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University College Cork, Ireland Coláiste na hOllscoile Corcaigh

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

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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 γ -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 a-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 one electron withdrawing group and one electron donating group (acceptor-donor) (**Figure 1.2**).⁴



Figure 1.2⁴

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 *p*-tolylsulfonyldiazomethane of will be discussed. А 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 1.1²⁰

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**).



Scheme 1.2

Class A type α -diazocarbonyl compounds may also be synthesised from **Class B** type **1.1**.²² А substrates demonstrated in Table number of 1-diazo-1as (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- α-		Yield (%)
		diazosulfone	diazosulfone	
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, K₂CO₃, NEt₃ 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.

		diazo tr	ansfer	reage	nt Q → R´	$S = R^1$	
starting material (SM)			se vent Iperatu	ıre	prod	N ₂ uct material (PM)	
Entry	R	R ¹	SM	PM	Diazo	Base/Solvent/	Yield
					transfer	Temp	(%)
127,28	Ph(CH ₂) ₃	Me	12	13	<i>p</i> -tosyl azide	K ₂ CO ₃ /CH ₃ CN/	62
						0 °C–rt	
227,28	Ph(CH ₂) ₄	OMe	14	15	<i>p</i> -tosyl azide	K ₂ CO ₃ /CH ₃ CN/	94
						0 °C–rt	
329	Me	(CH ₂) ₃ CH ₃	16	17	<i>p</i> -tosyl azide	K ₂ CO ₃ /CH ₃ CN/	86
						0 °C–rt	
429	Ph	(CH ₂) ₄ Ph	18	19	<i>p</i> -tosyl azide	K ₂ CO ₃ /CH ₃ CN/	87
						0 °C–rt	
5 ³⁰	CH ₃ (CH ₂) ₄	OEt	20	21	<i>p</i> -NBSA	(<i>i</i> -Pr) ₂ NEt/CH ₃ CN/	70
						-10 °C-rt	
631	<i>i</i> -Pr(CH ₂) ₃ O	OEt	22	23	mesyl azide	DBU/THF/	98
						-45 °C-rt	
7 ³²	Ph	(CH ₂) ₂ CH=CH ₂	24	25	p-tosyl azide	NEt ₃ /CH ₃ CN/	85
						0 °C–rt	
833	Ph	N(CH2Ph)(CH2)2Ph	26	27	p-ABSA	DBU/CH ₃ CN/	85-
						0 °C–rt	90

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

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 Muñoz³⁴ involved the use of *p*-tosyl azide and K₂CO₃ 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*-Pr₂)NEt, NEt₃ 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



Phl(OAc)₂

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



Lastly, Du Bois and co-workers has demonstrated that phenyliodonium ylides can be generated in situ using PhI=O and Cs₂CO₃, 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 1.4³⁹

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



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 azide⁴¹ 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 reaction⁴³



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 ¹⁵N 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



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.



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).



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% Rh₂(OAc)₄. 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



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.





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 Morehead⁶² 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 1.12⁶⁴

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 γ -lactone synthesis has been achieved⁶⁸ and values in excess of 95% ee have been reported in both β - and γ -lactam synthesis⁶⁹ (**Scheme 1.13**).



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 silver⁷³ 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.



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



Scheme 1.15⁷⁶

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 CuCl₂ 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-	L^*	cyclopentanone	Yield	% ee ^b
		diazosulfone			(%) ^a	
1	Ph	63	(4 <i>R</i>)-Bn 58	64 (2 <i>S</i> ,3 <i>S</i>)	62	82
2°	Ph	63	(4 <i>R</i>)-Bn 58	64 (2 <i>S</i> ,3 <i>S</i>)	40	8
3	Ph	63	(4 <i>R</i>)-Ph 59	64 (2 <i>S</i> ,3 <i>S</i>)	68	49
4	Ph	63	(4 <i>R</i> ,5 <i>S</i>)-di-Ph	64 (2 <i>S</i> ,3 <i>S</i>)	82	58
			60			
5	Ph	63	(4 <i>S</i>)- <i>t</i> -Bu 61	64 (2 <i>R</i> ,3 <i>R</i>)	55	64
6 ^d	Ph	63	(3 <i>S</i> ,8 <i>R</i>)-Ind 62	64 (2 <i>R</i> ,3 <i>R</i>)	87	89
7 ^e	Ph	63	(3 <i>S</i> ,8 <i>R</i>)-Ind 62	64 (2 <i>R</i> ,3 <i>R</i>)	59	91
8	Bn	19	(4 <i>R</i>)-Bn 58	65 (2 <i>S</i> ,3 <i>S</i>)	54	57
9	<i>i</i> -Pr	66	(4 <i>R</i>)-Bn 58	67 (2 <i>S</i> ,3 <i>S</i>)	95	60
10	Et	68	(4 <i>R</i>)-Bn 58	69 (2 <i>S</i> ,3 <i>R</i>)	70	62
11	Me	56	(4 <i>R</i>)-Bn 58	57 (2 <i>S</i> ,3 <i>R</i>)	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 CuCl₂, 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) >

(4R,5S)-di-Ph **60** (58% ee) > (4R)-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 (4R)-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 synthesis⁸³



Entry	EWG	α-	L*	cyclopentanone	Yield	ee
		diazocarbonyl			(%) ^a	(%) ^b
1	$CO_2CH(i-Pr)_2$	70	(4 <i>R</i>)-Bn 58	71 (+)	93	51
2	$CO_2CH(i-Pr)_2$	70	(3 <i>S</i> ,8 <i>R</i>)-Ind 62	71 (-)	89	65
3	$CO_2CH(i-Pr)_2$	70	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 60	71 (+)	53	61
4	PO(OMe) ₂	72	(4 <i>R</i>)-Bn 58	73 (-)	71	52
5	PO(OMe) ₂	72	(3 <i>S</i> ,8 <i>R</i>)-Ind 62	73 (+)	77	32
6	PO(OMe) ₂	72	(4 <i>R</i> ,5 <i>S</i>)-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 γ -lactams were of particular interest due to their biological importance.^{33,84} In a preliminary report by Jung and co-workers, γ -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.



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 γ -lactam **77** and **78** are formed, in comparison to the exclusive γ -lactam formation seen for phenylsulfonyl substrate **75** (**Scheme 1.16**).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 γ -lactam **81** exclusively (**Scheme 1.18**).⁸⁴


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



In subsequent reports by Jung, it was demonstrated that chiral γ -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 γ -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 *scis* 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}



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



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 sixmembered 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-\beta-oxo sulfones*⁸⁹



Entry	R ¹	R ²	R ³	catalyst	Temperature	Yield (%)	Yield
						thiopyran	(%)
							sulfolane
1	Me	Me	Me	Rh ₂ (pfb) ₄	reflux	Not	64
						detected	
2	Me	Н	Н	Rh ₂ (OAc) ₄	rt	65	9
3	Me	Н	Me	Rh ₂ (OAc) ₄	rt	40	24
4	Me	Н	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 Rh₂(*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). Rh₂(*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}



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

			Rh ₂ (L*) ₄	o o S		
		\bigvee_{N_2} OR	CH ₂ Cl ₂ ,rt		111	
Entry	R	α-	Catalyst	trans	Yield	de
		diazocarbonyl		thiopyran	(%)	(%)
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 Rh₂(*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-	δ -sultone	Yield
				diazocarbonyl		(%)
1 ³¹	Ph	Н	40 °C	97	98	85
2 ³¹	<i>i</i> -Pr	Н	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 -oxosulfones $sulfones^{27,78,79}$



Entry	R	R ¹	α-	thiopyran	Yield	ee (%)
			diazosulfone		(%)	
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 sulfones13 and 110



Entry	R	R ¹	a-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 αdiazosulfones⁹²



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- γ -sultams in moderate to excellent yields (up to 99%, **Table 1.14**, entry 1) *via* the Rh₂(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- γ -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* αdiazosulfonamides in the synthesis of benzo-γ-sultams⁹³



Entry	R	α-	benzo-y-	Yield (%) ^a
		diazosulfonamide	sultam	
1	Н	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 Rh₂(oct)₄ giving rise to the most efficient reaction and 1,2-dichloroethane (DCE) proving to be the best solvent, resulting in benzo- γ -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- γ -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 carbenoid employed, addition substituted was in establishing that high enantioselectivities could be achieved for this reaction when Rh₂(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

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



78 : 22 syn : anti

Scheme 1.26¹⁰³

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 1sulfonyl-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



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 Sloan¹¹⁰ 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 iminoidinane 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



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 Rh₂(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 1.30¹²⁵

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





a b

Entry	Catalyst	Product a	Product b
1	Rh ₂ (OAc) ₄	1	1.5
2	$Rh_2(O_2Ct-Bu)_4$	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 1.32¹²⁷

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-porphyrin¹²⁸ and ruthenium-imido¹²¹ 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}-NR¹ 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 Rh₂(*S*-nap)₄ as catalyst (**Scheme 1.33**).¹²⁹



Scheme 1.33¹²⁹

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*-CF₃ resulting in a modest 56% ee (**Table 1.16**, entry 3), highlighting the impact of electronic variation at the site of insertion.



Entry	R	α-	Product	Yield (%)	ee (%)
		diazosulfone			
1	Н	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 1.34¹²³

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.



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



Entry	R	Catalyst	Yield (%)	ee (%)
		mol%		
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 sixmembered 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 reactions⁴⁰



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



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



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

TpBr₃Cu(NCMe) was reported to successfully catalyse conversion of cyclohexane into N-(p-tolylsulfo-nyl)aminocyclohexane with PhINTs in a 65% yield (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



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



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 Rh₂(*S*-PTTL)₄, Rh₂(*S*-PTA)₄, Rh₂(*S*-PTV)₄ *etc*] revealed that Rh₂(*S*-PTTL)₄ was the most promising catalyst, resulting in enantioselectivities of up to 28% ee (**Table 1.19**, entry 1). Alteration of Rh₂(*S*-PTTL)₄ was subsequently made by replacing the four hydrogen atoms on the phthalimido group with electron withdrawing

groups. Replacing hydrogen with fluorine [Rh₂(*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 [Rh₂(*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 Rh₂(*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 catalysts¹³⁴



Entry	Catalyst	Temp	Time	Yield	ee (%)
		(°C)	(h)	(%)	
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





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



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 1.42¹²²

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 1.43¹³⁵

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 catalysts¹⁵⁷ 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 $Rh_2(4S-MEOX)_4$ has been employed in γ -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 Monteiro⁷⁵ 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}



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



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

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

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-	cyclo-	Temp	Time	Yield	ee (%)
				diazosulfone	propane		(h)	(%)	
1	Н	Η	Me	153	157	50 °C	2	90	98 (1 <i>R</i>)
2	Н	Н	Br	154	158	50 °C	2.5	63	98 (1 <i>S</i>)
3	Me	Me	Н	155	159	rt	5	84	92 (1 <i>R</i>)
4	Н	Н	CH ₂ OTr	156	160	rt,	3.5,	98	91 (1 <i>R</i>)
						50 °C,	13,		
						70 °C	7		

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

	Ν		n SO ₂ R	Cu(OTf) L* toluene	;	O RO ₂ S	H]	
Entry	R	R n α-		cyclo-	L	Temp	Time	Yield	ee
			diazosulfone	propane			(h)	(%)	(%)
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-diazosulfones167, 168



Entry	R	α -diazosulfone	cyclopropane	Yield	ee (%)
				(%)	
1	Н	167	169	95	96 (1 <i>R</i>)
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-diazosulfones171-176



Entry	Ar	α-diazosulfone	cyclopropane	Yield	ee (%)
				(%)	
1	real and rea	171	177	98	86
2	n n n n n n n n n n n n n n n n n n n	172	178	97	77
3	and the second s	173	179	95	69
4	n n n n n n n n n n n n n n n n n n n	174	180	82	91
5	non	175	181	82	91
6	A A A A A A A A A A A A A A A A A A A	176	182	91	62

Nakada and co-workers subsequently concentrated on substrates designed for sixmembered 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

 183-186¹⁶⁵



Entry	R	R ¹	L^*	SM	Temp	Time	Yield (%)	ee (%)	Yield (%)
						(h)	а	а	b and c (b : c)
1	Н	Ph	150	183	rt	2	58	92 (1 <i>R</i>)	19 (20 : 1)
2	Η	Ph	148	183	rt	14	41	89 (1 <i>R</i>)	14 (14 : 1)
3	Me	Ph	148	184	rt	2	62	93 (1 <i>R</i>)	15 (18 : 1)
4	Η	Mes	148	185	50 °C	16	31	98 (1 <i>R</i>)	17 (4 : 1)
5	Me	Mes	148	186	50 °C	4	43	98 (1 <i>R</i>)	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^tBu-ChenPhyrin)188 (3,5-Di^tBu-ZhuPhyrin)189 (2,6-DiMeO-ChenPhyrin)190 (2,6-DiMeO-ZhuPhyrin)Figure 1.7 (reproduced from reference²²)

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**



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

This catalyst system was further extended for reactions employing N₂CHMs and N₂CHNs 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 -diazosulfonesprecursors



Entry	R	L	X	Yield	trans : cis	%ee
				(%)		
1	Н	190	Ms	97	>99:1	96
2	Н	190	Ns	99	>99:1	90
3	<i>t</i> -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 1.8¹⁷⁵

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 $Cu(OTf)_2/(4S)$ -*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



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 1.53¹⁷⁹

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 1.54¹⁸⁰

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	Н	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 SESN3 ^{185,186,188,189}





SESN₃ = 2-(trimethylsilyl)ethanesulfonyl azide

Entry	\mathbf{R}^{1}	\mathbf{R}^2	R ³	Yield (%)	ee (%)
1	Н	Н	Н	99	>99
2	Н	Н	Cl	96	>99
3	Н	Cl	Н	96	>99
4	Cl	Н	Н	98	>99
5	Н	Н	OMe	92	>99
6	Н	OMe	Н	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 SESN3 ¹⁸⁷



Ar= 3,5-(CF₃)₂C₆H₃

Entry	R	catalyst	Yield (%)	ee (%)
		(mol%)		
1	Ph	0.5	99	90
2	p-ClC ₆ H ₄	1	96	90
3	<i>n</i> -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.



The synthesis of five-membered sulfone containing rings was achieved with enantioselectivities of up to 76% ee in the presence of $Rh_2(4S-MEOX)_4$ (**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 Rh₂(4S-MEOX)₄ catalysed intramolecular aziridination of 44, 198 and 199



Entry	R	Starting	Product	Yield	ee (%)
		material		(%)	
1	Н	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 Rh₂(4S-MEOX)₄ catalysed intramolecular aziridination of 203, 204 and 205



Entry	R	Starting	Product	Yield	ee
		Material		(%)	(%)
1	Н	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 ₃ CHO) 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



R=ester or sulfone

Scheme 1.57

R=ester or sulfone

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



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 Scott⁹ for copper catalysed intermolecular C–H insertionreactions of α -diazocarbonyls with cyclohexane.



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}



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 -cuparenone¹⁵ (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 Rh₂(*S*-BSP)₄ catalyst to yield 2-sulfonylcyclopentanone **8** in a 12% ee with a 90% yield¹⁶ (**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*-Pr₂) 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





Doyle and coworkers have had tremendous success with rhodium carboxamidate catalysts [for *e.g.* $Rh_2(5R-MEPY)_4$] 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'Riordan²³ and Flynn²⁴ 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 fivemembered 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 αdiazo-\beta-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 Novikov²⁵ 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



Entry	R	Rh(II) ^b	Thiopyran	Sulfolane
			(Yield %) ^a	(Yield %) ^a
1	Н	Rh ₂ (OAc) ₄	65	9
2	Н	Rh ₂ (esp) ₄	70	9
3	Н	Rh ₂ (cap) ₄	60	8
4	Н	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 Rh₂(*S*-PTTL)₄ and Rh₂(*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 Rh₂(*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 Rh₂(*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

		$\begin{array}{c} \text{Rh(II)} \\ \hline \\ \text{CH}_2\text{Cl}_2, \text{ rt} \end{array} \qquad \begin{array}{c} 0 & 0 \\ S \\ \hline \\ \end{array}$	OR OR	
	9 R=Et	11 R=E	Et	
	15 R=(-)-Menthy	yl 16 R=(–)-Menthyl	
	17 R=(+)-Menthyl 1		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.



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–H³⁵ 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-	cis	Yield	ee (%) ^b
			diazo-	thiopyrans	(%) ^a	
			β-οχο			
			sulfones			
1	Ph	Me	21	22a	30	85
2	Ph	Ph	23	24a	49	97
3°	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-	OMe	35	36 a	-	-
	nitrophenyl					
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 nonbenzylic 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



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-(4R)-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.
- 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.
- 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.
- 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 CuCl₂ and Cu(OTf)₂. The effect of the additive, both the nature and the amount, was explored by using KBARF, KPF₆, NaPF₆, LiPF₆, NaBF₄, KBARF, NaB(C₆H₅)₄. The influence of the nature of the bisoxazoline ligand was explored using a range of commercially available ligands (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.



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.



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

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*-diethyl amide substrates



N,N-dibenzyl amide substrate



Morpholine amide substrates



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 γ - 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 αdiazo-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

2.4 References

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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).



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.





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



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 procedure⁴ 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 4phenylbutyric 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

$$R \xrightarrow{OH} \frac{1.5 \text{ eq. PPh}_3, 1.5 \text{ eq. CBr}_4}{CH_3 \text{CN. rt}} R \xrightarrow{Br}$$

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. Flynn² 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 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



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 procedure⁷ 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 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 Flynn² for similar compounds (*p*-OMe, *p*-Me, *p*-NO₂ 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.



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	R	X	N,N-	Yield	Thiol	Time	Yield ^a
	Halide			dimethyldithiocarba	(%)		(h)	(%)
				mic acid derivatives				
1	71	Ph	Cl	72 ²	58 ^a	73 ^{2,9}	3	99 ^c

2	67	Bn	Ι	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

	1 eq. R ₂ NH, 1 eq. NEt ₃	
CI	0 °C, CH ₂ Cl ₂	

Table 3.3 Synthesis of α -chloroamide precursor	·S
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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 -oxosulfides 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	Χ	Time	β-οχο-	Crude
				(h)	sulfide	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	<i>n</i> -C ₁₂ H ₂₅	OBn	Br	19	82 ²	Quantitative
5	2'-	OEt	Br	19	83	97
	ethylphenyl					
6	2'-	Ph	Br	21	84	99
	ethylphenyl					
7	2'-	Me	Cl	20	85	68
	ethylphenyl					
8	Ph(CH ₂) ₃	N(CH ₂ Ph) ₂	Cl	21	86	69
9	Ph(CH ₂) ₃	morpholino	Cl	18	87	93 ^b
10	Ph(CH ₂) ₄	N(CH ₂ CH ₃) ₂	Cl	16	88	84
11	2'-	morpholino	Cl	19	89	92
	ethylphenyl					
12	2'-	N(CH ₂ CH ₂ CH ₃) ₂	Cl	21	90	95
	ethylphenyl					
13	<i>n</i> -C ₁₂ H ₂₅	morpholino	Cl	18	91	78

 $R-SH + X \overset{O}{\longleftarrow} R^{1} \overset{K_{2}CO_{3}, \text{ acetone } \Delta}{\longrightarrow} R^{S} \overset{O}{\longleftarrow} R^{1}$

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

R-2	х + HS	R S OMe				
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	Ι	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	$4-FC_6H_4(CH_2)_4$	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

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

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

$$R^{S} \xrightarrow{O} R^{1} \xrightarrow{mCPBA (2.2-2.5 \text{ eq., } 62-77\%)} R^{S} \xrightarrow{O O O} R^{S} \xrightarrow{R} R$$

Entry	R	R ¹	β-οχο-	Time	β-οχο-	Purified
			sulfide	(h)	sulfone	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	<i>n</i> -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 ₂ CH ₂ C	90	6	116	51 ^c
		$H_{3})_{2}$				
14	2'-ethylphenyl	morpholino	89	7	117	72
15	Ph(CH ₂) ₄	N(CH ₂ CH ₃) ₂	88	6	118	51
16	Ph(CH ₂) ₃	morpholino	87	19	119	76
17	Ph(CH ₂) ₃	N(CH ₂ Ph) ₂	86	25	120	65
18	<i>n</i> -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 ¹H NMR of the crude spectra.

c. After purification using column chromatography, followed by recrystallisation from IPA.



Oxidation of β -oxo-sulfides to the corresponding β -oxo-sulfones **104–121** was achieved using 2.2–2.5 equivalents of mCPBA 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 -sulforyl 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 ¹H 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 ¹H NMR spectra, in the region of 3.30–3.40 ppm for the CH₂ 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*



Scheme 3.9 *Pathway Two; β-amido-sulfone synthesis* 118

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	β-amido-	R ¹	R	Time	Yield ^a
	Acid	sulfones			(h)	(%)
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 mutigram 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	Yield ^a
				(h)	(%)
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 ¹H 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 NaIO₄ in aqueous methanol. Use of *m*CPBA was not attempted to avoid epoxide formation. The initial reaction of β -oxo-sulfide with NaIO₄ 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 -oxosulfoxide **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 ¹H 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 ¹H 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 β-oxo-sulfone		Yield ^a
		(h)		(%)
1	Н	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. ¹H NMR of crude product reveals that there is 47% starting sulfone **135** present.

c. Yield calculated accounting for unreacted starting material. ¹H 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 azide²⁶ 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 a-diazo-\beta-keto-sulfones and a-diazo-\beta-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=N₂ stretch seen in the region of v_{max}/cm⁻¹ 2103–2132 cm⁻¹. For safety purposes, reactions were conducted on scales of <3g.

|--|

0 0 0 R ^{-S} R ¹	K ₂ CO ₃ , ArSO ₂ N ₃	0 0 0		
	CH₃CN 0 °C–rt	$R^{-0} \xrightarrow{\ } R^1$ N_2		

Entry	R	R ¹	β-οχο-	ArSO ₂ N ₃	Time	α-diazo-	Purified
			sulfone		(h)	β-οχο-	Yield
						sulfone	(%) ^a
1	$Ph(CH_2)_3$	Me	104 ²	<i>p</i> -tosyl azide	3.5	41 ^{1,2}	70
2	Ph(CH ₂) ₄	Me	105 ²	<i>p</i> -tosyl azide	2.5	21 ^{1,2}	33
3	Ph(CH ₂) ₄	Ph	106 ²	<i>p</i> -tosyl azide	2.5	23 ^{1,2}	31
4	Ph(CH ₂) ₄	OMe	107 ²	<i>p</i> -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	<i>p</i> -tosyl azide	3	27 ^{1,2}	65
7	C ₆ H ₁₃	OMe	109 ²	p-ABSA	18.5	29 ^{1,2}	75
8	Ph(CH ₂) ₃	OEt		<i>p</i> -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	$4-FC_{6}H_{4}(CH_{2})_{4}^{b}$	OMe	112	<i>p</i> -tosyl azide	3.5	45	62
11	2-phenethyl ^b	OMe	122	<i>p</i> -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	<i>p</i> -ABSA ^d	0.75	63	65
16	$H_2C=CH(CH_2)_4^b$	OMe	129	<i>p</i> -ABSA ^{c,e}	0.17	59	60
17	$H_2C=CH(CH_2)_4^b$	Ph	131	<i>p</i> -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 ¹H 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 CH₂ in the starting sulfone material; inspection of Evans' pKa table³⁹ reveals that the methylene CH₂ 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.



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 ₂ N ₃	Temperature	Time (h)	Yield (%)
1 ^a	K ₂ CO ₃	<i>p</i> -tosyl	0 °C–rt	24	SM
		azide			
2 ^a	K ₂ CO ₃	<i>p</i> -ABSA	0 °C–rt	24	SM
3 ^a	DBU	<i>p</i> -NBSA	0 °C–rt	24	SM
4 ^b	DBU	<i>p</i> -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.

		1-1.1 eq. _D 1 eq. <i>p</i> -N	BU, IBSA	0,0	O ↓ _R¹	
	R ⁻⁰ N ⁻¹ R ¹	CH ₃ CN 40 °C	►	R ⁷ ℃ N ₂	N ¹	
Entry	R	R ¹	β- sulfonyl	Time (h)	α-	Purified
			amide		diazoace	Yield (%) ^a
					tamide	
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	$(\overline{CH_2CH_2})_2O$	117	1.25	58	32

Table 3.12 *Synthesis of* α *-diazo-\beta-amido-sulfones*

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 v_{max}/cm^{-1} 1639–1652 cm⁻¹, for the precursor sulfonyl amides, to v_{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.

¹H NMR characteristics
An interesting feature of the ¹H NMR spectra of α -sulfonyl amides is that the two CH₂ groups adjacent to the nitrogen appear as two separate 2H signals, while the corresponding signals in the ¹H 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 CH₃ of the *N*,*N*-dialkyl group. In the case of the α -diazo- β -amido sulfone one six hydrogen triplet appears for the two CH₃ groups, however in the case of the β -amido sulfone, two separate three hydrogen triplets are seen. An example of a ¹H NMR of β -oxo sulfone **118** and α -diazo- β -oxo sulfone **47** are shown in **Figure 3.4**.



Figure 3.4

¹³C characteristics

For a number of α -diazoamides **46–48**, **50**, **52** and precursor sulfonyl amide **121** the signal for the NCH₂ was noticeably broadened in the ¹³C 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 ¹H NMR, ¹³C 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.

¹H (300 MHz) and ¹³C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer. ¹H (400 MHz) and ¹³C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer. ¹H (500 MHz) and ¹³C (125.8 MHz) NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer. ¹H (600 MHz) and ¹³C (150.9 MHz) NMR spectra were recorded on a Bruker Avance 600 NMR spectrometer. Unless otherwise stated, all spectra were recorded in deuterated chloroform CDCl₃ using tetramethylsilane (TMS) as an internal standard at room temperature (~20 °C). Chemical shifts ($\delta_{\rm H}$ and $\delta_{\rm C}$) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ¹H 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 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. ¹³C NMR spectra were calibrated using the solvent signals, *i.e.* CDCl₃= 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. ¹H NMR spectra, IR spectra and melting point (m.p.) analysis were recorded for all previously prepared compounds, with ¹³C 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 LuxTM Amylose-2, LuxTM Cellulose-2 or LuxTM 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 ¹H 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 $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$.

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% acetonitrilewater 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 K α (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 programs³⁶ 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 (MgSO₄) 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} v_{max}/cm⁻¹ (film): 3340 (OH), 2935, 2860 (CH), 1604 (C=C, Ar), 1496, 1454 (C=C, Ar), 1061, 1030 (C–O); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.30 (1H, br s, OH), 1.56–1.78 [4H, m, C(2)H₂ and C(3)H₂], 2.65 [2H, t, *J* 7.5, C(4)H₂], 3.66 [2H, t, *J* 6.3, C(1)H₂], 7.15–7.22 (3H, m, ArH), 7.24–7.33 (2H, m, ArH).

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 Br 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 $(3 \times 20 \text{ mL})$. The combined organic layers were washed with brine (20 mL), dried (MgSO₄) and concentrated under reduced pressure. Following purification of the crude product by chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, 4phenyl-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} v_{max}/cm⁻¹ (film): 2938, 2857 (CH), 1603 1496, 1454 (C=C, Ar) 699; δ_H (CDCl₃, 400 MHz): 1.71–1.96 [4H, m, C(2)H₂ and C(3)H₂], 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)benzene⁴ 66

The title compound was prepared using the procedure for 4-phenyl-1-bromobutane **65**, described using 5-Br 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, (5bromopentyl)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 v_{max}/cm^{-1} (film): 2934, 2857 (CH), 1603, 1496, 1453 (C=C, Ar), 699; δ_H (CDCl₃, 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)H₂], 3.38 [2H, t, J 6.9, C(1)H₂], 7.11-7.12 (3H, m, ArH), 7.24-7.32 (2H, m, ArH).

Preparation of arylalkyl iodides

(4-Iodobutyl)benzene⁵ 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 (MgSO₄) 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 v_{max} /cm⁻¹ (film): 3026, 2934, 2856 (CH), 1603, 1496, 1454 (C=C, Ar), 1207, 600; $\delta_{\rm H}$ (CDCl₃, 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-fluorobenzene⁶ 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 (MgSO₄) 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 v_{max}/cm⁻¹ (film): 2939, 2860 (CH), 1601, 1510 (C=C, Ar), 1222; $\delta_{\rm H}$ (CDCl₃, 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 ester¹ 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 (MgSO₄) 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 v_{max}/cm⁻¹ (film): 2927, 2856 (CH), 1496, 1454 (C=C, Ar), 1374, 1253, 985, 700 (CS); $\delta_{\rm H}$ (CDCl₃, 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, NC*H*₃), 3.53 (3H, br s, NC*H*₃), 7.13–7.22 (3H, m, Ar*H*), 7.23–7.34 (2H, m, Ar*H*).

N,*N*-Dimethyldithiocarbamic acid 4-phenylbutyl ester² 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 v_{max}/cm⁻¹ (film): 2932, 2888 (CH), 1602, 1495 (C=C, Ar), 1370, 1251, 983, 740 (CS); $\delta_{\rm H}$ (CDCl₃, 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, NC*H*₃], 3.55 (3H, br s, NC*H*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

N,*N*-dimethyldithiocarbamic solution of acid 3-А phenylpropylester 72 (11.0 g, 46.0 mmol), in diethyl ether (50 ml), SH 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 (MgSO₄) 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 ¹H NMR analysis. Spectroscopic characteristics are consistent with those previously reported; 1,7 v_{max}/cm⁻¹ (film): 3027, 2933 (CH), 1604, 1497, 1454 (C=C, Ar), 744, 700 (SH); δ_H (CDCl₃, 400 MHz): 1.35 (1H, t, J 7.8, SH), 1.87–1.99 [2H, m, C(2)H₂], 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} v_{max}/cm^{-1} (film): 2933 (CH), 1640, 1604, 1496, 1453 (C=C, Ar), 699 (SH); $\delta_{\rm H}$ (CDCl₃, 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-morpholinoethanone⁹78

A solution of chloroacetyl chloride (10.0 g, 7.0 mL, 88.5 mmol) in Ο Cl 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 $(3 \times 40 \text{ mL})$ and hydrochloric acid $(2 \times 40 \text{ mL}, 2 \text{ M})$, brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 2-chloro-1morpholinoethanone 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 v_{max}/cm⁻¹ (film): 2968, 2923, 2860 (CH), 1651 (CO), 1440, 1270, 1234, 1115, 966 (C–O); δ_H (CDCl₃, 300 MHz): 3.40–3.52 (2H, m, morpholine CH₂), 3.58-3.61 (2H, m, morpholine CH₂), 3.65-3.71 (4H, m, morpholine CH₂), 4.08 (2H, s, $ClCH_2CO$).

2-Chloro-N,N-diethylacetamide¹⁰76



The title compound was prepared according to the method used for 2chloro-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 v_{max}/cm^{-1} (film): 2978, 2937 (CH), 1651 (CO), 1464, 1434, 1256, 1172, 792; δ_{H} (CDCl₃, 300 MHz): 1.10 (3H, t, *J* 7.2, one of NCH₂CH₃), 1.20 (3H, t, *J* 7.2, one of NCH₂CH₃), 3.32–3.46 (4H, m, NCH₂CH₃), 4.07 (2H, s, ClCH₂CO).

2-Chloro-N,N-dipropylacetamide¹¹77



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 v_{max} /cm⁻¹ (film): 2967, 2936, 2877 (CH), 1652 (CO), 1457, 1430, 1124, 794 (C-O); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 0.90 (3H, t, *J* 7.4, one of NCH₂CH₂CH₃), 0.95 (3H, t, *J* 7.4, one of NCH₂CH₂CH₃), 1.53–1.72 (4H, sym m, NCH₂CH₂CH₃), 3.22–3.41 (4H, sym m, NCH₂CH₂CH₃), 4.07 (2H, s, ClCH₂CO).

