathways can operate; into the sulfonyl chain to form thiopyrans/sulfolanes or into the amide substituent to form β/ɣ- lactams. In general, with conformationally mobile amides lactam formation is preferred, while the alternative pathway of insertion into the sulfonyl group competes only with amides, which through conformational or other factors, are not amenable to lactam formation. Accordingly, substrate control of reaction pathway is evident.

In general, for each of the heterocycles and carbocycles studied, the same bisoxazoline ligands gave rise to the highest levels of enantiocontrol for each compound in a particular group. In addition, the same regio- and diastereoselectivity and direction of enantioselectivity was observed for a particular series. One general exception to this was the synthesis of the *trans* sulfolane compounds. For each one of the compounds studied, a different ligand trend was displayed in terms of diastero- and enantioselectivity (**Figure 7.20**). In two instances, the direction of the enantioselectivity depending on the ligand stereochemistry was not as expected. Firstly the ligand trends in the synthesis of the fused morpholine amide **233b** displayed a very different pattern in terms of direction of enantioselection to the other compounds in this series (**Section 6.3.4**). Secondly the direction of enantioselection in the C–H insertion to form sulfolane **263b** displays uncharacteristic trends based on the ligands stereochemistry (**Section 7.2.2.2**). While

there were one other example in this instance as the % ee were very low the difference is not substantive (**Section 5.3.2**).

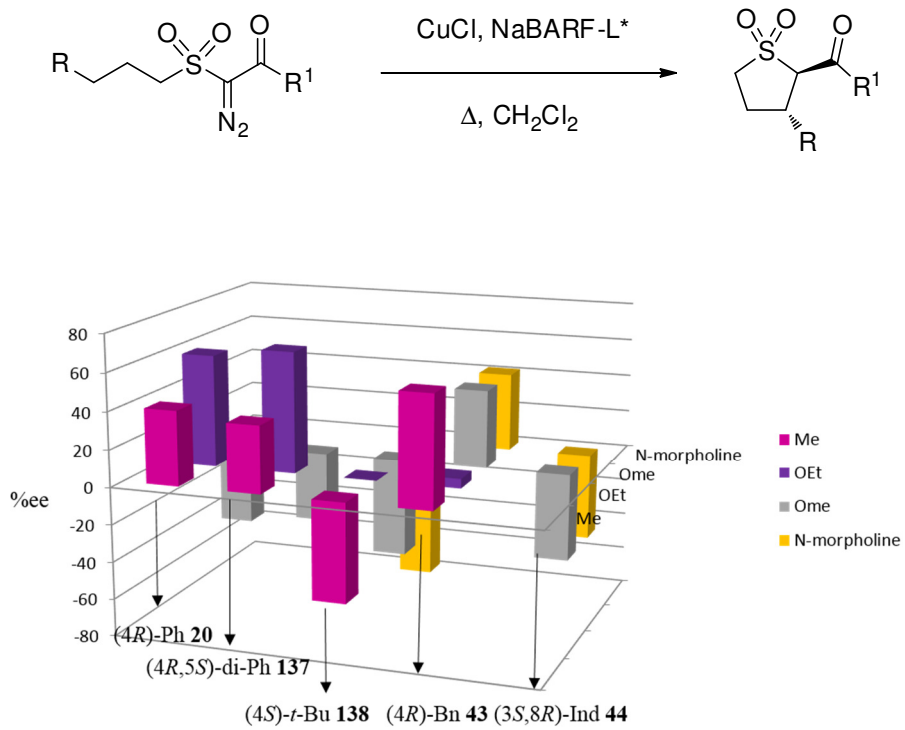


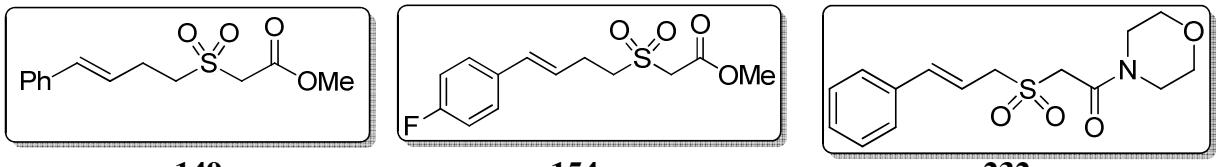
Figure 7.20 *Note R is phenyl is each case, with the exception of compound* ***263b****,(* R^1*=OMe, R=HC=C(Me)*$_2$*),* R^1*=OEt* ***40b****,* R^1*=Me* ***42b****,* R^1*=morpholino* ***231b***

In general, a CuCl-NaBARF-bisoxazoline gives rise to reaction products with the highest enantiopurities. However, in a few isolated instances, Cu[$(CH_3CN)_4PF_6$)]-bisoxazoline gave rise to higher enantioselectivities than the aforementioned catalyst system (**Section 6.3.1**). Similar instances of this have been seen in other projects.[56,62-63]

Throughout this work cyclisations have been explored with widely used chiral rhodium catalysts for comparison with the outcomes using copper-bisoxazoline system. Without exception higher enantioselectivities were achieved using the copper catalysts in all substrates studied in this work.

Throughout this work, products believed to arise from a competing hydride transfer pathway were seen for the transition metal catalysed reactions of a number α-diazo-β-

oxo-sulfones. This is consistent with literature reports for related systems.[58,61] A diverse number of products believed to arise from this pathway were seen throughout this work. For example, the formation of the diazo reduction product may form as a result of this pathway in an intermolecular sense; numerous examples have been seen throughout this project. In addition, hydride transfer may result in elimination products; these have been seen exclusively for substrates containing a benzylic C–H during this project. Examples of these products are shown in **Figure 7.21**.



149 **154** **232**

Figure 7.21

Competing hydride transfer processes are believed to be responsible for the generally low reaction efficiencies observed for the transition metal catalysed reactions of *N*,*N*-dibenzyl amide and the morpholine amides discussed in Chapter 6. In these instances, competing hydride transfer is believed to occur at the CH_2 α to the amide nitrogen, leading to unstable intermediates which subsequently break down to both known and unknown byproducts. In Chapter 7, for α-diazo-β-oxo-sulfones containing allylic bonds α to potential insertion sites, a number of unidentified byproducts were observed. These are largely believed to be due to competing hydride transfer processes. Therefore, hydride transfer is a significant pathway for the transition metal catalysed reactions of α-diazo-β-oxo-sulfones and the extent to which this occurs is determined by the substrate structure; hydride transfer at benzylic C–H bonds is often observed. While the hydride transfer products have been most commonly seen in copper catalysed processes there is also evidence for their formation with rhodium as minor byproducts.

More generally it is interesting to consider the overall efficiency of the insertion processes as evidenced by the H NMR spectra of the crude products. In the insertions to form the thiopyrans the cleanest transformations were generally seen with the esters while in the lactam series cyclisations of the *N*,*N*-dipropyl derivatives were remarkably clean, irrespective of whether a rhodium or a copper catalyst was employed. Evidently

competing reaction pathways are principally substrate controlled rather than catalyst controlled.

Overall substantial progress has been made over the course of this research in exploring the scope, chemo-, diastereo-and enantioselectivity in powerful synthetic transformations of a range of α-sulfonyl-α-diazo carbonyl compounds catalysed by copper-NaBARF-bisoxazoline catalysts providing useful mechanistic insight into the factors which determine the outcome in terms of reaction pathway and stereocontrol. The ultimate goal of design of a generally applicable catalyst across a wide range of different transformations remains feasible based on these studies.

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Appendix

Appendices

Appendix i-Chiral HPLC and Chiral shift ^{1}H NMR; Determination of enantiopurity

Appendix ii-Absolute stereochemistry determination

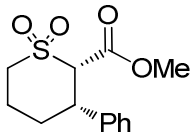
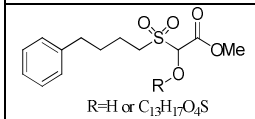
Appendix iii-Representative ^{1}H NMR spectra

Appendix iv-^{1}H NMR spectra of byproducts

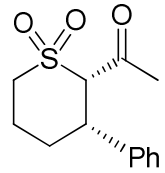
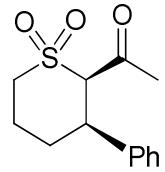
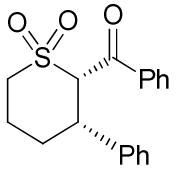
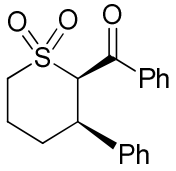
Appendix vi-Publications

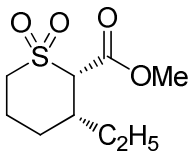
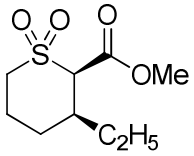
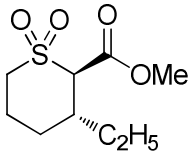
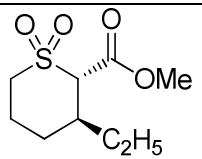
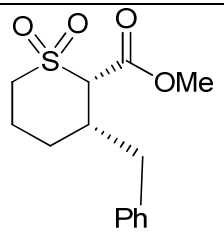
Appendix I *Chiral HPLC and Chiral shift ^{1}H NMR; Determination of enantiopurity*

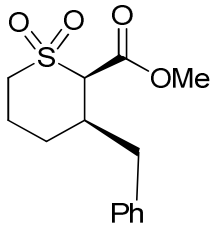
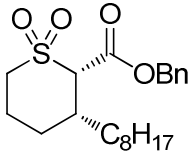
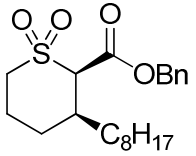
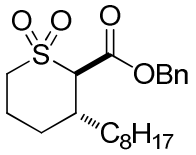
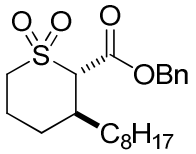
1) Samples for chiral stationary phase HPLC analysis were prepared at a concentration of ~1 mg/mL in IPA.
2) The injection volume was 10 μl for all compounds unless otherwise stated.
3) Chiral stationary phase HPLC was conducted at room temperature.
4) Retention times can change per injection (this is something that usually occurs for long run times); however, the order of elution of the enantiomers remains constant.

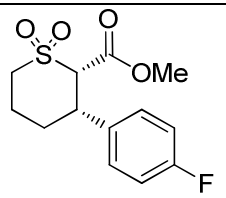
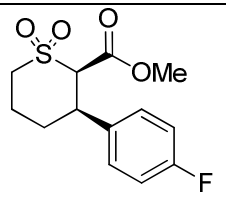
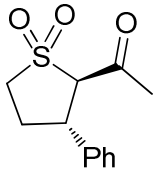
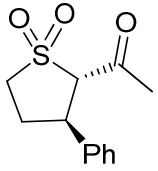
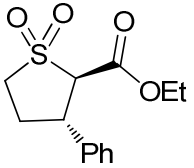
Compound	Condition Set	Column	λ (cm^{-1})	Flow Rate (mL/min)	Mobile Phase IPA:Hexane	Retention Time (min)	When to use
 **26a**	1	AS-H	210	1	20:80	(+)-(2*S*,3*S*) 15 (−)-(2*R*,3*R*) 20	For pure *cis* thiopyran **26a**
	2	OJ-H	210	1	10:90-30:70	(−)-(2*R*,3*R*) 31 (+)-(2*S*,3*S*) 36	When OH insertion product **148** is present
	3	OJ-H	210	1	Gradient: 2:98-4:96-6:94-8:92-10:90-30:70-10:90-98:2	(−)-(2*R*,3*R*) 68 (+)-(2*S*,3*S*) 83	When OH insertion product **148** is present in addition to other impurities
 R=H or $C_{13}H_{17}O_4S$ **148**	1	AS-H	210	1	10:90	Two peaks 22, 26	
	2	OJ-H	21	1	10:90-30:70	Two peaks, 111, 189	
	3	OJ-H	209	1	Gradient: 2:98-4:96-6:94-8:92-10:90-30:70-10:90-98:2	Two peaks, 140, 320	

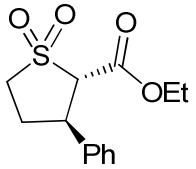
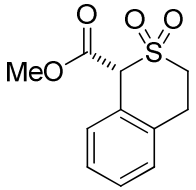
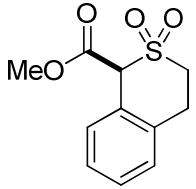
Chapter 4 continued

Compound	Column	λ Max	Mobile Phase (hexane : IPA)	Retention Time	
				Enantiomer	min
 **22a**	Chiralpak OJ-H	212	90 : 10	(+)-(2*S*,3*S*)	36
 **22a**				(−)-(2*R*,3*R*)	41
 **24a**	Chiralpak AS-H	210	5 : 95	(+)-(2*S*,3*S*)	51
 **24a**				(−)-(2*R*,3*R*)	59

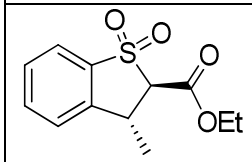
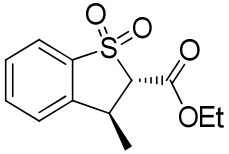
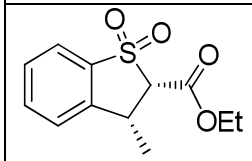
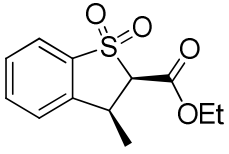
 **30a**	Chiralpak AS-H	210	90 : 10	(+)-(2*S*,3*R*)	22
 **30a**				(−)-(2*R*,3*S*)	25
 **30b**	Lux™ Cellulose-2	210	80 : 20	-[a]	30
 **30b**				-[a]	37
 **28a**	Chiralpak AS-H	210	80 : 20	(+)-(2*S*,3*S*)	18

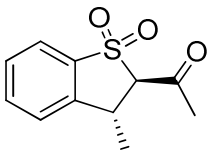
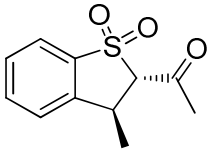
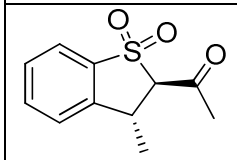
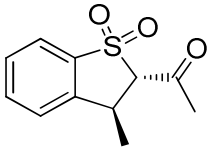
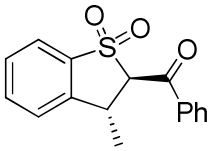
 **28a**				(−)-(2*R*,3*R*)	24
 **38a**	Chiralpak AS-H	210	90 : 10	(+)-(2*S*,3*R*)	11
 **38a**				(−)-(2*R*,3*S*)	19
 **38b**	Chiralpak AS-H	210	80 : 20	(+)[a]	12
 **38b**				(−)[a]	31