N,*N*-Dibenzyl-2-chloroacetamide¹²75



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); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 4.23 (2H, s, ClC*H*₂CO), 4.48 (2H, s, one of NC*H*₂Ph), 4.63 (2H, s, one of NC*H*₂Ph), 7.09–7.41 (10H, ArH).

General Procedure A for sulfide synthesis¹

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-one¹79

The title compound was prepared using general procedure **A**, using potassium carbonate (0.91 g, 6.6 mmol), 3phenylpropyl-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-(3phenylpropylthio)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 v_{max}/cm⁻¹ (film): 1708 (CO), 746, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.82–1.95 [2H, m, C(2')H₂], 2.28 (3H, s, COCH₃), 2.45–2.53 [2H, m, C(1')H₂ or C(3')H₂], 2.65–2.73 [2H, m, C(1')H₂ or C(3')H₂], 3.21 (2H, s, SCH₂CO), 7.12–7.22 (3H, m, ArH), 7.23–7.43 (2H, m, ArH).

1-(4-Phenylbutylthio)propan-2-one¹80



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 v_{max}/cm⁻¹ (film): 1705 (CO), 1604 (C=C, Ar), 700 (CS); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.51–1.79 [4H, m, C(2')*H*₂ and C(3')*H*₂], 2.27 (3H, s, COC*H*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, SC*H*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; v_{max}/cm^{-1} (film): 2967, 2932 (CH), 1712 (CO), 1470, 1443, (C=C, Ar), 1356, 1231, 1149, 751 (CS); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.24 (3H, t, *J* 7.5, ArCH₂CH₃), 2.27 (3H, s, COCH₃), 2.80 (2H, q, *J* 7.5, ArCH₂CH₃), 3.66 (2H, s, SCH₂CO₂CH₃), 7.12–7.22 (3H, m ArH), 7.23–7.28 (1H, m ArH).

2-(4-Phenylbutylthio)-1-phenylethanone¹ 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 v_{max}/cm⁻¹ (film): 2933 (CH), 1674 (CO), 1598, 1449 (C=C, Ar), 1277, 748, 700 (CS); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*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; v_{max}/cm^{-1} (film): 2967 (CH), 1693 (CO), 1466, 1450 (C=C, Ar), 751 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.18 (3H, t, *J* 7.5, ArCH₂CH₃), 2.76 (2H, q, *J* 7.5, ArCH₂CH₃), 4.24 (2H, s, SCH₂CO), 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 ¹H NMR) was isolated as a yellow oil which was used without further purification; v_{max}/cm^{-1} (film): 3028, 2952 (CH), 1730 (CO),

1604, 1498, 1436, 1455 (C=C, Ar), 1280, 1129 (CO₂Me), 699 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 2.90 [4H, s, C(2')*H*₂ and C(1')*H*₂], 3.22 (2H, s, SO₂C*H*₂CO), 3.72 (3H, s, COOC*H*₃), 7.16–7.24 (3H, m, Ar*H*), 7.25–7.33 (2H, m, Ar*H*).

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



thioglycolate (5.50 g, 4.6 mL, 51.8 mmol), (3chloropropyl)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; v_{max}/cm^{-1} (film): 3026, 2950, 2856 (CH), 1736 (CO), 1497, 1453 1436, 1279, 1128, 1008, 746, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.86–1.96 [2H, m, C(2')H₂], 2.59–2.65 [2H, m, C(3')H₂], 2.66–2.73 [2H, m, C(1')H₂], 3.20 (2H, s, SCH₂CO), 3.69 (3H, s, COOCH₃), 7.13–7.20 (3H, m, ArH), 7.23–7.30 (2H, m, ArH).

Methyl 2-(4-phenylbutylthio)acetate¹ 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

The title compound was prepared using general procedure

A, using potassium carbonate (7.91 g, 57.0 mmol), methyl

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 v_{max}/cm^{-1} (film): 2934 (CH), 1738 (CO), 1436 (C=C, Ar), 1279, 1136 (C–O), 700 (CS); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*₂CO), 3.72 (3H, s, COOC*H*₃), 7.10–7.21 (3H, m, Ar*H*), 7.30–7.32 (2H, m, Ar*H*).

Methyl 2-(5-phenylpentylthio)acetate¹ 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 v_{max}/cm^{-1} (film): 2935 (CH), 1737 (CO), 1436 (C=C, Ar), 1279, 1150 (C–O), 700 (CS); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*₂CO), 3.73 (3H, s, COOC*H*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; v_{max}/cm^{-1} (film): 2934 (CH), 1738 (CO), 1601 (C=C, Ar), 1510 (C=C, Ar), 1280, 1221, 1158 (C–O), 825, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*₂CO), 3.72 (3H, s, COOC*H*₃), 6.90–7.02 (2H, m, Ar*H*), 7.05–7.17 (2H, m, Ar*H*).

Methyl 2-(hexylthio)acetate¹ 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 v_{max}/cm^{-1} (film): 2929 (CH), 1739 (CO), 1278, 1135 (C–O); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*₂CO), 3.74 (3H, s, COOC*H*₃).

Benzyl 2-(dodecylthio)acetate¹ 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 v_{max}/cm⁻¹ (film): 2924, 2853 (CH) 1736 (CO), 1458 (C=C, Ar),1274, 1129 (C-O), 750, 696 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 0.88 [3H, t, *J* 6.9, C(12')H₃], 1.15–1.40 [18H, m, C(11')H₂, C(10')H₂, C(9')H₂, C(8')H₂, C(7')H₂, C(6')H₂, C(5')H₂, C(4')H₂, C(3')H₂], 1.50–1.63 [2H, m, C(2')H₂], 2.55–2.67 [2H, m, C(1')H₂], 3.25 (2H, s, SCH₂CO), 5.17 (2H, s, CO₂CH₂Ph), 7.25–7.46 (5H, m, ArH).

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-1ene (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; v_{max}/cm^{-1} (film): 2953, 2925 (CH), 1739 (CO), 1641 (C=C, Ar), 1437, 1281, 1134, 1009, 918 (CS); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*₂CO), 3.74 (3H, s, COOC*H*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; v_{max}/cm^{-1} (film): 2952, 2932 (CH), 1738 (CO), 1641 (C=C, Ar), 1437, 1279, 1134, 1010, 914 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.65–1.76 [2H, m, either C(2')H₂ or C(3')H₂], 2.09–2.22 [2H, m, either C(2')H₂ or C(3')H₂],

2.60–2.69 [2H, m, C(1')*H*₂], 3.23 (2H, s, SC*H*₂CO), 3.74 (3H, s, COOC*H*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), 2ethylbenzenethiol (6.00 g, 5.86 mL, 43.4 mmol) and ethyl 2bromoacetate (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; v_{max}/cm^{-1} (film): 2967 (CH), 1735 (CO), 1470 (C=C, Ar), 1268, 1129, 1029 (C–O), 750 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.17–1.28 (6H, two overlapping t, appears as m, ArCH₂CH₃ and OCH₂CH₃), 2.82 (2H, q, *J* 7.6, ArCH₂CH₃), 3.61 (2H, s, SCH₂CO₂Et), 4.15 (2H, q, *J* 7.2, OCH₂CH₃), 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; v_{max}/cm^{-1} (film): 2973 2932 (CH), 1640 (CO), 1454, 1431, 1282, 1110, 700 (CS); δ_{H} (CDCl₃, 400 MHz): 1.06 (3H, t, *J* 7.2, one of NCH₂CH₃), 1.15 (3H, t, *J* 7.2, one of NCH₂CH₃), 1.50–1.85 [4H, m, C(2')H₂ and C(3')H₂], 2.53–2.78 [4H, m, C(1')H₂ and C(4')H₂], 3.23 (2H, s, SCH₂CO), 3.31–3.48 (4H, sym m, 2 × NCH₂CH₃), 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), 2ethylbenzenethiol (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; v_{max}/cm^{-1} (film): 2964, 2932, 2873 (CH), 1642 (CO), 1466, 1102, 749 (C-O); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 0.84–0.96 (6H, two overlapping 3H t, 2 × NCH₂CH₂CH₃), 1.23 (3H, t, *J* 7.5, ArCH₂CH₃), 1.49–1.70 (4H, sym m, 2 × NCH₂CH₂CH₃), 2.82 (2H, q, *J* 7.5, ArCH₂CH₃), 3.17–3.25 (2H, sym m, one of NCH₂CH₂CH₃), 3.26–3.33 (2H, sym m, one of NCH₂CH₂CH₃), 3.71 (2H, s, SCH₂CO), 7.12–7.23 (3H, m, ArH), 7.41–7.45 (1H, m, ArH).

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, 1morpholino-2-[(3-phenylpropyl)thio]ethanone **87** (2.81 g, 93%) was isolated as an odorous brown oil, (~60% pure, by ¹H NMR contains unidentified material) which was used without further purification; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.90–2.14 [2H, m, C(2')H₂], 2.64–2.85 [4H, m, C(1')H₂ and C(3')H₂], 3.25–3.80 [10H, m, 8H morpholine CH₂ and SCH₂CO), 7.13–7.24 (3H, m, ArH), 7.25–7.34 (2H, m, ArH).

(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; v_{max}/cm^{-1} (film): 2919 (CH), 1649 (CO), 1459, 1274, 1117, 1040, 965, 850, 722 (CS); $\delta_{\rm H}$ (CDCl₃, 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, CH₂, SC*H*₂CO), 3.46–3.55 (2H, m, morpholine C*H*₂), 3.57–3.63 (2H, m, morpholine C*H*₂), 3.65–3.76 (4H, m, morpholine C*H*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), 2ethylbenzenethiol (2.37 g, 2.3 mL, 17.2 mmol) and 2-chloro-1morpholinoethanone **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]-1morpholinoethanone **89** (4.21 g, 92%) was isolated as a brown oil, which was used without further purification; v_{max}/cm^{-1} (film): 2965, 2927 2858 (CH), 1644 (CO) 1436, 1274, 1256, 1115, 1038, 752 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.24 (3H, t, *J* 7.5, ArCH₂CH₃), 2.81 (2H, q, *J* 7.5, ArCH₂CH₃), 3.43–3.51 (2H, m, morpholine CH₂), 3.58–3.68 (6H, m, morpholine CH₂), 3.69 (2H, s, SCH₂CO), 7.14–7.24 (3H, m, ArH), 7.43–7.48 (1H, m, ArH).

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; v_{max}/cm^{-1} (film): 3063, 3028, 2930 (CH), 1645 (CO), 1496, 1452, 1362, 1253, 1079, 745, 700 (CS); $\delta_{\rm H}$ (CDCl₃, 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, SC*H*₂CO), 4.54 (2H, s, one of NC*H*₂C₆H₅), 4.60 (2H, s, one of NC*H*₂C₆H₅), 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 °C 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 (MgSO₄) 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-one¹ 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 °C for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 3 h. Following the work up the ¹H 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 ¹H 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 v_{max}/cm⁻¹ (film): 1719 (CO), 1320, 1116 (SO₂); $\delta_{\rm H}$ (CDCl₃,400 MHz): 2.10–2.22 [2H, m, C(2')H₂], 2.39 (3H, s, COCH₃), 2.77 [2H, t, *J* 7.5, C(3')H₂], 3.05–3.13 [2H, m, C(1')H₂], 4.00 (2H, s, SO₂CH₂CO), 7.12–7.35 (5H, m, Ar*H*).

1-(4-Phenylbutylsulfonyl)propan-2-one¹ 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 °C for 1 h and slowly allowed to return to room temperature and stirred at room temperature for 3 h. Following the work up the ¹H 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 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 49–50 °C (Lit; mp 51–52 °C);¹ v_{max}/cm⁻¹ (KBr): 1728 (CO), 1297, 1077 (SO₂); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.69–1.96 [4H, m, C(2')*H*₂ and C(3')*H*₂], 2.42 (3H, s, COC*H*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, SO₂C*H*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 °C 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; v_{max}/cm^{-1} (film): 2928 (CH), 1717 (CO), 1311, 1150 (SO₂), 746 (CS); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.34 (3H, t, *J* 7.5, ArCH₂CH₃), 2.40 (3H, s, COCH₃), 3.06 (2H, q, *J* 7.5, ArCH₂CH₃), 4.18 (2H, s, SO₂CH₂CO₂CH₃), 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); $\delta_{\rm C}$ (CDCl₃, 75.5 MHz) 15.9 (CH₃, ArCH₂CH₃), 26.1 (CH₂, ArCH₂CH₃), 31.6 (CH₃, COCH₃), 67.9 (CH₂, SO₂CH₂CO), 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, *CO*); HRMS (ESI+): Exact mass calculated for C₁₁H₁₅O₃S [M+H]⁺, 227.0742. Found 227.0723.

NMR assignment was aided using COSY and HETCOR experiments

2-(4-Phenylbutylsulfonyl)-1-phenylethanone¹ 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 °C 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 °C (Lit; mp 92–93 °C);¹ v_{max}/cm⁻¹ (KBr): 1686 (CO) 1336, 1300, 1131 (SO₂); $\delta_{\rm H}$ (CDCl₃, 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, SO₂C*H*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 $(2 \times 20 \text{ mL})$. The combined organic layers were washed with brine (30 mL), dried with MgSO₄ and concentrated under reduced pressure. Following the work up, the analysis of the ¹H NMR spectrum of the crude product indicated that the reaction contained 53% sulfone and 47% starting material. [Relative amounts calculated from the ¹H NMR spectra of the crude product using SO₂CH₂CO signal; $\delta_{\rm H}$ =4.57 (2H, s, SO₂CH₂CO), for sulfone product **131** and $\delta_{\rm H}$ =4.61 (2H, s, SO₂CH₂CO), for starting material sulfone 135. An additional peak is observed for starting material sulfone 135; $\delta_{\rm H}$ =3.16 (3H, s, SO₂CH₃). 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)-1phenylethanone 131 (1.02 g, 40%) was isolated as a white solid. mp 65–66 °C, v_{max} /cm⁻¹ (KBr): 3053, 2961, 2920 (CH), 1688 (CO), 1642, 1599 (C=C, Ar), 1451, 1334, 1322, 1257, 1213, 1134, 1121 (SO₂), 995, 913, 895, 755, 689 (CS); δ_H (CDCl₃, 600 MHz): 1.96– 2.05 [2H, m, C(2')H₂], 2.19–2.29 [2H, m, C(3')H₂], 3.22–3.31 [2H, m, C(1')H₂], 4.57 (2H, s, SO₂CH₂CO), 5.02–5.17 [2H, m, C(5')H₂], 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 (CDCl₃, 150.9 MHz): 21.0 [CH₂, C(2')H₂], 32.1 [CH₂, C(3')H₂], 53.0 [CH₂, C(1')H₂], 59.6 (CH₂, SO₂CH₂CO), 116.7 [CH₂, C(5')H₂], 129.0 (2 × CH, aromatic CH_{meta}), 129.3 (2 × CH, aromatic CHortho), 134.7 (CH, aromatic CHpara), 135.7 (C, aromatic, C), 136.2 [CH, C(4')H], 189.3 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₃H₁₇O₃S [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 ¹H NMR of the crude product indicated that the reaction contained 33% sulfone and 67% starting material. [Relative amounts calculated from the ¹H NMR spectra of the crude product using SO₂CH₂CO signal; $\delta_{\rm H}$ =4.55 (2H, s, SO₂CH₂CO), for sulfone product **132** and $\delta_{\rm H}$ =4.61 (2H, s, SO₂CH₂CO), for starting material sulfone 135. An additional peak is observed for starting material sulfone 135; $\delta_{\rm H}=3.16$ (3H, s, SO₂CH₃). 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-1vl)sulfonvl]-1-phenvlethanone **132** (0.52 g, 22%) was isolated as a white crystalline solid; mp 59–60 °C, v_{max}/cm⁻¹ (KBr): 3060, 2998, 2959, 2918, 2874 (CH), 1687 (CO), 1600 (C=C), 1450, 1333, 1321, 1289, 1213, 1132, 1120 (SO₂), 995, 896, 753, 690 (CS); δ_H (CDCl₃, 600 MHz): 1.61 [3H, s, C(6')H₃ or CH₃], 1.71 [3H, s, C(6')H₃ or CH₃], 1.90–1.96 [2H, m, C(2')H₂], 2.13–2.19 [2H, m, C(3')H₂], 3.20–3.37 [2H, m, C(1')H₂], 4.55 (2H, s, SO₂CH₂CO), 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} (CDCl₃, 150.9 MHz): 17.8 [CH₃, C(6')H₃ or CH₃], 22.1 [CH₂, C(2')H₂], 25.7 [CH₃, C(6')H₃ or CH₃], 26.5 [CH₂, C(3')H₂], 53.2 [CH₂, $C(1')H_2$, 59.5 (CH₂, SO₂CH₂CO), 122.0 [CH, C(4')H], 129.0 (2 × CH, aromatic CH_{ortho}), 129.3 (2 × CH, aromatic CH_{meta}), 134.0 [C, aromatic, C or C(5')], 134.6 [CH, aromatic, CH_{para}], 135.7 [C, aromatic, C or C(5')], 189.3 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₅H₂₁O₃S [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 °C 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 °C (Found: C, 66.64; H, 5.47; $C_{16}H_{16}O_3S$ requires C, 66.64; H, 5.59%); v_{max}/cm^{-1} (KBr): 2983 (CH), 1675 (CO), 1316, 1214, 1154 (SO₂); δ_H (CDCl₃, 400 MHz): 1.32 (3H, t, J 7.5, ArCH₂CH₃), 3.07 (2H, q, J 7.5, ArCH₂CH₃), 4.76 (2H, s, SO₂CH₂CO), 7.27–7.35 (1H, m, ArH), 7.38–7.43 (1H, m, ArH), 7.44–7.52 (2H, m, ArH), 7.53–7.65 (2H, m, ArH), 7.88 (1H, dd, J 1.3, 8.0, Ar H^a), 7.93 (2H, ddd, J 1.6, 1.6, 8.5, Ar $H^{a'}$); δ_C (CDCl₃, 75.5) MHz): 15.9 (CH₃, ArCH₂CH₃), 26.2 (CH₂, ArCH₂CH₃), 63.7 (CH₂, SO₂CH₂CO), 126.4, 128.8, 129.4, 130.7, 131.1, 134.3 (6 signals seen for 7 aromatic CH carbons), 134.4 (C, aromatic C), 135.9 (C, aromatic C), 136.6 (C, aromatic C), 187.9 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₆H₁₇O₃S [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 °C. The reaction mixture was stirred at 0 °C 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 (MgSO₄) 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; v_{max}/cm^{-1} (film): 1744 (CO), 1319, 1116 (SO₂); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 3.10–3.24 [2H, m, C(1')H₂ or C(2')H₂], 3.49–3.60 [2H, m, C(2')H₂ or C(1')H₂], 3.80 (3H, s, COOCH₃), 3.88 (2H, s,

SO₂C*H*₂CO), 7.19–7.40 (5H, m, Ar*H*); δ_{C} (CDCl₃, 100.6 MHz): 28.2 [CH₂, *C*(1')H₂ or *C*(2')H₂], 53.3 (CH₃, COOCH₃), 54.8 [CH₂, *C*(1')H₂ or *C*(2')H₂], 57.5 (CH₂, SO₂CH₂CO), 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 C₁₁H₁₅O₄S [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 °C 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; v_{max}/cm^{-1} (film): 3028, 3005, 2954 (CH), 1744 (CO), 1455, 1438, 1323, 1218, 1143, 1116 (SO₂) 752, 702 (CS); $\delta_{\rm H}$ (CDCl₃, 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, COOC*H*₃), 3.94 (2H, s, SO₂C*H*₂CO), 7.19 (2H, d, *J* 7.4, Ar*H*_{ortho}), 7.23 (1H, t, *J* 7.4, Ar*H*_{para}), 7.31 (2H, t, *J* 7.5, Ar*H*_{meta}); $\delta_{\rm C}$ (CDCl₃, 150.9 MHz): 23.4 [CH₂, *C*(2')H₂], 34.1 [CH₂, *C*(3')H₂], 52.7 [CH₂, *C*(1')H₂], 53.3 (CH₃, COOC*H*₃), 57.3 (CH₂, SO₂C*H*₂CO), 126.6 (CH, aromatic *C*_{para}) 128.4 (2 × CH, aromatic *C*_{Ortho}), 128.7 (2 × CH, aromatic *C*_{Hmeta}), 139.7 (C, aromatic *C*), 163.5 (C, *CO*); (HRMS) (ESI+): Exact mass calculated for C₁₂H₁₇O₄S [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)acetate¹ 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 mCPBA (77% w/w,

10.19 g, 45.5 mmol) in dichloromethane (180 mL) stirred at 0 °C 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 v_{max} /cm⁻¹ (film): 1742 (CO), 1322, 1108 (SO₂); δ_{H} (CDCl₃, 400 MHz): 1.74–1.97 [4H, m, C(2')H₂ and C(3')H₂], 2.67 [2H, t, *J* 7.4, C(4')H₂], 3.22–3.32 [2H, m, C(1')H₂], 3.81 (3H, s, COOCH₃), 3.93 (2H, s, SO₂CH₂CO), 7.13–7.24 (3H, m, ArH), 7.24–7.32 (2H, m, ArH).

Methyl 2-(5-phenylpentylsulfonyl)acetate¹ 108



The title compound was prepared using general procedure \mathbf{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 °C 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 v_{max}/cm⁻¹ (film): 1743 (CO), 1324, 1106 (SO₂); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.42–1.56 [2H, m, C(3')H₂], 1.61–1.75 [2H, m, C(4')H₂], 1.83–1.95 [2H, m, C(2')H₂], 2.63 [2H, t, *J* 7.6, C(5')H₂], 3.19–3.28 [2H, m, C(1')H₂], 3.81 (3H, s, COOCH₃), 3.95 (2H, s, SO₂CH₂CO), 7.12–7.22 (3H, m, ArH), 7.24–7.32 (2H, m, ArH).

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 °C 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 °C; (Found: C, 53.85; H, 6.26; C₁₃H₁₇FO₄S requires C, 54.15; H, 5.94 %); v_{max}/cm^{-1} (KBr): 1746 (CO), 1510, 1277, 1217, 1141 (SO₂); δ_{H} (CDCl₃, 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, COOC*H*₃), 3.95 (2H, s, SO₂C*H*₂CO), 6.92–7.03 (2H, m, Ar*H*), 7.06–7.18 (2H, m, Ar*H*); δ_{C} (CDCl₃, 75.5 MHz): 21.4, 30.2 [2 × CH₂, *C*(2')H₂ and *C*(3')H₂], 34.5 [CH₂, *C*(4')H₂], 53.2 [CH₂, *C*(1')H₂], 53.4 (CH₃, OCH₃), 57.3 (CH₂, SO₂CH₂CO), 115.0 (2 × ArCH, d, ²*J*_{CF} 21.1, *C*(3)H, *C*(5)H], 129.7 [2 × ArCH, d, ³*J*_{CF} 7.7, *C*(2)H, *C*(6)H], 136.67 [C, d, ⁴*J*_{CF} 3.0, *C*(1)], 161.3 [C, ¹*J*_{CF} 243.5, *C*(4)], 163.6 (C, *CO*); HRMS (ESI+): Exact mass calculated for C₁₃H₁₈FO₄S [M+H]⁺, 289.0914. Found 289.0910. m/z (ESI+): 289.1 [M+H]⁺.

Methyl 2-(hexylsulfonyl)acetate¹ 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 °C 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 °C; v_{max}/cm^{-1} (KBr): 1758, 1746 (CO), 1318, 1281, 1149, 1111 (SO₂); δ_{H} (CDCl₃, 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, COOC*H*₃), 3.96 (2H, s, SO₂C*H*₂CO).

Benzyl 2-(dodecylsulfonyl)acetate¹ 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 °C 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 °C (Lit. mp 62–64 °C)¹; v_{max}/cm⁻¹ (KBr): 1734 (CO), 1327, 1161 (SO₂); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 0.88 [3H, t, *J* 6.8, C(12')H₃], 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, SC H_2 CO), 5.24 (2H, s, CO₂C H_2 Ph), 7.37 (5H, br s, ArH).

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

A solution of sodium (meta)periodate (> 99.8% ACS 0.0 Ο reagent) (17.9 g, 83.6 mmol) in distilled water (150 mL) was OMe 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 $(4 \times 50 \text{ mL})$, the combined organic layers were washed with brine (50 mL), dried with MgSO4 and concentrated under reduced pressure. Following the work up, analysis of the ¹H NMR spectrum of the crude reaction mixture indicated 63% sulfone and 37% sulfoxide formation. [Relative amounts were calculated from the ¹H NMR spectra of the crude product using OMe signal; $\delta_{\rm H}$ =3.82 (3H, s, COOCH₃) for sulfone **129** and $\delta_{\rm H}$ =3.79 (3H, s, COOCH₃) 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-1ylsulfonyl)acetate **129** (3.45g, 46%, 70% corrected for sulfoxide, using the ¹H 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%); v_{max}/cm^{-1} (film): 3003, 2980, 2955 (CH), 1745 (CO), 1642 (C=C, Ar), 1439, 1323, 1141, 1112 (SO₂), 917 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.94–2.05 [2H, m, C(2')H₂], 2.21–2.28 [2H, m, C(3')H₂], 3.23–3.29 [2H, m, C(1')H₂], 3.82 (3H, s, COOCH₃), 3.98 (2H, s, SO₂CH₂CO), 5.05–5.14 [2H, m, C(5')H₂], 5.72–5.82 [1H, m, C(4')H]; δ_C (CDCl₃, 150.9 MHz): 21.0 [CH₂, C(2')H2], 32.1 [CH2, C(3')H2], 52.8 [CH2, C(1')H2], 53.4 (CH3, COOCH3), 57.3 (CH2, SO₂CH₂CO), 116.8 [CH₂, C(5')H₂], 136.1 [CH, C(4')H], 163.6 (C, CO); Exact mass calculated for C₈H₁₅O₄S [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**; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 3.67 (1H, A part of ABq, *J* 13.7, one of

SOCH₂CO), 3.72 (1H, B part of ABq, J 13.7, one of SOCH₂CO), 3.79 (3H, s, COOCH₃).

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

The title compound was prepared using the procedure described Ő Ö for methyl 2-(pent-4-en-1-ylsulfonyl)acetate 129, using methyl ЭМе 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 ¹H NMR spectrum of the crude product indicated 50% sulfone and 50% sulfoxide formation. [Relative amounts were calculated from the ¹H NMR spectra of the crude product using the OMe signal; δ_{H} =3.83 (3H, s, COOCH₃) for sulfone **130** and δ_{H} =3.80 (3H, s, COOCH₃) 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 ¹H NMR spectra of the crude product mixture) was isolated as a colourless oil; v_{max}/cm^{-1} (film): 3005, 2955 (CH), 1744 (CO), 1643 (C=C, Ar), 1438, 1401, 1321, 1219, 1140, 1112, 1002 (SO₂), 915, 823 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 2.60–2.68 [2H, sym m, C(2')H₂], 3.32–3.40 [2H, m, C(1')H₂], 3.83 (3H, s, COOCH₃), 4.00 (2H, s, SO₂CH₂CO), 5.12–5.25 [2H, m, C(4')H₂], 5.79–5.89 [1H, m, C(3')H]; δ_C (CDCl₃, 150.9 MHz) 26.2 [CH₂, C(2')H₂], 52.6 [CH₂, C(1')H₂], 53.4 (CH₃, COOCH₃), 57.5 (CH₂, SO₂CH₂CO), 117.9 [CH₂, C(4')H₂], 133.5 [CH, C(3')H], 163.5 (C, CO); HRMS (ESI+): Exact mass calculated for C₇H₁₃O₄S [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**; $\delta_{\rm H}$ (CDCl₃, 400 MHz) 3.70 (1H, A part of ABq, *J* 13.7, one of SOC*H*₂CO), 3.77 (1H, B part of ABq, *J* 13.7, one of SOC*H*₂CO), 3.80 (3H, s, COOC*H*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 °C 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 acetatehexane (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, C₁₂H₁₆O₄S requires C, 56.23; H, 6.29%); v_{max}/cm^{-1} (film): 2982 (CH), 1743 (CO), 1323, 1155 (SO₂); δ_{H} (CDCl₃, 300 MHz): 1.14 (3H, t, *J* 7.1, OCH₂CH₃), 1.34 (3H, t, *J* 7.5, ArCH₂CH₃), 3.07 (2H, q, *J* 7.5, ArCH₂CH₃), 4.09 (2H, q, *J* 7.1, OCH₂CH₃), 4.15 (2H, s, SO₂CH₂CO₂Et), 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^e), 7.97 (1H, dd, *J* 8.0, 1.3, ArH^a); δ_{C} (CDCl₃, 75.5 MHz): 13.7 (CH₃, OCH₂CH₃), 15.8 (CH₃, ArCH₂CH₃), 26.0 (CH₂, ArCH₂CH₃), 61.1 (CH₂, SO₂CH₂CO), 62.2 (CH₂, OCH₂CH₃), 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, CO); HRMS (ESI+): Exact mass calculated for C₁₂H₁₇O₄S [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 °C 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; v_{max}/cm^{-1} (film): 2977, 2937 (CH), 1641 (CO), 1455, 1318,

1149, 1128, 1114 (SO₂), 752, 702 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.15 (3H, t, *J* 7.2, one of NCH₂CH₃), 1.22 (3H, t, *J* 7.2, one of NCH₂CH₃), 2.16–2.27 [2H, m, C(2')H₂], 2.78 [2H, t, *J* 7.6, C(3')H₂], 3.27–3.34 [2H, m, C(1')H₂], 3.37–3.51 (4H × 2, overlapping q appears as sym m, 2 × NCH₂CH₃), 3.97 (2H, s, SO₂CH₂CO), 7.16–7.23 (3H, m, ArH), 7.26–7.34 (2H, m, ArH); $\delta_{\rm C}$ (CDCl₃, 150.9 MHz); 12.8 (CH₃, one of NCH₂CH₃), 14.3 (CH₃, one of NCH₂CH₃), 23.6 [CH₂, *C*(2')H₂], 34.2 [CH₂, *C*(3')H₂], 41.1 (CH₂, one of NCH₂CH₃), 43.3 (CH₂, one of NCH₂CH₃), 52.9 [CH₂, *C*(1')H₂], 56.0 (CH₂, SO₂CH₂CO), 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 C₁₅H₂₄NO₃S [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 mCPBA (66% w/w, 14.5 g, 57.3 mmol) in dichloromethane (250 mL), stirred at 0 °C 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-[(4phenylbutyl)sulfonyl]acetamide 118 (3.61 g, 51%) was isolated as a colourless oil; v_{max}/cm^{-1} (film): 2934 (CH), 1639 (CO), 1452, 1317, 1148 (SO₂), 751 (CS); δ_{H} (CDCl₃, 300 MHz): 1.16 (3H, t, J 7.2, one of NCH₂CH₃), 1.23 (3H, t, J 7.2, one of NCH₂CH₃), 1.72–1.84 [2H, m, C(2')H₂ or C(3')H₂], 1.86–1.99 [2H, m, C(2')H₂ or C(3')H₂], 2.61–2.72 $[2H, m, C(4')H_2], 3.29-3.36 [2H, m, C(1')H_2], 3.37-3.51 (4H, sym m, 2 \times NCH_2CH_3),$ 3.98 (2H, s, SO₂CH₂CO), 7.12–7.22 (3H, m, ArH), 7.23–7.32 (2H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 12.8 (CH₃, one of NCH₂CH₃), 14.4 (CH₃, one of NCH₂CH₃), 21.6 [CH₂, C(2')H₂ or C(3')H₂], 30.1 [CH₂, C(2')H₂ or C(3')H₂], 35.4 [CH₂, C(4')H₂], 41.2 [CH₂, one of NCH₂CH₃], 43.4 [CH₂, one of NCH₂CH₃], 53.4 [CH₂, C(1')H₂], 56.0 (CH₂, SO₂CH₂CO), 126.0 (CH, aromatic CH), 128.3 (CH, 2 × aromatic CH), 128.4 (CH, 2 × aromatic CH), 141.4 (C, aromatic C), 161.5 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₆H₂₆NO₃S [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 °C 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-[(3phenylpropyl)sulfonyl]-N,N-dipropylacetamide 127 (1.56 g, 53%) was isolated as a colourless oil; v_{max}/cm⁻¹ (film): 2965, 2936, 2876 (CH), 1641 (CO), 1455, 1319, 1149, 1115 (SO₂), 749, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 0.91 (3H, t, J 7.4, one of NCH₂CH₂CH₃), 0.93 (3H, t, J 7.4, one of NCH₂CH₂CH₃), 1.52–1.69 (4H, sym m, 2 × NCH₂CH₂CH₃), 2.16–2.25 [2H, m, C(2')H₂], 2.78 [2H, t, J 7.6, C(3')H₂], 3.27–3.39 [6H, m, $2 \times \text{NCH}_2\text{CH}_2\text{CH}_3$ and $C(1')H_2$], 3.99 (2H, s, SO₂CH₂CO), 7.16–7.23 (3H, m, ArH), 7.24–7.32 (2H, m, ArH); δ_{C} (CDCl₃, 150.9 MHz): 11.2 (CH₃, one of NCH₂CH₂CH₃), 11.3 (CH₃, one of NCH₂CH₂CH₃), 20.8 (CH₂, one of NCH₂CH₂CH₃), 22.4 (CH₂, one of NCH₂CH₂CH₃), 23.6 [CH₂, C(2')H₂], 34.3 [CH₂, C(3')H₂], 48.4, 50.7, 52.9 (3 × CH₂, 2 × NCH₂CH₂CH₃ and C(1')H₂], 56.1 (CH₂, SO₂CH₂CO), 126.4 (CH, aromatic CH) 128.5 (2 \times CH, aromatic CH), 128.6 (2 \times CH, aromatic CH), 140.1 (C, aromatic C), 161.9 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₇H₂₈NO₃S [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 $^{\circ}$ C 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 (10:90-20:80-40:60-50:50-80:20) ethvl acetate-hexane as eluent. 2-[(4phenylbutyl)sulfonyl]-N,N-dipropylacetamide 126 (2.23 g, 56%) was isolated as a colourless oil; v_{max}/cm⁻¹ (film): 2964, 2937 (CH), 1641 (CO), 1455, 1319, 1149 (SO₂), 701 (CS); δ_H (CDCl₃, 400 MHz): 0.91 (3H, t, J 7.3, one of NCH₂CH₂CH₃), 0.94 (3H, t, J 7.3, one of NCH₂CH₂CH₃), 1.53–1.69 (4H, m, $2 \times NCH_2CH_2CH_3$), 1.73–1.84 [2H, m, C(3')H₂], 1.87–1.97 [2H, m, C(2')H₂], 2.62–2.70 [2H, m, C(4')H₂], 3.26–3.41 [6H, m, 2 × NCH₂CH₂CH₃ and C(1')H₂], 3.98 (2H, s, SO₂CH₂CO), 7.13–7.21 (3H, m, ArH), 7.23– 7.33 (2H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 11.2 (CH₃, one of NCH₂CH₂CH₃), 11.3 (CH₃, one of NCH₂CH₂CH₃), 20.8 (CH₂, one of NCH₂CH₂CH₃), 21.7 [CH₂, C(2')H₂], 22.4 (CH₂, one of NCH₂CH₂CH₃), 30.1 [CH₂, C(3')H₂], 35.4 [CH₂, C(4')H₂], 48.4, 50.7, 53.4 $(3 \times CH_2, 2 \times NCH_2CH_2CH_3 \text{ and } C(1')H_2], 56.0 (CH_2, SO_2CH_2CO), 126.0 (CH, aromatic)$ CH), 128.3 ($2 \times CH$, aromatic CH), 128.4 ($2 \times CH$, aromatic CH), 141.4 (C, aromatic C), 161.9 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₈H₃₀NO₃S [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 °C 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 °C; v_{max}/cm^{-1} (KBr): 2976, 2963, 2936 (CH), 1647 (CO), 1469, 1458, 1313, 1150 (SO₂), 808, 772 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 0.86 (3H, t, *J* 7.4, one of NCH₂CH₂CH₃), 0.94 (3H, t, *J* 7.4 one of NCH₂CH₂CH₃), 1.35 (3H, t, *J* 7.5, ArCH₂CH₃), 1.45–1.54 (2H, m, one of NCH₂CH₂CH₃), 3.19–3.26 (2H, m, one of NCH₂CH₂CH₃), 3.37–3.46 (2H, m, one of NCH₂CH₂CH₃), 4.25 (2H, s, SO₂CH₂CO), 7.35 (1H, dd appears as t, *J* 7.7, Ar*H*^{*a*}); $\delta_{\rm C}$

(CDCl₃,150.9 MHz): 11.2 (CH₃, one of NCH₂CH₂CH₃), 11.3 (CH₃, one of NCH₂CH₂CH₃), 15.8 (CH₃, ArCH₂CH₃), 20.6 (CH₂, one of NCH₂CH₂CH₃), 22.2 (CH₂, one of NCH₂CH₂CH₃), 26.2 (CH₂, ArCH₂CH₃), 48.1 (CH₂, one of NCH₂CH₂CH₃), 50.6 (CH₂, one of NCH₂CH₂CH₃), 60.0 (CH₂, SO₂CH₂CO), 126.2 (CH, aromatic *C*H^b), 130.5 (CH, aromatic *C*H^a), 130.9 (CH, aromatic *C*H^d), 134.2 (CH, aromatic *C*H^c), 136.6 (C, aromatic *C*), 144.7 (C, aromatic *C*), 160.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for C₁₆H₂₆NO₃S [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 °C 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, 1morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone 119 (2.13 g, 76%) was isolated as a white crystalline solid; mp 125–127 °C; (Found: C, 57.69; H, 6.86, N 4.42, C₁₅H₂₁NO₄S requires C, 57.86; H, 6.80, N 4.50%); v_{max}/cm⁻¹ (neat, ATR): 2968, 2853 (CH), 1639, 1615 (CO), 1461, 1313, 1163, 1130, 1114 (SO₂), 751, 701 (CS); δ_H (CDCl₃, 600 MHz): 2.17-2.29 [2H, m, C(2')H₂], 2.79 [2H, t, J 7.6, C(3')H₂], 3.18-3.27 [2H, m, C(1')H₂], 3.56–3.64 [2H, sym m, morpholine CH₂], 3.65–3.72 (4H, sym m, morpholine CH₂), 3.73–3.78 [2H, sym m, morpholine CH₂], 4.04 (2H, s, SO₂CH₂CO), 7.16–7.25 (3H, m, ArH), 7.27–7.34 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 23.5 [CH₂, C(2')H₂], 34.1 [CH₂, C(3')H₂], 42.7 [CH₂, morpholine NCH₂], 47.6 [CH₂, morpholine NCH₂], 52.8 [CH₂, C(1')H₂], 55.9 (CH₂, SO₂CH₂CO), 66.4 (CH₂, morpholine OCH₂), 66.5 (CH₂, morpholine OCH₂), 126.5 (CH, aromatic CH), 128.4 (CH, 2 × aromatic CH), 128.6 (CH, 2 × aromatic CH), 139.8 (C, aromatic C), 160.6 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₅H₂₂NO₄S [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 °C 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 °C (Found: C, 58.95; H, 7.11, N 4.05, C₁₆H₂₃NO₄S requires C, 59.05; H, 7.12, N 4.30%); v_{max}/cm⁻¹ (neat, ATR): 1648, 1636 (CO), 1437, 1273, 1131, 1115 1033 (SO₂) 750 (CS); δ_H (CDCl₃, 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')H₂], 3.58–3.64 (2H, m, morpholine CH₂), 3.65–3.72 (4H, m, morpholine CH₂), 3.74–3.78 (2H, m, morpholine CH₂), 4.05 (2H, s, SO₂CH₂CO), 7.14–7.22 (3H, m, ArH), 7.25–7.31 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 21.5 [CH₂, C(2')H₂], 30.0 [CH₂, C(3')H₂], 35.3 [CH₂, C(4')H₂], 42.7 (CH₂, morpholine NCH₂), 47.6 (CH₂, morpholine NCH₂), 53.4 [CH₂, C(1')H₂], 55.8 (CH₂, SO₂CH₂CO), 66.4 (CH₂, morpholine OCH₂), 66.5 (CH₂, morpholine OCH₂), 126.0 (CH, aromatic CH), 128.4 (CH, $2 \times \text{aromatic CH})$, 128.5 (CH, 2 × aromatic CH), 141.2 (C, aromatic C), 160.7 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₆H₂₂N₃O₄S [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 °C 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 °C (Found: C, 59.73; H, 9.51, N 3.80, S 8.67, C₁₈H₃₅NO4S requires C, 59.80; H, 9.76, N 3.87, S 8.87%); v_{max}/cm^{-1} (KBr): 2957, 2921, 2850 (CH), 1647 (CO), 1474, 1445, 1272, 1116, 1041 (SO₂), 722 (CS); δ_{H} (CDCl₃, 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 C*H*₂), 3.66–3.74 (4H, m, morpholine C*H*₂), 3.75–3.79 (2H, m, morpholine C*H*₂), 4.05 (2H, s, SO₂C*H*₂CO); δ_{C} (CDCl₃, 150.9 MHz): 14.3 [CH₃, C(12')H₃], 21.8, 22.7, 28.3, 29.1, 29.3, 29.4, 29.5, 29.6 (2 signals overlapping), 31.9 [10 × CH₂, C(11')H₂, C(10')H₂, C(9')H₂, C(8')H₂, C(7')H₂, C(6')H₂, C(5')H₂, C(4')H₂, C(3')H₂, C(2')H₂,], 42.7 (CH₂, br, morpholine NCH₂), 47.6 (CH₂, br, morpholine NCH₂), 53.6 [CH₂, C(1')H₂], 55.8 (CH₂, SO₂CH₂CO), 66.5 (CH₂, morpholine OCH₂), 66.6 (CH₂, morpholine OCH₂), 160.6 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₈H₃₆NO₄S [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 °C 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 °C (Found: C, 56.76; H, 6.52, N 4.81, S 10.43, C₁₄H₁₉NO4S requires C, 56.55; H, 6.44, N 4.71, S 10.78%); v_{max}/cm^{-1} (KBr): 3005, 2954, 2850 (CH), 1645 (CO), 1464, 1439, 1313, 1276, 1258, 1230, 1161, 1116, 1035 (SO₂), 815, 776, 751 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.35 (3H, t, *J* 7.5, ArCH₂CH₃), 3.10 (2H, q, *J* 7.5, ArCH₂CH₃), 3.56–3.62 [2H, sym m, morpholine CH₂], 4.27 (2H, s, SO₂CH₂CO), 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); $\delta_{\rm C}$ (CDCl₃, 75.5 MHz): 15.9 (CH₃, ArCH₂CH₃), 26.2 (CH₂,

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Ar*C*H₂CH₃), 42.7 (CH₂, morpholine N*C*H₂), 47.6 (CH₂, morpholine N*C*H₂), 59.9 (CH₂, SO₂*C*H₂CO), 66.6 (CH₂, morpholine O*C*H₂), 66.7 (CH₂, morpholine O*C*H₂), 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 C₁₄H₂₀NO₄S [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 °C 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,Ndibenzyl-2-[(3-phenylpropyl)sulfonyl]acetamide 120 (2.56 g, 65%) was isolated as a white crystalline solid; mp 81–82 °C v_{max}/cm⁻¹ (KBr): 3031, 2946, 2956, 2914 (CH), 1652 (CO), 1497, 1420, 1320, 1283, 1221, 1129 (SO₂), 752, 699 (CS); δ_H (CDCl₃, 400 MHz): 2.19–2.31 [2H, m, C(2')H₂], 2.80 [2H, t, J 7.6, C(3')H₂], 3.31–3.39 [2H, m, C(1')H₂] 4.05 (2H, s, SO₂CH₂CO), 4.66 (2H, s, one of NCH₂C₆H₅), 4.68 (2H, s, one of NCH₂C₆H₅), 7.11–7.16 (2H, m, ArH), 7.17–7.41 (13H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 23.6 [CH₂, *C*(2')H₂], 34.2 [CH₂, *C*(3')H₂], 49.4 (CH₂, one of N*C*H₂Ar), 51.2 (CH₂, one of N*C*H₂Ar), 53.0 [CH₂, C(1')H₂], 56.3 (CH₂, SO₂CH₂CO), 126.2 (2 × CH, aromatic CH), 126.5 (CH, aromatic CH), 127.6 (3 × CH, aromatic CH), 128.1 (CH, aromatic CH), 128.5 (2 × CH, aromatic CH), 128.6 (2 \times CH, aromatic CH), 128.8 (2 \times CH, aromatic CH), 129.2 (2 \times CH, aromatic CH), 135.3 (C, aromatic C), 135.9 (C, aromatic C), 139.9 (C, aromatic C), 163.2 (C, CO); HRMS (ESI+): Exact mass calculated for C₂₅H₂₈NO₃S [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-[(3phenylpropyl)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 °C 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-[(3phenylpropyl)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 $(2 \times 50 \text{ mL})$, 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-[(3phenylpropyl)sulfonyl]acetic acid 123 as a white solid (7.17 g, 76%); mp 95–97 °C, (Found: C, 54.40; H, 5.75, C₁₁H₁₄O₄S requires C, 54.53; H, 5.82,%); v_{max}/cm⁻¹ (KBr): 3014 (OH), 2953 (CH) 1703 (CO), 1427, 1317, 1291, 1263, 1147, 1120 (SO₂), 910, 748, 695 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 2.13–2.26 [2H, sym m, C(2')H₂], 2.79 [2H, t, J 7.5, C(3')H₂], 3.20–3.31 [2H, m, C(1')H₂], 3.99 (2H, s, SO₂CH₂CO), 6.08 (1H, br s, OH), 7.19 (2H, d, J7.6, ArHortho), 7.23 (1H, t, J7.3, ArHpara), 7.31 (2H, t, J7.5, ArHmeta); δ_C (CDCl₃, 150.9 MHz): 23.4 [CH₂, C(2')H₂], 34.1 [CH₂, C(3')H₂], 52.9 [CH₂, C(1')H₂], 57.2 (CH₂, br, SO₂CH₂CO), 126.6 (CH, aromatic CH_{para}) 128.4 (2 × CH, aromatic CH_{ortho}), 128.7 (2 x CH, aromatic CH_{meta}), 139.6 (C, aromatic C), 166.2 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₁H₁₅O₄S [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 $(2 \times 30 \text{ mL})$, 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-[(4phenylbutyl)sulfonyl]acetic acid 124 as a white solid (4.22 g, 89%); mp 82-83 °C, v_{max}/cm⁻¹ (KBr): 3063, 3028, 3005 (OH), 2938, 2855 (CH), 1717 (CO), 1458, 1423, 1330, 1297, 1284, 1273, 1226, 1129 (SO₂), 911, 761, 744, 699, 609 (CS); δ_H (CDCl₃, 400 MHz): 1.75–1.86 [2H, m, C(3')H₂], 1.87–1.96 [2H, m, C(2')H₂], 2.68 [2H, t, J 7.4, C(4')H₂], 3.23–3.32 [2H, sym m, C(1')H₂], 3.98 (2H, s, SO₂CH₂CO), 5.92 (1H, br s, OH), 7.12– 7.23 (3H, m, ArH), 7.24–7.36 (2H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 21.4, 30.0 [2 × CH₂, $C(2')H_2$ and $C(3')H_2$, 35.2 [CH₂, $C(4')H_2$], 53.6 [CH₂, $C(1')H_2$], 57.2 (CH₂, br, SO₂CH₂CO), 126.2 (CH, aromatic CH) 128.4 (2 × CH, aromatic CH), 128.5 (2 × CH, aromatic CH), 141.1 (C, aromatic C), 166.4 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₂H₁₅O₄S [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.

Procedure A

Potassium carbonate (ACS reagent, $\geq 99.0\%$) 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 °C. 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 0° 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, \geq 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 °C. 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 °C, 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 °C. 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 °C, and stirring was continued at 40 °C, 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 °C 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 °C 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} v_{max}/cm^{-1} (film): 2134 (C=N₂), 1665 (CO), 1325, 1269, 1142 (SO₂); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 2.07–2.23 [2H, m, C(2')H₂], 2.31 (3H, s, COCH₃), 2.78 [2H, t, *J* 7.4, C(3')H₂], 3.23–3.41 [2H, m, C(1')H₂], 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 °C 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} v_{max}/cm^{-1} (KBr): 2126 (C=N₂), 1655 (CO), 1324, 1286, 1140 (SO₂); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.72–1.93 [4H, m, C(2')H₂ and C(3')H₂], 2.36 (3H, s, COCH₃), 2.67 [2H, t, *J* 7.1, C(4')H₂], 3.28–3.41 [2H, m, C(1')H₂], 7.12–7.35 (5H, m, ArH).

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-[(2ethylphenyl)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; C₁₁H₁₂N₂O₃S requires; C, 52.37; H, 4.79; N, 11.0; %); v_{max}/cm^{-1} (film): 2974, 2938, 2878 (CH), 2115 (C=N₂), 1668 (CO), 1364, 1332, 1256, 1155 (SO₂), 764, 696 (CS); δ_{H} (CDCl₃, 300 MHz): 1.31 (3H, t, *J* 7.5, ArCH₂CH₃), 2.19 (3H, s, COCH₃), 2.98 (1H, q, *J* 7.5, ArCH₂CH₃), 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} (CDCl₃, 75.5 MHz): 15.0 (CH₃, ArCH₂CH₃), 25.7 (CH₂, ArCH₂CH₃), 27.0 (CH₃, CH₃), 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, CO) (Diazo carbon not seen); HRMS (ESI+): Exact mass calculated for C₁₁H₁₃N₂O₃S [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 °C 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} v_{max}/cm^{-1} (KBr): 2115 (C=N₂), 1649 (CO), 1331, 1283, 1225, 1138 (SO₂); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.70–1.97 [4H, m, C(2')H₂ 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 °C) 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-1ylsulfonyl)-1-phenylethanone **60** (0.68 g, 95%) as a yellow solid; mp 93–94 °C, v_{max}/cm^{-1} (KBr): 2955, 2921, 2898, 2434 (CH), 2125 (C=N₂), 1651 (CO), 1599, 1579 (C=C, Ar), 1449, 1331, 1283, 1283, 1222, 1142, 1110 (SO₂), 924, 854, 770, 784, 708, 673 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.93–2.00 [2H, m, C(2')H₂], 2.23 [2H, apparent q, J 7.1, C(3')H₂], 3.51–3.58 [2H, m, C(1')H₂], 5.04–5.11 [2H, m, C(5')H₂], 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 (CDCl₃, 150.9 MHz): 21.8 [CH₂, C(2')H₂], 31.8 [CH₂, C(3')H₂], 56.1 [CH₂, C(1')H₂], 80.3 $(C, C=N_2)$, 116.8 [CH₂, $C(5')H_2$], 127.4 (2 × CH, aromatic, CH_{ortho}), 129.1 (2 × CH, aromatic CH_{meta}), 133.4 (CH, aromatic CH_{para}), 135.6 (C, aromatic, C), 136.0 [CH, C(4')H], 183.4 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₃H₁₅N₂O₃S [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 °C), 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 4acetamidobenzenesulfonyl 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 °C, v_{max}/cm^{-1} (KBr): 2958, 2932, 2917, 2878 (CH), 2112 (C=N₂), 1646 (CO), 1599, 1580 (C=C), 1462, 1446, 1409, 1337, 1317, 1286, 1226, 1184, 1141, 1129, 1110 (SO₂), 721, 699 (CS); δ_{H} (CDCl₃, 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, Ar*H*_{meta}), 7.62 (1H, t, *J* 7.5, Ar*H*_{para}), 7.68 (2H, d, *J* 7.7, Ar*H*_{ortho}); δ_{C} (CDCl₃, 150.9 MHz): 17.8 [CH₃, *C*(6')H₃ or *CH*₃], 22.9 [CH₂, *C*(2')H₂], 25.7 [CH₃, *C*(6')H₃ or *CH*₃], 26.3 [CH₂, *C*(3')H₂], 56.2 [CH₂, *C*(1')H₂], 80.2 (C, *C*=N₂), 121.8 [CH, *C*(4')H], 127.4 (2 × CH, aromatic *CH*_{ortho}), 129.1 (2 × CH, aromatic *CH*_{meta}), 133.4 (CH, aromatic, *CH*_{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 C₁₅H₁₉N₂O₃S [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 acetatehexane (20:80–30:70) as eluent to afford 2-diazo-2-[2-(ethylphenyl)sulfonyl]-1phenylethanone **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, C₁₆H₁₄N₂O₃S requires C, 61.13; H, 4.49; N 8.91%); v_{max}/cm⁻¹ (KBr): 2967 (CH), 2117 (C=N₂), 1659 (CO), 1332, 1279, 1153 (SO₂); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.32 (3H, t, *J* 7.5, ArCH₂CH₃), 3.02 (2H, quartet, *J* 7.5, ArCH₂CH₃), 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, Ar*H*^{*a*}); $\delta_{\rm C}$ (CDCl₃, 75.5 MHz): 15.2 (CH₃, ArCH₂CH₃), 25.8 (CH₂, CH₂CH₃), 126.3 (CH, aromatic CH), 127.4 (CH, aromatic CH × 2), 128.8 (CH, aromatic CH × 2), 130.7 (CH, aromatic CH), 131.6 (CH, aromatic CH), 132.9 (CH, aromatic CH), 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 C₁₆H₁₅N₂O₃S [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; C₁₁H₁₂N₂O₄S requires; C, 49.24; H 4.51; N, 10.44; S 11.95 %); v_{max}/cm⁻¹ (KBr): 2960, 2925 (CH), 2136 (C=N₂), 1718 (CO), 1401, 1325, 1302, 1128, 1192 (SO₂), 751, 738, 713, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 3.08–3.24 [2H, m, C(1')H₂ or C(2')H₂], 3.65–3.74 [2H, m, C(1')H₂ or C(2')H₂], 3.78 (3H, s, COOCH₃), 7.15–7.20 (2H, m, ArH), 7.21–7.27 (1H, m, ArH), 7.29–7.34 (2H, m, ArH); $\delta_{\rm C}$ (CDCl₃, 150.9 MHz): 29.1 [CH₂, *C*(1')H₂ or *C*(2')H₂], 53.0 (CH₃, COOCH₃) 57.1 [CH₂, *C*(1')H₂ or *C*(2')H₂], 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, CO); HRMS (ESI+): Exact mass calculated for C₁₁H₁₃N₂O₄S [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]acetate¹⁴ **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 °C 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; v_{max}/cm^{-1} (film): 2129 (C=N₂), 1711 (CO), 1335, 1291, 1148 (SO₂);

δ_H (CDCl₃, 300 MHz): 1.28 (3H, t, *J* 7.1, OCH₂CH₃), 2.09–2.25 (2H, m, C(2')H₂), 2.78 [2H, t, *J* 7.4, C(3')H₂], 3.30–3.43 [2H, m, C(1')H₂], 4.29 (2H, q, *J* 7.1 OCH₂CH₃), 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 °C 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} v_{max}/cm⁻¹ (film): 2131 (C=N₂), 1718 (CO), 1338, 1224, 1148 (SO₂); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.73–1.92 [4H, m, C(2')H₂ and C(3')H₂], 2.66 [2H, t, *J* 7.3, C(4')H₂], 3.43–3.46 [2H, m, C(1')H₂], 3.86 (3H, s, COOCH₃), 7.12–7.26 (3H, m, ArH), 7.24–7.36 (2H, m, ArH).

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 °C 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; v_{max}/cm^{-1} (film): 2130 (C=N₂), 1716 (CO), 1337, 1298, 1147 (SO₂); $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.43–1.53, 1.62–1.73 [2 × 2H, m, C(3')H₂ and C(4')H₂], 1.79–1.91 [2H, m, C(2')H₂], 2.63 [2H, t, *J* 7.6, C(5')H₂], 3.23–3.41 [2H, m, C(1')H₂], 3.86 (3H, s, COOCH₃), 7.12–7.23 (3H, m, ArH), 7.24–7.32 (2H, m, ArH).

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-(4fluorophenylbutyl)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 °C. 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 ¹H NMR analysis; v_{max}/cm^{-1} (film): 2132 (C=N₂), 1718 (CO), 1510, 1336, 1299, 1222, 1145 (SO₂); δ_H (CDCl₃, 300 MHz): 1.67–1.94 [4H, m, C(2')H₂, C(3')H₂], 2.63 [2H, t, J 7.3, C(4')H₂], 3.35–3.43 [2H, m, C(1')H₂], 3.86 (3H, s, OCH₃), 6.92–7.03 (2H, m, ArH), 7.06–7.16 (2H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 22.0, 29.8 [2 × CH₂, *C*(2')H₂, *C*(3')H₂], 34.4 [CH₂, *C*(4')H₂], 53.2 (CH₃, OCH₃), 56.4 [CH₂, *C*(1')H₂], 72.9 (C, $C=N_2$), 115.2 [2 × ArCH, d, ² J_{CF} 21.1, C(3)H, C(5)H], 129.7 [2 × ArCH, d, ³ J_{CF} 7.7, *C*(2)H, *C*(6)H], 136.7 [C, d, ⁴*J*_{CF} 3.2, *C*(1)], 160.5 (C, *CO*), 161.4 [C, ¹*J*_{CF} 243.8, *C*(4)]; HRMS (ESI+): Exact mass calculated for C₁₃H₁₆FN₂O₄S [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, 1 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 °C 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} v_{max}/cm^{-1} (film): 2128

(C=N₂), 1719 (CO), 1336, 1297, 1145 (SO₂); $\delta_{\rm H}$ (CDCl₃, 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, COOC*H*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 °C 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}); v_{max} /cm⁻¹ (KBr): 2129 (C=N₂), 1727 (CO), 1339, 1297, 1219, 1144 (SO₂); $\delta_{\rm H}$ (CDCl₃, 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, CO₂C*H*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 $^{\circ}$ C but instead heating to 40 $^{\circ}$ C 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; v_{max}/cm^{-1} (film): 2959, 2359 (CH), 2131 (C=N₂), 1715 (CO), 1645 (C=C, Ar), 1436, 1338, 1297, 1222, 1144, 1085 (SO₂), 742 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 2.55–2.64 [2H, sym m, C(2')H₂], 3.45–3.53 [2H, m, C(1')H₂], 3.88 (3H, s, COOCH₃), 5.10–5.23 [2H, sym m, C(4')H₂], 5.73–5.84 [1H, sym m, C(3')H]; $\delta_{\rm C}$ (CDCl₃, 150.9 MHz) 27.2 [CH₂, *C*(2')H₂], 53.1 (CH₃, COOCH₃), 55.8 [CH₂, *C*(1')H₂], 73.3 (C, *C*=N₂), 117.6 [CH₂, 1202]

C(4')H₂], 133.3 [CH, *C*(3')H], 160.5 (C, *CO*); HRMS (ESI+): Exact mass calculated for C₇H₁₁N₂O₄S [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 °C), 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 acetatehexane (10:90-20:80)as eluent to afford methyl 2-diazo-2-(pent-4-en-1ylsulfonyl)acetate **59** (0.75 g, 60%) as a pale yellow oil; v_{max}/cm^{-1} (neat, ATR): 2957 (CH), 2126 (C=N₂), 1713 (CO), 1642 (C=C, Ar), 1437, 1332, 1293, 1219, 1143, 1082 (SO_2) , 740 (CS); δ_H (CDCl₃, 300 MHz): 1.87–2.02 [2H, m, C(2')H₂], 2.22 [2H, apparent q, J 7.1, C(3')H₂], 3.33–3.45 [2H, m, C(1')H₂], 3.88 (3H, s, COOCH₃), 5.03–5.14 [2H, m, C(4')H₂], 5.67–5.84 [1H, m, C(5')H₂]; δ_C (CDCl₃, 75.5 MHz): 21.8 [CH₂, C(2')H₂], 31.8 [CH₂, C(3')H₂], 53.1 (CH₃, COOCH₃) 55.9 [CH₂, C(1')H₂], 73.0 (C, C=N₂), 116.8 [CH₂, C(5')H₂], 136.0 [CH, C(4')H], 160.5 (C, CO); HRMS (ESI+): Exact mass calculated for C₈H₁₃N₂O₄S [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, C₁₂H₁₄N₂O₄S requires C, 51.05; H, 5.00; N 9.92%); v_{max}/cm^{-1} (film): 2982 (CH), 2126 (C=N₂), 1719 (CO), 1337, 1292, 1159 (SO₂); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 1.17 (3H, t, *J* 7.1, OCH₂CH₃), 1.31 (3H, t, *J* 7.5, ArCH₂CH₃), 3.00 (2H, quartet, *J* 7.5, ArCH₂CH₃), 4.16 (2H, quartet, *J* 7.1, OCH₂CH₃), 7.32–7.48 (2H, overlapping dd and ddd, appears as m, ArH^{*d*} and ArH^{*b*}), 7.57 (1H, ddd, *J* 1.4, 5.9, 7.6, ArH^{*c*}), 8.10 (1H, dd, *J* 1.3, 8.0, ArH^{*a*}); $\delta_{\rm C}$ (CDCl₃, 75.5 MHz): 14.0 (CH₃, OCH₂CH₃), 15.2 (CH₃, ArCH₂CH₃), 25.8 (CH₂, ArCH₂CH₃), 62.3 (CH₂, OCH₂CH₃), 126.2 (CH, aromatic CH^b), 130.8 (CH, aromatic CH^a), 131.4 (CH, aromatic CH^d), 134.1 (CH, aromatic CH^c), 138.9 (C, aromatic *C*), 143.6 (C, aromatic *C*), 159.7 (C, *CO*); HRMS (ESI+): Exact mass calculated for C₁₂H₁₄N₂O₄S [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 °C, in accordance with procedure C. The mixture was heated to 40 °C and stirred at 40 °C 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 acetatehexane (20:80-30:70)as eluent to give 2-diazo-N,N-diethyl-2-[(3phenylpropyl)sulfonyl]acetamide **51** (0.75 g, 63%) as a yellow oil; $v_{max}cm^{-1}$ (film): 2980, 2938 (CH), 2096 (C=N₂), 1634 (CO), 1455, 1423, 1329, 1166, 1141 (SO₂), 751, 702 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.19 (6H, t, J 7.1, 2 × NCH₂CH₃), 2.12–2.25 [2H, m, C(2')H₂], 2.78 [2H, t, J 7.6, C(3')H₂], 3.37 [4H, q, J 7.1, 2 × NCH₂CH₃], 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 (CDCl₃, 150.9 MHz): 13.1 (CH₃, 2 × NCH₂CH₃), 24.5 [CH₂, C(2')H₂], 34.1 [CH₂, C(3')H₂], 41.9 [CH₂, 2 × NCH₂CH₃], 56.9 [CH₂, C(1')H₂], 68.9 (C, C=N₂), 126.5 (CH, aromatic CH), 128.5 (CH, 2 × aromatic CH), 128.7 (CH, 2 × aromatic CH), 140.0 (C, aromatic C), 158.5 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₅H₂₂N₃O₃S [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 4nitrobenzenesulfonyl azide (0.42 g, 1.86 mmol) in acetonitrile (15 mL). The mixture was stirred at 40 °C 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, C₁₆H₂₃N₃O₃S requires C, 56.95; H, 6.87; N 12.45%); v_{max}/cm⁻¹ (film): 2986, 2946 (CH), 2098 (C=N₂), 1638 (CO), 1423, 1325, 1140 (SO₂), 701 (CS); δ_H (CDCl₃, 600 MHz): 1.19 (6H, t, J 7.1, 2 × NCH₂CH₃), 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 × NCH₂CH₃], 3.57–3.65 [2H, m, C(1') H_2], 7.11–7.22 (3H, m, ArH), 7.23–7.34 (2H, m, ArH); δ_C $(CDCl_3, 150.9 \text{ MHz})$: 13.1 $(CH_3, 2 \times NCH_2CH_3)$, 22.4 $[CH_2, C(2')H_2]$, 29.8 $[CH_2,$ $C(3')H_2$, 35.3 [CH₂, $C(4')H_2$], 41.8 [CH₂, br, 2 × NCH₂CH₃], 57.3 [CH₂, $C(1')H_2$], 68.7 (C, C=N₂), 126.0 (CH, aromatic CH), 128.3 (CH, 2 × aromatic CH), 128.4 (CH, 2 × aromatic CH), 141.3 (C, aromatic C), 158.5 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₆H₂₄N₃O₃S [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 °C 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,Ndipropylacetamide 50 (0.68 g, 63%) was isolated as a yellow oil; (Found: C, 57.82; H, 7.22, N, 11.50, C₁₇H₂₅N₃O₃S requires C, 58.09; H, 7.17, N, 11.96%); v_{max}/cm⁻¹ (film): 2966, 2877 (CH), 2094 (C=N₂), 1632 (CO), 1497, 1419, 1329, 1234, 1141 (SO₂), 751, 702 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 0.91 (6H, t, J 7.4, 2 × NCH₂CH₂CH₃), 1.52–1.67 (4H, sym m, 2 × NCH₂CH₂CH₃), 2.13–2.24 [2H, m, C(2')H₂], 2.78 [2H, t, J 7.6, C(3')H₂], 3.21-3.29 [4H, m, 2 × NCH₂CH₂CH₃], 3.54-3.63 [2H, m, C(1')H₂], 7.14-7.24 (3H, m, Ar*H*), 7.26–7.34 (2H, m, Ar*H*); δ_C (CDCl₃, 150.9 MHz): 11.2 (CH₃, 2 × NCH₂CH₂CH₃), 21.3 (CH₂, br, 2 × NCH₂CH₂CH₃), 22.5 [CH₂, C(2')H₂], 34.1 [CH₂, C(3')H₂], 49.4 (CH₂, br, $2 \times \text{NCH}_2\text{CH}_2\text{CH}_3$), 56.9 [CH₂, $C(1')\text{H}_2$], 68.9 (C, $C=N_2$), 126.5 (CH, aromatic CH), 128.4 (CH, 2 × aromatic CH), 128.6 (CH, 2 × aromatic CH), 140.0 (C, aromatic C), 158.6 (C, CO); 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 °C 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; v_{max}/cm^{-1} (film): 2966, 2936 (CH), 2095 (C=N₂), 1636 (CO), 1420, 1331, 1141 (SO₂), 749, 701 (CS); δ_{H} (CDCl₃, 600 MHz): 0.92 (6H, t, *J* 7.4, 2 × NCH₂CH₂CH₃), 1.55–1.64 (4H, m, 2 × NCH₂CH₂CH₃), 1.74–1.81 [2H, m, C(3')H₂], 1.85–1.91 [2H, m, C(2')H₂], 2.66 [2H, t, *J* 7.6, C(4')H₂], 3.22–3.27 (4H, m, 2 × NCH₂CH₂CH₃), 3.58–3.63 [2H, m, C(1')H₂], 7.14–7.21 (3H, m, ArH), 7.25–7.30 (2H, m, 24)