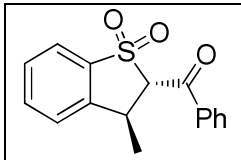
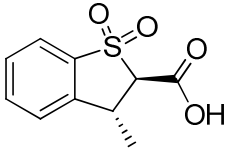
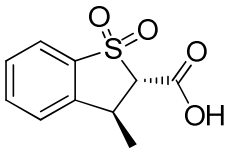
 **145a**	Chiralpak AS-H	210	80 : 20	(+)-(2*S*,3*S*)	22
 **145a**				(−)-(2*R*,3*S*)	42
 **42b**	Chiralpak AS-H	210	80 : 20	(+)-(2*R*,3*S*)	30
 **42b**				(−)-(2*S*,3*R*)	41
	Chiralpak AS-H	210	95 :5	(+)-(2*R*,3*S*)	72

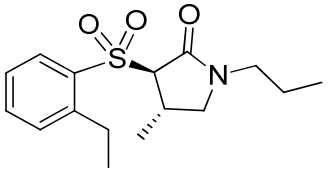
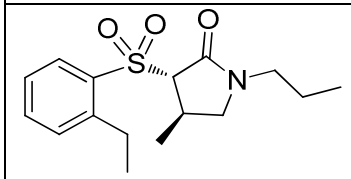
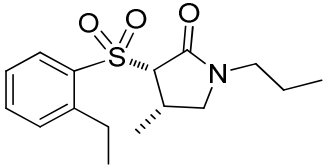
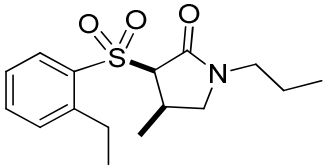
40b					
 **40b**				(−)-(2*S*,3*R*)	51
 **146**	Chiralpak OJ-H	210	80 :20	-[a]	51
 **146**				-[a]	109

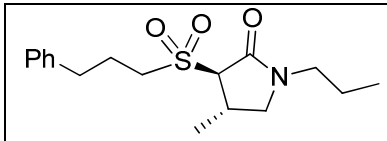
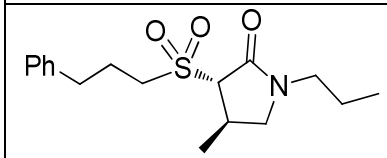
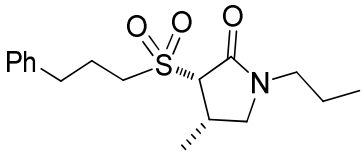
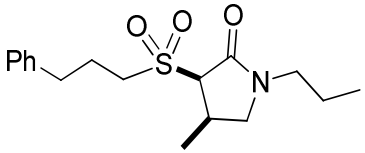
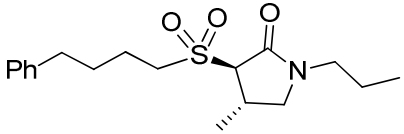
a. Absolute stereochemistry for this series is unknown, therefore the assignment of an enantiomer to a HPLC peak is not made.

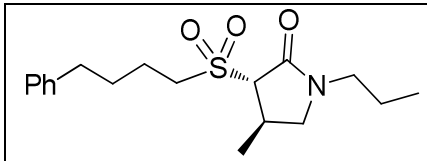
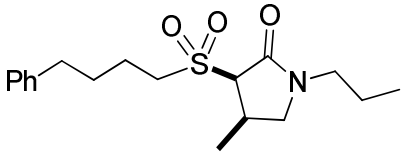
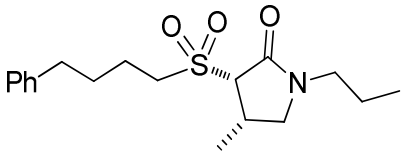
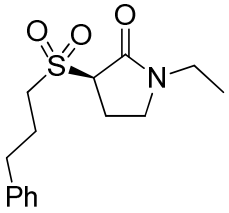
Compound	Column	λ Max	Mobile Phase (hexane : IPA)	Retention Time	
				Enantiomer	min
 **165b**	Chiralpak AS-H	209	80 : 20	(−)-(2*R*,3*R*)	29
 **165b**				(+)-(2*S*,3*S*)	21
 **165a**				(2*S*,3*R*)	38
 **165a**				(2*R*,3*S*)	46

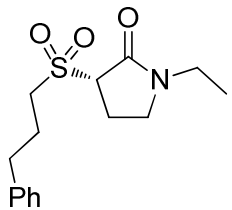
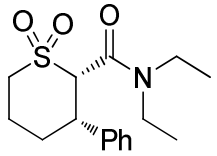
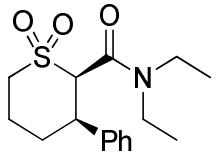
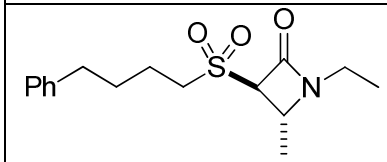
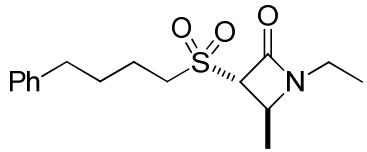
 **166b**	Chiralpak OJ-H	209	95 : 5	(−)-(2*R*,3*R*)	66
 **166b**				(+)-(2*S*,3*S*)	113
 **166b**	Lux™ Cellulose-2	209	95 : 5	(−)-(2*R*,3*R*)	40
 **166b**				(+)-(2*S*,3*S*)	37
 **167b**	Chiralpak AS-H	209	80 : 20	(−)-(2*R*,3*R*)	42

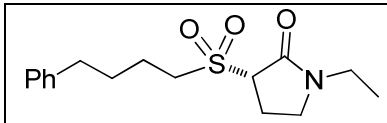
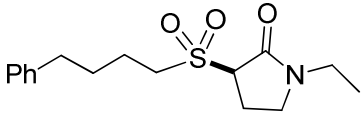
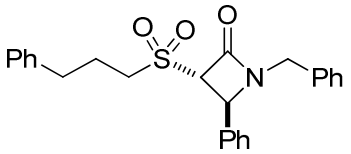
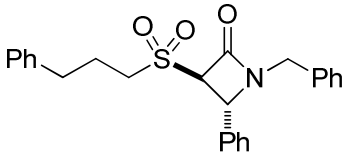
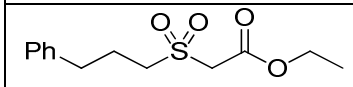
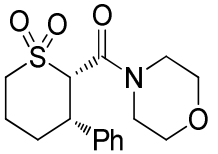
 **167b**				(+)-(2*S*,3*S*)	26
 **170b**	Chiralpak AS-H	209	80 : 20	(−)-(2*R*,3*R*)	28
 **170b**				(+)-(2*S*,3*S*)	20

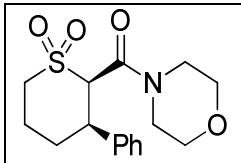
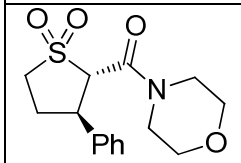
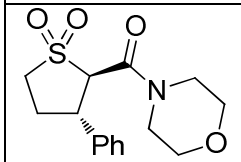
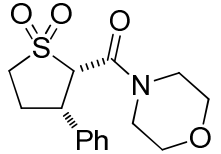
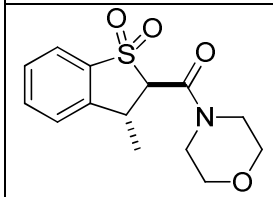
Compound	Column	Flow mL/min	λ Max (min)	Mobile Phase (hexane : IPA)	Retention Time	
					Enantiomer	min
 **208b**	Lux™ Cellulose- 4	1	210	90 : 10 (80 : 20)	(−)-(3*R*,4*S*)	40 (22)
 **208b**					(+)-(3*S*,4*R*)	73 (45)
 **208a**	Lux™ Cellulose-4	1	210	90 : 10 (80 : 20)	-[a]	23-25 (10)
 **208a**					-[a]	26-28 (12)

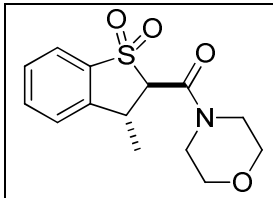
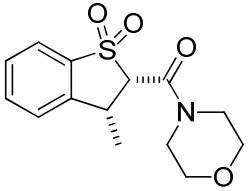
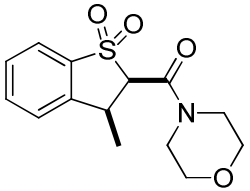
 **210b**	Lux™ Cellulose-2	1	210	90 : 10	(−)-(3*R*,4*S*)	27
 **210b**					(+)- (3*S*,4*R*)	43
 **210a**	Lux™ Cellulose-2	1	210	90 : 10	-[a]	28
 **210b**					-[a]	32
 **209b**	Lux™ Cellulose-2	1	210	90 : 10	(−)-(3*R*,4*S*)	26

 **209b**					(+)- (3*S*,4*R*)	41
 **209a**	Lux™ Cellulose-2	1	210	90 : 10	-[a]	29
 **209a**					-[a]	36
 **216**	Chiralpak AS-H	1	210	90 : 10	-[a]	28

 **216**					-[a]	30
 **220a**	Chiralpak AS-H	1	210	95 : 5	(+)-(2*S*,3*S*)	21
 **220a**					(−)-(2*R*,3*R*)	18
 **221b**	Lux™ Cellulose-4	1	210	10 : 90	-[a]	37
 **221b**					-[a]	49

 **219**	Chiralpak AS-H	1	210	80 : 20	-[a]	15
 **219**					-[a]	23
 **226b**	Lux™ Cellulose-4	1	210	90 : 10	(+)[a]	40-55
 **226b**					(−)[a]	66-85
 **227**					-	~34
 **224a**	Chiralpak AS-H	1	210	90 : 10	(+)-(2*S*,3*S*)	43

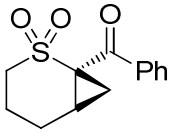
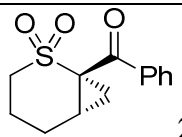
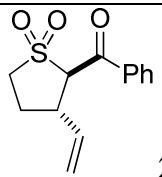
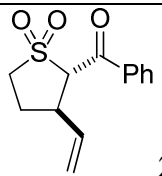
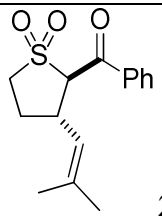
 **224a**					(−)-(2*R*,3*R*)	39
 **231b**	Lux™ Cellulose-4	1	210	70 : 30	(+)[a]	33
 **231b**					(−)[a]	44
 **231a**	Lux™ Cellulose-4	1	210	70 : 30	-[a]	53
 **233b**					-[a]	39

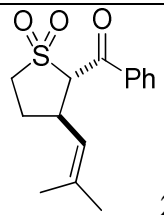
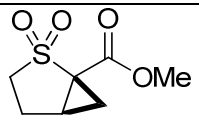
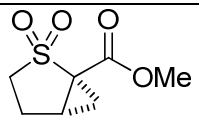
 **233b**	Lux™ Cellulose-2	1	212	70 : 30	-[a]	45
 **233a**					-[a]	43
 **233a**					-[a]	62

a. Absolute stereochemistry for this series is unknown, therefore the assignment of an enantiomer to a HPLC peak is made.

Chapter 7

Compound	Column	λ Max (min)	Mobile Phase (hexane : IPA)	Retention Time	
				Enantiomer	min

 **259a**	Lux™ Amylose-2	214	80 :20	(+)-(1*R*,6*S*)	36
 **259a**				(−)-(1*S*,6*R*)	52
 **260b**	Lux™ Amylose-2	220	80 : 20	-[a]	34
 **260b**				-[a]	61
 **263b**	Lux™ Amylose-2		80 : 20	-[a]	36

 **263b**				-[a]	75
 **270a**	Lux™ Amylose-2	209	70:30	-[a]	33[b]
 **270a**				-[a]	36[b]

a. Absolute stereochemistry for this series is unknown, therefore the assignment of an enantiomer to a HPLC peak is not made.

b. Analysis carried out on an Agilent Technologies 1120 LC fitted with a UV detector and a light scattering detector (Agilent Technologies 385-ELSD).

Determination of Relative Stereochemistry using Chiral Shift Reagent.

The use of a chiral shift reagent [(+)-Eu(hfc)$_3$] in the ^{1}H NMR spectroscopy was used to measure the relative stereochemistry in one instance. This was done by adding 5 mg of (+)-Eu(hfc)$_3$ to a sample of 10 mg of **257a** in 0.6 mL of $CDCl_3$. An attempt to measure the enantiopurity of samples of 257a was also made using chiral HPLC. Chiralpak OJ-H was used as the chiral column, with flow rate of 1 mL per minute, using 10% IPA : 90% hexane. Two peaks at 71 min and 76 min were detected and are believed to be the two enantiomers of **257a**. However, the absorbance was extremely low and therefore this method was not perused.