Ar*H*); δ_{C} (CDCl₃, 150.9 MHz): 11.2 (CH₃, 2 × NCH₂CH₂CH₃), 21.3 (CH₂, br, 2 × NCH₂CH₂CH₃), 22.4 [CH₂, *C*(2')H₂], 29.8 [CH₂, *C*(3')H₂], 35.3 [CH₂, *C*(4')H₂], 49.4 (CH₂, br, 2 × NCH₂CH₂CH₃), 57.3 [CH₂, *C*(1')H₂], 68.8 (C, *C*=N₂), 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 C₁₈H₂₈N₃O₃S [M+H]⁺, 366.1851. Found 366.1853. m/z (ESI+): 338.3 [(M-N₂)+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 °C 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; v_{max}/cm⁻¹ (film): 2967, 2936, 2877 (CH), 2089 (C=N₂), 1638 (CO), 1420, 1329, 1153 (SO_2) , 687 (CS); δ_H (CDCl₃, 600 MHz): 0.85 (6H, t, J 7.4, 2 × NCH₂CH₂CH₃), 1.31 (3H, t, J 7.5, ArCH₂CH₃), 1.48–1.56 (4H, m, $2 \times \text{NCH}_2\text{CH}_2\text{CH}_3$) 2.99 (2H, q, J 7.5, ArCH₂CH₃), 3.21-3.27 (4H, m, $2 \times \text{NCH}_2\text{CH}_2\text{CH}_3$), 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, Ar H^a); δ_C (CDCl₃, 150.9 MHz): 11.1 (CH₃, 2 × NCH₂CH₂CH₃), 15.1 (CH₃, ArCH₂CH₃), 21.2 (CH₂, 2 × NCH₂CH₂CH₃), 25.9 (CH₂, ArCH₂CH₃), 49.2 (4H, m, 2 × NCH₂CH₂CH₃), 73.0 (C, C=N₂), 126.3 (CH, aromatic CH^b), 130.7 (2 × CH, aromatic CH^a and aromatic CH^d), 133.7 (CH, aromatic CH^c), 139.9 (C, aromatic C), 143.3 (C, aromatic C), 158.3 (C, CO); 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 °C 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 °C (Found: C, 53.41; H, 5.79, N 12.27, C₁₅H₁₉N₃O₄S requires C, 53.40; H, 5.68, N, 12.45%); v_{max}/cm⁻¹ (KBr): 2858 (CH), 2110 (C=N₂), 1636 (CO), 1440, 1427, 1322, 1286, 1227, 1140, 1112 (SO₂), 857, 774, 751, 706 (CS); δ_H (CDCl₃, 600 MHz): 2.14–2.22 [2H, m, C(2')H₂], 2.78 [2H, t, J7.6, $C(3')H_2$, 3.47–3.58 [6H, m, $C(1')H_2$ and morpholine CH_2], 3.63–3.73 [4H, m, morpholine CH₂], 7.16–7.20 (2H, m, ArH), 7.21–7.25 (1H, m, ArH), 7.28–7.32 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 24.4 [CH₂, *C*(2')H₂], 33.9 [CH₂, *C*(3')H₂], 45.6 (CH₂, br, morpholine NCH₂), 56.9 [CH₂, C(1')H₂], 66.4 (CH₂, morpholine OCH₂), 69.6 (C, C=N₂), 126.5 (CH, aromatic CH), 128.4 (CH, 2 × aromatic CH), 128.7 (CH, 2 × aromatic CH), 139.8 (C, aromatic C), 158.7 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₅H₂₀N₃O₄S [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 °C 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 °C 186

 v_{max}/cm^{-1} (KBr): 2925, 2858 (CH), 2107 (C=N₂), 1627 (CO), 1436, 1317, 1290, 1142, 1110 (SO₂) 711, 698 (CS); δ_{H} (CDCl₃, 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 C*H*₂], 3.69–3.72 [4H, m, morpholine C*H*₂], 7.14–7.22 (3H, m, Ar*H*), 7.25–7.31 (2H, m, Ar*H*); δ_{C} (CDCl₃, 150.9 MHz): 22.4 [CH₂, *C*(2')H₂], 29.8 [CH₂, *C*(3')H₂], 35.3 [CH₂, *C*(4')H₂], 45.6 [CH₂, br morpholine NCH₂], 57.5 [CH₂, *C*(1')H₂], 66.4 [CH₂, morpholine OCH₂], 69.4 (C, *C*=N₂), 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, *CO*); HRMS (ESI+): Exact mass calculated for C₁₆H₂₂N₃O₄S [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 4nitrobenzenesulfonyl azide (0.95 g, 4.15 mmol) in acetonitrile (10 mL). The mixture was stirred at 40 °C 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)-1morpholinoethanone 49 (1.02 g, 63%) as a yellow solid; (Found: C, 56.10; H, 8.73, N 10.63, S 8.02, C₁₈H₃₃N₃O₄S requires C, 55.79; H, 8.58, N 10.84, S 8.27%); mp 76–77 °C; v_{max}/cm⁻¹ (KBr): 2921, 2851 (CH), 2115 (C=N₂), 1624 (CO), 1437, 1329, 1279, 1124 (SO₂), 776, 717 (CS); δ_H (CDCl₃, 300 MHz): 0.88 [3H, t, J 6.7, C(12')H₃], 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')H₂], 1.76–1.95 [2H, m, C(2')H₂], 3.43–3.59 [6H, m, C(1')H₂ and morpholine CH₂], 3.68–3.76 [4H, sym m, morpholine CH₂]; δ_C (CDCl₃, 75.5 MHz): 14.1 [CH₃, C(12')H₃], 22.7, 22.8, 28.1, 29.0, 29.2, 29.3, 29.5, 29.6 (2 signals overlapping), $31.9 [10 \times CH_2, C(11')H_2, C(10')H_2, C(9')H_2, C(8')H_2, C(7')H_2, C(6')H_2, C(5')H_2, C(4')H_2, C(4')$ C(3')H₂, C(2')H₂], 45.7 (CH₂, morpholine NCH₂), 57.7 [CH₂, C(1')H₂], 66.4 (CH₂, morpholine OCH₂), 69.5 (C, C=N₂), 158.8 (C, CO); HRMS (ESI+): Exact mass

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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 °C 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 acetatehexane (20:80–30:70–40:60) as eluent to give 2-diazo-2-[(2-ethylphenyl)sulfonyl]-1morpholinoethanone **58** (0.43 g, 32%) as a yellow solid; mp 53–54 °C; v_{max}/cm^{-1} (KBr): 2967, 2923, 2859 (CH), 2108 (C=N₂), 1645 (CO), 1423, 1323, 1148, 1117 (SO₂), 716 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.32 (3H, t, J 7.5, ArCH₂CH₃), 3.00 (2H, q, J 7.5, ArCH2CH3), 3.49-3.54 [4H, sym m, morpholine CH2], 3.65-3.71 [4H, sym m, morpholine CH₂], 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 (CDCl₃, 150.9 MHz): 15.2 (CH₃, ArCH₂CH₃), 25.8 (CH₂, ArCH₂CH₃), 46.1 (CH₂, morpholine NCH₂), 66.5 (CH₂, morpholine OCH₂), 74.2 (C, C=N₂), 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, CO); HRMS (ESI+): Exact mass calculated for C₁₄H₁₈N₃O₄S [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; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 7.34–7.40 (1H, ddd appears as m, Ar*H*^d), 7.41–7.46 (1H, dd appears as m, Ar*H*^d) 7.57 (1H, ddd, *J* 7.6, 7.6, 1.4, Ar*H*^c), 8.04 (1H, dd, *J* 8.0, 1.3 Ar*H*^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 °C 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 °C (Found: C, 66.80; H, 5.65; N 9.38, C₂₅H₂₅N₃O₃S requires C, 67.09; H, 5.63; N 9.39%); v_{max}/cm⁻¹ (KBr): 3026, 2926 (CH), 2097 (C=N₂), 1638 (CO), 1458, 1436, 1421, 1329, 1139 (SO₂), 752, 699 (CS); δ_H (CDCl₃, 300 MHz): 2.13–2.28 [2H, m, C(2')H₂], 2.80 [2H, t, J 7.6, C(3')H₂], 3.57–3.68 [2H, m, C(1')H₂], 4.52 (4H, s, 2 × NCH₂Ph), 7.11–7.43 (15H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 24.4 [CH₂, C(2')H₂], 34.1 [CH₂, C(3')H₂], 50.1 (CH₂, 2 × NCH₂Ph), 56.9 [CH₂, C(1')H₂], 69.5 (C, C=N₂), 126.5 (CH, aromatic CH), 127.4 (CH, 3 × aromatic CH), 128.1 (CH, 2 × aromatic CH), 128.5 (CH, 2 × aromatic CH), 128.7 (CH, 2 × aromatic CH), 129.0 (CH, 5 × aromatic CH), 135.0 (C, 2 × aromatic C), 139.9 (C, aromatic C), 160.0 (C, CO); HRMS (ESI+): Exact mass calculated for C₂₅H₂₆N₃O₃S [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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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, CuCl₂ and Cu(OTf)₂, and the additive, for example NaBARF, KBARF, NaPF₆, KPF₆, LiPF₆, NaBF₄, 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 series³ 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.



Scheme 4.2

Recently, in this research group, Buckley⁷ carried out a similar set of experiments for the synthesis of *cis* thiopyran **26a** using CuCl₂/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 ¹H 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 ¹H 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 ¹H 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 ¹H NMR spectra of crude product mixture and purified compounds (*Table 4.6*, entry 2) in CDCl₃, 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 ¹H 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 ¹H 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 ¹H NMR spectra of crude product mixtures (400 MHz)

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

Examination of the ¹H 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.





In the crude spectra, characteristic singlets are frequently seen in the region of $\delta_{\rm H}$ 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



The next structure we envisaged to explain the singlets between $\delta_{\rm H}$ 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.



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 Mountjoy¹¹ and Pirrung and co-workers,¹² when α -diazoketones were exposed to rhodium catalysts (**Scheme 4.6**).



Scheme 4.6^{11,12}

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



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.



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 H¹NMR 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 compounds¹⁶ 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.



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



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

- a. Efficiency and relative ratios of isomers calculated using ¹H 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, OCH₃), *trans* thiopyran 26b; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*]. [¹H NMR signal used for calculation of X–H insertion product 148; δ_H 5.08 (1H, s, SO₂CHXCO)].
- b. Approx 2–4% hydride elimination product **149** observed in the ¹H NMR spectra of the crude product.
- c. Fraction contains *approx* 93% *cis* thiopyran **26a**, 3% *trans* thiopyran **26b**. Additional peaks observed in the ¹H NMR spectra of the purified product; δ_H 3.35 (s), 3.86 (s), 4.73 (s). Buckely⁷ 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.
- 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 ¹H 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 $\geq 81\%$ 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 by Novikov and co-workers using Rh₂(pfb)₄.²¹

While minor amounts of unidentified byproducts were detected in the ¹H NMR spectra of all of the crude reactions mixtures, the presence of hydride elimination product 149 (2-4%) was confirmed in the ¹H NMR spectrum of the reaction with (4R)-Bn **43** and (4S)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).



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}



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 (3S,8R)-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 <i>R</i>)-Ph 20	3	50-60 ^b	Crude Ratio: Purified Yield (%):	86 61% (95% ee) ^c (2 <i>S</i> ,3 <i>S</i>)	4	10
2	CuCl ₂	12	(4 <i>R</i>)-Ph 20	3	70–80 ^d	Crude Ratio: Purified Yield (%):	- 52% (98% ee) (2 <i>S</i> ,3 <i>S</i>)	-	-
3	CuCl ₂	6	(4 <i>R</i>)-Bn 43	3	70–80 ^b	Crude Ratio: Purified Yield (%):	88 67% (67% ee) ^e (2 <i>S</i> ,3 <i>S</i>)	9	3
4	Cu(OTf) ₂	12	(4 <i>R</i>)-Ph 20	2	40–50 ^d	Crude Ratio: Purified Yield (%):	- 38% (98% ee) (2 <i>S</i> ,3 <i>S</i>)	-	-
5	Cu(OTf) ₂	12	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	2	30-40 ^b	Crude Ratio: Purified Yield (%):	80 32% (94% ee) (2 <i>S</i> ,3 <i>S</i>)	10	10
6	Cu(OTf) ₂	12	(4 <i>R</i>)-Bn 43	2	30-40 ^{b,d}	Crude Ratio: Purified Yield (%):	- 28% (66% ee) (2 <i>S</i> ,3 <i>S</i>)	-	-

7	Cu(OTf) ₂	12	(4 <i>S</i>)- <i>t</i> -Bu 138	1.5	50-60 ^{b,d}	Crude Ratio:		-	-
						Purified Yield (%):	42% (70% ee)		
							(2R, 3R)		
8	Cu(OTf) ₂	6	(4 <i>R</i>)-Ph 20	6	30-40	Crude Ratio:	90	3	7
						Purified Yield (%):	11% (97% ee) ^f		
							(2S, 3S)		
9	Cu(OTf) ₂	-	(4 <i>R</i>)-Ph 20	1 week	10-20 ^g	Crude Ratio:	87	13	-
						Purified Yield (%):	17% (89% ee) ^h		
							(2S, 3S)		
10	CuCl ₂	-	(4 <i>R</i>)-Ph 20	98	10-20 ⁱ	Crude Ratio:	~86	~7	~7
						Purified Yield (%):	48% (79% ee)		
							31:11:58 ^j		
		1							

a. Efficiency and relative ratios of isomers were calculated using ¹H 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, OCH₃), *trans* thiopyran 26b; δ_H 4.16 [1H, d, *J* 12.1, C(2)*H*]. ¹H NMR signal used for calculation of X–H insertion product 148; δ_H 5.08 (1H, s, SO₂CHXCO).

- b. Approx 1–13% X–H insertion product 148 observed in the ¹H 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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 ¹H 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 CuCl₂ 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, CuCl₂ 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 CuCl₂ (**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 ¹H 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.



Variation in reaction time is strongly dependent 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 CuCl₂, 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



NaBARF=78% ee no additive=37% ee

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.



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 NaPF₆ 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 NaBF₄ 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}



89% ee with NaBARF 14% ee no NaBARF

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**.

Ph (1, 1, 1) (1, 1, 1) (o o o s ↓ 0<u>0</u> ∐ `OMe + `OMe х́н -Ph Ph 25 26 (a and b) 147b 148 Entry Additive Ligand Crude **Crude Ratio:** Product ratios^a Time Purified Yield (%)^b Efficiency ^a (h) (% ee)^c 26b 147b 26a 148 (4*R*)-Ph **20** 19 **_** d LiPF₆ **Crude Ratio:** 1 _ --Purified Yield (%): 47% 82% 8% --(% ee) (83% ee) LiPF₆ (4R)-Bn 43 21 _d **Crude Ratio:** 2 ----**Purified Yield (%): 35%** 30% 7% 4% -(% ee) (69% ee) 3 NaPF₆ (4*R*)-Bn **43** 6 30-40^e **Crude Ratio:** 76 14 10 _e **Purified Yield (%):** <u>48%</u> 70 5 --(73% ee) (% ee)

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

4	NaPF ₆	(4 <i>R</i>)-Ph 20	6	30–40 ^e	Crude Ratio:	80	11	9	- ^e
					Purified Yield (%): 38%	71%	-	-	3%
					(% ee)	(97% ee)			
5	KBARF	(4 <i>R</i>)-Ph 20	3	50-60 ^e	Crude Ratio:	89	3	8	_e
					Purified Yield (%): 46%	80%	-	-	1%
					(% ee)	(98% ee)			
						× ,			
6	KBARF	(4 <i>R</i>)-Bn 43	2	60–70 ^e	Crude Ratio:	94	3	3	_ e
-		× ,			Purified Yield (%): 51%	90%	-	-	1%
					(% ee)	(62% ee)			
					((
7	KPF ₆	(4 <i>R</i>)-Ph 20	30	30-40 ^e	Crude Ratio:	~ 80	~10	~10	_e
,		(111) 111 20	50	50 10	Purified Vield (%): 45%	72%	-	-	8%
					(% ee)	(92% ee)			0 /0
8	KDE.	(<i>AP</i>) Bn /3	18	30 40°	Crude Datio:	()270 00)	. 16	. 7	e
0	KI I'6	(4 <i>K</i>)-Dii 4 3	40	50-40	Durified Vield (%): 48%	520%	70%	~ /	-
					Further field ($\frac{70}{10}$): $\frac{4370}{100}$	52%	170	-	270
					(% ee)	(70% ee)			
0		(4D) DL 20	50	:10f					f
9	$NaB(C_6H_5)_4$	(4R)-Ph 20	50	<10*	Crude Ratio:	-	-	-	-
					Purified Yield (%): 4%	12%	-	-	45%
					(% ee)				
				- h					
10	$NaB(C_6H_5)_4$	(4 <i>R</i>)-Bn 43	56	On	Crude Ratio:	-	-	-	-
					Purified Yield (%):				
					(% ee)				
11	NaBF ₄	(4 <i>R</i>)-Ph 20	24	<10 ^e	Crude Ratio:	~80	~10	~10	- ^e

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

a. Efficiency and relative ratios of isomers calculated using ¹H 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: ¹H NMR signal used for calculation of X–H insertion product 148; δ_H 5.08 (1H, s, SO₂CHXCO). 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. ¹H NMR spectra of the crude product not obtained due to hazardous nature of LiPF₆, the crude material was immediately purified by flash chromatography.
- e. Complex mixture containing between 1–10% X–H insertion product **148**.
- f. ¹H 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 ¹H 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. ¹H 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: (4R)-Ph 20 and (4R)-Bn 43. In the initial studies with NaBARF (4R)-Ph 20 gave rise to cis thiopyran 26a in 98% ee (Section 4.2.1, Table 4.1) and (4R)-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 ¹H 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>NaPF₆~KPF₆>NaBF₄~NaB(C₆H₅)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 (4R)-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 219

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(C₆H₅)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(C₆H₅)₄ or NaBF₄ (**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 carbon 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 (4R)-Ph 20 or the (4R)-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 (4S)-t-Bu 138 and the (4R,5S)-di-Ph 137 ligands led to additional signals in the ¹H 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 (4R)-Ph 20 ligand was employed, ^{1,2} using (4R, 5S)-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.

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

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

a. Crude efficiency was calculated using the ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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 COC*H*₃] 17% *trans* 22b [4.35 ppm, *J* 12.1, C(2)*H*, 2.19 COC*H*₃]and 70% *trans* sulfolane 150b [3.78 ppm, *J* 9.0, C(2)*H*, 2.20 ppm, COC*H*₃]-tentative.
- i. A ¹H 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 ¹H 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 \sim 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 (4R)-Ph **20** and (4S)-*t*-Bu **138** ligands giving only *cis* thiopyran **24a** and (4R,5S)-di-Ph **137** and (4R)-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.



*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**



R=Bn, R^1 =Me 28

Entry	α-	R	R ¹	Ligand	Crude efficiency	Time (h)	Crude ratio		Products ^{a,b,c}		
	diazosulfone				(%) ^a			cis	trans	cis	trans
							Purified Yield (%)	thiopyran th	iopyran s	ulfolane	sulfolane
							0 7				
							% ee				
1	37	Oct	OBn	(4 <i>R</i>)-di-Ph 137	80–90 ^d	22	Crude ratio	62	11	5	22
							Purified Yield (%) ^e	12%	-	-	6%
							% ee	79% ee (2 <i>S</i> ,3 <i>R</i>)	-	-	-
								38a	38b	139a	139b
2	37	Oct	OBn	(4S)-t-Bu 138	80-90 ^d	21	Crude ratio	60	14	4	22
							Purified Yield (%) ^e	51%	10%	-	13%
							% ee	81% ee (2 <i>R</i> ,3 <i>S</i>)	59% ee	-	-
								38a	38b	139a	139b
3	37	Oct	OBn	(4R)-Bn 43	80-90 ^d	20	Crude ratio	70	13	-	17
							Purified Yield (%) ^e	51%	4%	-	13%
							% ee	80% (2 <i>S</i> ,3 <i>R</i>)	10% ee	-	-

								38a	38b	139a	139b
4	29	Et	OMe	(4 <i>R</i>)-di-Ph 137	70-80	21	Crude ratio	69	9	-	21
							Purified Yield (%) ^e	30%	-	-	9%
							% ee	>99% ee (2 <i>S</i> ,3 <i>R</i>)	-	-	-
								30a	30b		151b
5	29	Et	OMe	(4 <i>S</i>)- <i>t</i> -Bu 138	80-90	21	Crude ratio	67	11	-	22
							Purified Yield (%) ^e	49%	6%	-	10%
							% ee	92% ee (2 <i>R</i> ,3 <i>S</i>)	57% ee	-	-
								30a	30b		151b
6	29	Et	OMe	(4 <i>R</i>)-Bn 43	80–90	21	Crude ratio	67	12	-	21
							Purified Yield (%) ^e	56%	5%	-	10%
							% ee	87% ee (2 <i>S</i> ,3 <i>R</i>)	6% ee	-	-
								50a	300		1510
7	27	Bn	OMe	(4 <i>R</i>)-Ph 20	70-80 ^f	7	Crude Ratio	-	-	-	-
							Purified Yield (%)	42%	-	-	-
							% ee	96% ee (2 <i>S</i> ,3 <i>S</i>)	-	-	-
								28a			
8	27	Bn	OMe	(4 <i>R</i>)-di-Ph 137	80–90 ^g	22	Crude ratio	-	-	-	-
							Purified Yield (%)	37%	-	-	
							% ee	94% ee (2 <i>S</i> ,3 <i>S</i>)	-	-	
								28a			
9	27	Bn	OMe	(4 <i>S</i>)- <i>t</i> -Bu 138	80-90 ^h	8	Crude Ratio	-	-	-	-
							Purified Yield (%)	2%	-	-	-
							% ee	90% ee (2 <i>R</i> ,3 <i>R</i>)	-	-	-
								28a			
10	27	Bn	OMe	(4 <i>R</i>)-Bn 43	70-80	24	Crude ratio	-	-	-	-
							Purified Yield (%)	21%	-	-	-
							% ee	80% ee (2 <i>S</i> ,3 <i>S</i>)	-	-	-
								28a			

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

a. Efficiency and relative ratios of isomers calculated using ¹H 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 ¹H 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; $[\delta_H 3.63 (d, J 9.5)]$ (*approx* 23%) and $[\delta_H 3.74 (d, J 10.1)]$ (*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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{H} 2.32 2.49$ (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; [$\delta_{H} 3.63$ (d, *J* 9.5)] (*approx* 16%) and [$\delta_{H} 3.74$ (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 ¹H 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 ¹H 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.



*=OBn ester, in all other cases OMe ester

Et

Ph

Figure 4.16

Oct*

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 (4R)-Ph 20 and (4R,5S)-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 (4S)-t-Bu 138 and (4R)-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 $\geq 80\%$ (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.



*=OBn ester, in all other cases OMe ester

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 Rh₂(*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



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

						% ee	(55% ee) (2 <i>S</i> ,3 <i>S</i>)		
							145a		
6 ^e	31	Me	(4 <i>R</i>)-Ph 20	80–90%	5	Crude	Exclusive	-	-
						Purified Yield (%)	product		
						% ee	64%		
							(96% ee) (2 <i>S</i> ,3 <i>S</i>)		
							32a		
7 ^e	33	OMe	(4 <i>R</i>)-Ph 20	80–90%	22	Crude	80	20	-
						Purified Yield (%)	56%	14%	
						% ee	(91% ee) (2 <i>S</i> ,3 <i>S</i>)	12% ee	
							34a		
8 ^e	35	NO ₂	(4 <i>R</i>)-Ph 20	Not formed	2.5	Crude	Not formed	-	-

a. Efficiency and relative ratios of isomers calculated using ¹H 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 (4R)-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 ¹H NMR, ¹³C NMR, IR spectroscopy and high resolution mass spectrometry.



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 $\geq 80\%$ with *cis* thiopyran **145a** accounting for $\geq 80\%$ 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**).



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).





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



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 -oxosulfones 41 and 39



Entry	α-Diazosulfone	Sulfolane	R	L^*	Time	Crude	trans
					(h)	Efficiency	Sulfolane
						(%) ^a	Yield (%)
							(% ee)
1	39	40b	OEt	(4R, 5S)-	48	80-90	69 (65% ee)
				di-Ph		(50:50,	(2R, 3S)
				137		cis:trans)	
2	39	40b	OEt	(4 <i>S</i>)- <i>t</i> -	3	80–90	61 (0% ee)
				Bu 138			(2S, 3R)
3	39	40b	OEt	(4 <i>R</i>)-Bn	26	80–90	53 (5% ee)
				43			(2R, 3S)
4	41	42b	Me	(4R, 5S)-	21	70-80	19 (36% ee)
				di-Ph			(2R, 3S)
				137			
5	41	42b	Me	(4 <i>S</i>)- <i>t</i> -	26	80–90	53 (51% ee)
				Bu 138			(2S, 3R)
6	41	42b	Me	(4 <i>R</i>)-Bn	21	80–90	33 (59% ee)
				43			(2R, 3S)
7 ^b	39	40b	OEt	(4 <i>R</i>)-Ph	5	complex	57 (60% ee) ^b
				20			(2R, 3S)
8 ^b	41	42b	Me	(4 <i>R</i>)-Ph	3	~60	40 (40% ee) ^b
				20			(2R, 3S)
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 ¹H 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 Rh₂(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 (4R)-Ph and (4R,5S)-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 (4S)-t-Bu and (4R)-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 (4R)-Ph 43 (59% ee) and (4S)-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.



(4R)-Ph 20 (4R,5S)-di-Ph 137 (4S)-t-Bu 138 (4R)-Bn 43

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.



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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**.

$\bigcup_{N_2} O O O O O O O O O O O O O O O O O O O$										
	62		1	146						
Entry	Crude	Ligand	Time (h)	Yield (%)	ee (%)					
	Efficiency ^a									
1	~80–90%	(4 <i>R</i>)-Ph 20	2	70	0					
2	~85-90%	(4 <i>R</i> ,5 <i>S</i>)-di-	2	68	0					
		Ph 137								
3	~80-90%	(4 <i>S</i>)- <i>t</i> -Bu	3	69	0					
		138								
4	~80–90%	(4 <i>R</i>)-Bn 43	2	66	0					

Table 4.9 Aromatic C-H insertion

a. Efficiency and relative ratios of isomers calculated from the ¹H 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-1,3dihydrobenzo[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



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 (4R)-Ph **20** or di-phenyl (4R,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 porbital overlaps with the σ -orbital of the C–H bond undergoing insertion, followed by formation of the C–C and C–H bond as Rh₂L₄ catalyst dissociates as depicted in **Scheme 4.12**.⁴⁴ This mechanism is characterised by a three centred, two electron concerted transition state.



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



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



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* γ -lactams products are formed.



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-SO₂-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



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=CHCO₂Me, 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 copperbisoxazoline 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**.



Figure 4.25 adapted from ref³⁶

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 2R, 3*S*. The absolute stereochemistry of the methyl ketone *trans* sulfolane **42b** was then assigned by analogy.



The origin of enantioselectivity for the *trans* sulfolane compounds, arising from reaction in the presence of CuCl-NaBARF-(4R)-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 f rom the less sterically hindered f ace of the carbenoid, leading to sulf olane with the observed stereochemistry*



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).