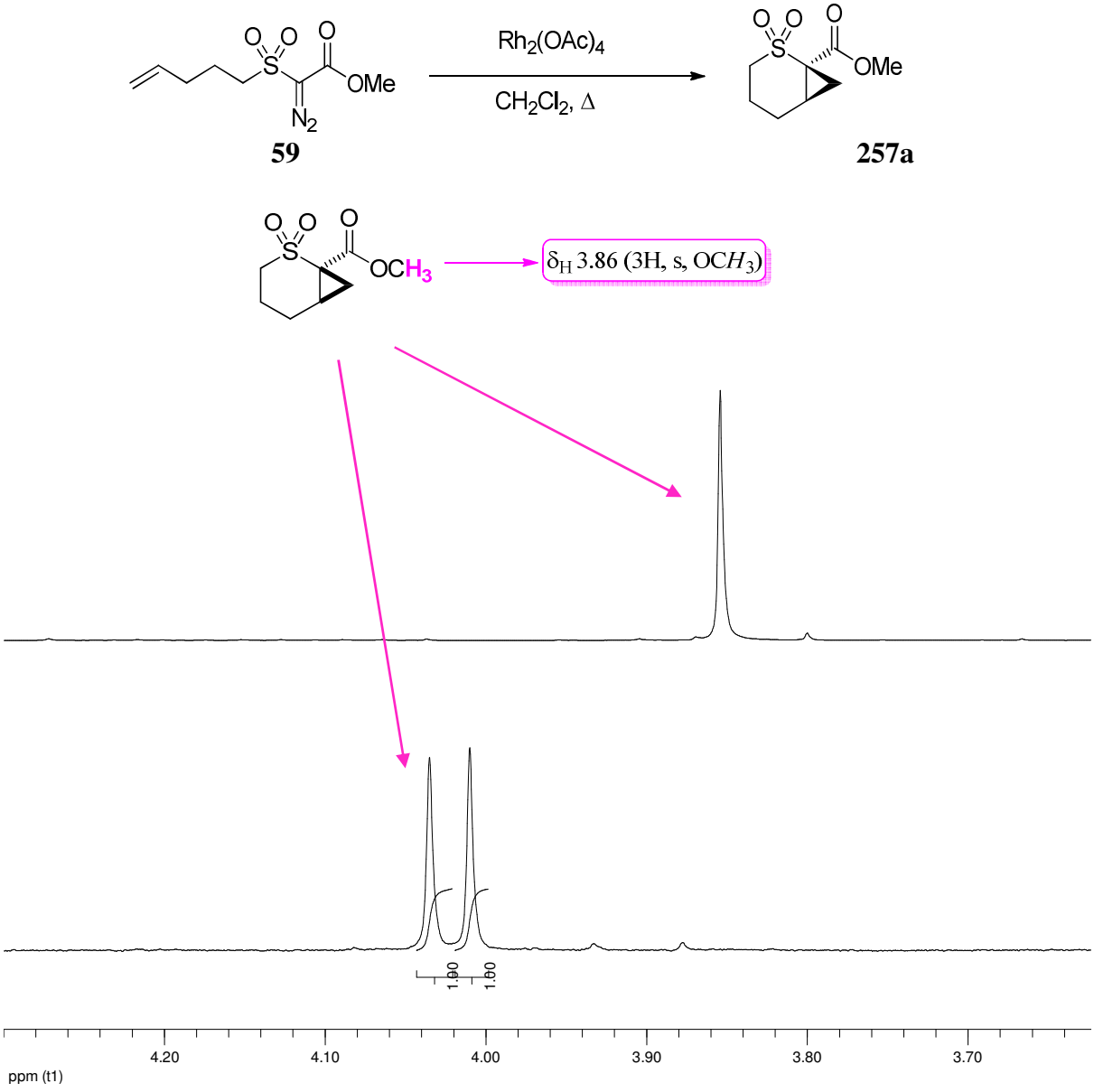
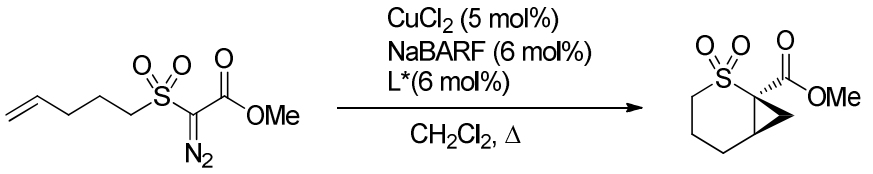
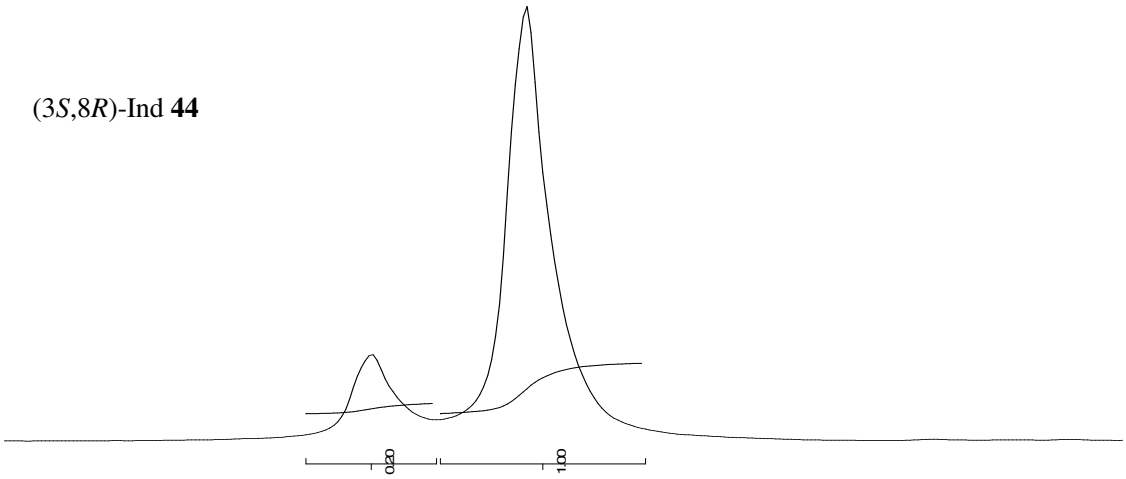


Figure 1 *^{1}H NMR spectra recorded in ($CDCl_3$, 400 MHz)*



59 **257a**

(3*S*,8*R*)-Ind **44**



(4*R*)-Ph **20**

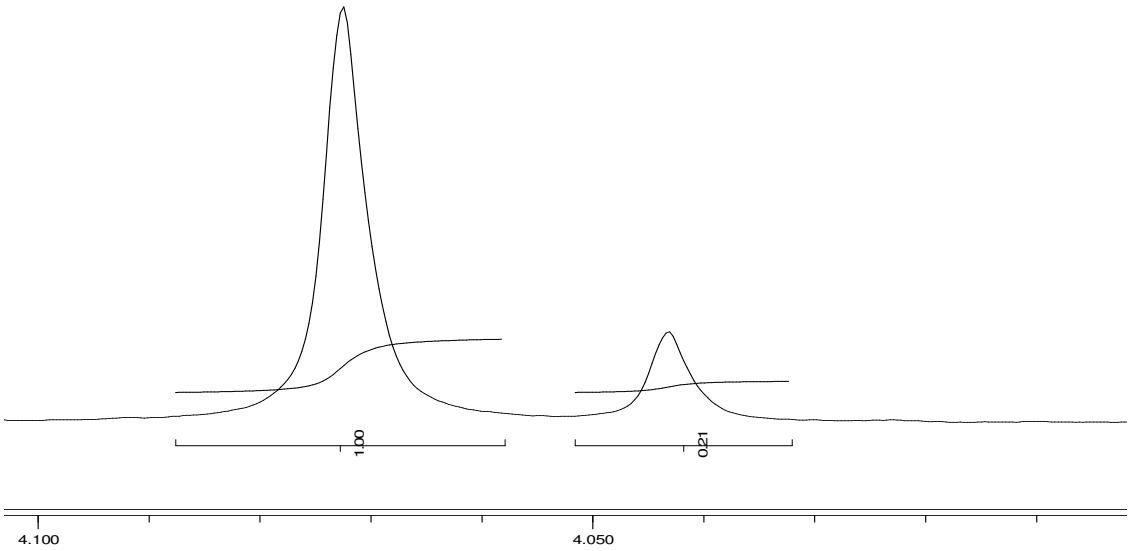
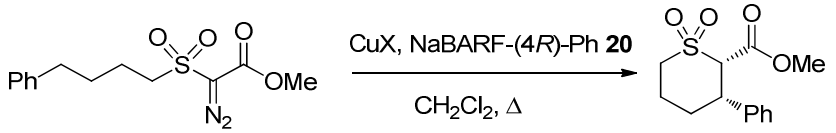


Figure 2*^{1}H NMR spectra recorded in* (*$CDCl_3$, 400 MHz)*

Appendix II *Determination of Absolute Stereochemistry*

Determination of **the Absolute Stereochemistry of *cis* thiopyrans**

The determination of the absolute stereochemistry of the *cis* thiopyran compounds reported in this thesis is based on work previously carried out by Flynn. Flynn carried out a $Cu(OTf)_2$ catalysed reaction of **25**, leading to a racemic sample of **26**, which allowed the development of chiral HPLC condition for the separation of the enantiomers of **26a**. The cyclisation of α-diazo-β-oxo sulfone **25** in the presence of CuCl-NaBARF-(4*R*)-Ph ligand **20** was subsequently carried out. The *cis* thiopyran **26a** that resulted was isolated with 98% ee, and a positive optical rotation $[\alpha]_D^{20}$ +103.8 (**Figure 3**). X-ray analysis of a single crystal of *cis* thiopyran **26a**, obtained from this reaction, showed that the absolute stereochemistry of *cis* thiopyran **26a** was (2*S*,3*S*). This crystal was subsequently dissolved in IPA and HPLC analysis was conducted. This confirmed that the (2*S*,3*S*) enantiomer was the major enantiomer and therefore a peak on the HPLC could be assigned to an enantiomer. Flynn assigned the absolute stereochemistry of the remaining *cis* thipyrans, **22a**, **24a**, **30a**, **28a**, **38a** by analogy. This was based on the fact that these *cis* thiopyrans, which arose from cyclisations using of CuCl-NaBARF-(4*R*)-Ph **20** had positive optical rotation. Therefore assignment of *cis* thipyrans, **22a**, **24a**, **26a**, **30a**, **28a** and **38a** made in this project were made with respect to Flynn's assignments.[1,2]

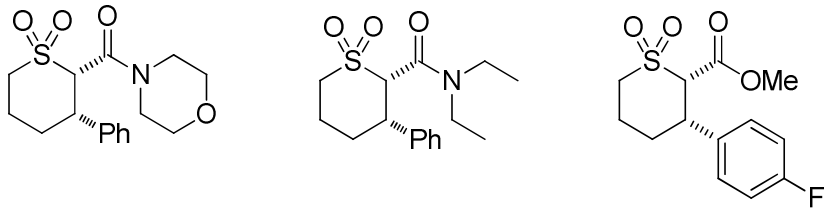


25 **26a** (2*S*,3*S*)

$[\alpha]_D^{20}$ +103.8

Figure 3

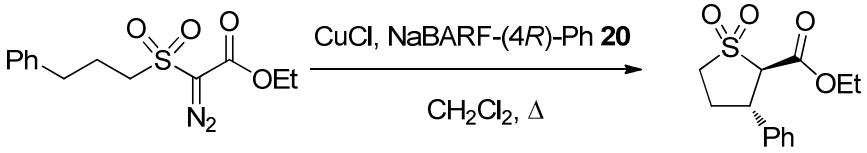
Three novel *cis* thiopyrans were synthesised during this work (**Figure 4**). Each of the cis thiopyrans **224a, 220a** and **145a** had a positive optical rotation arising from reaction with CuCl-NaBARF-(4*R*)-Ph **20** catalyst system. As this is consistent with results obtained by Flynn, the absolute stereochemistry of each of these was assigned as (2*S*,3*S*).



224a **220a** **145a**

Figure 4

The determination of the absolute stereochemistry of the *trans* sulfolanes reported in this thesis is also based on work previously carried out by Flynn. Flynn carried out CuCl-NaBARF-(4*R*)-Ph **20** cyclisation of **39** leading to *trans* sulfolane **40b** (**Figure 5**) with 60% ee and a positive rotation-Lit[1,2] $[\alpha]_D^{20}$ +21.3. X-ray analysis of **40b** showed that its absolute stereochemistry was (2*R*,3*S*). The single crystal that was used for X-ray analysis was dissolved in IPA and HPLC analysis showed that (2*R*,3*S*) enantiomer was the major product. Flynn assigned the absolute stereochemistry of *trans* sulfolane **42b** by analogy. These were the basis of the assignments used in this project.[1,2]



39 **40b** (2*R*,3*S*)

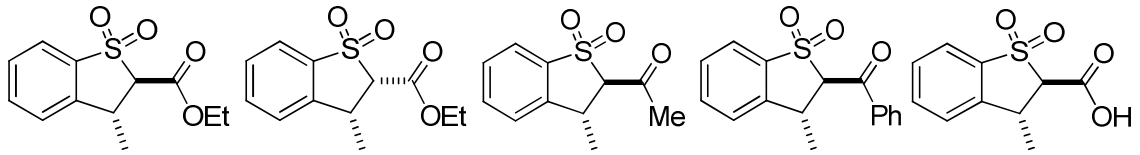
$[\alpha]_D^{20}$ +21.3

Figure 5

During this work the absolute stereochemistry of sulfolanes **40b** and **42b** were assigned on the basis of Flynn's assignment. For the novel sulfolanes **260b**, **263b** and **231b**, while the enantiopurity was determined by chiral HPLC it was not possible to assign the absolute stereochemistry of these compounds by analogy as the trends in sense of enantioselection on variation of the ligand stereochemistry were uncharacteristic.

Determination of Absolute Stereochemistry; fused sulfolanes

The absolute stereochemistry of the compounds shown in **Figure 6** is reported in Chapter Five.



165b **165a** **166b** **167b** **170b**

Figure 6

The methods used to detremine the absolute stereochemistry of the fused sulfolanes discussed in Chapter Five are further documented in this Section. The C–H insertion reaction of α-diazo-β-oxo sulfone **54** catalysed by $Cu(OTf)_2$ was first undertaken with the aim of synthesising racemic sulfolane **165b**. As can be seen in **Figure 7**, sulfolane **165b** was formed as mixture of diastereomers [50 : 50, *cis* (a): *trans (b)*], with nearly complete epimerisation to the *trans* isomer taking place after chromatography on silica gel [7 : 93., *cis* (a): *trans (b)*]. With the racemic sample of sulfolane **165b** in hand adequate HPLC conditions were developed for the separation of the enantiomers of the *trans* sulfolane **165b** (**Figure 7**).

Conversion of ethyl ester sulfolane **165b** (colourless oil) to carboxylic acid **170b** (white solid) was achieved using potassium hydroxide in aqueous methanol. Separation of the enantiomers of carboxylic acid *trans* sulfolane **170b** was achieved using chiral HPLC. With suitable HPLC conditions for the separation of the enantiomers of ethyl ester sulfolane **165b** and carboxylic acid sulfolane **170b** enantioselectivities of the enantioenriched samples subsequently began.

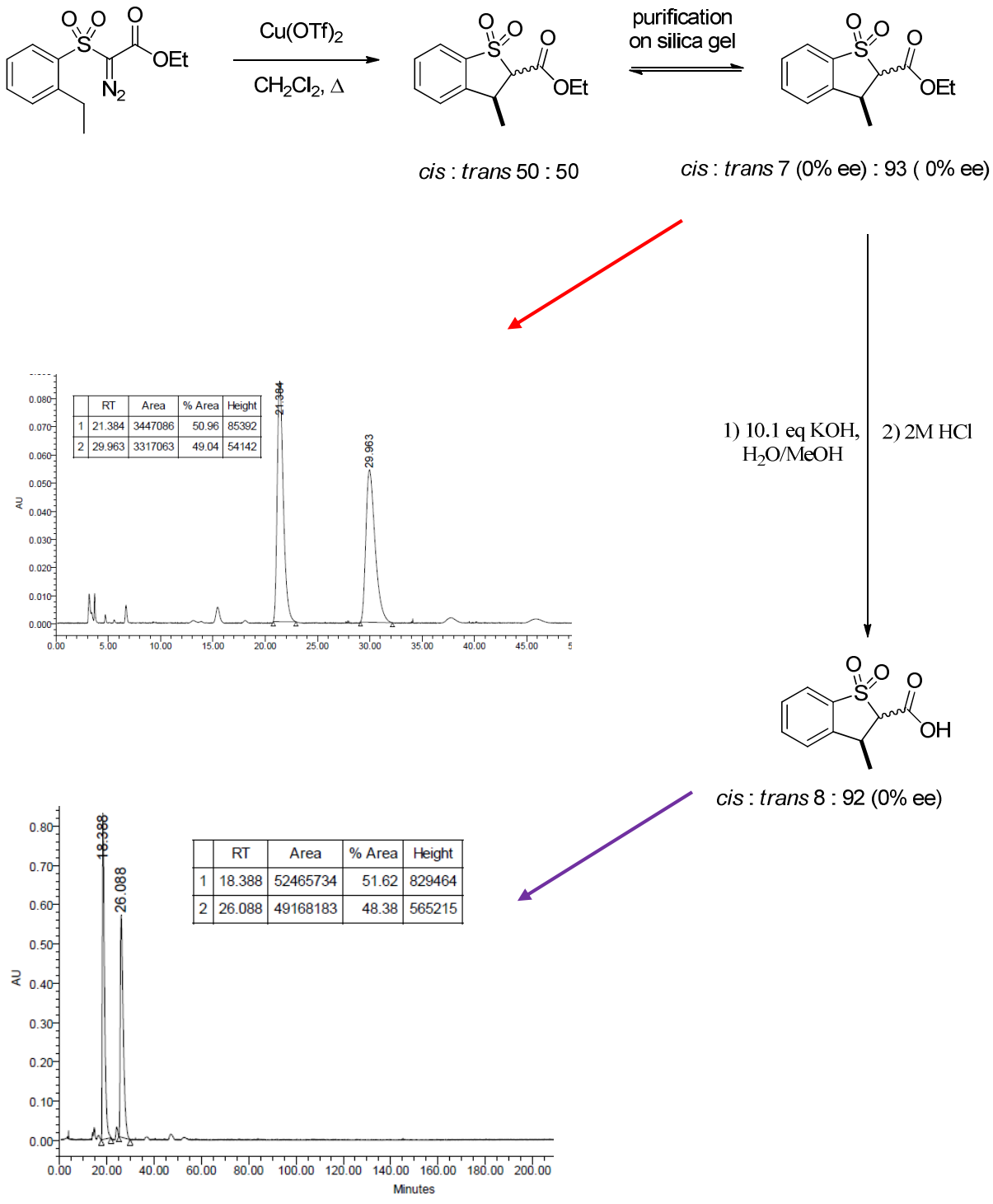

Cu(OTf)2
CH2Cl2, Δ
purification on silica gel
cis : trans 50 : 50
cis : trans 7 (0% ee) : 93 (0% ee)
1) 10.1 eq KOH, H2O/MeOH
2) 2M HCl
cis : trans 8 : 92 (0% ee)
RT Area % Area Height
1 21.384 3447086 50.96 85392
2 29.963 3317063 49.04 54142
AU
Minutes
RT Area % Area Height
1 18.388 52465734 51.62 829464
2 26.088 49168183 48.38 565215

Figure 7

As cyclisation of α-diazo-β-oxo sulfone **54** using $CuCl_2$-NaBARF-(4*R*)-Ph **20** catalyst system resulted in the formation of *trans* sulfolane **165b** with the best enantiopurity, material from this reaction was chosen to be used in the determination of the absolute stereochemistry of **165b**. The crude reaction consisted of predominately the *cis* isomer **165a** which after chromatography on silica gel epimerised to give predominately *trans* sulfolane **165b**, which was subsequently converted to give carboxylic acid **170b** as a white solid using a hydrolysis reaction. On slow recrystallisation from IPA of carboxylic acid **170b** a crystalline white solid suitable for X-ray crystal structure analysis was obtained and gave rise to the crystal structure shown in with an absolute stereochemistry of (2*R*,3*R*). The single crystal was dissolved in IPA and reinjected on the chiral column (**Figure 8**).

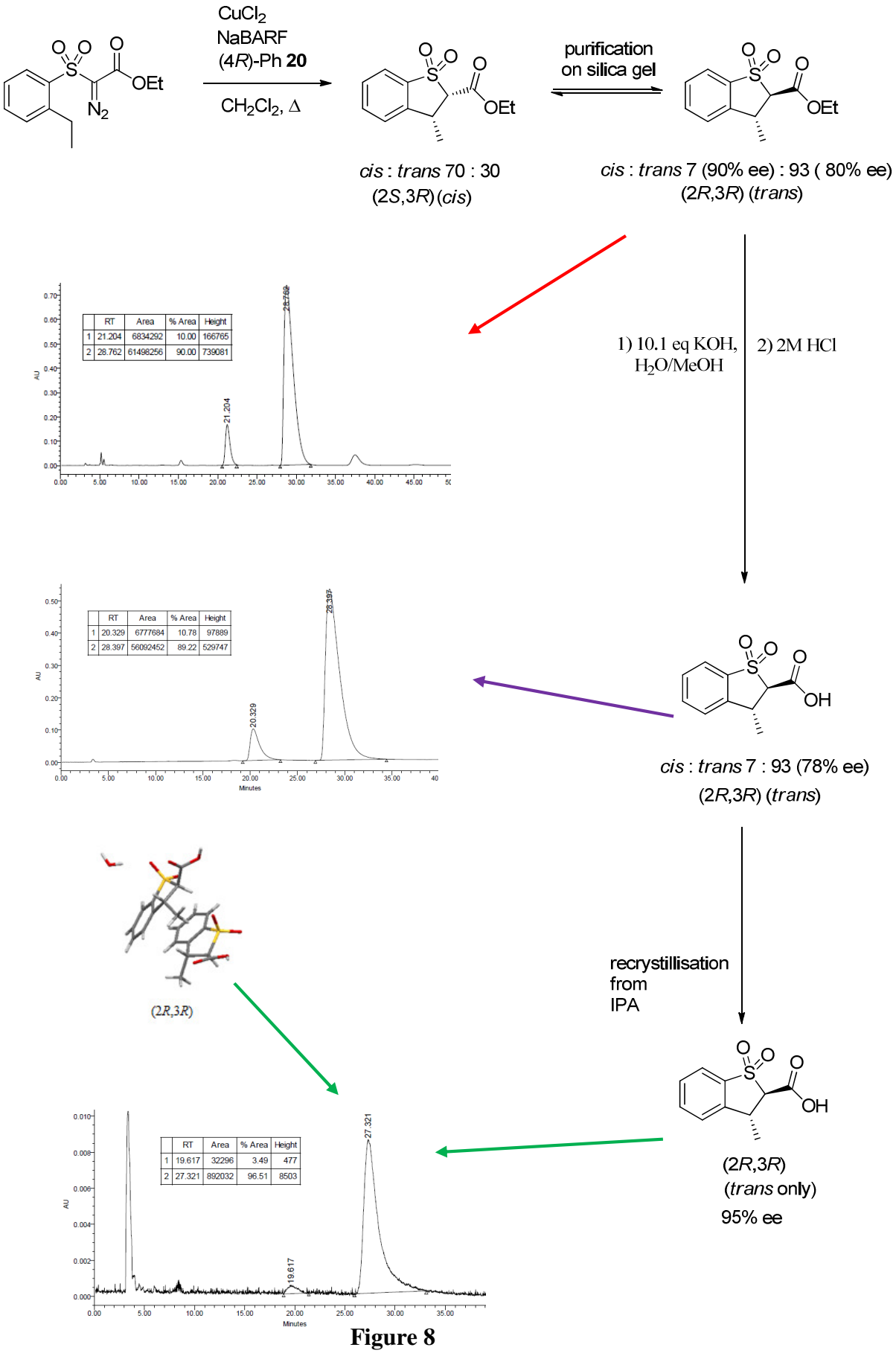
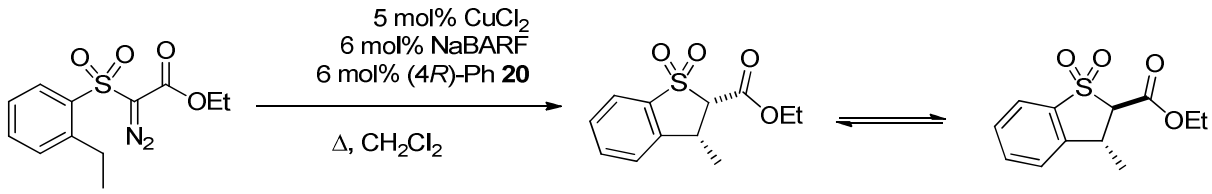

CuCl2
NaBARF
(4R)-Ph 20
CH2Cl2, Δ
purification on silica gel
cis : trans 70 : 30
(2S,3R) (cis)
cis : trans 7 (90% ee) : 93 (80% ee)
(2R,3R) (trans)
1) 10.1 eq KOH, H2O/MeOH
2) 2M HCl
cis : trans 7 : 93 (78% ee)
(2R,3R) (trans)
recrystillisation from IPA
(2R,3R)
(trans only)
95% ee
(2R,3R)
RT Area % Area Height
1 21.204 6834292 10.00 166765
2 28.762 61498256 90.00 739081
RT Area % Area Height
1 20.329 6777684 10.78 97889
2 28.397 56092452 89.22 529747
RT Area % Area Height
1 19.617 32296 3.49 477
2 27.321 892032 96.51 8503
AU
Minutes

Figure 8

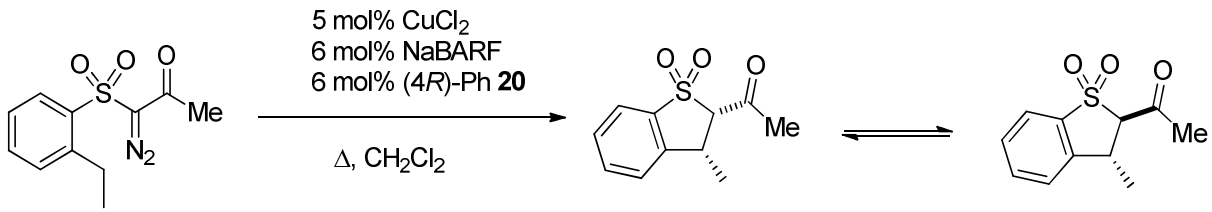
The absolute stereochemistry of the remaining *trans* sulfolanes **166b** and **167b** were assigned by analogy on the basis of optical rotations **Figure 9**.



165b (2*R*,3*R*) by X-ray

7 : 93 *cis* : *trans*, 80% ee *trans*

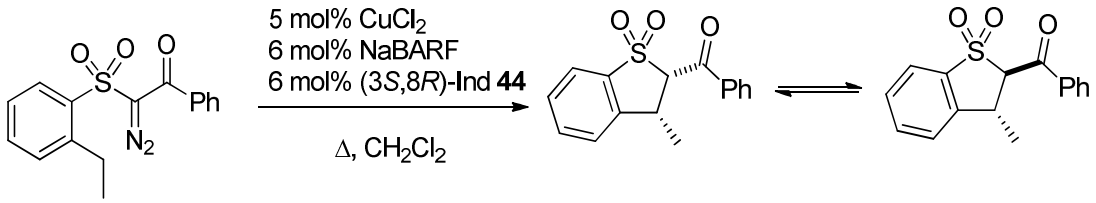
$[\alpha]_D^{20}$ −29.0 (*c*, 1.0 CH_2Cl_2)



166b (2*R*,3*R*)

2 : 98 *cis* : *trans,* 64 % ee *trans*

$[\alpha]_D^{20}$ −2.0 (*c*, 0.1 CH_2Cl_2).



167b (2*S*,3*S*)

7 : 93 *cis* : *trans,* 13 % ee *trans*

$[\alpha]_D^{20}$ +16.0 (*c*, 0.1 CH_2Cl_2).

Figure 9

The absolute stereochemistry was not directly determined for this series as all compounds obtained were oils, making structural determination by X-ray crystallography impossible. However, Ring obtained a crystal structure for a similar substrate **211b** and determined the absolute stereochemistry to be (3*S*,4*R*) when (3*R*,8*S*)-Ind **161** ligand was employed.[3] Therefore, the absolute stereochemistry of **208b** was assigned by analogy as (3*S*,4*R*) when (3*S*,8*R*)-Ind **44** ligand was employed. Additional evidence that supports that both α-diazocarbonyl compounds proceed through similar transition states comes from the optical rotation data of ɣ-lactam **211b** and **208b**; employing (3*R*,8*S*)-Ind **161** results in ɣ-lactam **211b** having a negative specific rotation $[\alpha]_D^{20}$ −9.5 (*c* 0.11, $CHCl_3$, 66% ee) and using (3*S*,8*R*)-Ind **44** leads to ɣ-lactam **208b** having a positive specific rotation $[\alpha]_D^{20}$ +41.11 (*c* 0.09, CH_2Cl_2, 82% ee). By comparing rotation data for **208b**, **209b** and **210b** and the order of elution of enantiomers of **210b** and **209b** on the HPLC, depending on the ligand employed, the absolute stereochemistry of **210b** and **209b** was assigned by analogy to **208b** (**Figure 10**).

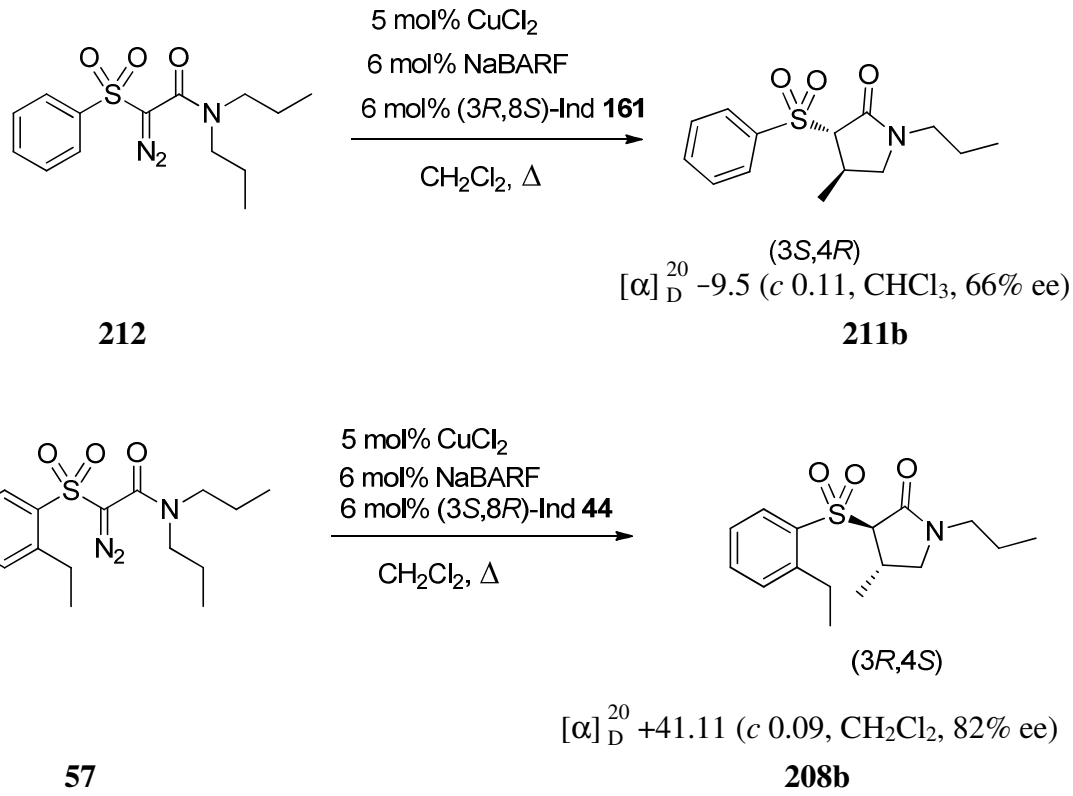


Figure 10

Determination of the absolute stereochemistry of cyclopropanes

The absolute stereochemistry of **259a** was determined as follows; α-diazo-β-oxo sulfone **60** was cyclised using rhodium acetate as a catalyst, yielding a racemic sample of cyclopropane **259a**. Chiral HPLC condition were developed for the separation of both of the enantiomers of **259a** (**Figure 11**).