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.]



favoured transition state for the (4R)-Ph ligand



Unfavourable transition state leading to trans diastereomer



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 ¹H 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 ¹H NMR spectroscopy, IR spectroscopy and chiral HPLC. In the case of novel compounds ¹³C 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[(4R)-4-phenyl-2-oxzoline] **20**, (+)-2,2'-isopropylidenebis[(4R)-4-benzyl-2-oxzoline] **43**, 2,2'-isopropylidenebis[(4S)-4-*tert*-butyl-2-oxzoline] **138**, 2,2'-methylenebis[(4R, 5S)-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 [(3S,8R)-Ind **44** and (3S,8R)-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 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 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 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.

(2S,3S)-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-(4phenylbutylsulfonyl)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 (4R)-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. ¹H 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, (2S,3S)-methyl 2-(3-phenyl-1,1-dioxohexahydrothiopyran-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 CH₂Cl₂), (Lit $[\alpha]_{D}^{20}$ +103.8, for 98% ee)^{1,2}, >99% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (KBr): 2952, 2931 (CH), 1726 (CO), 1323, 1295, 1116 (SO₂); δ_H (CDCl₃, 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)H₂], 3.54 (3H, s, OCH₃), 3.62–3.74 [2H, m, one of C(6)H₂ and C(3)H], 3.99 [1H, dd, J 4.5, 2.9, C(2)H], 7.16–7.20 (2H, m, ArH), 7.26-7.36 (3H, m, ArH).

Table 4.10 Additional products were observed in the ¹H NMR of the crude products fromthe cyclisations of methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate**25** (previouslycharacterised).²

Entry	Compound	Characteristic
		signals in ¹ H NMR
1		δн 3.19–3.32 [1Н, т,
	OMe	one of $C(6)H_2$], 3.58
		(3H, s, OCH ₃), 4.16
		[1H, d, J 12.1, C(2)H]
	26b	
2		δ _H 6.12–6.25 [1H, m,
	S S	C(3')H], 6.54 [1H, d,
	Ullie Ullie	J 15.8, C(4')H]
	149	
3	0,00	δ _H 2.71–2.83 (1H, m,
	Š	one of $ArCH_2$), 2.87–
	∫ ∫ `OMe	2.97 (1H, m, one of
		ArCH ₂), 3.26 [1H,
	- 111 1470	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 ¹H NMR spectra of the crude products from the cyclisations of methyl 2-diazo-2-(4phenylbutylsulfonyl)acetate **25**. This compound was

occasionally isolated as a less polar fraction than the cyclised product **148**, as a colourless oil; $v_{max/cm^{-1}}$ (film): 1752 (C=O), 1334, 1117 (SO₂); δ_{H} (500 MHz, CDCl₃): 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, COOC*H*₃), 5.08 [1H, s, SO₂C*H*(OR)CO], 7.13–7.23 (3H, m, Ar*H*), 7.24–7.31 (2H, m, Ar*H*); δ_{C} (125.8 MHz, CDCl₃): 20.54 [CH₂, *C*(2')H₂], 30.12 [CH₂, *C*(3')H₂], 35.24 [CH₂, *C*(4')H₂], 48.99 [CH₂, *C*(1')H₂], 54.51 (CH₃, OCH₃), 68.97 [CH, SO₂CH(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.

Entry	Copper	NaBARF	Ligand	Time (h)	Crude	Products ^a			
	Source	(mol%)			Efficiency ^a (%)		<i>trans</i> : sulfolane ^a 147b	trans : thiopyran ^a 26b	<i>cis</i> thiopyranª 26a
1	CuCl	6	(4 <i>R</i>)-Ph 20	21	80–90 ^b	Crude Ratio: Purified Yield (%):	9	7	84 52% (>99%ee) ^c (2 <i>S</i> ,3 <i>S</i>)
2	CuCl	6	(4 <i>R</i>)-Bn 43	21	60-70 ^d	Crude Ratio: Purified Yield (%):	3	9	88 36% (66%ee) ^c (2 <i>S</i> ,3 <i>S</i>)
3	CuCl	6	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	21	80–90 ^e	Crude Ratio: Purified Yield (%):	11	8	81 45% (95%ee) ^c (2 <i>S</i> ,3 <i>S</i>)
4	CuCl	6	(4 <i>S</i>)- <i>t</i> -Bu 138	21	70-80 ^f	Crude Ratio: Purified Yield (%):	6	6	88 33% (71%ee) ^c (2 <i>R</i> ,3 <i>R</i>)
5	CuCl	6	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	21	60–70 ^g	Crude Ratio: Purified Yield (%):	3	8	89 57% (62%ee) ^{h,c} (2 <i>R</i> ,3 <i>R</i>)
6	CuCl ₂	6	(4 <i>R</i>)-Ph 20	3	50-60 ⁱ	Crude Ratio: Purified Yield (%):	10	4	86 61% (95%ee) ^{j,k} (2 <i>S</i> ,3 <i>S</i>)
7	CuCl ₂	12	(4 <i>R</i>)-Ph 20	3	70–80 ¹	Crude Ratio: Purified Yield (%):	_1	- 1	_1 52% (98%ee) ^c

Table 4.11 Asymmetric copper catalysed C–H insertion reactions of α -diazo- β -oxo sulfone **25** (Method A)

									(2S, 3S)
8	CuCl ₂	6	(4 <i>R</i>)-Bn 43	3	70–80 ^m	Crude Ratio: Purified Yield (%):	3	9	88 67% (67%ee) ^{n,k} (2 <i>S</i> ,3 <i>S</i>)
9	Cu(OTf) ₂	12	(4 <i>R</i>)-Ph 20	2	40–50°	Crude Ratio: Purified Yield (%):	_0	_0	_° 38% (98%ee) ^c (2 <i>S</i> ,3 <i>S</i>)
10	Cu(OTf) ₂	12	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	2	30-40 ^p	Crude Ratio: Purified Yield (%):	10	10	80 32% (94%ee) ^c (2\$,3\$)
11	Cu(OTf) ₂	12	(4 <i>R</i>)-Bn 43	2	30-40 ^q	Crude Ratio: Yield (purified):	_q	_q	_q 28% (66%ee) ^c (2 <i>S</i> ,3 <i>S</i>)
12	Cu(OTf) ₂	12	(4 <i>S</i>)- <i>t</i> -Bu 138	1.5	50–60 ^r	Crude Ratio: Purified Yield (%):	_r	_r	
13	Cu(OTf) ₂	6	(4 <i>R</i>)-Ph 20	6	30-40 ^s	Crude Ratio: Purified Yield (%):	7	3	90 11% (97%ee) ^{t,u} (2 <i>S</i> ,3 <i>S</i>)
14	Cu(OTf) ₂	-	(4 <i>R</i>)-Ph 20	1 week	10–20 ^v	Crude Ratio: Purified Yield (%):	-	13	87 17% (89%ee) ^{w,u} (2 <i>S</i> ,3 <i>S</i>)

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for *cis* thiopyran **26a**; $\delta_{\rm H}$ 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**; $\delta_{\rm H}$ 3.74 (3H, s, OCH₃), *trans* thiopyran **26b**; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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).
- 1. 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_H 3.84-3.87$ (m), 4.69 (s). Additional less polar fraction obtained (6 mg) obtained with the following spectral characteristics; $\delta_H 1.69-1.82$ (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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_H 3.74-3.95$ (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; $\delta_H 1.73-1.94$ (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 ¹H 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), 4.42 (s).

Entry	Additive	Ligand	Time	Crude	Products ^a			
			(h)	Efficiency ^a		<i>trans</i> sulfolane ^a 147b	trans thiopyran ^a 26b	<i>cis</i> thiopyran ^a (2 <i>S</i> ,3 <i>S</i>) 26a
1	LiPF ₆	(4 <i>R</i>)-Ph 20	19	_b	Crude Ratio: Purified Yield (%):	_b	_ ^b	_ ^b 47% (83% ee) ^{c,d}
2	LiPF ₆	(4 <i>R</i>)-Bn 43	21	_b	Crude Ratio: Purified Yield (%):	_b	_ ^b	_ ^b 35% (69% ee) ^{d,e}
3	NaPF ₆	(4 <i>R</i>)-Bn 43	6	30-40 ^f	Crude Ratio: Purified Yield (%):	10	14	76 48% (73% ee) ^{d,g}

Table 4.12 Asymmetric copper catalysed C-H insertion reactions of α -diazo- β -oxo sulfone 25, variation of additive (Method A)

4	NaPF ₆	(4 <i>R</i>)-Ph 20	6	30-40 ^h	Crude Ratio: Purified Yield (%):	9	11	80 38% (97% ee) ^{d,i}
5	KBARF	(4 <i>R</i>)-Ph 20	3	50–60 ^j	Crude Ratio: Purified Yield (%):	8	3	89 46% (98% ee) ^{k,l,m}
6	KBARF	(4 <i>R</i>)-Bn 43	2	60–70 ⁿ	Crude Ratio: Purified Yield (%):	3	3	94 51% (62% ee) ^{d,l,o}
7	KPF6	(4 <i>R</i>)-Ph 20	30	30–40 ^p	Crude Ratio: Purified Yield (%):	~10	~10	~ 80 45 (92% ee) ^{d,q}
8	KPF ₆	(4 <i>R</i>)-Bn 43	48	30-40 ^r	Crude Ratio: Purified Yield (%):	~7	~16	~77 48 (70% ee) ^{s,d}
9	NaB(C ₆ H ₅) ₄	(4 <i>R</i>)-Ph 20	56	<10 ^t	Crude Ratio: Purified Yield (%):	_ ^t	_t	_t 4% ^u
10	NaB(C ₆ H ₅) ₄	(4 <i>R</i>)-Bn 43	56	0 ^v	Crude Ratio: Purified Yield (%):	_v	_v	_v _w
11	NaBF ₄	(4 <i>R</i>)-Ph 20	24	<10 ^x	Crude Ratio: Purified Yield (%):	~10	~10	~80 43% (93% ee) ^{m,y}
12	NaBF ₄	(4 <i>R</i>)-Bn 43	48	10–20 ^z	Crude Ratio: Purified Yield (%):	~10 ^z	~ 10	~80 22% ^{aa}
13	-	(4 <i>R</i>)-Ph 20	98	10–20 ^{bb}	Crude Ratio: Purified Yield (%):	~7	~7	~86 48% (79% ee) ^{m,cc}
14	-	(4 <i>R</i>)-Bn 43	1 week	_dd	Crude Ratio:	_dd	-	_dd

		starting	Purified Yield (%):		
		material only			

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for *cis* thiopyran **26a**; $\delta_{\rm H}$ 3.99 [1H, dd, *J* 4.5, 2.9 C(2)*H*], *trans* sulfolane **147b**, $\delta_{\rm H}$ 3.74 (3H, s, OC*H*₃), *trans* thiopyran **26b**; $\delta_{\rm H}$ 4.16 [1H, d, *J* 12.1, C(2)*H*].

- b. ¹H NMR spectra of the crude product not obtained due to hazardous nature of LiPF₆, the crude material was immediately purified by flash chromatography.
- c. ¹H NMR spectra of the purified product contains 82% *cis* thiopyran **26a**, 8% X–H insertion product **148** {¹H NMR signal used for calculation of X–H insertion product; $\delta_{\rm H}$ 5.08 [1H, s, SO₂CH(OR)CO], and an additional unknown compound; $\delta_{\rm H}$ 3.87 (s), (additional peaks may be present but may not be observed to overlapping signals in the ¹H 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. ¹H 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 ¹H NMR spectra of the purified fraction; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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 in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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), 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 3.35 (s), 3.85 (s), 4.69 (s).
- 1. 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H} 2.55-2.77$ (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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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 ¹H NMR spectra of this fraction include; $\delta_{\rm H}$ 3.81 (s), 3.83 (s), 3.85 (s), 3.86 (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ 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 ¹H NMR spectra of this fraction include; $\delta_{\rm H}$ 3.85 (s), 3.86 (s), 3.92 (s), 4.10 (s).
- t. ¹H 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 ¹H NMR spectra of the crude product. (A series of overlapping multiplets 1.50–2.70 and 3.00–4.10 ppm appear in ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 3.85 (s), 4.70 (s). Two additional less polar fractions obtained. The least polar fraction obtained (3%) obtained has the following spectral characteristics; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ 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 ¹H NMR spectra of this fraction include; $\delta_{\rm H}$ 3.85 (s), 4.68 (s).
- v. ¹H 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_H 4.69$ (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 ¹H 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). ¹H NMR analysis of the more polar of the two fractions (5 mg) reveals the following signals; $\delta_{\rm H} 1.74-2.07$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H} 3.73$ (s), 3.75 (s), 3.77 (s), 3.81(s), 3.82 (s), 3.85 (s), 3.97 (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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.

(2S,3S)-1-(Phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)ethanone cis 22a^{1,2}



The title compound was prepared according to the procedure described for (2S,3S)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2yl)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), bisoxazoline ligand (4R,5S)-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. ¹H 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 (*trans* 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, (2S,3S)-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 CH₂Cl₂) (Lit^{1,2} $[\alpha]_{D}^{20}$ +42.4 for 85% ee); 73% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (KBr): 1717 (CO), 1453 (C=C, Ar), 1362, 1314, 1297, 1119 (SO₂), 762, 702 (CS); δ_H (CDCl₃, 300 MHz): 1.77–1.87 [4H, m, one of C(4)H₂ incorporating at 1.81, 3H, s, COCH₃], 2.13–2.21 [1H, m, one of C(5)H₂], 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)H₂], 3.50–3.71 [2H m, C(3)H and one of C(6)H₂], 4.21 [1H, dd, J 4.2, 3.1, C(2)H], 7.17–7.24 (2H, m, ArH), 7.27–7.40 (3H, m ArH).

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, COC*H*₃] 17% *trans* thiopyran **22b** (4.35 ppm, d, *J* 12.1, C(2)*H*, 2.19 ppm, s, COC*H*₃) and 70% *trans* sulfolane **150b** [3.78 ppm, d, *J* 9.0, C(2)*H*, 2.20 ppm, s, COC*H*₃]. The assignment of *trans* sulfolane **150b** is tentative.

Note; A ¹H 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**.

(2S,3S)-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-2yl)carboxylate *cis*-**26a**, using 2-(4-phenylbutylsulfonyl)-2-diazo-1phenylethanone **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**. ¹H 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 CH₂Cl₂); 83% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (KBr): 2959 (CH), 1668 (CO), 1595, 1446, (C=C, Ar), 1321, 1298, 1230, 1207, 1122 (SO₂), 759, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 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(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*).

Entry	Ligand	Time	Crude	Yield	%ee	[a] ²⁰
		(h)	Efficiency ^a	(%)		[u] D
1	(4 <i>R</i>)-Bn 43	20	>70% 24a	55	83 (2 <i>S</i> ,3 <i>S</i>)	+50.1 (c 0.40)
2	(4 <i>R</i> ,5 <i>S</i>)-di-	6	>80% (all	41	93 (2 <i>S</i> ,3 <i>S</i>)	+89.1 (c 0.40)
	Ph 137		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			
3	(4 <i>S</i>)- <i>t</i> -Bu	20	>80% (all	51	78 (2 <i>R</i> ,3 <i>R</i>)	-62.5 (c 0.10)
	138		included-			
			~60% 24a)			
			Mixture			
			containing			
			majority 24a ,			
			one additional			
			compound in			
			crude; doublet of			
			doublets at 4.60			
			ppm (~20%)			

Table 4.13 Asymmetric copper-bisoxazoline catalysed C-H insertion reactions of α -
diazo- β -oxo sulfone 23(Method A)

a. Efficiency calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **24a**; $\delta_{\rm H}$ 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 ¹H 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 ¹H NMR signal; 4.60 (dd, *J* 13.8, 11.1)

Note; A ¹H 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 Ο Ő Ö described 2-(3-phenyl-1,1-dioxofor (2S,3S)-methyl оМе (R) (S) hexahydrothiopyran-2-yl)carboxylate cis-26a, using methyl 2-diazo-2-C₂H₅ (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 (4S)-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 ¹H NMR spectrum of the crude reaction mixture shows a mixture of products, including cis (2R,3S) **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 (2R,3S)- 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); v_{max}/cm⁻¹ (film): 2938 (CH), 1736 (CO), 1321, 1296, 1161 (SO₂); δ_H (CDCl₃, 400 MHz): 0.97 [3H, t, J 7.4, C(2')H₃], 1.24– 1.45 [2H, m, C(1')H₂], 1.63–1.87 [2H, m, C(4)H₂], 1.99–2.19 [2H, m, C(5)H₂], 2.22–2.34 [1H, m, C(3)H], 2.95 [1H, apparent dq, J 13.9, 3.2, one of C(6)H₂], 3.53–3.64 [1H, m, one of C(6)H₂], 3.80 (3H, s, OCH₃), 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; v_{max}/cm^{-1} (KBr): 2940 (CH), 1732 (CO), 1319, 1269 (SO₂); $\delta_{\rm H}$ (CDCl₃, 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, OC H_3).



The most polar fraction (*trans* thiopyran **30b**) (11 mg, 6%) was isolated as a white solid; 57% ee (determined by chiral-HPLC); v_{max}/cm^{-1} (KBr): 2946 (CH), 1729 (CO) 1317, 1293, 1129 (SO₂); $\delta_{\rm H}$ (CDCl₃, 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, OCH₃).

Entry	Time (h)	Ligand	Crude	Product ^a						
			Efficiency (%) ^a		cis thiopyran 30a :	trans thiopyran	trans sulfolane ^a			
						30b :	151b			
1	21	(4 <i>S</i>)- <i>t</i> -Bu 138	80–90	Crude Ratio:	67 :	11 :	22			
				Purified Yield(%):	48% (92% ee)	6% (57% ee) ^c	11% ^d			
					(2R, 3S)					
				Overall Yield ^b	49%		10%			
2	21	(4 <i>R</i>)-Bn 43	80–90	Crude Ratio:	67 :	12 :	21			
				Purified Yield(%):	38% (87% ee)	5% (6% ee) ^e	$14\%^{\rm f}, 8\%^{\rm g}$			
					(2S, 3R)					
				Overall Yield ^b	56%		10%			
3	21	(4 <i>R</i> ,5 <i>S</i>)-di-Ph	70–80	Crude Ratio:	69 :	9 :	21			
		137		Purified Yield(%):	21% (>99% ee)	- ^h	18% ⁱ			
					(2S, 3R)					
				Overall Yield^b	30%		9%			

Table 4.14 Asymmetric copper-bisoxazoline catalysed C–H insertion reactions of α -diazo- β -oxo sulfone **29** (Method A)

a. Efficiencies and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₃, *cis* thiopyran **30a**; $\delta_{\rm H}$ 3.80 (3H, s, OCH₃), *trans* thiopyran **30b**; $\delta_{\rm H}$ 3.85 (3H, s, OCH₃), *trans* sulfolane **151b**; $\delta_{\rm H}$ 3.86 (3H, s, OCH₃).

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 (2S,3S)-methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2yl)carboxylate *cis*-**26a**, using methyl 2-diazo-2-(5phenylpentylsulfonyl) 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**. ¹H 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} [α]²⁰_D +35.8 (*c* 0.123 in CH₂Cl₂); 80% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (film): 2932 (CH), 1732 (CO), 1455, 1437 (C=C, Ar), 1322, 1249, 1168, 1117 (SO₂), 749, 703 (CS); $\delta_{\rm H}$ (CDCl₃, 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 C*H*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, OC*H*₃], 7.06–7.22 (2H, m, Ar*H*), 7.23–7.40 (3H, m, Ar*H*).

Entry	Ligand	Time	Crude	Crude (%)	cis thiopyran 28a
		(h)	Efficiency ^a	Purified Yield (%)	(2 <i>S</i> ,3 <i>S</i>)
			(total)		
			(%)		
1	(4 <i>R</i>)-Bn	24	70–80 ^b	Crude (%):	70–80%
	43			Purified Yield (%):	21% (80% ee)
					(2 <i>S</i> ,3 <i>S</i>)
					$[\alpha]_{\rm D}^{20}$ +35.8
					(c 0.123)
2	(4R, 5S)-	22	80–90°	Crude (%):	45%
	di-Ph			Purified Yield (%):	37% (94% ee)
	137				(2 <i>S</i> ,3 <i>S</i>)
3	(4 <i>S</i>)- <i>t</i> -	8	80-90 ^d	Crude (%):	58%
	Bu 138			Purified Yield (%):	22% (90% ee)
					(2R, 3R)
					$\left[\alpha\right]_{\rm D}^{20}$
					-39.3
					(c 0.37)
4	(4 <i>R</i>)-Ph	7	70–80 ^e	Crude (%):	41%
	20			Purified Yield (%):	(2 <i>S</i> ,3 <i>S</i>)
					12% (96% ee)

Table 4.15 Asymmetric copper bisoxazoline catalysed C–H insertion reactions of α diazo- β -oxo-sulfone 27 (Method A)

- a. Efficiencies calculated using ¹H 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 ¹H NMR spectra of crude product; $\delta_H 2.36-2.54$ (m), 2.79–2.84 (m), 3.04–3.41 (m).
- c. Additional signals observed in the ¹H NMR spectra of crude product; $\delta_H 2.27-2.35$ (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 ¹H 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 ¹H NMR spectra of the crude product. (See footnote a)
- d. Additional signals observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H} 2.32-2.49$ (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 ¹H NMR spectra of the crude product; compound [$\delta_{\rm H} 3.63$ (d, *J* 9.5)], (*approx* 16%) and compound p [$\delta_{\rm H} 3.74$ (d, *J* 10.1)] (*approx* 13%). (See footnote a).

e. Additional signals observed ¹H NMR spectra of crude product; $\delta_H 2.28-2.51$ (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 ¹H NMR spectra of the crude product; compound [$\delta_H 3.63$ (d, *J* 9.5)] (*approx* 23%), and compound[$\delta_H 3.74$ (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* (2R,3S) 38a, *trans* (+) 38b^{1,2}

The title compounds were prepared according to the procedure described for (2S,3S)-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 (4S)-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. ¹H NMR spectroscopy of the crude product showed that the reaction was approx. 80–90% efficient. The ¹H NMR spectrum shows a mixture of products, including trans-139b, cis (2S,3R)-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 (2R,3S)-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 CH₂Cl₂) (Lit^{1,2} $[\alpha]_{D}^{20}$ +16.1, for 90% eeopposite major enantiomer), 82% ee (determined by chiral-HPLC); $v_{max}/cm^{-1}(KBr)$: 2957, 2927, 2855 (CH), 1720 (CO), 1467, 1458 (C=C, Ar), 1326, 1295, 1256, 1172, 1119 (SO₂), 871, 851, 750, 698 (CS); δ_H (CDCl₃, 400 MHz): 0.88 [3H, t, J 7.0, C(8')H₃], 1.10– 1.36 [14H, m, C(7')H₂, C(6')H₂, C(5')H₂, C(4')H₂, C(3')H₂, C(2')H₂, C(1')H₂], 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)H₂], 3.59 [1H, apparent dt, J 13.6, 4.6, one of C(6)H₂], 3.90 [1H, dd, J 4.4, 2.9, C(2)H], 5.14 (1H, d, H_A of AB system, J 12.1, CH₂Ar), 5.30 (1H, d, H_B of AB system, J 12.1, CH₂Ar), 7.33–7.39 (5H, m, ArH)



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, C*H*₂Ar), 7.29–7.43 (5H, m, Ar*H*).

This fraction also contains *approx*. 4% reduction product **111**, signals in ¹H NMR spectra appears at $\delta_{\rm H}$ 3.98 (2H, s, SCH₂CO), 1.35–1.50 [18 H, m, C(11')H₂, C(10')H₂, C(9')H₂, C(8')H₂, C(7')H₂, C(6')H₂, C(5')H₂, C(4')H₂, C(3')H₂].



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 CH₂Cl₂) (Lit $[\alpha]_D^{20}$ +3.9, for 45% ee-opposite major enantiomer);^{1,2} 59% ee

(determined by chiral-HPLC); $v_{max}/cm^{-1}(KBr)$: 2927, 2855 (CH), 1729 (CO), 1457 (C=C, Ar), 1314, 1272, 1195, 1131 (SO₂), 699 (CS); $\delta_{\rm H}$ (CDCl₃, 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, CH₂Ar), 7.29–7.42 (5H, m, Ar*H*).

Entry	Ligand	Time (h)	Crude Efficiency (%) ^{a,b}		Products ^a				
					cis :	cis thiopyran ^{a,c} :	<i>trans</i> thiopyran ^{a,c} :	trans	
					sulfolane ^{a, c,d}			sulfolane ^{a,c}	
1	(4 <i>S</i>)- <i>t</i> -Bu 138	21	80–90	Crude Ratio: Purified Yield (%) Overall Yield ^g	4 :	$ \begin{array}{c} 60 & : \\ 51\% (81\% \text{ ee})^{\text{e}} \\ (2R, 3S) \\ 51\% \\ \left[\alpha\right]_{\text{D}}^{20} -23.7(c \ 0.12) \end{array} $	$\begin{array}{c} 14 & : \\ 10\% \ (59\% \ ee) \\ 10\% \\ \left[\alpha\right]_{\rm D}^{20} -10.0 \ (c \ 0.1) \end{array}$	22 13% ^f 13%	
2	(4 <i>R</i>)-Bn 43	20	80–90 ^h	Crude Ratio Purified Yield (%) Overall Yield ⁿ	- :	$70 : 49\% (80\% \text{ ee})^{i} (2S, 3R) 51\% [\alpha]_{D}^{20} + 13.64 (c 0.11)$	13 : $4\% (10\% \text{ ee})^{j}$ $[\alpha]_{D}^{20} +9.5 (c \ 0.1)$	17 10%, 6% ^k 13%	

Table 4.16 Asymmetric copper bisoxazoline catalysed C–H insertion reactions of α -diazo- β -oxo-sulfone 37 (Method A)

3	(4R, 5S)-	22	80–90	Crude Ratio	5 :	62 :	11 :	22
	di-Ph 137			Purified Yield (%)	-	$12\% (79\% \text{ ee})^{1}$	_ ^m	7% ⁿ
						(2S, 3R)		
				Overall Yield ⁿ		12%		6%

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **139a**, $\delta_{\rm H}$ 3.92 [1H, d, *J* 6.5, C(2)*H*], *cis* thiopyran **38a**, $\delta_{\rm H}$ 3.90 [1H, dd, *J* 4.4, 2.9, C(2)*H*]; *trans* thiopyran **38b**, $\delta_{\rm H}$ 3.68 [1H, d, *J* 10.5, C(2)*H*]; *trans* sulfolane **139b**, $\delta_{\rm H}$ 3.61 [1H, d, *J* 9.5, C(2)*H*].

b. ~1% reduction product **111** observed in all ¹H NMR spectra of crude products; δ_H 3.98 (2H, s, SCH₂CO).

c. Estimation due to peak overlap.

d. Signal in ¹H NMR spectra for *cis* sulfolane **139a**; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_H 4.68$ (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 $\delta_{\rm H}$ 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**.
- 1. 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 1,1dioxide *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[3,5bis(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. ¹H 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, (2S,3S)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; $[\alpha]_{\rm D}^{20}$ +92.0 (*c*, 1.0 CH₂Cl₂) 98% ee (determined by chiral-HPLC); (Found C, 54.57; H 5.31; S, 11.44, C₁₃H₁₅O₄FS requires C, 54.53; H, 5.28; S, 11.20%); v_{max}/cm⁻¹ (KBr): 2956, 2939 (CH) 1735 (CO), 1512 (C=C, Ar), 1317, 1114 (SO₂) 840; δ_H (CDCl₃, 300 MHz): 1.84 [1H, apparent dq, J 13.6, 3.2, one of C(4)H₂], 2.10–2.36 [2H, m, C(5)H₂], 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, OCH₃), 3.61-3.73 [2H, m, one of C(6)H₂and C(3)H], 3.96 [1H, dd, J 4.5, 2.9 C(2)H], 6.95-7.07 (2H, m, ArH), 7.12–7.23 (2H, m, ArH); δ_c (CDCl₃, 75.5 MHz): 22.9, 23.8 [2 × CH₂, C(4)H₂, C(5)H₂], 43.8 [CH, C(3)H], 47.8 [CH₂, C(6)H₂], 52.7 (CH₃, OCH₃), 70.4 [CH, C(2)H], 115.8 [2 × ArCH, d, ² J_{CF} 21.4, C(3')H, C(5')H], 128.6 [2 × ArCH, d, ³ J_{CF} 8.1, *C*(2')H, *C*(6')H], 135.3 [C, d, ⁴*J*_{CF} 3.3, *C*(1')], 162.1 [C, ¹*J*_{CF} 246.9, *C*(4')], 166.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for C₁₃H₁₆O₄FS [M+H] ⁺, 287.0753. Found 287.0767.

Stereochemistry assigned by analogy

Coppercatalysedreactionsofethyl2-diazo-2-{[4-(4-fluorophenyl)butyl]sulfonyl}acetate45yielded(2S,3S)-methyl3-(4-fluorophenyl)tetrahydro-2H-thiopyran-2-carboxylate1,1-dioxidecis-145aas the major

product. Additional products were observed in the crude mixtures. The following table (**Table 4.17**) shows these products and signals from ¹H 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



Entry	Compound	¹ H NMR
1	O O O O O O O O O O O O O O O O O O O	δ _H 3.59 (3H, s, OCH ₃), 4.10 [1H, d, <i>J</i> 12.1, C(2) <i>H</i>].
2	153b	$ δ_{\rm H} 2.68-2.75 (1H, m, H_{\rm A} of CH_2Ar), 2.85-2.91 (1H, m, H_{\rm B} of CH_2Ar), 3.28 [1H, ddd, J 12.3, 7.1, 1.5, H_{\rm B} of CH_2Ar C(5)H_2], 3.75 (3H, s, OCH_3). $
3	F 154	$\delta_{\rm H}$ 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	Crude	Crude			
		(h)	Efficiency ^a	Ratio			
				(cis thiopyran	(cis	thiopyran 1	45a)
				145a:			
				trans	Yield	% ee	[a] ²⁰
				thiopyran 145b	(%)		[α] _D
				: trans			
				sulfolane			
				153b) ^a			
1	(4 <i>R</i>)-Ph	21	~75-85%	91:4:5	49	98 (2 <i>S</i> ,3 <i>S</i>)	+92
	20						(<i>c</i> 1.000)
2	(4R, 5S)-	21	~75-85%	84 :7 : 9 ^b	55	98	
	di-Ph 137					(2S, 3S)	
3	(4 <i>S</i>)- <i>t</i> -Bu	48	~75-85%	84 : 12 : 5 ^b	52	80	-68.5
	138					(2R, 3R)	(<i>c</i> 1.000)
4	(4 <i>R</i>)-Bn	21	~37%	84:12:5	25°	53 (2 <i>S</i> ,3 <i>S</i>)	
	43		Complex				
			Mixture of				
			Products				
5	Cu(OTf)2 ^d	48	~30%	78 : 19 : 2 [.]	24	-	-
			efficient.				
			Complex				
			mixture				
			Hydride				
			elimination				
			154 ~6%				

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₃, *cis* thiopyran **145a**; δ_H 3.56 (3H, s, OCH₃), *trans* thiopyran **145b**; δ_H 3.59 (3H, s, OCH₃), *trans* sulfolane **153b**; δ_H 3.75(3H, s, OCH₃). (see **Table 4.17**)

b. A shift in the singlet for *trans* thiopyran **145b** was observed in the ¹H NMR spectra of the crude product of *entries* **2** and **3** from $\delta_H 3.59$ (3H, s, OCH₃) (entries 1, 4 and 5) to $\delta_H 3.57$ (3H, s, OCH₃) (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) $\delta_{\rm H}$ 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.