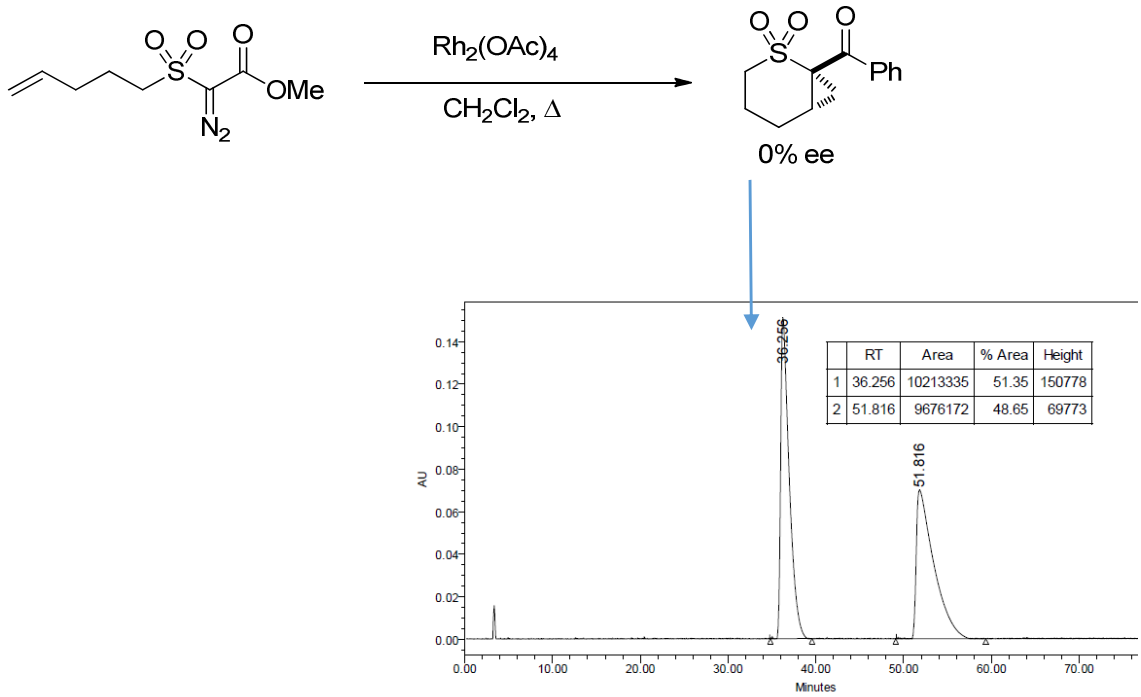
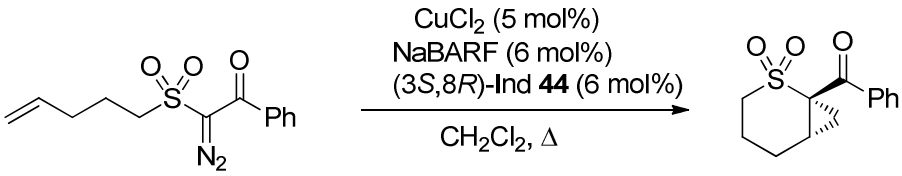


Figure 11

Cyclisation of α-diazo-β-oxo sulfone **60** using $CuCl_2$-NaBARF-(3*S*,8*R*)-Ind **44** as catalyst yielded **259a** with 80% ee (**Figure 12**).



60 **259a**

Determined using X-ray crystallography

80% ee $[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH_2Cl_2)

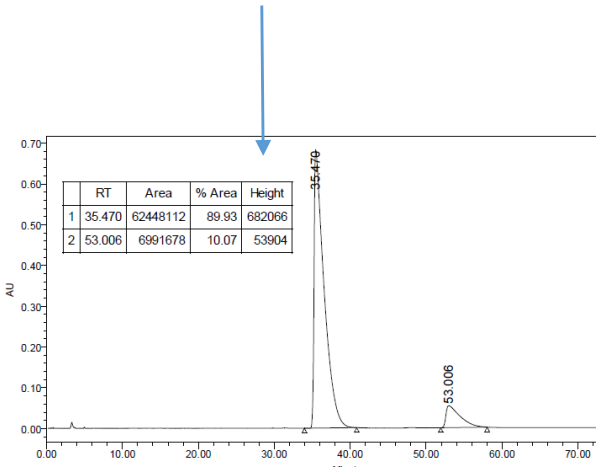


Figure 12

A sample of **259a** obtained from this reaction was recrystallised from IPA. A crystal structure was obtained using X-ray analysis and showed the major enantiomer to be (1*R*,6*S*), which was confirmed by dissolving the crystal in IPA and analysing it using HPLC (**Figure 13**).

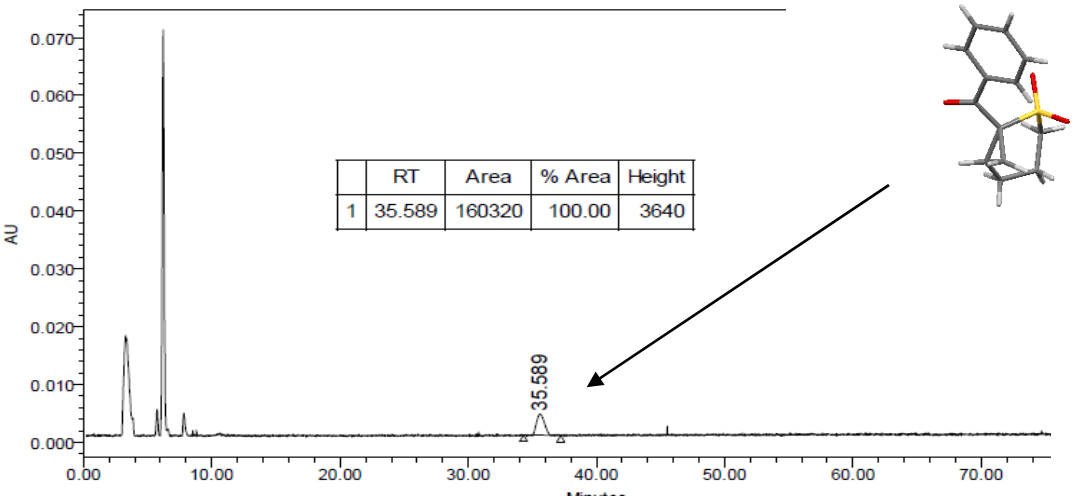
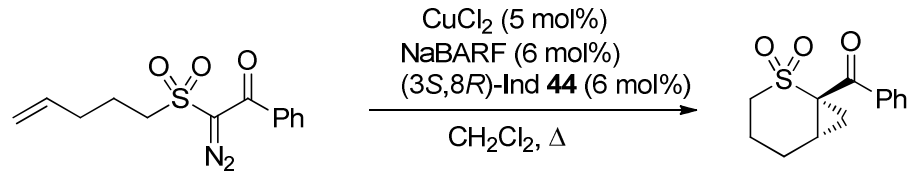


Figure 13

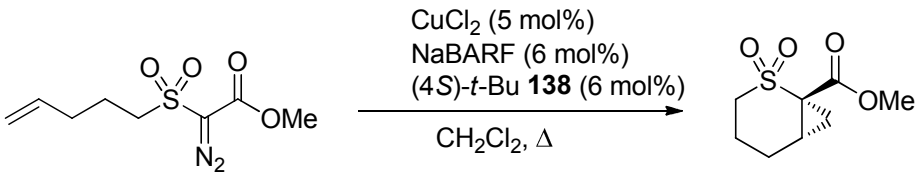
The absolute stereochemistry of **257a** was assigned by analogy for this series. The absolute stereochemistry of phenyl ketone cyclopropane **259a** was determined using X-ray crystallography. To ensure the correct assignment, the single crystal was dissolved in IPA and injected onto a chiral HPLC column. The absolute stereochemistry for this compound, generated using (3*S*,8*R*)-Ind **44** as a ligand, was determined to be (1*R*,6S) and the rotation of this sample was positive $[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH_2Cl_2) (**Figure 14**). In comparison with the methyl ester series **257a**, a positive rotation was also obtained when (4*S*)-*t*-Bu **138** was employed as a ligand and a negative rotation was obtained through use of (4*R*)-Bn **43**.



60 **259a**

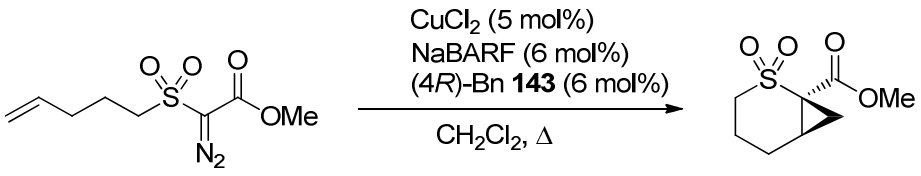
Determined using X-ray crystallography

$[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH_2Cl_2).



59 **257a**

$[\alpha]_D^{20}$ +15.7 (*c* 0.15, CH_2Cl_2).



59 **257a**

$[\alpha]_D^{20}$ -13.0 (*c* 0.1, CH_2Cl_2).

Figure 14

Appendix iii *Representative ^1H NMR spectra*

Throughout the course of this work, a number of heterocycles and carbocycles were synthesised. These included, *cis* thiopyrans, *trans* sulfolanes, ɣ-lactams, β-lactams and cyclopropanes. The majority of these compounds were novel and were fully characterised. The ^{1}H NMR spectra of a selection of these compounds is given in this Appendix.