(2R,3S)-1-(3-Phenyl-1, 1-dioxo-tetrahydrothiophen-2-yl)ethanone trans 42b^{1,2}



CuCl (1.10 mg, 11.2 μ mol), 1-(phenylpropylsulfonyl)-1-diazopropan-2one **41** (60.00 mg, 0.23 mmol), sodium tetrakis[3, 5bis(trifluoromethyl)phenyl]borate (NaBARF) (11.97 mg, 13.5 μ mol) and bisoxazoline ligand (4*R*)-Bn **43** (4.90 mg, 13.5 μ mol) 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. ¹H 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} [α]²⁰_D +63.8 (*c* 0.112 in CH₂Cl₂) (Lit^{1,2} [α]²⁰_D +49.9, for 40% ee), 59% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (KBr): 1714 (CO), 1605, 1497, 1458, 1412 (C=C, Ar), 1365, 1296, 1169, 1122 (SO₂), 753, 702 (CS); $\delta_{\rm H}$ (CDCl₃, 300 MHz): 2.24–2.43 [4H, 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 ¹H 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 -

Entry	Ligand	Time	Crude	Yield	ee (%)	$\left[\boldsymbol{\alpha}\right]_{\mathrm{D}}^{20}$
		(h)	Efficiency ^a	(%)		
1	(4 <i>R</i>)-Bn	21	>90% 42b	33	59 (2 <i>R</i> ,3 <i>S</i>)	+63.8(c 0.112)
	43					
2	(4R,5S)-	21	>80% 42b	19	36 (2 <i>R</i> ,3 <i>S</i>)	-
	di-Ph 137					
3	(4 <i>S</i>)- <i>t</i> -Bu	26	>90% 42b	53	51(3 <i>R</i> ,2 <i>S</i>)	-76.6 (<i>c</i> 0.113)
	138					

 $diazo-\beta$ -oxo sulfone **41** (Method A)

a. Efficiency calculated using C(2)*H*, $\delta_{\rm H}$ 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 (2R,3S)-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

 μ mol) and bisoxazoline ligand (4*R*)-Bn 43, (7.32 mg, 20.2 μ mol) in dichloromethane (15 mL), stirred while heating under reflux for 26 h, in accordance with Method A. ¹H 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 eluent, (2R,3S)-ethyl (10:90)as 2-(3-phenyl-1, 1-dioxotetrahydrothiophen-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 CH₂Cl₂) (Lit^{1,2} $[\alpha]_{D}^{20}$ +21.3, for 60% ee); 5% ee (determined by chiral-HPLC); v_{max}/cm^{-1} (KBr) 1739 (CO), 1456 (C=C, Ar), 1380, 1317, 1277, 1195, 1123 (SO₂), 759, 702 (CS); δ_H (CDCl₃, 300 MHz) 1.28 (3H, t, J 7.2, OCH₂CH₃), 2.26-2.43 [1H, m, one of C(4)H₂], 2.46-2.59 [1H, m, one of C(4)H₂], 3.23 [1H, apparent dt, J 12.9, 6.9, one of C(5)H₂], 3.45 [1H, ddd, J 12.9, 6.8, 1.6, one of C(5)H₂], 3.89-4.08 [2H, m, C(2)H and C(3)H], 4.12-4.39 (2H, m, OCH₂CH₃), 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	Crude	Yield	% ee	[α] ²⁰ _D
		(h)	Efficiency	(%)		
			(%) ^a			
1	(4 <i>R</i>)-Bn	26	>90% 40b	53	5 (2 <i>R</i> ,3 <i>S</i>)	+1.7 (c 1.000)
	43					
2	(4R, 5S)-	48	> 90%	69	65 (2 <i>R</i> ,3 <i>S</i>)	+42.3 (c 0.122)
	di-Ph 137		(1:1)			
			(40a : 40b)			
3	(4 <i>S</i>)- <i>t</i> -Bu	3	>90% 40b	61	0(2S,3R)	-
	138					

a. Efficiency calculated using ¹H NMR spectra of the crude product using signals for C(2)*H* and C(3)*H*, *trans* sulfolane **40b**; $\delta_{\rm H}$ 3.89-4.08 [2H, m, C(2)*H* and C(3)*H*].

Note; A ¹H 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 (2R,3S)-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), CuCl₂ (2.0 mg, 15 µmol), sodium tetrakis[3,5bis(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. ¹H 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); v_{max}/cm^{-1} (KBr): 2936 (CH), 1736 (CO), 1429 (C=C, ArH), 1321, 1312, 1298, 1121 (SO₂), 740 (CS); δ_{H} (CDCl₃, 600 MHz): 3.22 (1H, dddd, *J* 14.1, 5.1, 3.8, 2.6 one of SO₂CH₂), 3.43–3.59 (2H, m, SO₂CH₂CH₂), 3.84 (3H, s, OCH₃), 3.93–4.01 (1H, ddd, *J* 14.1, 11.4, 5.7, one of SO₂CH₂), 4.99 (1H, d, *J* 2.5, SO₂CH), 7.11–7.14 (1H, m, ArH), 7.24–7.29 (2H, m, ArH), 7.31–7.36 (1H, m, ArH); δ_{c} (CDCl₃, 150.9 MHz) 29.0 (CH₂, SO₂CH₂CH₂), 45.9 (CH₂, SO₂CH₂), 53.8 (CH₃, OCH₃), 67.8 (CH, SO₂CH), 127.4 (CH, aromatic CH), 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, *CO*); HRMS (ESI+): Exact mass calculated for C₁₁H₁₃O₄S [M+H]⁺, 241.0535. Found 241.0527.

Assignments made with aid of 2D NMR experiments.

Entry	Crude	Ligand	Time (h)	Yield (%)	% ee
	Efficiency ^a				
1	~85–90% ^b	(4 <i>R</i> ,5 <i>S</i>)-di-Ph	2	68	0
		137			
2	~80–90%	(4 <i>R</i>)-Bn 43	2	66	0
3	~80–90%	(4 <i>S</i>)- <i>t</i> -Bu 138	3	69	0
4	~80–90%°	(4 <i>R</i>)-Ph 20	2	70 ^d	0

Table 4.21 Copper catalysed C–H insertion reaction of α -diazo- β -oxo sulfone 62

(Mathad A	١
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a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for **146** C(2)*H*; $\delta_{\rm H}$ 4.99 [1H, d, *J* 2.5, SO₂C*H*].

b. Additional product observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the pure product; $\delta_{\rm H}$ 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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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 wornout 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**)



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	l catalysed C–H insertio	n reactions of α-diazo-	β -oxo sulfones 54-56
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$ \begin{array}{c} 0 & 0 & 0 \\ \hline \\ S & R \end{array} \xrightarrow{(N_2)} R \end{array} \xrightarrow{(Catalyst)} A \xrightarrow{(Catalyst)} R \xrightarrow$								R	
Entry	Method	R	М	Crude	Yield		cis	:	trans
				Efficiency	(%)		% ee		% ee
1	С	OEt	Cu(OTf) ₂ ^a	~60–70% ^b		Crude:	50		50
			(5 mol%)		29°	Purified:	7		93
			(0)				(0% ee)		(0% ee)
							165a		165b
2	Е	Ph	Rh ₂ (OAc) ₄	~70-80% ^d		Crude:	10		90
			(1 107)		40		1		00
			(1 mol%)		40	Purified:	1		99
					(80%				(0% ee)
					16 7) ^e		167a		167b
3	Е	Me	Rh ₂ (OAc) ₄	~95% ^f		Crude:	9		91
			(1 mol%)		56	Purified:	2		98
		1							(0% ee)
							166a		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 ¹H NMR spectra of the crude product using signals for OCH₂CH₃, *cis* sulfolane **165a**, δ_H 1.26 (3H, t, *J* 7.1, OCH₂CH₃); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH₂CH₃).
- c. Additional material present, including X-H insertion product 168.
- d. Efficiency and relative ratios of isomers calculated using the ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **167a**, $\delta_{\rm H}$ 5.45 [1H, d, *J* 5.4, C(2)*H*]; *trans* sulfolane **167b**, $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **166a**, $\delta_{\rm H}$ 4.44 [1H, d, *J* 6.5, C(2)*H*]; *trans* sulfolane **166b**, $\delta_{\rm H}$ 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 v_{max} 2126 cm⁻¹ (C=N₂) after 21 hours indicated that the reaction was complete; however, examination of the ¹H 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 ¹H 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.

Rh₂(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% Rh₂(OAc)₄ in refluxing dichloromethane. The disappearance of the diazo stretch at $v_{max} 2117 \text{ cm}^{-1}$ (C=N₂) for α diazo- α -sulfonyl phenyl ketone **56** and at v_{max} 2115 cm⁻¹ (C=N₂) for α -diazo- α -sulfonyl methyl ketone 55 indicated that the reactions were finished. Inspection of the ¹H 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 ¹H NMR, ¹³C 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.



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 ¹H 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 ¹H NMR spectra.



Figure 5.5¹H NMR spectra recorded in CDCl₃ (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 CuCl₂-NaBARF-(4R)-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 ¹H NMR spectrum in CDCl₃ was obtained, to enable determination of the cis: trans ratio, with the initial sample being held in CDCl₃. 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 ¹H NMR.

Table 5.2 Study on factors affecting the ratio of epimerisation of cis sulfolane 165a totrans sulfolane 165b

	CuCl ₂ -NaBARF-(4 <i>R</i>)-Ph 20	S S	° ° ° °			
	Δ, CH ₂ Cl ₂	OEt	OEt			

Entry	Time	Solvent	Temperature	cis : trans ^b	
1 ^a	1h	CH ₂ Cl ₂	Reflux*	88%:12%	
	20 h	CDCl ₃	rt	87%:13%	
	9 days	CDCl ₃	rt	33%:67%	
2	3h	CH ₂ Cl ₂	reflux	87% : 13%	
3	21h	CH ₂ Cl ₂	reflux	84% : 16%	
4	30h	CH ₂ Cl ₂	reflux	81%:19%	
5	9 days	CH ₂ Cl ₂	2 day reflux,	60% : 40%	
			7 days rt		
6°	~0.5 h	Silica gel	Room temperature	Crude:	
				70% :30%	
				Purified :	
				7%:93%	

- a. The initial sample was held in CDCl₃ and two further ¹H NMR spectra of this sample were obtained, one after 20 h in CDCl₃ and one after 9 days in CDCl₃.
- b. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃, *cis* sulfolane; 1.26 (3H, t, *J* 7.1, OCH₂CH₃) *trans* sulfolane; $\delta_{\rm H}$ 1.37 (3H, t, *J* 7.1, OCH₂CH₃).
- 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 CDCl₃ 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 CDCl₃. 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.







Figure 5.6¹H NMR spectra recorded in CDCl₃ (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 CH₃ 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.



Scheme 5.3²⁵

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% CuCl₂, 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, preforming 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 ¹H 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 insertionreactions of α -diazo- β -oxo sulfone 54



Entry	Method	CuX	Time	Crude	Yield	Product	cis	:	trans
			(h)	Efficiency ^a	(%) ^b	Ratio	% ee ^c		% ee ^c
1	Α	CuCl ₂	2	~90%	91	Crude:	89		11
	catalyst								
	not pre-					Purified:	6		94
	formed						(82% ee)		(80% ee)
							(2S, 3R)		(2R, 3R)
2 ^d	Α	CuCl ₂	5	~90%	78	Crude:	70		30
	catalyst								
	not pre-					Purified:	7		93
	formed						(90% ee)		(80% ee)
							(2S, 3R)		(2R, 3R)
3	В	CuCl ₂	3	~90%	81	Crude:	84		16
	pre-								
	formed					Purified:	8		92
	catalyst						(86% ee) ^e		(80% ee)
							(2S, 3R)		(2R, 3R)
4	В	CuCl	30	~90%	77	Crude:	38		62
	pre-								
	formed					Purified:	7(-) ^{f,g}		93
	catalyst								(80% ee)
									(2R, 3R)

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃, *cis* sulfolane **165a**; 1.26 (3H, t, *J* 7.1, OCH₂CH₃) *trans* sulfolane **165b**; $\delta_{\rm H}$ 1.37 (3H, t, *J* 7.1, OCH₂CH₃).

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-[α] $^{20}_{D}$ -29.0 (*c*, 1.0 CH₂Cl₂)
- f. Rotation measured on mixed fraction-[α] $\frac{20}{D}$ -39.5 (*c*, 1.0 CH₂Cl₂)
- 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 CuCl₂ 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 CuCl₂. 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 CuCl₂ 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 insertionreactions of α -diazo- β -oxo sulfone 54

O C	$ \begin{array}{c} 5n \\ 6n \\ 6n \\ N_2 \end{array} $	nol% CuCl ₂ nol% NaBARF nol% L*	•	S S D D D D D D D D D D D D D D D D D D		o c Ś	0 OEt	
	54			165a		165b		
Entry	L*	Crude Efficiency ^a	Yield (%) ^b	Product Ratio	cis % ee ^c	:	<i>trans</i> % ee ^c	
1	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	~90%		Crude:	83		17	
			67	Purified:	14 (83% ee) (2 <i>S</i> ,3 <i>R</i>)		86 (75 % ee) (2 <i>R</i> ,3 <i>R</i>)	
2	(4 <i>R</i>)-Bn 43	~90%		Crude:	32		68	
			75	Purified:	7 (18% ee) (2 <i>S</i> ,3 <i>R</i>)		93 (15% ee) (2 <i>R</i> ,3 <i>R</i>)	
3	(4 <i>S</i>)- <i>t</i> -Bu 138	~82%		Crude:	52		48	
			61	Purified:	11 (54% ee) (2 <i>R</i> ,3 <i>S</i>)		89 (49% ee) (2 <i>S</i> ,3 <i>S</i>)	
4	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	~90%		Crude:	63		37	
			84	Purified:	7 (3% ee) (2 <i>R</i> ,3 <i>S</i>)		93 (2% ee) (2 <i>S</i> ,3 <i>S</i>)	

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃, *cis* sulfolane **165a**;1.26 (3H, t, *J* 7.1, OCH₂CH₃); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH₂CH₃).

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 (4R)-Ph 20 (Table 5.3, entry 1) and (4R)-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 (4S)-t-Bu ligand 138 giving rise to trans sulfolane 165b with 49% ee (Table 5.4, entry 3) and enantioselectivity falls off dramatically when (4R)-Bn 43 and (3S,8R)-Ind 44 are used with values of <20% ee attained in both instances. (Table 5.4, entries 2 and 4). The (4R)-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 (3S, 8R)-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 (3S, 8R)-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-(4R)-Ph **159**, Py-(4S)-*i*-Pr **160** and CN-(4S)-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



165a

165b

Entry	Ligand	Crude	Yield		<i>cis</i> 165a	:	trans 165a
		Efficiency ^a	(%) ^b		% ee ^c		% ee ^c
1	CN-(4S)-Ph 158	~80% ^d	35	Crude:	33		67
				Purified:	6		94
					-		(28% ee) ^e
							(2S, 3S)
2	Py-(4 <i>R</i>)-Ph 159	Starting		Crude:	-		-
		material only					
				Purified:	-		-
					-		-
3	Py-(4 <i>S</i>)- <i>i</i> -Pr 160	50-60% ^f	26	Crude:	10		90
	-						
				Purified:	10		90
					(10% ee) ^e		(10% ee) ^e

Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃, *cis* sulfolane **165a**; 1.26 (3H, t, J 7.1, OCH₂CH₃) *trans* sulfolane **165b**; δ_H 1.37 (3H, t, *J* 7.1, OCH₂CH₃).

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.

- Enantioselectivity was measured using chiral HPLC analysis, details of which can be found in c. 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.
- The crude material contains ~5% starting material α -diazo- β -oxo sulfone 54. d.
- The enantioselectivity given here is estimated and could not be accurately determined due to peak e. 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-(4R)-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-(4S)-Ph 158 and the Py-(4S)-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 ₂ L ₄	Time	Crude	Yield	Product	cis	:	trans
			(h)	Efficiency ^a	(%) ^b	Ratios	% ee ^c		% ee ^c
1	F	$Rh_2(S-$	6	80–90%	44	Crude:	58		42
		PTTL) ₄							
		0 °C-rt				Purified:	7 (20% ee)		93 (30% ee)
							(2S, 3R)		(2R, 3R)
2	F	$Rh_2(S-$	6	80–90%	61	Crude:	62		48
		PTPA) ₄							
		0 °C-rt				Purified:	5 (13% ee)		95 (16% ee)
							(2S, 3R)		(2R, 3R)
3	F	$Rh_2(S-$	2	80–90%	52	Crude:	50		50
		DOSP) ₄							
		0 °C-rt				Purified:	8		92 (8% ee)
									(2S, 3S)
4	G	$Rh_2(S-$	30,90 ^d	50–60% ^e	25	Crude:	47		53
		$MEPY)_4$							
		$0 ^{\circ}\text{C-rt-}\Delta$				Purified:	10 (0% ee)		$90 (2\% \text{ ee})^{\text{f}}$
									(2R, 3R)
5	F	$Rh_2(S-$	6	80–90%	58	Crude:	45		55
		mand) ₄				Purified:	7 (5% ee)		93 (6% ee)
		0 °C-rt					(2R, 3S)		(2S, 3S)

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃, *cis* sulfolane **165a**, 1.26 (3H, t, *J*7.1, OCH₂CH₃); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J*7.1, OCH₂CH₃).

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 Rh₂(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 Rh₂(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 Table5.3, entry 2



78% ee-trans

Entry	Ester 165b	Yield	Product	Acid ^a		
	(trans : cis)	(%)	Ratio			
	(% ee-trans)					
				cis ^b	trans	
				(170a)	(170b)	
1	80% ^c (93 : 7)	78%	Ratio (% ee)	5(-) ^b	95 (78% ee)	
	(2R, 3R)					
	Table 5.3, entry 2					
2	0% (93 : 7)	65%	Ratio (% ee)	8(-) ^b	92 (0% ee)	
	Table 5.1, entry 1					

a. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for *cis* sulfolane **170a**; $\delta_{\rm H}$ 4.46 [1H, d, *J* 6.8 C(2)H], *trans* sulfolane **170b**; $\delta_{\rm H}$ 4.13 [1H, d, *J* 7.3, C(2)H].

b. Peaks for *cis* sulfolane **170a** not detected during HPLC analysis.

80% ee-trans

c. Result obtained from a reaction catalysed using (4R)-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 (¹H 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 (2R,3R) 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 (2R,3R) stereochemistry (80% ee, **Table 5.3**, entry 2), which upon saponification gave rise to carboxylic acid **170b** with (2R,3R) 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**.



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 CH₂Cl₂) 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 CH₂Cl₂) 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 CH₂Cl₂) 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**.





167b (2*S*,3*S*) 7 : 93 *cis* : *trans*, 13 % ee *trans* $[\alpha]_{\rm D}^{20}$ +16.0 (*c*, 0.1 CH₂Cl₂).

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 Rh₂(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



55, R=Me

167a R=Ph
1((- D M.
100a K=Me

166b R=Me

Entry	α-diazosulfone	R	L*	Time	Crude	Combined Yield	Product Ratio	cis	 trans
				(h)	Efficiency (%)	(cis and trans) $(\%)^{a}$		% ee	% ee ^b
1	56	Ph	(4 <i>R</i>)-Ph 20	5	~65%°	38 ^d	Crude ratio:	9	91 905
							Purified ratio:	1	(71% ee) (2R 3R)
2	56	Ph	(4 <i>R</i> ,5 <i>S</i>) di-Ph	3	~72% ^c	50 ^f	Crude ratio:	54	46
			137				Purified ratio:	1	99 (70% ee) ^{g,h} (2 <i>R</i> ,3 <i>R</i>)
3	56	Ph	(4 <i>S</i>)- <i>t</i> -Bu 138	21	~70% ^c	55	Crude ratio: Purified ratio:	42 1	58 99 ⁱ (39% ee) (2 <i>S</i> ,3 <i>S</i>)
4	56	Ph	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	24	~65%°	42	Crude ratio: Purified ratio:	7 1	93 99 (13% ee) ^j (2 <i>S</i> ,3 <i>S</i>)
5	56	Ph	(4 <i>R</i>)-Bn 43	50	~65% ^c	48	Crude ratio:	Trace	>99

							Purified ratio:	1	99 $(12\% \text{ ee})^k$ (2R.3R)
6	55	Me	(4 <i>R</i>)-Ph 20	3	>90%1	65	Crude ratio: Purified ratio:	2 2	98 98 $(64\% \text{ ee})^{m}$ (2R,3R)
7	55	Me	(4 <i>R</i> ,5 <i>S</i>) di-Ph 137	7	~55% ^{l,n}	42	Crude ratio: Purified ratio:	2 1	98 99 (76% ee) ^{0,p} (2 <i>R</i> ,3 <i>R</i>)
8	55	Me	(4 <i>S</i>)- <i>t</i> -Bu 138	30	41% starting material left, of remaining 59%;43% efficient ¹	38	Crude ratio: Purified ratio:	2 2	98 98 (12% ee) (2 <i>S</i> ,3 <i>S</i>)
9	55	Me	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	5	~60-70% ^{l,q}	45	Crude ratio: Purified ratio:	5 2	95 98 (16% ee) ^{r,s} (2 <i>R</i> ,3 <i>R</i>)
10	55	Me	(4 <i>R</i>)-Bn 43	4	~70% ¹	60	Crude ratio: Purified ratio:	4 1	96 99 (13% ee) (2 <i>R</i> ,3 <i>R</i>)

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 ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **167a**, $\delta_{\rm H}$ 5.45 [1H, d, *J* 5.4, C(2)*H*]; *trans* sulfolane **167b**, $\delta_{\rm H}$ 5.02 [1H, d, *J* 6.9, C(2)*H*].

d. Additional less polar fraction isolated after chromatography (3 mg); $\delta_{\rm H}$ 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 selfdisproportionation. 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; $\delta_{\rm H}$ 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 selfdisproportionation .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 CH₂Cl₂), measured on fraction five (see g).
- i. Rotation measured on combined mixed - $[\alpha]_{D}^{20}$ +73.5 (*c*, 0.1 CH₂Cl₂).
- j. Rotation measured on combined mixed -[α] $_{D}^{20}$ +16.0 (c, 0.1 CH₂Cl₂).
- k. Rotation measured on combined mixed -[α] $_{D}^{20}$ +26.8 (c, 0.276 CH₂Cl₂), the direction of specific rotation is inconsistent with HPLC data.
- 1. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* sulfolane **166a**, $\delta_{\rm H}$ 4.44 [1H, d, *J* 6.5, C(2)*H*]; *trans* sulfolane **166b**, $\delta_{\rm H}$ 4.17 [1H, d, *J* 7.0, C(2)*H*].
- m. Rotation measured on mixed fraction- $[\alpha]_{D}^{20}$ -2.0 (*c*, 0.1 CH₂Cl₂).
- n. Additional peaks observed in ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 CH₂Cl₂), measured on fraction one (see o).
- q. Additional peaks observed in ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 CH₂Cl₂).

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 ¹H 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 ¹H 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 ¹H 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 tables²⁸ 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 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 (4R)-Ph **20** or (4R,5S)-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 (4R)-Ph **20** and (4R,5S) 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 (2R,3S)-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),

CuCl₂ (3.53 mg, 26.6 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (28mg, 31.9 μ mol) and bisoxazoline ligand (4*R*)-Ph **20** (10.6 mg, 31.9 μ mol) in dichloromethane (20 mL), stirred while heating under reflux for 2 h, in accordance with Method A. ¹H 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, (2R,3R) 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. v_{max}/cm⁻¹ (film): 1741 (CO), 1317, 1282, 1251, 1213, 1180 (SO₂), 761 (CS); δ_H (CDCl₃, 300 MHz): 1.37 (3H, t, *J* 7.1, OCH₂CH₃), 1.55 [3H, d, *J* 6.70, C(1')H₃], 3.93–4.08 [2H, m, C(2)H and C(3)H], 4.17–4.47 (2H, sym m, OCH₂CH₃), 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 (CDCl₃, 75.5 MHz): 14.1 (CH₃, OCH₂CH₃), 18.7 [CH₃, C(1')H₃], 35.7 [CH, C(3)H], 62.9 (CH₂, OCH₂CH₃), 72.3 [CH, C(2)H], 121.6 (CH, aromatic CH), 125.4 (CH, aromatic CH), 129.0 (CH, aromatic CH), 134.1 (CH, aromatic CH), 137.4 (C, aromatic C), 140.3 (C, aromatic C), 164.0 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₂H₁₅O₄S [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**.



¹H NMR spectral characteristics of *cis* **165a** were determined from the spectra of the crude product; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.26 (3H, t, *J* 7.1, OCH₂CH₃), 1.55 [3H, d, *J* 7.1, C(1')H₃], 3.92 [1H, apparent quint, *J* 6.8, C(3)H], 4.16–4.32 (2H, m, OCH₂CH₃), 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 the¹H 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 CDCl₃ and in CH₂Cl₂. A reaction was set up identical to that reported for ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2carboxylate 1,1-dioxide **165b**. The reaction was deemed complete after 1 h, at which point a ¹H 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 ¹H NMR analysis.

effects	Table 5.9 Investi	gation into the ra	tte of epimerisation	n of 165a to 16	5b ; solvent and hear
			effects		

Entry	Time	Solvent	Temperature	<i>cis</i> 165a :
				trans 165b ^b
1 ^a	1h	CH ₂ Cl 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 ₂ Cl ₂	reflux	84% : 16%
6	30h	CH_2Cl_2	reflux	81%:19%
7	9 days	CH ₂ Cl ₂	2 day reflux,	60%:40%
			7 days rt	

a. The initial ¹H NMR of the crude mixture was kept in CDCl₃. Two further ¹H NMR were measured for this sample, one after 20 h in CDCl₃ and one after 9 days in CDCl₃.

b. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃; *cis* sulfolane **165a**, δ_H 1.26 (3H, t, *J* 7.1, OCH₂CH₃); *trans* sulfolane **165b**, δ_H 1.37 (3H, t, *J* 7.1, OCH₂CH₃).

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 \sim 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.

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency ^a	Yield (%) ^b	Crude ratios ^a Purified ratios ^a	cis 165a %ee ^c	:	<i>trans</i> 165b %ee ^c
1	Α	CuCl₂/∆	(4 <i>R</i>)-Ph 20	2	~90%	91	Crude ratio: Purified ratio:	89 6 (82% ee) (2 <i>S</i> ,3 <i>R</i>)		11 94 (80% ee) (2 <i>R</i> ,3 <i>R</i>)
2 ^d	Α	CuCl₂/∆	(4 <i>R</i>)-Ph 20	5	~90%	78	Crude ratio: Purified ratio:	70 7 (90% ee) (2 <i>S</i> ,3 <i>R</i>)		30 93 (80% ee) (2 <i>R</i> ,3 <i>R</i>)
3	С	Cu(OTf)₂ [¢] /∆	-	21	~60–70%	29 ^f	Crude ratio: Purified ratio:	50 7 (0% ee)		50 93 (0% ee)
4	Α	CuCl ₂ /Δ	(3 <i>S</i> ,8 <i>R</i>)-Ind 4 4	3	~90%	84	Crude ratio: Purified ratio:	63 7 (3% ee) (2 <i>R</i> ,3 <i>S</i>)		37 93 (2% ee) (2 <i>S</i> ,3 <i>S</i>)
5	Α	CuCl ₂ /Δ	(4 <i>R</i>)-Bn 43	3	~90%	75	Crude ratio: Purified ratio:	32 7 (18% ee) (2 <i>S</i> ,3 <i>R</i>)		68 93 (15% ee) (2 <i>R</i> ,3 <i>R</i>)
6	Α	CuCl ₂ /Δ	(4 <i>S</i>)- <i>t</i> -Bu 138	3	~82%	61	Crude ratio: Purified ratio:	52 11 (54% ee) (2 <i>R</i> ,3 <i>S</i>)		48 89 (49% ee) (2 <i>S</i> ,3 <i>S</i>)

Table 5.10 Copper and rhodium catalysed C–H insertion reactions of α -diazo- β -oxo sulfone 54

7	A	CuCl ₂ /Δ	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	3	~90%	67	Crude ratio: Purified ratio:	83 14 (83% ee) (2 <i>S</i> ,3 <i>R</i>)	17 86 (75% ee) (2 <i>R</i> ,3 <i>R</i>)
8	В	CuCl ₂ /Δ	(4 <i>R</i>)-Ph 20	3	~90%	81	Crude ratio: Purified ratio:	84 8 (86% ee) ^g (2 <i>S</i> ,3 <i>R</i>)	$ \begin{array}{c} 16 \\ 92 (80\% \text{ ee})^{\text{g}} \\ (2R,3R) \end{array} $
9	В	CuCl/Δ	(4 <i>R</i>)-Ph 20	30	~90%	77	Crude ratio: Purified ratio:	38 7 (-) ^h	$ \begin{array}{c} 62 \\ 93 (80\% \text{ ee})^{i} \\ (2R,3R) \end{array} $
10	В	CuCl ₂ /Δ	CN-(4 <i>S</i>)-Ph 158	120	~80% ^j	35	Crude ratio: Purified ratio:	33 6	67 94 (28% ee) ^k (2 <i>S</i> ,3 <i>S</i>)
11	B	CuCl ₂ /Δ	Py-(4 <i>R</i>)-Ph 159	120	Starting material only	-	Crude ratio: Purified ratio:	-	-
12	В	CuCl ₂ /Δ	Py-(4 <i>S</i>)- <i>i</i> -Pr 160	120	50-60%1	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 <i>S</i> ,3 <i>R</i>)	42 93 (30% ee) (2 <i>R</i> ,3 <i>R</i>)
14	F	Rh ₂ (S- PTPA) ₄ 0 °C-rt	-	6	80–90%	61	Crude ratio: Purified ratio:	62 5 (13% ee) (2 <i>S</i> ,3 <i>R</i>)	48 95 (16% ee) (2 <i>R</i> ,3 <i>R</i>)
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 <i>S</i> ,3 <i>S</i>)

16	G	Rh ₂ (S-MEPY) ₄	-	120	50-60% ^m	25	Crude ratio:	47	53
		0 °C-rt-∆					Purified ratio:	10 (0% ee)	90 (2% ee) ^k
									(2R, 3R)
17	F	$Rh_2(S-mand)_4$	-	6	80–90%	58	Crude ratio:	45	55
		0 °C-rt					Purified ratio:	7 (5% ee)	93 (6% ee)
								(2R.3S)	(2S.3S)

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for OCH₂CH₃; *cis* sulfolane **165a**, $\delta_{\rm H}$ 1.26 (3H, t, *J* 7.1, OCH₂CH₃); *trans* sulfolane **165b**, $\delta_{\rm H}$ 1.37 (3H, t, *J* 7.1, OCH₂CH₃).

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**; v_{max}/cm⁻¹ 2126 (C=N₂), 1720 (CO); $\delta_{\rm H}$ (CDCl₃, 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- $[\alpha]_{\rm D}^{20}$ -29.0 (c, 1.0 CH₂Cl₂)
- h. Result could not be determined accurately.
- i. Rotation measured on mixed fraction- $[\alpha]_{D}^{20}$ -39.5 (c, 1.0 CH₂Cl₂)
- 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.
- 1. Contains ~30% starting material α -diazo- β -oxo sulfone 54.
- m. Contains ~25% starting material α -diazo- β -oxo sulfone 54.