***trans* sulfolanes**

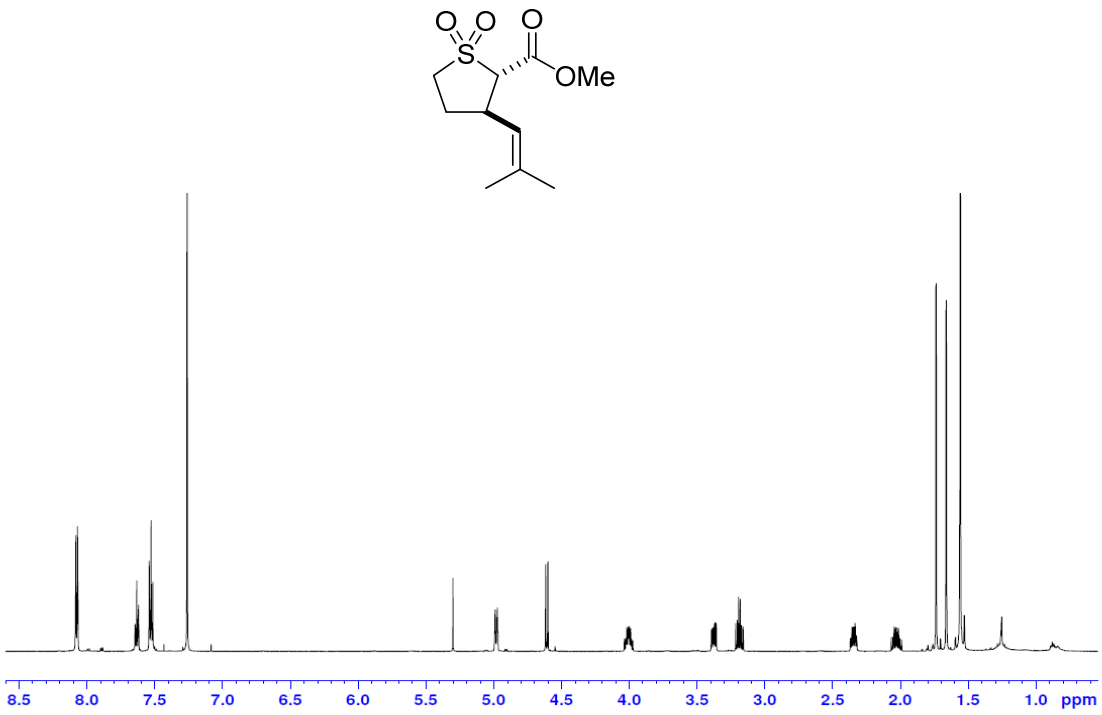


Figure 15 *^1H NMR spectrum of **236b** recorded in ($CDCl_3$, 600 MHz)*

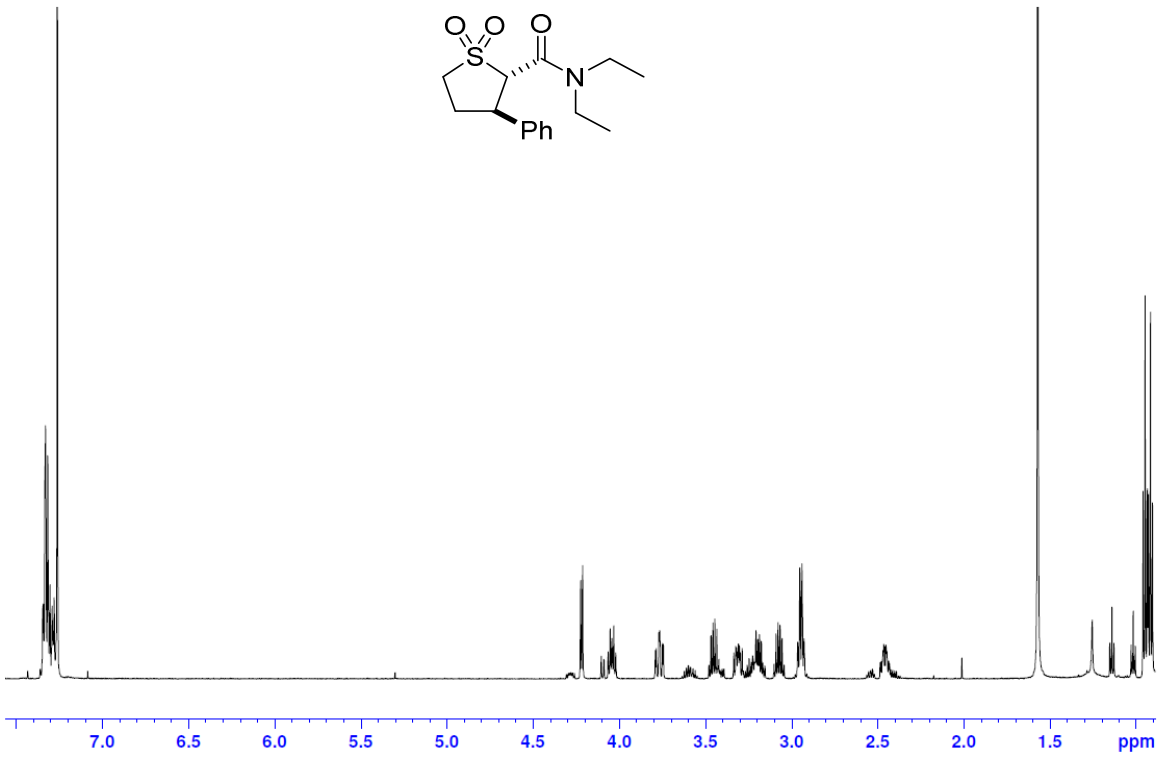


Figure 16 *^{1}H NMR spectrum of **218b** recorded in ($CDCl_3$, 600 MHz)*

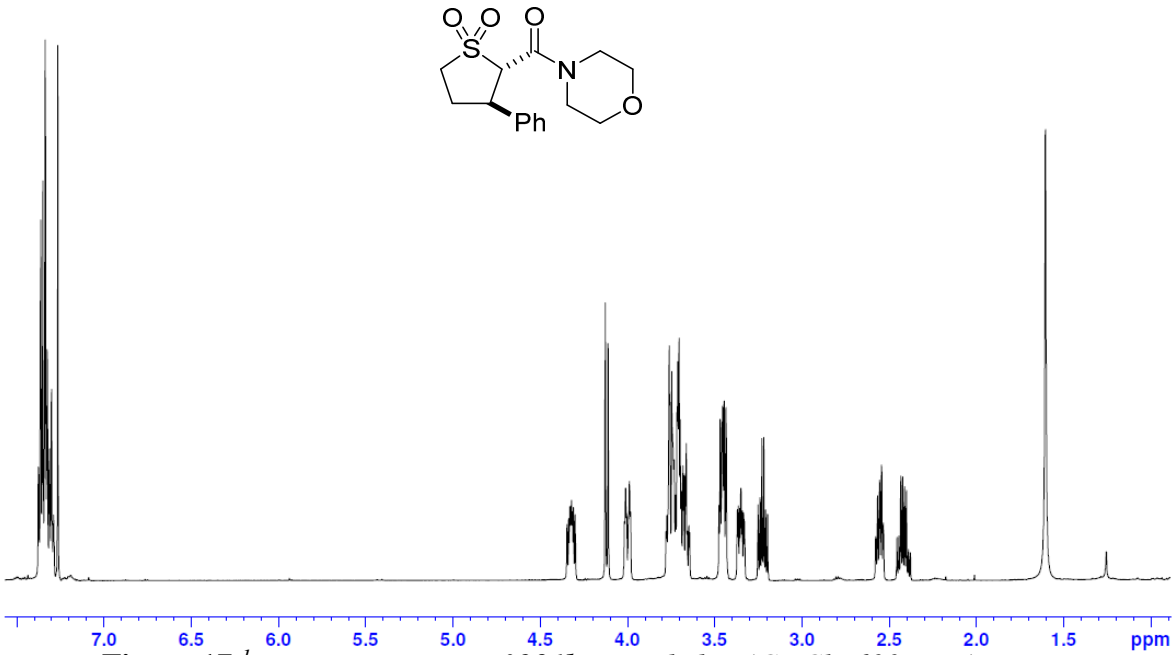


Figure 17 *^{1}H NMR spectrum of **231b** recorded in ($CDCl_3$, 600 MHz)*

***cis* thiopyrans**

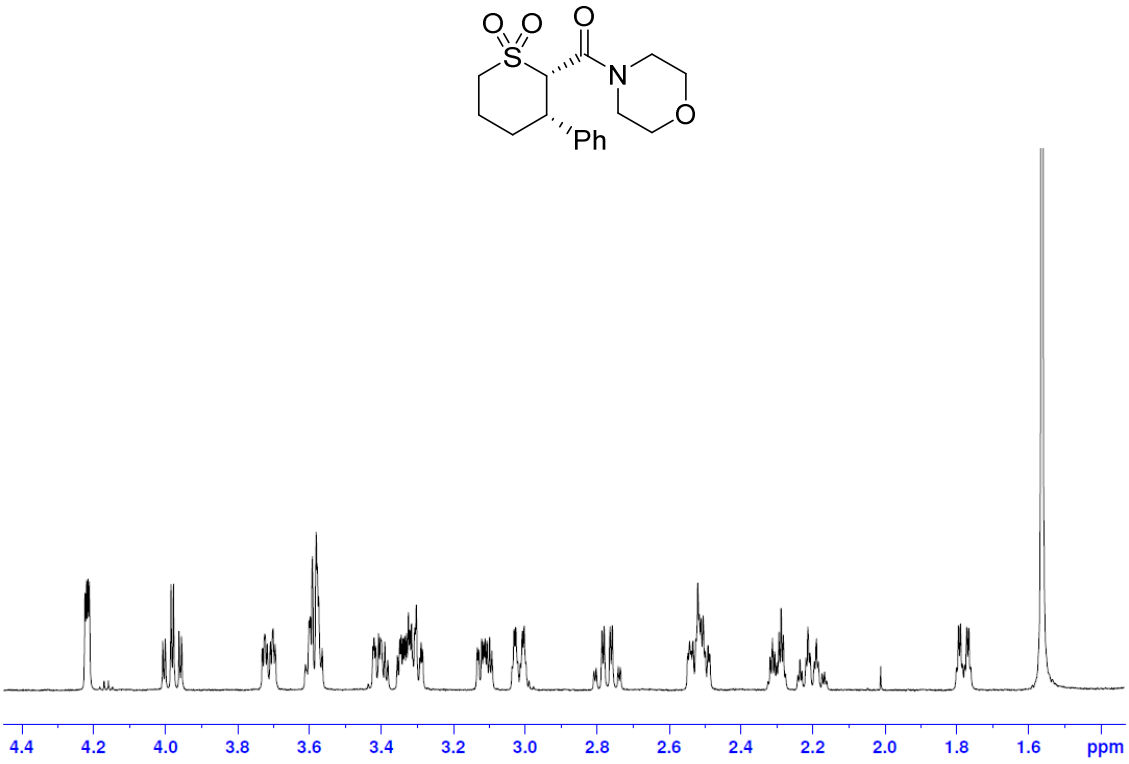


Figure 18 *^{1}H NMR spectrum of* ***224a*** *recorded in* ($CDCl_3$, *600 MHz*)

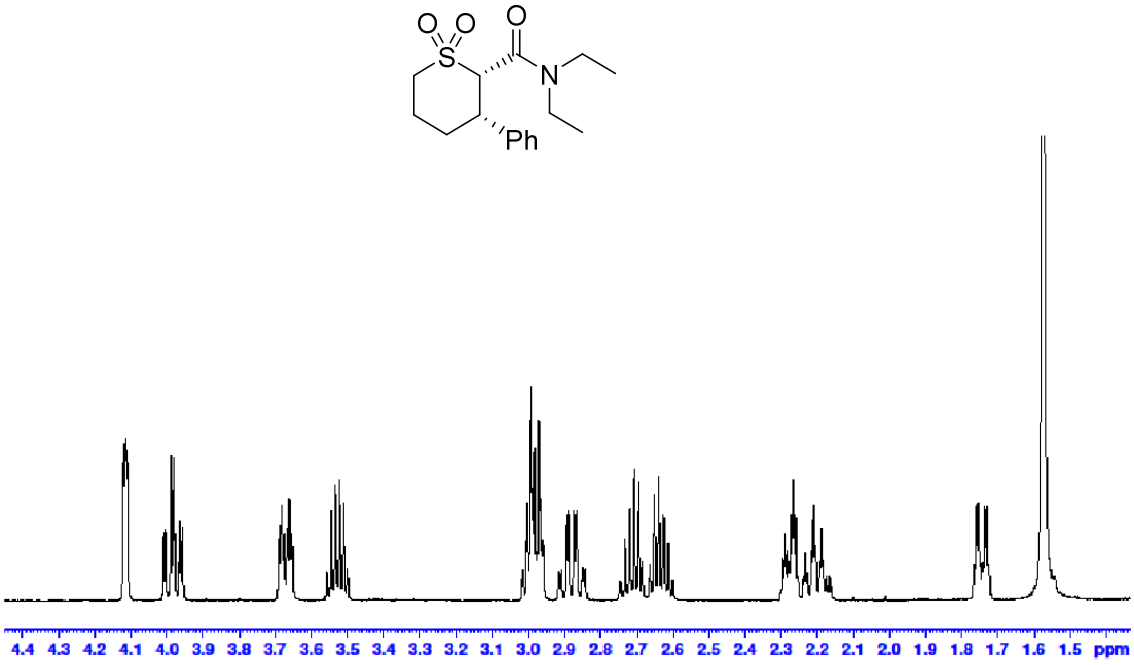


Figure 19 *^{1}H NMR spectrum of* ***220a*** *recorded in* ($CDCl_3$, *600 MHz*)

ɣ-lactams

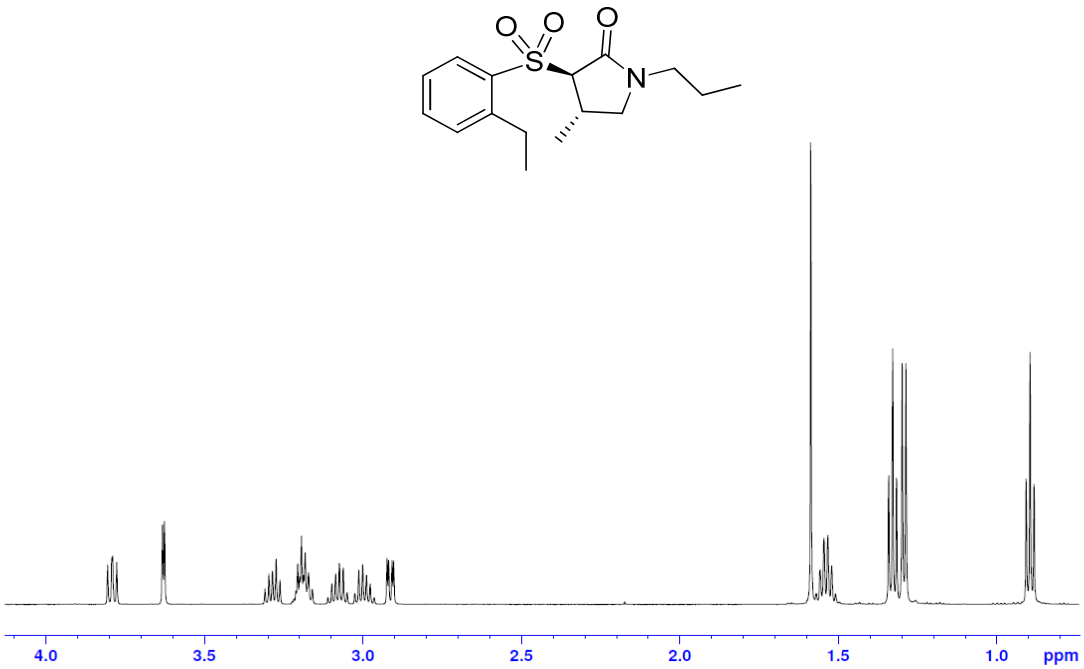


Figure 20 *^{1}H NMR spectrum of **208b** recorded in ($CDCl_3$, 600 MHz)*

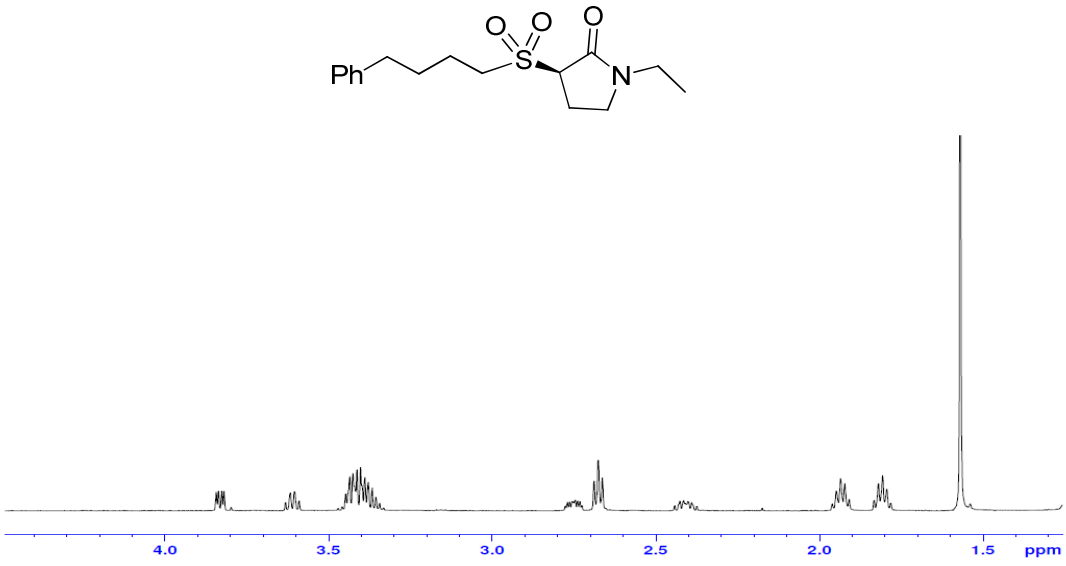
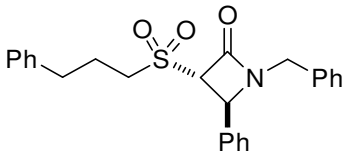


Figure 21 *^{1}H NMR spectrum of **219** recorded in ($CDCl_3$, 600 MHz)*



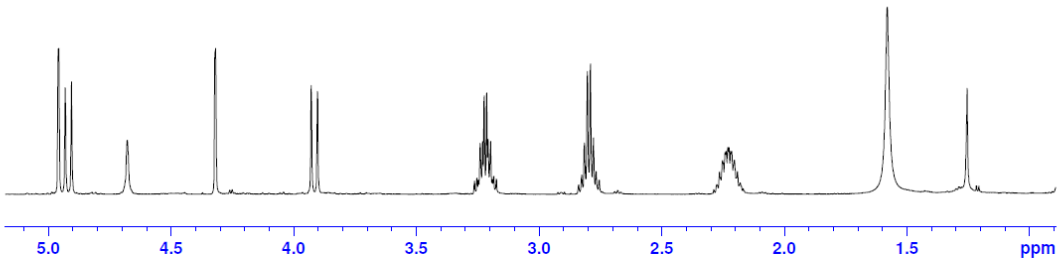


Figure 22 *^{1}H NMR spectrum of **226b** recorded in ($CDCl_3$, 600 MHz)*

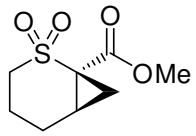


Figure 23 *^{1}H NMR spectrum of **257a** recorded in ($CDCl_3$, 400 MHz)*

Fused sulfolanes

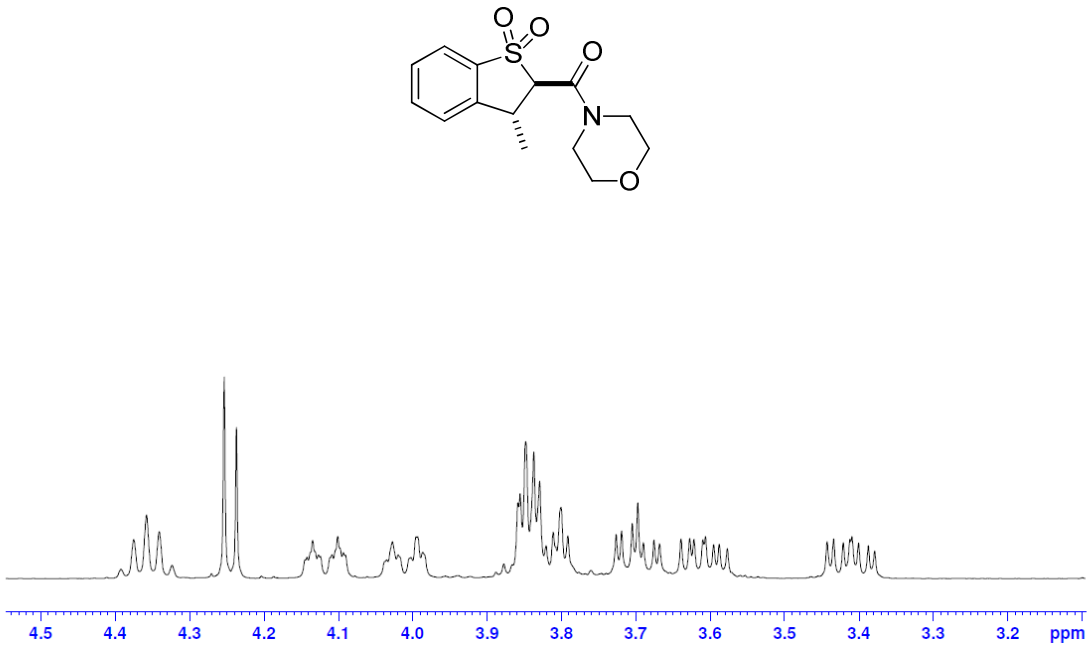


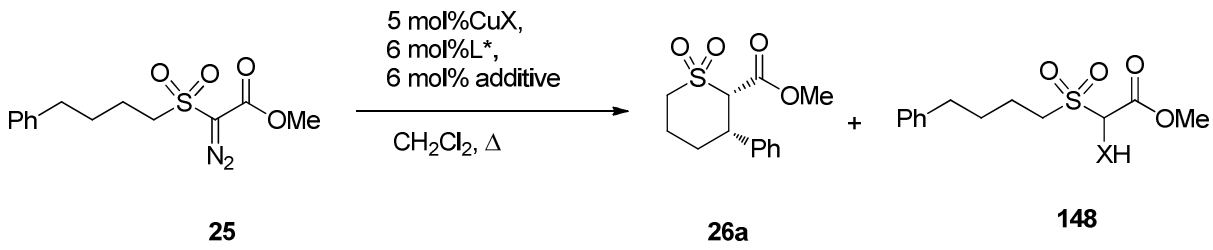
Figure 24 *^{1}H NMR spectrum of **233b** recorded in ($CDCl_3$, 400 MHz)*

Appendix iv *^{1}H NMR spectra of byproducts*

A number of identified and unidentified byproducts were observed throughout the course of this work. These byproducts were seen in either the ^{1}H NMR spectra of the crude product mixtures were isolated after chromatography. In the latter case these byproducts were isolated either as mixed fractions containing addition material or as an individual compound. This Appendix contains the ^{1}H NMR spectra of a number of these byproducts.

Chapter 4

Throughout this thesis, the formation of an X–H insertion product has been discussed. In certain instances, it was isolated after purification by column chromatography. In other cases, the presence of signals in the ^{1}H NMR spectra of the crude products, consistent with X–H insertion product, were observed. The identity of these X–H insertion products has not been confirmed. A number of possible structure have been put forward; the most likely product is now thought to be a chloride abstraction product. A notable example of the formation of this product was seen in the $CuCl_2$-NaBARF-bisoxazoline catalysed reactions of **25**; the formation of *cis* thiopyran **26a** was the major C–H insertion product, with X–H insertion **148** also forming on occasion. A COSY spectrum of purified **148** is shown in **Figure 25**.



25 **26a** **148**

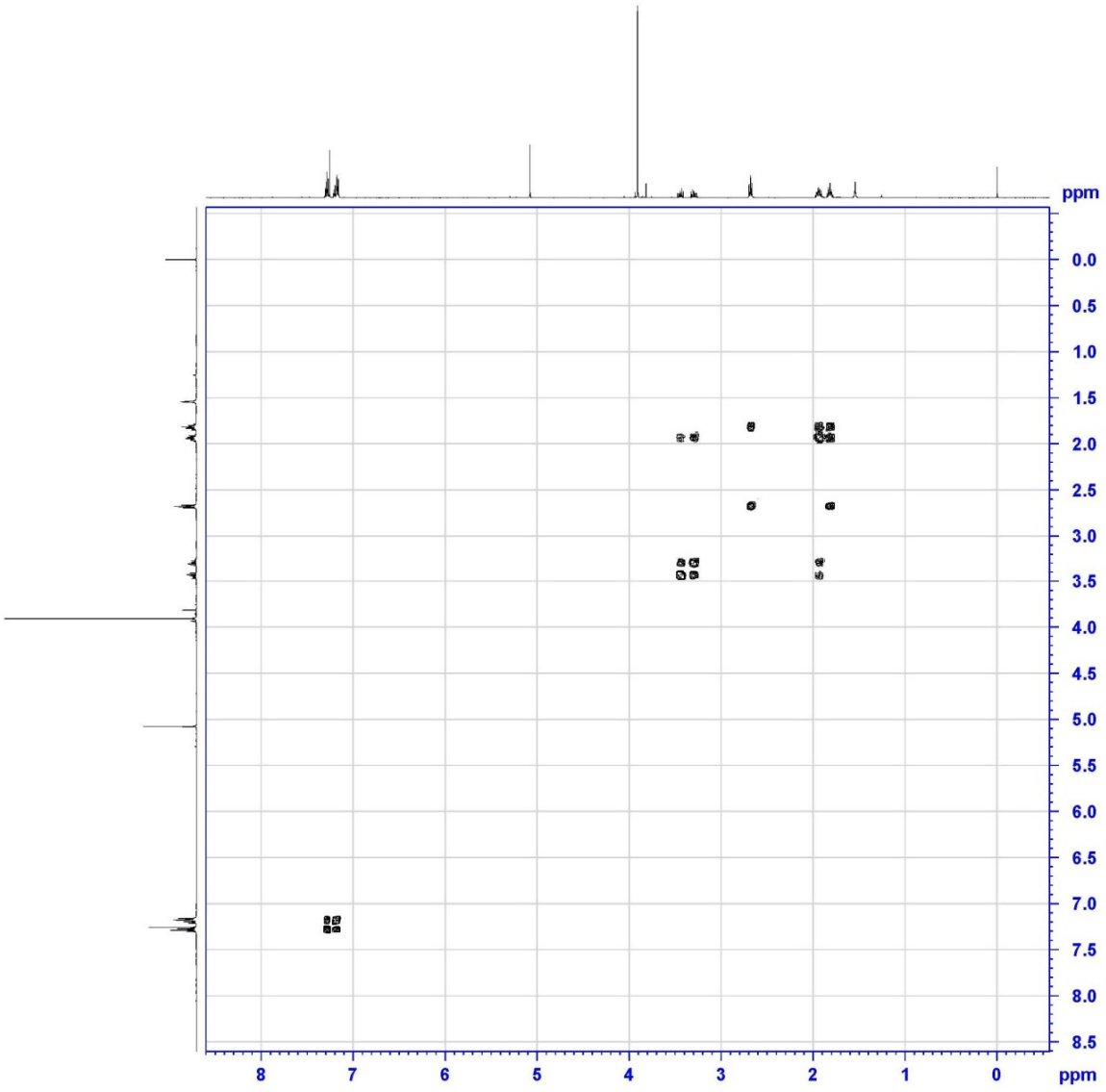
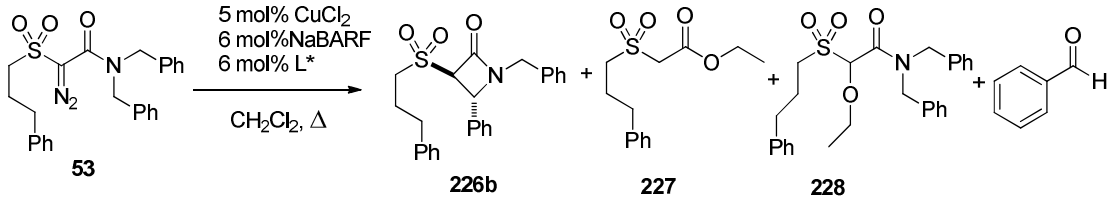
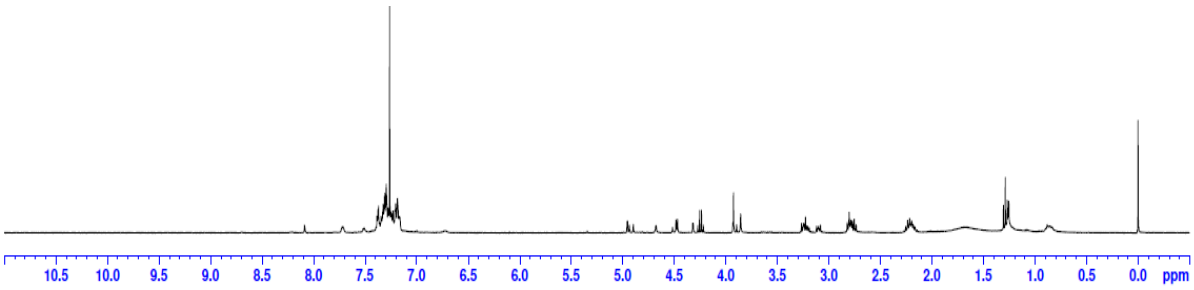


Figure 25 *Two dimensional NMR (COSY) of unidentified byproduct **148** ($CDCl_3$,*500 MHz)

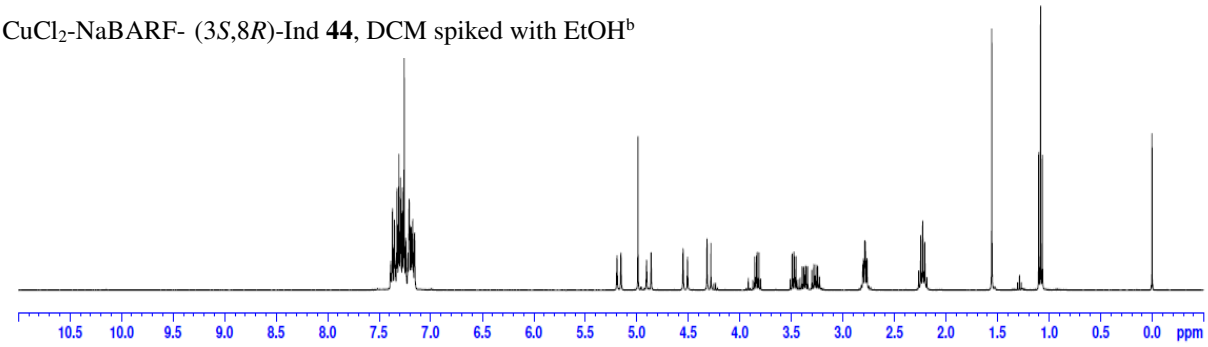
In the $CuCl_2$-NaBARF-bisoxazoline and $Rh_2(OAc)_4$ catalysed reactions of **53** the only identifiable C–H insertion product was β-lactam **226b**. However, a number of byproducts were also observed. Two of these byproducts **227** and **228** formed in the presence of adventitious ethanol. In addition, benzaldehyde was seen in the ^{1}H NMR spectra of the majority of the crude product mixtures. Herein, the ^{1}H NMR spectra of the crude product mixture of these cyclisations are presented.



$CuCl_2$-NaBARF- (3*S*,8*R*)-Ind **44**, adventitious EtOH in DCM[a]



$CuCl_2$-NaBARF- (3*S*,8*R*)-Ind **44**, DCM spiked with EtOH[b]



$CuCl_2$-NaBARF- (3*S*,8*R*)-Ind **44**, HPLC grade DCM[a]

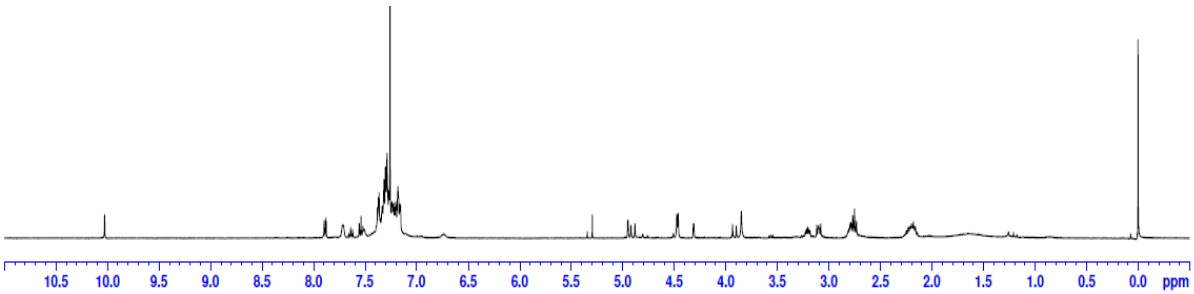


Figure 26 *^{1}H NMR spectra ($CDCl_3$, 400 MHz), (a of crude product, b of purified product)*