The presence of $\delta_{\rm H}$ 5.76 (s) in the ¹H 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**. ¹H 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)1-(3-methyl-1,1-dioxido-2,3as eluent, 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**. v_{max}/cm^{-1} (film): 2912 (CH), 1726 (CO), 1647, 1595 (C=C, Ar), 1299, 1209, 1173, 1126 (SO₂), 768 (CS); δ_H (CDCl₃, 400 MHz): 1.49 [3H, d, J 7.0, C(1')H₃], 2.55 (3H, s, COCH₃), 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 (CDCl₃, 150.9 MHz): 18.7 [CH₃, C(1')H₃], 31.1 [CH₃, COCH₃], 34.3 [CH, C(3)H], 78.5 [CH, C(2)H], 121.5 (CH, aromatic CH), 125.5 (CH, aromatic CH), 129.0 (CH, aromatic CH), 134.2 (CH, aromatic CH), 137.0 (C, aromatic C), 140.8 (C, aromatic C), 195.8 (C, CO); 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 (2R,3S)-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), CuCl₂ (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**. ¹H 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 ¹H NMR spectra of the crude product and are tentatively assigned to *cis* **166a**; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.51 [3H, d, *J* 5.4, C(1')*H*₃], 2.42 (3H, s, COC*H*₃), 3.89 [1H, apparent quint *J* 6.5, C(3)*H*], 4.44 [1H, d, *J* 6.5, C(2)*H*].

Entry	Method	М	Ligand	Time (h)	Crude Efficiency ^a	Yield (%) ^b	Crude ratios ^a Purified ratios ^a	<i>cis</i> % ee ^c	:	trans % ee ^c
1	Α	CuCl ₂ /Δ	(4 <i>R</i>)-Ph 20	3	>90% ^d	65 ^e	Crude ratio: Purified ratio:	2 2		98 98 (64% ee) ^f (2 <i>R</i> ,3 <i>R</i>)
2	A	CuCl ₂ /Δ	(4 <i>R</i> ,5 <i>S</i>) di-Ph 137	7	~55% ^g	42	Crude ratio: Purified ratio:	2 1		98 99 (76% ee) ^{h,i} (2R,3R)
3	A	CuCl₂/∆	(4 <i>S</i>)- <i>t</i> -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 <i>S</i> ,3 <i>S</i>)
4	A	CuCl ₂ /Δ	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	5	~60-70% ^k	45 ^{d,1}	Crude ratio: Purified ratio:	5 2		95 98 (16% ee) ^{m,n} (2 <i>R</i> ,3 <i>R</i>)
5	A	CuCl₂/∆	(4 <i>R</i>)-Bn 43	4	~70%	60	Crude ratio: Purified ratio:	4		96 99 (13% ee) (2 <i>R</i> ,3 <i>R</i>)
6	E	Rh ₂ (OAc) ₄ / Δ	-	21	~95%	56 ^d	Crude ratio: Purified ratio:	9 2		91 98 (0% ee)

Table 5.11 Asymmetric copper-bisoxazoline and rhodium acetate catalysed C-H insertion reactions of α -diazo- β -oxo sulfone 55

- a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*; *cis* sulfolane **166a**, $\delta_{\rm H}$ 4.44 [1H, d, *J* 6.5, C(2)*H*]; *trans* sulfolane **166b**, $\delta_{\rm H}$ 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 $73-74^{\circ}$ C).
- e. Additional peaks observed in ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 CH₂Cl₂).
- g. Additional peaks observed in ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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: $\left[\alpha\right]_{D}^{20}$ -2.0 (*c*, 0.1 CH₂Cl₂).
- j. Impurity(ies) observed in ¹H NMR spectra of the crude and purified product. Signals listed for ¹H NMR of purified product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; δ_H 3.01–3.11 (m), 5.12 (s).
- 1. Additional peaks observed in the ¹H 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 CH₂Cl₂).



The presence of $\delta_{\rm H}$ 5.12 (s) in the ¹H 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 (2R,3S)-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), CuCl₂ (2.2 mg, 16 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (16.9 mg, 19 μ mol) and (4R)-Ph 20 (6.4 mg, 19 μ mol) in dichloromethane (25 mL), stirred while heating under reflux for 5 h, in accordance with Method A. ¹H 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, [(2R,3R)-3-methyl-1,1-dioxido-2,3-methdihydrobenzo[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); v_{max}/cm⁻¹ (film): 2922, 2851 (CH), 1684 (CO), 1597 (C=C, Ar), 1309, 1156 (SO_2) , 751 (CS); δ_H (CDCl₃, 400 MHz): 1.54 [3H, d, J 7.0, C(1')H₃], 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, ArH), 7.63-7.72 (3H, m, ArH), 8.19–8.22 (2H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 18.8 [CH₃, C(1')H₃], 35.7 [CH, C(3)H], 73.8 [CH, C(2)H], 121.6 (CH, aromatic CH), 125.4, 129.1 (× 2), 129.5 (× 2), 134.2, 134.6 (6 signals seen for 7 aromatic CH carbons), 136.3 (C, aromatic C), 137.3 (C, aromatic C), 141.2 (C, aromatic C), 188.2 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₆H₁₅O₃S [M+H]⁺, 287.0742. Found 287.0732.



The following signals appear in ¹H NMR spectra of the crude product and are tentatively assigned to *cis* **167a**; $\delta_{\rm H}$ (CDCl₃, 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)

Entry	Method	M	Ligand	Time (h)	Crude Efficiency ^a	Yield (%) ^b	Crude ratios ^a Purified ratios ^a	cis % ee ^c	:	<i>trans</i> % ee ^c
1	Α	CuCl ₂ /Δ	(4 <i>R</i>)-Ph 20	5	~65%	38 ^d (oil)	Crude ratio: Purified ratio:	9 1 ^e		91 99 ^e (71% ee) (2 <i>R</i> ,3 <i>R</i>)
2	A	CuCl ₂ /Δ	(4 <i>R</i> ,5 <i>S</i>) di- Ph 137	3	~72% ^f	50 ^g (oil)	Crude ratio: Purified ratio:	54 1		46 99 $(70\% \text{ ee})^{h,i}$ (2R,3R)
3	A	CuCl ₂ /Δ	(4 <i>S</i>)- <i>t</i> -Bu 138	21	~70%	55 ^j (solid)	Crude ratio: Purified ratio:	42 1 ^j		58 99 ^{j,k} (39% ee) (2 <i>S</i> ,3 <i>S</i>)
4	A	CuCl ₂ /Δ	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	24	~65%1	42 (solid) ^m	Crude ratio: Purified ratio:	7 1		93 99 (13% ee) ⁿ (2 <i>S</i> ,3 <i>S</i>)
5	A	CuCl ₂ /Δ	(4 <i>R</i>)-Bn 43	50	~65%	48 (solid)	Crude ratio: Purified ratio:	Trace 1		>99 99 (12% ee) ^o (2 <i>R</i> ,3 <i>R</i>)
6	Ε	$Rh_2(OAc)_4/\Delta$	-	21	~70-80%	40	Crude ratio: Purified ratio:	10 1		90 99 (0% ee)

Table 5.12 Asymmetric copper-bisoxazoline and rhodium acetate catalysed C–H insertion reactions of α -diazo- β -oxo sulfone 56

			(80%		
			167b)		
			(solid)		

- a. Efficiency and relative ratios of isomers calculated using the ¹H NMR spectra of the crude product using signals for C(2)*H*; *cis* sulfolane **167a**, $\delta_{\rm H}$ 5.45 [1H, d, *J* 5.4, C(2)*H*]; *trans* sulfolane **167b**, $\delta_{\rm H}$ 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 selfdisproportionation. 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 ¹H NMR spectra of the crude product; $\delta_H 2.50-2.33$ (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; $\delta_{\rm H}$ 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 selfdisproportionation. 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 CH₂Cl₂)
- j. Additional peaks present in the ¹H 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-[α] $\frac{20}{D}$ +73.5 (*c*, 0.1 CH₂Cl₂)
- 1. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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-[α] $^{20}_{D}$ +16.0 (*c*, 0.1 CH₂Cl₂).
- o. Rotation measured on mixed fraction- $[\alpha]_{D}^{20}$ +26.8 (c, 0.276 CH₂Cl₂)



The presence of $\delta_{\rm H}$ 6.14 (s) in the ¹H NMR spectra of some of the crude products may indicate the presence of an X–H insertion product 180, however, this is not confirmed.

(2R,3R)-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 (2S,3R)] : trans 165b [80%ee (2R,3R)], 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 $(3 \times 20 \text{ mL})$. The combined organic layers were washed with brine (40 mL), dried with MgSO₄ and concentrated under reduced pressure to yield (2R,3R) 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, CH₂Cl₂); 78% ee (trans 170a) (determined by chiral-HPLC); (Found: C, 51.50; H, 4.53; C₁₀H₁₀O₄S.0.5H₂O requires C, 51.05; H, 4.71 %); v_{max}/cm⁻¹ (neat): 3176 (OH), 2926 (CH), 1725 (CO), 1281, 1151, 1123 (SO₂), 764 (CS); The following spectral characteristics are reported for trans 170b. δ_H (CDCl₃, 600 MHz): 1.57 [3H, d, J 7.0, C(1')H₃], 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, COOH), 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 (CDCl₃, 75.5 MHz): 18.5 [CH₃, *C*(1')H₃], 35.8 [CH, *C*(3)H], 72.2 [CH, br, *C*(2)H], 121.7 (CH, aromatic CH^a), 125.1 (CH, aromatic CH^b or CH^d), 129.1 (CH, aromatic CH^b or CH^d), 134.3 (CH, aromatic CH^c), 137.0 (C, aromatic C), 140.3 (C, aromatic C), 167.4 (C, CO).

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 C₂₀H₂₂O₉S₂, M_R = 470.49, *a* = 8.1731(8) Å, *b* = 8.5779(9) Å, *c* = 9.0489(9) Å, *a* = 74.180(2)°, *β* = 76.474(2)°, *γ* = 63.539(2)°, *U* = 541.75(10) Å³, *F*(000) = 246, μ (Mo K α) = 0.295 mm⁻¹, *R*(F₀) = 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 K α radiation, $\lambda = 0.71073$ Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F² 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.



¹H NMR spectral characteristics of *cis* **170a** were determined from spectra of purified product; $\delta_{\rm H}$ (CDCl₃, 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	Yield		Carboxylic acid ^a		
	cis 165a : trans	(%)				
	165b					
	(trans %ee)			<i>cis</i> 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)	

Relative ratios of isomers calculated using ¹H 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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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 γ -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 γ -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 γ -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 γ -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 y-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 y-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 y-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 6.1⁷

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 γ -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}



increasing reactivity

Figure 6.1⁶

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 γ -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 γ -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	Ra	atio
		(%)	β	Y
125	COCH ₃	9	49	51
2^{28}	PhSO ₂	95	none	only
326	PO(OEt) ₂	81	none	only

6.1.2 Effect of substituents near to the insertion centre

In determining whether β - or γ -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 6.2²⁶

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, y-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 y-lactam product outweighs this preference. The exclusive synthesis of y-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 y-lactam formation (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 γ -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 γ -lactam product, which has been rationalised by the stabilising effect of the phenylsulfonyl moiety.²⁸



Scheme 6.5²⁸

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 γ -lactam **193**; cleavage of both the phenylsulfonyl moiety and the *N*-benzyl group occurred simultaneously upon exposure to Li/NH₃ which afforded rolipram **194** in an excellent yield of 90%.³⁸



Scheme 6.6³⁸

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.* Rh₂(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.* Rh₂(acam)₄] (**Figure 6.3**).^{2,7,39,40}



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 γ -lactam **197** formation (**Table 6.2**, entry 3). ²⁵

Table 6.2 C-H insertion reactions of α -diazoacetamide **196** employing electronically
different rhodium catalysts²⁵



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 γ -lactams.^{3,5–7} For example, Hashimoto and coworkers reported the synthesis of β -lactam **198** in 74% ee, employing Rh₂(*S*-PTPA)₄ as a catalyst and the synthesis of γ -lactam **199**, an important intermediate in the synthesis of R-(-)-rolipram, in 88% ee when Rh₂(*S*-BPTTL)₄ was utilised as a catalyst (**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 γ -lactams (**Scheme 6.8**). The synthesis of β -lactam **202** was reported with a value of 97% ee, when Rh₂(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; γ -lactam **203** was the major product, isolated in 98% ee with Rh₂(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 y-lactam product.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 [RuCl₂(*p*-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}



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 6.10³³

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





46

50

N,*N*-diethyl amide substrates



N,N-dibenzyl amide substrate



Morpholine amide substrates



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 y 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 -/ γ 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.



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 amide⁴⁵



Entry	α-diazo sulfone	R	Time (h)	Crude Efficiency (%)	Yield (%) ^a	Product Ratio:	<i>cis</i> (% ee)	trans (% ee)
1	57	2'-	18	~80–90% ^b	52	Crude:	8	92
		ethylphenyl				Pure:	5 (0% ee)	95 (0% ee)
							208a	208b
2	46	Ph(CH ₂) ₄	6	>90%°	60	Crude:	5	95
						Pure:	5 (0% ee)	95 (0% ee)
							209a	209b
3	50	Ph(CH ₂) ₃	2	~80–90% ^d	57	Crude:	12	88
						Pure:	10 (0% ee)	90 (0% ee)
							210a	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 ¹H 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 ¹H NMR spectra of the crude product using signals for NCH₂CH₂CH₃, *cis* γ-lactam **209a**, δ_H 0.93 (3H, t, *J* 7.4, NCH₂CH₂CH₃); *trans* γ-lactam **209b**, δ_H 0.92 (3H, t, *J* 7.4, NCH₂CH₂CH₃). Relative ratios for *cis* and *trans* isomers are estimated due to partial peak overlap.
- d. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for NCH₂CH₂CH₃, *cis* γ-lactam **210a**, δ_H 0.95 (3H, t, *J* 7.4, NCH₂CH₂CH₃); *trans* γ-lactam **210a**, δ_H 0.92 (3H, t, *J* 7.4, NCH₂CH₂CH₃). 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 ¹H NMR spectroscopy. In the cases where

reactions were not complete within $\sim 6-7$ 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 CH₂ group β to the nitrogen, leading to y-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 y- 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). y-Lactams 208–210 are novel compounds and were fully characterised using ¹H NMR, ¹³C NMR, IR and high resolution mass spectrometry. Both *cis* and *trans* y-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* y-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 γ -lactam **211** formed by C–H insertion reaction of the related α -diazoacetamide **212**, which confirmed the *trans* stereochemistry of the lactam. ¹H NMR characteristics of Ring's γ -lactam **211** were consistent with those seen for γ -lactam **208b**.



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 ¹HNMR signals (in CDCl₃) for the identification of cis and trans y- 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 ¹H 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 γ -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* γ -lactams through a single injection.

¹H NMR spectra of the crude product and the purified γ -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 ¹H NMR (CDCl₃, 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 amide⁴⁵



Entry	α-diazosulfone	R	Ligand	Time	Crude	Yield	Product	cis ^b	<i>trans^b</i>
				(h)	Efficiency	(%) ^a	Ratio	(% ee)	(% ee)
					(%) ^b				
1	57	2'-ethylphenyl	(4 <i>R</i>)-Ph 20	21	~75-85%		Crude:	14	86
						48	Pure:	10 (43% ee)	90 (48% ee)
									(3S, 4R)
								208a	208b
2	57	2'-ethylphenyl	(4 <i>R</i> ,5 <i>S</i>)-di-	21	~80-90%		Crude:	15	85
			Ph 137			53	Pure:	7 (53% ee)	93 (34% ee)
									(3S, 4R)
								208a	208b
3	57	2'-ethylphenyl	(4 <i>R</i>)-Bn 43	21	~80-90%		Crude:	12	88
						59	Pure:	0	100 (52% ee)
									(3S, 4R)
								208a	208b

4	57	2'-ethylphenyl	(4 <i>S</i>)- <i>t</i> -Bu	48	~70-80%		Crude:	8	92
			138			45	Pure:	6 (38% ee)	94 (70% ee)
									(3R, 4S)
								208a	208b
5°	57	2'-ethylphenyl	(3 <i>S</i> ,8 <i>R</i>)-Ind	6	~80–90%		Crude:	4	96
			44			61	Pure:	-	99 (82% ee)
									(3R, 4S)
								208a	208b
6	46	$Ph(CH_2)_4$	(4 <i>R</i>)-Ph	21	>90%		Crude:	3	97
			20			49	Pure:	3	97 (12% ee)
								209a	(3S, 4R)
									209b
7	46	$Ph(CH_2)_4$	(4 <i>R</i> ,5 <i>S</i>)-di-	21	>90%		Crude:	5	95
			Ph			49	Pure:	5	95 (3% ee)
			137						(3S, 4R)
								209a	209b
8	46	Ph(CH ₂) ₄	(4 <i>R</i>)-Bn	21	>90%		Crude:	5	95
			43			51	Pure:	0	100 (45% ee)
									(3S, 4R)
								209a	209b
9	46	$Ph(CH_2)_4$	(4 <i>S</i>)- <i>t</i> -Bu	50	>90%		Crude:	3	97
			138			60	Pure:	3	97 (62% ee)
									(3R, 4S)
								209a	209b
10 ^d	46	$Ph(CH_2)_4$	(4 <i>S</i>)- <i>t</i> -Bu	21	>90%		Crude:	8	92
			138			52	Pure:	6	94 (72% ee)
									(3R, 4S)
								209a	209b
11	46	$Ph(CH_2)_4$	(3 <i>S</i> ,8 <i>R</i>)-Ind	21	>90%		Crude:	2	98
			44			61	Pure:	2	98 (54% ee)
									(3R, 4S)

								209a	209b
12 ^d	46	$Ph(CH_2)_4$	(3 <i>S</i> ,8 <i>R</i>)-Ind	21	>90%		Crude:	5	95
			44			60	Pure:	2	98 (67% ee)
									(3R, 4S)
								209a	209b
13	50	$Ph(CH_2)_3$	(4 <i>R</i>)-Ph	18	~80–90%		Crude:	5	95
			20			76	Pure:	3	97(13% ee)
									(3S, 4R)
								210a	210b
14ª	50	$Ph(CH_2)_3$	(4 <i>R</i>)-Ph 20	1	>90%		Crude:	15	85
						69	Pure:	12	88 (0% ee)
									(3S,4R)
								210a	210b
15	50	$Ph(CH_2)_3$	(4R,5S)-di-	30	>90%		Crude:	15	85
			Ph 137			67	Pure:	10	90 (4% ee)
									(3S,4R)
							~ .	210a	210b
16	50	$Ph(CH_2)_3$	(4 <i>R</i>)-Bn 43	31	_e		Crude:	-	-
						65	Pure:	1	99 (48% ee)
									(3S,4R)
15			D	10	0.0 %			210a	210b
17	50	$Ph(CH_2)_3$	(4 <i>S</i>)- <i>t</i> -Bu	40	>90%		Crude:	<10	>90
			138			66	Pure:	3	97 (67% ee)
									(3R,4S)
- 10							~ .	210a	210b
18	50	$Ph(CH_2)_3$	(3 <i>S</i> ,8 <i>R</i>)-Ind	16	>90%	50	Crude:	<10	90
			44			58	Pure:	1	99 (61% ee)
									(3R,4S)
1								210a	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(CH₃CN)₄PF₆ was the copper source used. NaBARF was not employed in these reactions.
- e. Data not available.

With racemic samples of y-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% CuCl₂, 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* y-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 γ -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 γ -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 γ -lactam products, with the *trans* diastereomer dominating.²⁸

There is literature precedent for the selective formation of *trans* χ -lactams in the rhodium catalysed intramolecular C–H insertion reactions of α -diazoacetamides. Both Taber and co-workers^{46,47} and Nakamura and co-workers³⁶ 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* χ -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 y-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 (3S,8R)-Ind 44 ligand.⁴⁵ This marks the highest enantiocontrol for the synthesis of a y-lactam using chiral copper catalysis to date. The (4S)-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 (4R,5S)-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 (4S)-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 ylactams 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(CH₂)₄], with the (4*S*)-*t*-Bu **138** ligand giving the best enantiocontrol at 62% ee (Table 6.4, entry 9), followed closely by (3S,8R)-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(CH₃CN)₄PF₆ is used as a copper source, instead of CuCl₂-NABARF, an increase of 62% ee to 72% ee was observed in the presence of the (4S)-t-Bu 138 ligand (Table 6.4, entries 9 and 10) and an increase from 54% ee to 67% ee was seen for (3S,8R)-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 CuCl₂-NABARF, for (4R)-Ph 20 ligand, going from 13 to 0% ee (Table 6.4, entries 13 and 14). The enantiocontrol achieved for substrate 210b [Ph(CH₂)₃] with the various ligands in descending order is as follows (4S)-t-Bu 138 (67%) ee) > (3S,8R)-Ind 44 (61% ee) > (4R)-Bn 43 (48% ee) > (4R)-Ph 20 (13% ee) > (4R,5S)di-Ph 137 (3% ee) (Table 6.4, entries 13, 15–18). Therefore, the best ligands for achieving high enantiocontrol in this series are (4S)-t-Bu 138 and (3S,8R)-Ind 44. This trend is clearly illustrated in Figure 6.11. This is in contrast to the thiopyran and sulfolane series, where (4R)-Ph 20 and (4R,5S)-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(CH₃CN)₄PF₆-bisoxazoline is employed as a catalyst, lower enantioselectivities are observed than when a CuCl₂-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 y-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 γ -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 γ -lactam **213** in a 64% yield as colourless oil, demonstrating the synthetic potential of these reaction pathways. (**Scheme 6.12**).



Scheme 6.12





Entry	L*	Time (h)	Crude Efficiency (%) ^a	Yield (%)	Product Ratio	<i>cis</i> (% ee)	trans (% ee)
1	CN-(4S)-Ph 158	30	~70-80%		Crude:	9	91
				32	Pure:	5 (6% ee)	95 (4% ee) (3 <i>R</i> ,4 <i>S</i>)
2	Py-(4 <i>R</i>)-Ph 159	21	~60–70%		Crude:	20	80
				39	Pure:	15 (8% ee)	85 (3% ee) (3 <i>S</i> ,4 <i>R</i>)
3	Py-(4 <i>S</i>)- <i>i</i> -Pr 160	72	~40–50% reaction		Crude:	26	74
	100		approx 50% complete	22	Pure:	26 (46% ee)	74 (24% ee) (3 <i>R</i> ,4 <i>S</i>)

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 catalysis⁴⁵



Entry	α-	R	Rh(II)	Time	Crude	Yield	Product	% ee cis	% ee trans
	diazo-			(h)	Efficiency	(%)	Ratio		
	sulfone				(%) ^a				
1	57	2'-ethylphenyl	Rh ₂ (S-DOSP) ₄	48	~80–90%		Crude:	22	78
			0 °C−rt−∆						
			30 h, 18 h			62	Pure:	24 (20% ee)	76 (6% ee)
									(3R, 4S)
								208a	208b
2	57	2'-ethylphenyl	Rh ₂ (5S-	72	~70-80%		Crude:	13	87
			MEPY) ₄	(reaction~90					
			0 °C−rt−∆	% complete)		25	Pure:	7 (-% ee)	93 (0% ee)
			30 h, 42 h					208a	208b
3	57	2'-ethylphenyl	$Rh_2(S-mand)_4$	7	~80–90%		Crude:	18	82
			0 °C–rt						
						61	Pure:	9 (20% ee)	91 (27% ee)
									(3S, 4R)
								208a	208b
4	57	2'-ethylphenyl	Rh ₂ (S-PTPA) ₄	21	~80–90%		Crude:	23	77
			0 °C–rt						
						59	Pure:	17 (60% ee)	83 (41% ee)

									(3 <i>R</i> ,4 <i>S</i>)
								208a	208b
5	57	2'-ethylphenyl	Rh ₂ (S-PTTL) ₄	30	>90%		Crude:	11	89
		••••	0 °C–rt						
						65	Pure:	11	89 (71% ee)
								(75% ee)	(3R, 4S)
								208a	208b
6	50	$Ph(CH_2)_3$	Rh ₂ (S-PTTL) ₄	4	~80–90%		Crude:	10	90
			0 °C–rt						
						74	Pure:	5	95 (51% ee)
									(3R, 4S)
								210a	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* γ-lactams, have been included in a publication.⁴⁵

The synthesis of y-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 diazoacetamides, with only achiral catalysts described for these sulfonyl 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 -sulforyl 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 [Rh₂(S-DOSP)₄, Rh₂(S-mand)₄, Rh₂(S-PTPA)₄ and Rh₂(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 Rh₂(S-PTTL)4, which gave trans y-lactam 208b in 71% ee (Table 6.6, entry 5), all other catalysts gave poor to modest enantioselectivities. While enantiopurities of the minor ylactam 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, Rh₂(5S-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 Rh₂(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 (3S,4R) when (3R,8S)-Ind **161** ligand was employed.⁵¹ Therefore, the absolute stereochemistry of **208b** was assigned by analogy as (3S,4R) when (3S,8R)-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 γ -lactam **211b** and **208b**; employing (3*R*,8*S*)-Ind **161** results in γ lactam **211b** having a negative specific rotation $[\alpha]_D^{20}$ -9.5 (*c* 0.11, CHCl₃, 66% ee) and using (3*S*,8*R*)-Ind **44** leads to γ -lactam **208b** having a positive specific rotation $[\alpha]_D^{20}$ +41.11 (*c* 0.09, CH₂Cl₂, 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**.









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* γ -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* γ -lactams **210b** and **209b**.



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 γ - lactams, whereas substrate **51** does not allow thiopyran formation.



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 γ -lactam than the reaction of the *N*,*N*-dipropyl analogue **50**.

While γ -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 γ -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 CH₃ 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 $\gamma : \beta$ 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 γ -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 CH₃ relative to the CH₂ 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 ¹H NMR spectrum of the crude product mixture for reaction employing Cu[CH₃CN)₄]PF₆-NaBARF-(4*R*) Ph **20** and the purified products are presented in **Figure 6.13**.



Figure 6.13 ¹H NMR (CDCl₃, 400 HHz)

The use of chiral copper catalysis was next employed. The CuCl₂-NaBARF-(4R)-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 $\sim 37\%$ when CuCl₂-NaBARF-(4*R*)-Ph **20** was used as a catalyst (Table 6,7, entries 1 and 3). Therefore, proportionately less y-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 y-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-(4R)-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 ylactam 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 CuCl₂.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 $Cu(CH_3CN)_4PF_6-(4R)$ -Ph 20 was employed as the catalyst system. Remarkably, the enantiopurity of the y-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.





	51			218b		218a	217b		216
Entry	Method	М	Ligand	Time (h)	Crude Efficiency (%) ^a			Products	<u>5</u>
						Crude Ratio			
						Purified Yield %	<i>trans</i> sulfolane ^b	β-lactam ^b	y-lactam
						Overall Yield (%)	218b Least polar	217b Mid	216 Most polar
1	R		$(AR)_{-}$	21	80-90°	Crude Ratio	2	27	61
1	D	CuCl ₂ /A	Ph 20	21	00 70	Ci duc Natio	2	51	01
						Purified Yield (%)	0.8% ^d	_ ^e	27% ^f (46% ee)
						<u>Overall Yield (%)</u>	0.68%	_ ^e	26%

2	B	$CuCl_2/\Delta$	(4 <i>R</i>)- Ph 20	21	80–90	Crude Ratio	2	38	60
						Purified Yield (%)	0.7% ^g	12% ^h	$9\%^{i}(47\% \text{ ee})$ + 12% ^j (32% ee) + 5% ^k (39% ee)
						Overall Yield (%)	0.65%	12%	21% (45% ee)
3	E	$Rh_2(OAc)_4/\Delta$	-	4	80–90 ¹	Crude Ratio	2	7	91
		No NaBARF				Purified Yield %	-	3% ^m	45% (0% ee)
						Overall Yield (%)	0.18%	2.6%	45%
4	B	Cu(CH ₃ CN)PF ₆ / Δ	(4R)-	2	60–70 ⁿ	Crude Ratio	2	23	75
		No NaBARF	Pn 20			Purified Yield (%)	1.5%°	8% ^p	28% (69% ee)
						Overall Yield (%)	1.3%	4%	28%

a. Efficiency and relative ratios calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *trans* sulfolane **218b**, $\delta_{\rm H}$ 4.38 [1H, d, *J* 5.3, C(2)*H*]; β -lactam **217b**, $\delta_{\rm H}$ 4.24 [1H, apparent qd, *J* 6.1, 1.6, C(4)*H*] and γ -lactam **216**, $\delta_{\rm H}$ 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 ¹H 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; $\delta_{\rm H}$ 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% y-lactam **216**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H NMR spectra; $\delta_{\rm H}$ 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% y-lactam **216**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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% y-lactam **216**. Additional peaks present in the ¹H 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 ¹H NMR spectra; $\delta_H 3.07 3.14$ (m), 4.64–4.72 (m), 5.21–5.28 (m).
- 1. Additional peaks may be present in the ¹H 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; $\delta_{\rm H}$ 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 ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H 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; $\delta_{\rm H}$ 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, SO₂CH₂CO). Additional peaks present in the ¹H 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 CuCl₂-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 $\delta_H 0.79$ (t, *J* 7.1), 1.01 (t, *J* 7.2) and a doublet at $\delta_H 4.24$ (d, *J* 11.4) in the ¹H 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.



Figure 6.14

The, crude product mixtures were very complex, with just three of the products detectable by ¹H NMR, namely; γ -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 ¹H NMR spectra of γ -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 ¹H NMR spectra of both mixtures. Other unidentified byproducts were also evident.



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 ¹H NMR spectrum of the crude product mixtures allows the identification of a variety of isomers formed in these reactions. For example, the ¹H NMR spectrum for the reaction employing CuCl₂-NaBARF and (3*S*,8*R*)-Ind **44** and (3*R*,8*S*)-Ind **161** in 1 : 1 ratio is shown in **Figure**

5 mol% CuCl₂ 6 mol% NaBARF 6 mol% [1 : 1 С 0 Q 0 Q 0 0 (3S, 8R) Ind 44 : 0 (3R, 8S) Ind 161] Ъ н́ Ν₂ CH_2Cl_2, Δ Ph Ph Ph Ph 47 221b 220a 118 219 Crude ٨٨ β-lactam 221b \mathbb{M} MM cis thiopyran 220a M y-lactam 219 Λ 3.80 4.10 4.00 4.20 3.90 ppm (t1)

6.16, along with the purified products.