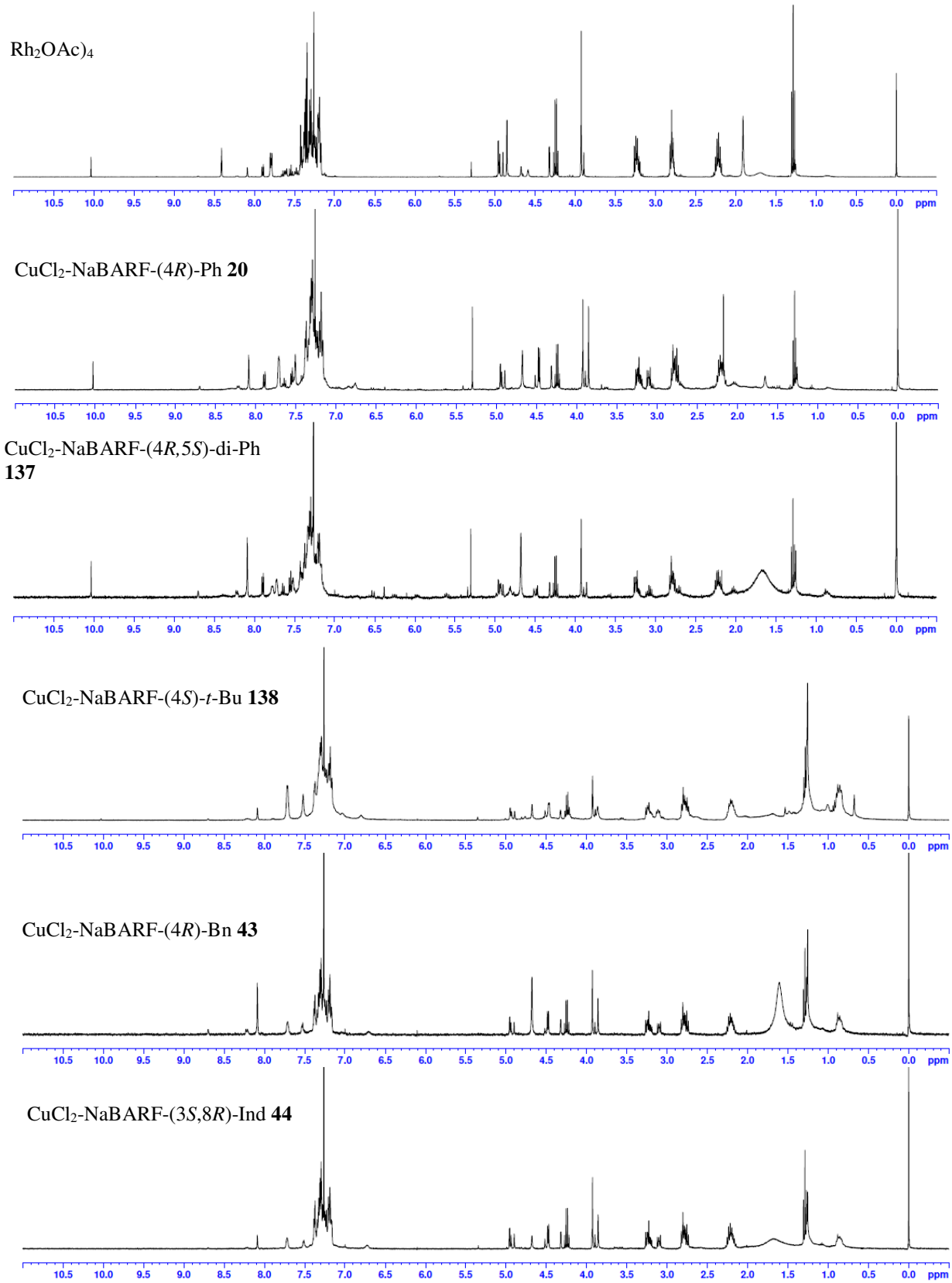


Figure 27 (*$CDCl_3$, 400 MHz)*

Chapter 7

In the $CuCl_2$-NaBARF-bisoxazoline and $Rh_2(OAc)_4$ catalysed reactions of **61**, C–H insertion products **263a** and **263b** were the main reaction products. However, an additional product was also observed, unknown byproduct **264**. A ^1H NMR spectrum of a mixture of byproduct **28b** and **263b** is illustrated in **Figure 28**.

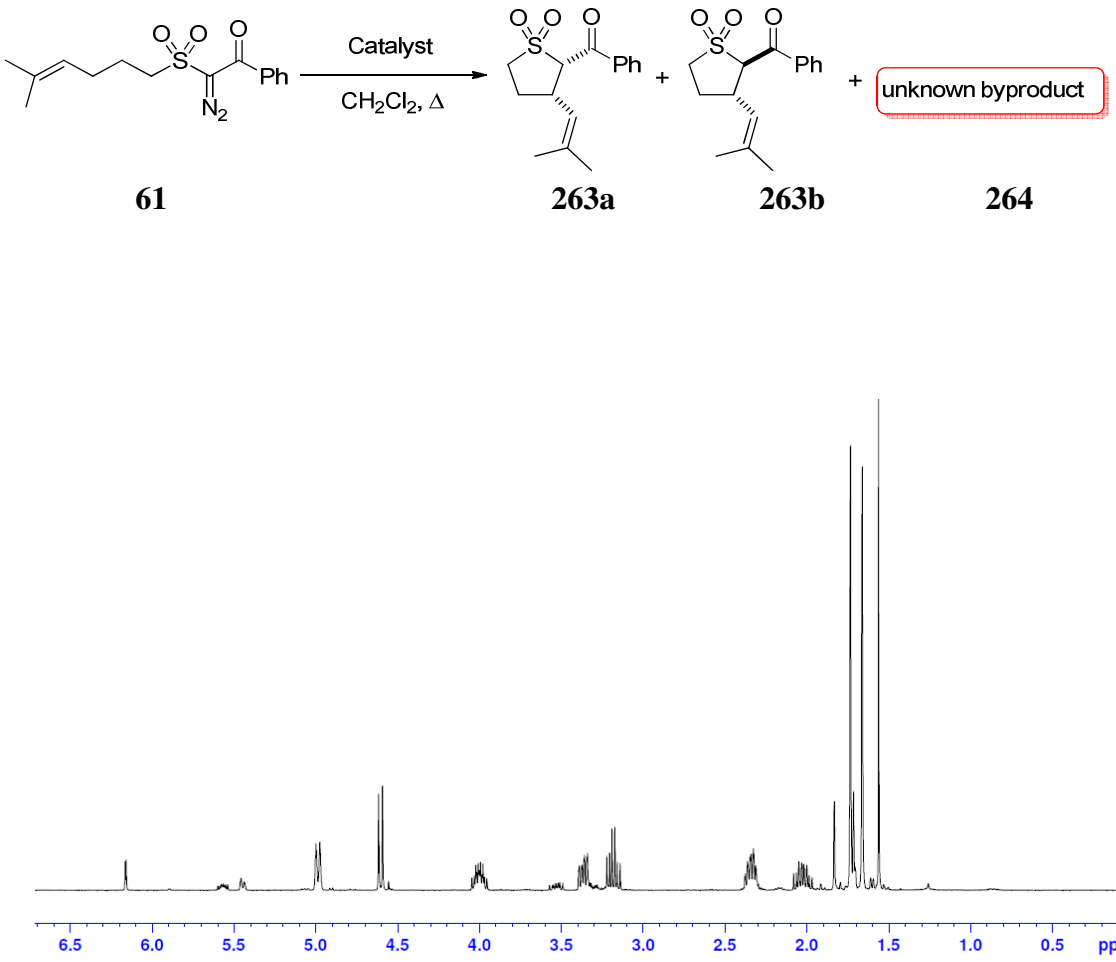
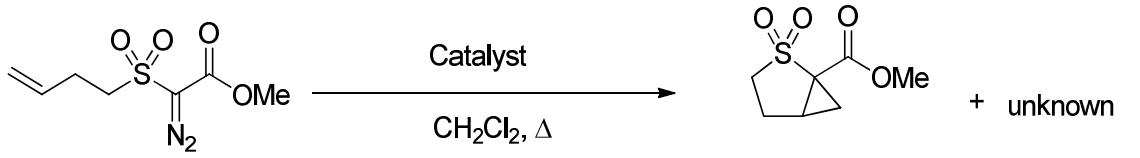


Figure 28 *^1H NMR spectra ($CDCl_3$, 400 MHz)*

In the $CuCl_2$-NaBARF-bisoxazoline and $Rh_2(OAc)_4$ catalysed reactions of **63**, cyclopropane **270** was the main reaction product. However, an additional product was also observed, unknown byproduct **271**. A ^1H NMR spectrum of a mixture of byproduct **271** and **270a** is illustrated in **Figure 29**.



63 **270a**

271

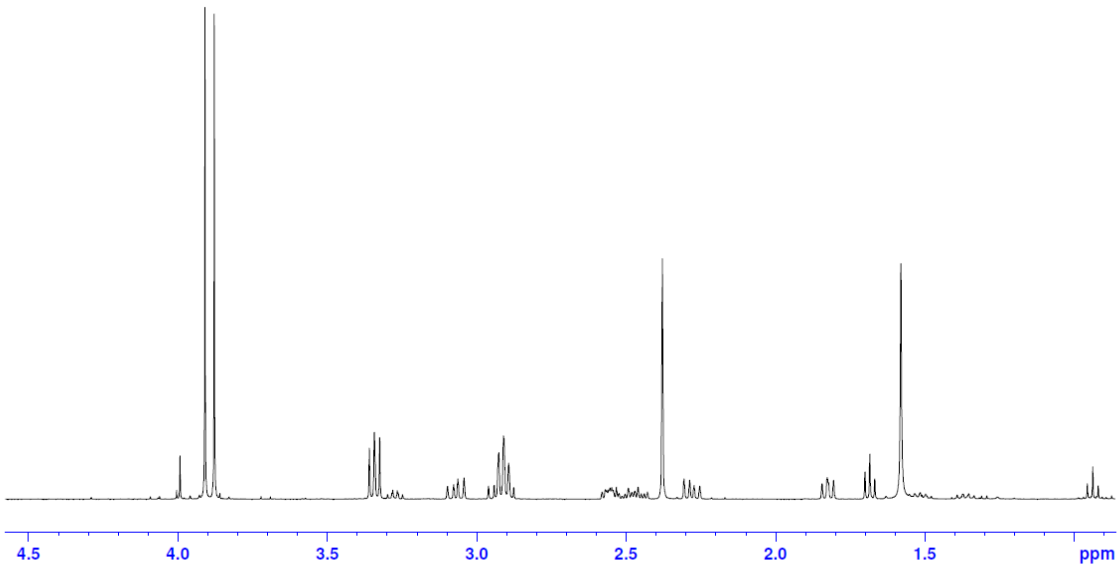


Figure 29 *^1H NMR spectra ($CDCl_3$, 400 MHz)*

Appendix V *Abbreviations*

Abbreviations	
p-ABSA	*para* acetamidobenzenesulfonyl azide
Ar	aryl
Bu	butyl
BuLi	butyl lithium
Bn	benzyl
Bp	boiling point
br s	broad singlet
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dddd	doublet of doublets of doublets of doublets
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCE	dichloroethane
DEPT	distortionless enhancement of polarisation transfer
ee	enantiomeric excess
equiv or eq	equivalents
Ether	diethyl ether
EtOH	ethanol
Eu(hfc)	*tris*-[3-Heptafluoropropyl-hydroxymethylene-(+)-camphorato] europium(III) derivative
Fr	fraction
g	gram
h	hour
HETCOR	Heteronuclear chemical shift correlation
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	hertz
IPA	isopropyl alcohol
i-Pr	isopropyl
IR	Infrared
Lit.	literature
m	mutiplet
min	minute
mand	mandelate
MeOH	Methanol
Mg	Milligram
MHz	Megahertz
ml	millilitre
mmol	millimole
mol	Mole
m.p.	Melting point
NaBARF	sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate
p-NBSA	*para* nitrobenzenesulfonylazide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect Spectroscopy
OAc	Acetate
pfb	perfluorobutyrate
Ph	phenyl
q	quartet

r.t.	room temperature
s	singlet
sym	symmetrical
t	triplet
T	Time
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Oct	octyl

$Rh_2(acam)_4$	rhodium acetamide
$Rh_2(S\text{-BSP})_4$	rhodium *N*-benzenesulfonylprolinate
$Rh_2(4S,2'S\text{-BSPIM})_4$	rhodium *N*-benzenesulfonylprolinoylimidazolidinone
$Rh_2(cap)_4$	rhodium caprolactam
$Rh_2(S\text{-DOSP})_4$	rhodium *N*-dodecylbenzenesulfonylprolinate
$Rh_2(OAc)_4$	rhodium acetate
$Rh_2(Ooct)_4$	rhodium octanoate
$Rh_2(pfb)_4$	rhodium perfluorobutyrate
$Rh_2(4S\text{-MACIM})_4$	rhodium methylesteracetylimidazolidinone
$Rh_2(S\text{-mand})_4$	rhodium mandelate
$Rh_2(4S,2'S,3'S\text{-MCPIM})_4$	rhodium methylestercyclopropylimidazolidinone
$Rh_2(S\text{-MEOX})_4$	rhodium methylesteroxazolidinone
$Rh_2(S\text{-MEPY})_4$	rhodium methylesterpyrrolidinone
$Rh_2(S\text{-MPPIM})_4$	rhodium methylesterphenylpropanoylimidazolidinone
$Rh_2(S\text{-PTPA})_4$	rhodium phthaloylphenylalanine
$Rh_2(S\text{-PTTL})_4$	rhodium phthaloyl-*t*-leucine
$Rh_2(S\text{-TBSP})_4$	rhodium *N*-*t*-butylbenzenesulfonylprolinate
$Rh_2(tfa)_4$	rhodium trifluoroacetate
$Rh_2(tfacm)_4$	rhodium trifluoroacetamide
$Rh_2(TPA)_4$	rhodium triphenylacetate

Appendix VI *Publications*

Enantioselective copper catalysed C–H insertion reaction of 2-sulfonyl-2-diazoacetamides to form γ-lactams

Leslie-Ann Clarke, Aoife Ring, Alan Ford, Abhijeet S. Sinha, Simon E. Lawrence, Anita R. Maguire
Organic & Biomolecular Chemistry, **2014**, *12*, 7612–28

Catalyst, additive and counterion effects on the efficiency and enantioselectivity of copper-catalysed C–H insertion reactions of α-diazosulfones

Catherine N. Slattery, Leslie-Ann Clarke, Alan Ford, Anita R. Maguire
Tetrahedron, **2013**, *69*, 1297–1301

Investigation of additive effects in enantioselective copper-catalysed C–H insewrtion reaction and aromatic addition reactions of α-diazocarbonyl compounds

Catherine N. Slattery, Leslie-Ann Clarke, Shane O'Neill, Aoife Ring, Alan Ford, Anita R. Maguire
Synlett, **2012**, 23, 765–767

Substrate and Catalyst effects in the enantioselective copper mediated C–H insertion of α-diazo-β-oxo sulfones

Leslie-Ann Clarke, Christopher J. Flynn, Alan Ford, Abhijeet S. Sinha, Simon E. Lawrence, Anita R. Maguire
Manuscript in preparation.

References

1) Flynn, C. J.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. *J. Am. Chem. Soc.* **2010**, *132*, 1184–1185.
2) Flynn, C. J. Ph.D Thesis, National University of Ireland, Cork, 2011.
3) Ring, A. PhD Thesis, National University of Ireland, Cork, thesis in progress, 2015.