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	Crude Ratio ^a Purified Vield (%) ^a		Products	
					(10)	(% ee) ^a	<i>cis</i> : thiopyran ^a	β : lactam ^{a,b}	y lactam ^a
							least polar	more polar	most polar
1	В	$CuCl_2/\Delta$	(3 <i>S</i> ,8 <i>R</i>)- Ind 44	48	70–80°	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 (%)	<u>20% (92% ee)</u>	<u>11%</u>	<u>18%</u>
							$\begin{bmatrix} \alpha \end{bmatrix}_{\rm D}^{20} -67.0 (c \\ 0.05, \rm CH_2Cl_2)$	5.8% total estimated for sulfone 118	

2	B	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph	21	70–80 ^j	Crude Ratio	17	20	63
			20						
						Purified Yield (%)	4% (>99% ee) (2 <i>S</i> ,3 <i>S</i>) + 6% (96% ee) (2 <i>S</i> ,3 <i>S</i>)	$2\% + 7\%^{k} + 3\%^{1}$	12% ^m (54% ee) + 8% ⁿ (51% ee) + 6% (49% ee)
						Overall Yield (%)	$\frac{10\% (97\% \text{ ee})}{[\alpha]_{\text{D}}^{20} + 74.0}$ (c 0.05, CH ₂ Cl ₂)	<u>10%</u> <u>0.77%</u> total	<u>26% (52% ее)</u>
								estimated for sulfone 118	
3	D	CuCl ₂ /Δ	(3S, 8R)-	21	70–80	Crude Ratio	38	30	32
			and			Purified Yield (%)	15% (0% ee)	12%°(0%ee)	16% ^p (0% ee)
			(<i>3R</i> ,85)- Ind 161			Overall Yield (%)	<u>15% (0% ee)</u>	<u>9% (0% ee)</u>	<u>14% (0% ee)</u>
			(1:1)					0.96% total estimated for sulfone 118	

a. Efficiency and relative ratios calculated using ¹H 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 ¹H 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, SO₂CH₂CO). Additional peaks may be present in the ¹H 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, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 2.78–2.84 (m).
- f. Fraction contains 30% β -lactam 217b and 59% sulfone 118 3.98 (2H, s, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 2.77–2.84 (m).
- g. Fraction contains 85% γ -lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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**; $\delta_{\rm H}$ 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 4.24 (d, *J* 11.2).
- h. Fraction contains 86% γ -lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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**; $\delta_{\rm H}$ 0.79 (t, *J* 6.9), 1.05 (t, *J* 7.4), 4.24 (d, *J* 11.2).
- i. Fraction contains 83% γ lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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**; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product but cannot be distinguished due to peak overlap. Additional less polar fraction obtained (4 mg), $\delta_{\rm H}$ 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**; $\delta_{\rm H}$ 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** $\delta_{\rm H}$ 3.98 (2H, s, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 2.76–2.84 (m), 4.47 (d, *J* 6.8).
- 1. Fraction contains 62% β -lactam 217b and 14% sulfone 118 δ_H 3.98 (2H, s, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; δ_H 2.77–2.84 (m).
- m. Fraction contains >99% y-lactam 219. Additional peaks present in the ¹H NMR spectra; $\delta_H 3.19 3.34$, 4.08–4.20 (m), 4.65–4.71 (m), 5.20–5.26 (m).
- n. Fraction contains >99% y-lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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, SO₂CH₂CO). Additional peaks present in the ¹H 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% γ -lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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**; $\delta_{\rm H}$ 0.79 (t, *J* 7.1), 1.01 (t, *J* 7.2), 4.24 (d, *J* 11.4).

Two ligands were chosen for investigation: (3S, 8R)-Ind **44** as it had previously given the best enantioselectivity for the y-lactam series and (4R)-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 y-lactam 219 and more cis thiopyran 220a is seen for (3S,8R)-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 (3S,8R)-Ind 44 and 97% ee observed for (4R)-Ph 20 (Table 6.8, entries 1 and 2). While the high enantioselectivity achieved using (4R)-Ph 20 is in agreement with previous trends, the high enantioselectivity achieved using (3S, 8R)-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 CH₂ in the *N*,*N*-dibenzyl substituent is doubly activated by the presence of an adjacent nitrogen atom and phenyl substituent; insertion into a benzylic CH₂ is known to be favourable electronically for C–H insertion processes⁵⁶ (Scheme 6.16).



Scheme 6.16⁵⁶

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**.



The two main potential reaction pathways, β -lactam and sulfolane formation are demonstrated in **Scheme 6.17**. C–H insertion to lead to γ -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

Rh₂(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

CuCl₂-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)-CH₃ and C(4)*H* and C(4)-CH₃.



Figure 6.18⁵⁶

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 CH₂ 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 CuCl₂-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 ¹H 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 ¹H 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 ¹H 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 sulforyl 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 ¹H 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, Jung³⁸ 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



Scheme 6.19⁵⁸

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 γ-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 γ -lactam formation, despite significant conformational and electronic differences in the pathway leading to four and fivemembered ring formation. It is important to note since γ -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(CH₂)₃





210b R=Ph(CH₂)₃ **209b** R=Ph(CH₂)₄ **208b** R= 2'ethylphenyl





216 Ph(CH₂)₃ **219** R=Ph(CH₂)₄

Scheme 6.20





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; ¹H 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 γ -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 γ -lactam series. The transition state model drawn in **Scheme 6.21** is based on the same model leading to γ -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.



favourable transition state: reacting C-H approaches less sterically hindered carbenoid face leading to the observed stereochemistry

Scheme 6.21

5 mol% CuCl₂ 6 mol%NaBARF 6 mol% L* Ph_____S o o ∬ Ph. , + Ph. 🧄 CH_2CI_2, Δ Ph Ρ̈́h 53 226b 227 Sulfone Purified Yield Entry Method Metal Solvent Purity Ligand Time Crude Fraction βof Efficiency (h) 227 ratios (%)^a Lactam ββ-% ee^a Solvent Lactam (%) (%)^a **Crude**^a Lactam: Lactam, Sulfone Sulfone CH₂Cl₂ 50-60^b 13% 13^c 55 % ee^d B $CuCl_2/\Delta$ Doubly (4*R*)-Bn 30 Fr1 1 _ distilled, 43 Lactam EtOH only absent $39\% ee^d$ 2 B CH_2Cl_2 Doubly (4*R*)-Ph 21 $30 - 40^{e}$ 40-45 Fr 1 38:62 $CuCl_2/\Delta$ 8 $37\% ee^d$ distilled, 20 Fr 2 50:50 6^g 2^{f} Fr 3 $70:30^{f}$ -

Table 6.9 *Rhodium acetate and asymmetric copper catalysed* C-H *insertion reactions of* α -*diazo-\beta-oxo sulfone* **53**

				trace					Overall		(7.44%,	
				EtOH					<u>Yield</u>		8.56%)	
3	В	$CuCl_2/\Delta$	CH ₂ Cl ₂	Doubly	(4 <i>R</i>)-Bn	24	30-40 ^h	40-45	Fr 1	30:70	4	59 % ee ^d
				distilled,	43				Fr 2	43:64	6	$56\% ee^d$
				trace					Fr 3	$58:42^{i}$	5	$56 \% ee^d$
				EtOH					Fr 4	69 : 31 ⁱ	7	57 % ee ^d
									<u>Overall</u>		(11.51%,	
									<u>Yield</u>		10.91%)	
4	В	$CuCl_2/\Delta$	CH ₂ Cl ₂	Doubly	(4R, 5S)-	30	10–20 ^j	20–30	Fr1	33:67	8	52 % ee ^d
				distilled,	di-Ph				Fr 2	64:36	10 ^k	$56\% ee^d$
				trace	137				<u>Overall</u>		(9.04%,	
				EtOH					<u>Yield</u>		8.96%)	
5	В	$CuCl_2/\Delta$	CH ₂ Cl ₂	Doubly	(4 <i>S</i>)- <i>t</i> -	50	$20-30^{1}$	35–45	Fr 1 ^{m,n}	42:58	5	53 % ee ^p
				distilled,	Bu 138				Fr 2°	35 : 65	10	78 % ee ^p
				trace					Fr 3°	58:42	9	48 % ee ^p
				EtOH					<u>Overall</u>		(10.82%,	
									<u>Yield</u>		13.18%)	

6	В	$CuCl_2/\Delta$	CH ₂ Cl ₂	Doubly distilled, trace	(3 <i>S</i> ,8 <i>R</i>)- 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
				EtOH					Fr 4 Overall	68 : 32	4 (11.36% ,	84 % ee ^p
									<u>Yield</u>		9.64%)	
7	В	CuCl ₂ /Δ	CH_2Cl_2	Doubly	(3S, 8R)-	24	_r		Fr1	38:62	5	85 % ee ^p
				distilled,	Ind 44				Fr 2	50 : 50	9 ^s	81 % ee ^p
				spiked					<u>Overall</u>		(6.4%,	
				with					<u>Yield</u>		7.6%)	
				EtOH								
8	В	CuCl ₂ /Δ	CH ₂ Cl ₂	HPLC	(3S, 8R)-	30	30–40 ^t		Fr1	-	9	89 % ee ^p
				grade,	Ind 44				Fr2	-	12 ^u	77 %
				no					<u>Overall</u>		21%	ee ^{p,v}
				EtOH					<u>Yield</u>		Lactam	
											only	
9	Ε	$Rh_2(OAc)_4/\Delta$	CH_2Cl_2	Doubly	-	18	50-60 ^w		Fr1	37 : 63 ^x	6	0 % ee
				distilled,					Fr2	67 : 33 ^x	10	

		trace			Overall	(8.92%,	
		EtOH			<u>Yield</u>	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 OCH₂CH₃ for sulfone **227**, δ_H 4.24 (2H, q, *J* 7.2 OCH₂CH₃). 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 ¹H 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 ¹H NMR spectra of the pure product; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of Fr 3 (2 mg); $\delta_{\rm H}$ 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 ¹H NMR spectra; $\delta_{\rm H} 3.02-3.08$ (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; $\delta_{\rm H}$ (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). $\delta_{\rm H}$ (minor signals) 4.64-4.71 (m), 5.19-5.26 (m).
- h. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_H 3.04-3.13$ (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 ¹H NMR spectra; $\delta_{\rm H} 3.02-3.07$ (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; $\delta_{\rm H}$ series of overlapping signals 1.50–5.00 (m), 5.43 (s), 6.99–7.43 (m)
- 1. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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; $\delta_H 2.63-2.87(m)$, 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 ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product showed that *approx* 5% of the starting material α -diazocarbonyl **53** was present. Additional signals observed in the ¹H NMR spectra of the crude product; $\delta_H 3.06-3.14$ (m), 3.86 (s), 4.68 (s), 6.73 (br s).
- r. ¹H 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; $\delta_H 2.12-2.23$ (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 ¹H NMR spectra of the crude product; $\delta_H 3.05-3.13$ (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 ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_H 4.59$ (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 ¹H 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**.



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

$$5 \text{ mol}\% \text{ NaBARF}$$

$$5 \text{ mol}\% \text{ L*}$$

$$CH_2Cl_2, \Delta$$



224a R= Ph **229a** R= Oct

Entry	R	Ligand	Time	Crude	Fraction after	Yield	% ee
			(h)	Efficiency	purification by	(%)	
				(%)	chromatography		
1	Ph	(3 <i>S</i> , 8 <i>R</i>)- Ind 44 and (3 <i>R</i> , 8 <i>S</i>)- Ind 161 (1:1)	21	60–70ª	Fraction 1	20	0
2	Ph	(4 <i>R</i>)-Ph	21	40–50 ^a			-
		20			Fraction 1	4 ^b	
					Fraction 2	15	98
							(2 <i>S</i> ,3 <i>S</i>)
							$[\alpha]_{D}^{20} +$
							40.0 (<i>c</i>
							0.05,
							CH ₂ Cl ₂)
3	Ph	(3 <i>S</i> ,8 <i>R</i>)- Ind 44	21	40–50 ^a	Fraction 1	6 ^c	
					Fraction 2	7	86
							(2R, 3R)
							$\left[\alpha \right] _{\mathrm{D}}^{20}$ -
							57.0 (<i>c</i> 0.1,
							CH ₂ Cl ₂)

4	Oct	(3 <i>S</i> , 8 <i>R</i>)- Ind 44 and (3 <i>R</i> , 8 <i>S</i>)- Ind 161 (1:1)	75	10–20 ^{d,e}	Not purified	_f	_f
5	Oct	(4 <i>R</i>)-Ph 20	96	10–20 ^{d,g}	Not purified	_f	_f
6	Oct	(3 <i>S</i> ,8 <i>R</i>)- Ind 44	72	10–20 ^{d,h}	Purified	<i>cis</i> thiopyran isolated as an impure fraction ⁱ	_i

- a. Efficiency calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **224a** $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **229a**, $\delta_{\rm H}$ 4.10 [1H, dd, *J* 4.0, 2.1, C(2)*H*].
- e. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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, CuCl₂ (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 ¹H 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 ¹H 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}



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 copperbisoxazoline 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 ¹H 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 ¹H 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**.



Two ligands were selected for investigation into the asymmetric copper-catalysed C-H insertion reactions of α -diazoacetamides 48 and 49; (4R)-Ph 20, as this ligand had resulted in the best enantioselectivities in cis thiopyran synthesis and (3S,8R)-Ind 44, as this ligand gave rise to *N*,*N*-diethyl *cis* thiopyran **220a** with extremely high enantiopurity. Furthermore, the (3S,8R)-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 CuCl₂-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 ylactam formation respectively. However, presumably due to conformational restraints, neither β - nor y-lactam products were observed. Reaction efficiencies were moderate, with 40–50% efficiency being obtained in the presence of (4R)-Ph 20 and (3S,8R)-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 ¹H 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 (2S,3S) when using the (4R)-Ph **20** ligand. During this work, the stereochemistry of the morpholine derivative **224a** is assigned as (2S,3S) when using the same ligand (4R)-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 (4R)-Ph **20** and (3S,8R)-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 CuCl₂, 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 CuCl₂-NaBARF-(4*R*)-Ph **20** (**Table 6.10**, entry 5) and CuCl₂-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 CuCl₂-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 γ -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 γ -lactam **219**. As has been discussed in **Section 6.3.2**, γ -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 ¹H 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 ¹H 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	Pro cis : sulfolane more polar 231a	ducts <i>trans</i> sulfolane less polar 231b
1	В	CuCl ₂ /Δ	(4 <i>S</i>)- <i>t</i> -Bu 138	48	60–70 ^b	Crude Ratio Purified Yield (%) <u>Overall Yield (%)</u>	20 8% ^c <u>7</u>	$\begin{array}{c} 80\\ 22\%^{\rm d}(77\%\ {\rm ee})^{\rm e}\\ \underline{23}\\ \left[\alpha\right]_{\rm D}^{20}-22.78\ (c\\ 0.09,\ {\rm CH}_2{\rm Cl}_2)\end{array}$

2	В	CuCl ₂ /Δ	(4 <i>R</i>)-Bn	60	60–70 ^f	Crude Ratio	20	80
		_	43			Purified Yield (%)	5%	8% ^g (45% ee) ^h
								$[\alpha]_{\rm D}^{20}$ +1.961 (c
								$0.102, CH_2Cl_2)$
								+
								11 (43% ee) ^h
								$[\alpha]_{\rm D}^{20}$ +7.692 (c
								0.13, CH ₂ Cl ₂)
						Overall Yield (%)	5%	+
								28% (42% ee) ⁱ
3	В	CuCl ₂ /Δ	(3S, 8R)-	21	60-70% ^j	Crude Ratio	30	70
		_	Ind 44			Purified Yield (%)		
							-	$17\%^{\rm k} (47\% {\rm ee})^{\rm e}$
								$[\alpha]_{\rm D}^{20}$ -9.542
								(<i>c</i> 0.105,
								CH ₂ Cl ₂)
4	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph 20	21	60–70% ¹	Crude Ratio	70	30
						Burified Vield (%)	1 9 07_m	607.n
5	P		(AP 5 5) di	21	60 70%°	Crudo Datio	60	40
5	D	$CuCl_2/\Delta$	(4 <i>N</i> ,55)-ul-	21	00-70%	Durified Vield (%)	150/m	40 80%n
			Ph 137				1370	0 70
6	Е	Rh ₂ (OAc) ₄ /		6	50-60% ^p	Crude Ratio	60	40
		Δ				Purified Yield (%)	-	14% ^q

- a. Efficiency and relative ratios were calculated using ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra were observed; $\delta_H 2.15-2.29$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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.
- 1. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_H 4.71$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR; $\delta_{\rm H}$ 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-[(3phenylpropyl)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 ¹H 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 ¹H 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 ¹H NMR, including NOESY, with characteristics observed resembling those seen for the ester **40b** and ketone series **42b** (Figure 6.27).

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Subsequently asymmetric copper catalysed reactions were carried out on 2-diazo-1morpholino-2-[(3-phenylpropyl)sulfonyl]ethanone **52** using five commercially available bisoxazoline ligands (4S)-t-Bu 138, (4R)-Bn 43, (3S, 8R)-Ind 44, (4R)-Ph 20 and (4R,5S)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 (3S,8R)-Ind 44 and (4S)-t-Bu 138 (Table 6.11, entries 1 and 3), and was obtained in low quantities as the most polar fraction from cyclisation employing (3S,8R)-Ind 44. Due to limited amounts of sample only a ¹H NMR analysis was obtained. However, the allylic sulfone signals are very characteristic enabling structure assignment.



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 (4R)-Ph 20 and (4R,5S)-di-Ph 137 ligands, the cis isomer was the major reaction product. For (4R)-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 ¹H 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 (4R)-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, (3S,8R)-Ind 44, (4S)-t-Bu 138 and (4R)-Bn 43, the *trans* isomer predominated, accounting for 80% of the insertion products for (4S)-t-Bu 138 and (4R)-Bn 43, while constituting 70% of the insertion products for (3S,8R)-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 (3S,8R)-Ind 44, (4S)-t-Bu 138 and (4R)-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 (4R)-Bn 43 and (3S,8R)-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 (4R)-Ph 20 and (4R,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 (4R,5S)-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 γ -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, γ -lactam is the major product formed.



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 γ -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-\beta-oxo sulfone* **58**



		58			2	233b		233a	117			
Entry	Method	Metal	Ligand	Time	Crude	Sulfone	Yield		Products ratios			
				(h)	Efficiency of C–H insertion (%) ^a	117 (%Crude) b	(%)		trans 233b	cis 233a	(S) 117	
1	Е	$Rh_2(OAc)_4/\Delta$	-	21	>90%	-		Crude ratio	96	4	-	
							46%	Purified ratio	99 (0% ee)	1		
2	В	$CuCl_2/\Delta$	(3S, 8R)-	24	50–60% ^c	10–15%		Crude ratio	44	44	12	
			1110 44					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	
							<u>Total</u>		9.28%	1.46%	2.26%	

3	В	$CuCl_2/\Delta$	(4R,5S)- di-Ph 137	21	50-60% ^g	10–15%		Crude ratio	36	52	12
			ui-i ii 1 57				_	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		<u>9.48%</u>		1.52%
4	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph 20	6	50-55% ¹	~8%		Crude ratio	20	68	12
							En1 107-m	Purified	$anly (00\% as)^{1.0}$	-	-
							Ff1 1%	rauo	0111y (90% ee),*	-	-
							Fr2 3%		only (70% ee) ^j		
							Fr3 2%		only (60% ee) ^j	-	-
							<u>Total</u>		<u>6%</u>		
5	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Bn	21	50-60% ^p	~5%		Crude ratio	68	30	2
			45					Purified ratio			
							Fr1 4% ^q		78 (43% ee) ^{e,r}	22 ^{s,t}	-
							Fr2 6% ^q		73 (37% ee) ^{e,}	27 ^{s,t}	
							Fr3 4% ^q		74 (32% ee) ^{e,r}	22 ^{s,t}	2
							Total		<u>10.46%</u>	3.38%	0.08%
6	В	$CuCl_2/\Delta$	$(\overline{4S})$ -t-Bu	30	50-60	~5%		Crude ratio	74	22	4
			130					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
							<u>Total</u>		7.24%	<u>1.76%</u>	
7	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Bn	24	50–60	~1%		Crude ratio	72	27	1
			43					Purified ratio		-	-
							Fr1 5%		Only (37% ee) ^e	-	-
							Fr2 7% ^v		Only (33% ee) ^e		
							<u>Total</u>		<u>13%</u>		
8	В	$CuCl_2/\Delta$	(4 <i>S</i>)- <i>t</i> -Bu	48	50-60 ^w	~1%		Crude ratio	80	19	1
			150					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 ¹H 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 ¹H NMR using the following signals: $\delta_{\rm H}$ 4.27 (2H, s, SO₂CH₂CO). Additional signals were observed for sulfone **117**; $\delta_{\rm H}$ 1.35 (3H, t, *J* 7.5, ArCH₂CH₃), 3.10 (2H, q, *J* 7.5, ArCH₂CH₃).

c. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; δ_{H} 5.17 (s), 5.59 (s).
- h. Impure fraction. Additional peaks present in the ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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.
- 1. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 5.17 (s), 5.60 (s), 9.41 (s).
- m. Impure fraction. Additional peaks present in the ¹H NMR spectra of the purified product; $\delta_H 3.77-3.99$ (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 ¹H NMR spectra of the crude product; $\delta_{H} 5.17$ (s), 6.11-6.24 (m), 6.44-6.52 (m).
- q. Contains dioctyl phthalate (placticiser), detected by ¹H 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 4.20–4.25 (m overlapping), 4.30 (d, J 5.4).
- w. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_H 4.91$ (s), 5.59 (s), 6.54–6.61 (m).
- x. Contains ~5% additional compound that contains the following peaks in the ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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 CH₂ signal at 4.27 ppm (2H, s, SO₂CH₂CO). 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 CH₂ 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 ¹H 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 (4R,5S)-di-Ph 137 and (4R)-Ph 20 (Table 6.12, entries 3–4) resulting in predominately *cis* 233a, while ligands (4*R*)-Bn 43 and (4S)-t-Bu 138 (Table 6.12, entries 5–8) lead to predominately trans 233b in the crude product mixtures, (3S, 8R)-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*R*)-tr-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 ligandsubstrate interactions in the transition state for the C–H insertion process. A number of specific 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 γ -lactam formation was seen in reactions with dipropyl amide. The impact of conformational properties on reaction outcome is in line with observations by Doyle

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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 γ -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 γ -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 γ -lactam synthesis; the highest reported value for γ -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 γ -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 γ -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).



one of the insertion products

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 γ -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 6.34⁵¹ 445

(3S,4R) 3-[(2-Ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one 208b



CuCl₂ (2.0 mg, 14.8 μ mol), (+)-2,2'isopropylidenebis[(4*R*)-4-benzyl-2-oxazoline] **43** (6.4 mg, 17.8 μ mol) and sodium tetrakis[3, 5bis(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 2-diazo-2-[(2-ethylphenyl)sulfonyl]-N,N-B. А solution of 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. ¹H 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-[(2ethylphenyl)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 ¹H 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, (3S,4R) 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, CH₂Cl₂); v_{max}/cm⁻¹ (film): 2967, 2935, 2876 (CH), 1699 (CO), 1439, 1308, 1151, 1133 (SO₂); δ_H (CDCl₃, 600 MHz): 0.89 (3H, t, J 7.4, NCH₂CH₂CH₃), 1.29 [3H, d, J 7.1, CH₃-C(4)], 1.33 (3H, t, J 7.5, ArCH₂CH₃), 1.47–1.60 (2H, m, NCH₂CH₂CH₃), 2.91 [1H, dd, J 9.6, 3.2, one of C(5)H₂], 2.94–3.31 (2H, m ArCH₂CH₃), 3.14–3.23 [2H, m, C(4)H and one of NCH₂CH₂CH₃], 3.24–3.33 (1H, m, one of NCH₂CH₂CH₃), 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 (CDCl₃, 150.9 MHz): 11.1 (CH₃, NCH₂CH₂CH₃), 16.1 (CH₃, ArCH₂CH₃), 20.3 (CH₂, NCH₂CH₂CH₃), 20.9 [CH₃, CH₃-C(4)], 26.4 (CH₂, ArCH₂CH₃), 27.5 [CH, C(4)H], 44.7 (CH₂, NCH₂CH₂CH₃), 53.0 [CH₂, C(5)H₂], 73.1 [CH, C(3)H], 126.2 (CH, aromatic CH), 130.9 (CH, aromatic CH), 131.5 (CH, aromatic CH), 134.2 (CH, aromatic CH), 135.7 (C,

aromatic *C*), 144.8 (C, aromatic *C*), 164.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for C₁₆H₂₄NO₃S [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 ¹H 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 ¹H NMR spectral characteristics; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.65 [3H, d, *J* 7.2, CH₃-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.

Entry	Method	Metal	Ligand	Time	Crude	Yield	Crude Ratio ^a :	<i>cis</i> (% ee) ^a	:	trans (% ee) ^a
				(h)	Efficiency ^a	(%) ^a	Purified Ratio ^a :			
1	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Bn	21	~80–90%	59	Crude Ratio:	12		88
			43				Purified Ratio:	-(-) ^b		100 (52% ee) ^b
										(3S, 4R)
2	B	$CuCl_2/\Delta$	(3S, 8R)-	6	~80–90%	61	Crude Ratio:	4		96
			Ind 44				Purified Ratio:	1(-) ^c		99 (82% ee) ^c
										(3R, 4S)
3	B	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph	21	~75-85% ^d	48	Crude Ratio:	14		86
			20				Purified Ratio:	10 (43% ee) ^e		90 (48% ee) ^f
										(3S, 4R)
4	B	$CuCl_2/\Delta$	(4 <i>S</i>)- <i>t</i> -Bu	48	~70-80% ^g	45	Crude Ratio:	8		92
			138				Purified Ratio:	6 (38% ee) ^{h,i}		94 (70% ee) ^h
										(3R, 4S)
5	B	$CuCl_2/\Delta$	(4R, 5S)-	21	~80–90%	53	Crude Ratio:	15		85
			di-Ph 137				Purified Ratio:	7 (53% ee) ^e		93 (34% ee) ^j
										(3S, 4R)
6	B	$CuCl_2/\Delta$	CN-(4 <i>S</i>)-	30	~70-80% ^k	32	Crude Ratio:	9		91
			Ph 158				Purified Ratio:	$5 (6\% \text{ ee})^{i}$		95 (4% ee)
										(3R, 4S)
7	B	$CuCl_2/\Delta$	Py-(4 <i>R</i>)-	21	~60-70% ¹	39	Crude Ratio:	20		80
			Ph 159				Purified Ratio:	15 (8% ee) ^e		85 (3% ee) ^m
										(3S, 4R)

Table 6.13 Copper and rhodium catalysed C–H insertion reactions of α -diazo- β -oxo sulfone 57

8	B	$CuCl_2/\Delta$	Py-(4 <i>S</i>)- <i>i</i> - Pr 160	72	~40-50% ⁿ	22	Crude Ratio: Purified Ratio:	26 26 (46% ee) ⁱ	74 74 (24% ee)
									(3R, 4S)
9	F	Rh ₂ (S-PTTL) ₄	-	30	>90%	65	Crude Ratio:	11	89
		0 °C–rt					Purified Ratio:	11 (75% ee) ⁱ	89 (71% ee)
									(3R, 4S)
10	F	Rh ₂ (S-PTPA) ₄	-	21	~80–90%°	59	Crude Ratio:	23	77
		0 °C–rt					Purified Ratio:	17 (60% ee) ⁱ	83 (41% ee)
									(3R, 4S)
11	G	Rh ₂ (S-DOSP) ₄	-	48	~80–90% ^p	62	Crude Ratio:	22	78
		0 °C−rt−∆					Purified Ratio:	24 (20% ee) ⁱ	76 (6% ee)
		30 h, 18 h							(3R, 4S)
12	G	Rh ₂ (5 <i>S</i> -	-	72	~70-80% ^q	25 ^r	Crude Ratio:	13	87
		MEPY) ₄					Purified Ratio:	7 (-% ee)	93 (0% ee)
		0 °C–rt–Δ							
		30 h, 42 h							
		,							
13	F	$Rh_2(S-mand)_4$	-	7	~80–90% ^s	61	Crude Ratio:	18	82
		0 °C–rt					Purified Ratio:	$9 (20\% \text{ ee})^{\text{e}}$	91 (27% ee)
								~ /	(3S,4R)
14	E	$Rh_2(OAc)_4/\Delta$	-	18	~80–90%	52	Crude Ratio:	8	92
							Purified Ratio:	5 (0% ee)	95 (0% ee)
15 ^t	B	$CuCl_2/\Delta$	(3S, 8R)-	21	~70-80%	64	Crude Ratio:	3	97
			Ind 44				Purified Ratio:	2 (-)	98 (78% ee)
									(3R, 4S)

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product and ¹H NMR spectra of the purified 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*]. 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 CH₂Cl₂). A second purification using column chromatography on silica gel was carried out due to the presence of additional peaks in the ¹H NMR spectra of the purified product; $\delta_H 4.21-4.32$ (m). These peaks were also observed on the ¹H 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 ¹H NMR spectra of the purified product; $\delta_H 4.22 4.34$ (m). These peaks were also observed in the ¹H NMR spectra of the crude product. Enantioselectivity of *cis* **208a** was not determined due to peak overlap on the HPLC.
- d. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of fraction two; $\delta_{\rm H}$ 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 [α] $_{\rm D}^{20}$ +36.0 (*c* 0.1014 in CH₂Cl₂), Rotation measured on fraction two [α] $_{\rm D}^{20}$ +33.90 (*c* 0.103, CH₂Cl₂).
- 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}4.21-4.30$ (m). These peaks were also observed on the ¹H 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 ¹H NMR spectra of the crude product; $\delta_H 3.95 3.99$ (m), 4.15 (s), 4.15-4.29 (m), 4.63 (d, *J* 6.3), 5.54 (s).
- 1. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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. ¹H NMR spectra of the crude product contains *approx* 50% of α -diazocarbonyl **57**. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 3.95–3.99 (m), 4.24 (s), 5.55 (s), 9.45 (s).
- o. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 4.15 (s), 4.20–4.28 (m), 7.19–7.21 (m), 7.67–7.77 (m).
- p. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 4.11 (s), 4.20–4.31 (m), 9.45 (s).
- q. Analysis of the ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 4.14 (s), 4.20–4.31 (m), 5.56 (s), 6.10 (s), 6.99 (s).
- r. Additional peaks observed in the ¹H NMR spectra of the purified product; $\delta_H 3.50$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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**

mg, 0.57 mmol), CuCl₂ (3.8 mg, 28.4 µmol), sodium tetrakis[3,5-(200)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**. ¹H 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 acetatehexane (10:90)eluent, (3S, 4R)4-methyl-3-[(3-phenylpropyl]sulfonyl)-1as 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); v_{max}/cm⁻¹ (film): 2965, 2934, 2876 (CH), 1693 (CO), 1454, 1308, 1139, 1125 (SO₂), 701 (CS); δ_H (CDCl₃, 600 MHz): 0.92 (3H, t, J 7.4, NCH₂CH₂CH₃), 1.29 [3H, d, J 7.0, CH₃-C(4)], 1.50–1.62 (2H, m, NCH₂CH₂CH₃), 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)H₂], 3.05–3.14 [1H, m, C(4)H], 3.19–3.28 (1H, m, one of NCH₂CH₂CH₃), 3.29–3.36 (1H, m, one of NCH₂CH₂CH₃), 3.37–3.43 [2H, m, C(1')H₂], 3.45 [1H, d, J 4.7, C(3)H], 3.67–3.77 [1H, m, one of C(5)H₂], 7.16–7.24 (3H, m, ArH), 7.25–7.33 (2H, ArH); δ_C (CDCl₃, 150.9 MHz): 11.1 (CH₃, NCH₂CH₂CH₃), 20.3 (CH₂, NCH₂CH₂CH₃), 20.9 [CH₃, CH₃-C(4)], 23.4 [CH₂, C(2')H₂], 25.8 [CH, C(4)H], 34.4 [CH₂, C(3')H₂], 44.8 (CH₂, NCH₂CH₂CH₃), 51.8 [CH₂, C(1')H₂], 53.3 [CH, C(5)H], 69.8 [CH, C(3)H], 126.3 (CH, aromatic CH), 128.4 (CH, 2 × aromatic CH), 128.7 (CH, 2 × aromatic CH), 140.2 (C, aromatic C), 165.7 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₇H₂₆NO₃S [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 ¹H 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 ¹H 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**; $\delta_{\rm H}$ (CDCl₃, 400 MHz): 0.95 (3H, t, *J* 7.4, NCH₂CH₂CH₃), 3.73 [1H, d, *J* 8.6, C(3)*H*]. A second set of signals were observed in the ¹³C NMR of *trans* **210b** and are tentatively assigned to *cis* **210a**; $\delta_{\rm C}$ (CDCl₃, 150.9 MHz) 13.8 (CH or CH₃), 20.5 (CH₂), 23.4 (CH₂), 31.9 (CH or CH₃), 44.8 (CH₂), 53.3 (CH₂), 53.5 (CH₂), 65.7 (CH or *C*H₃), 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.

Entry	Method	Metal	Ligand	Time	Crude	Yield	Crude Ratio ^a	cis ^{a,b}	:	<i>trans</i> (% ee) ^a
				(h)	Efficiency ^a	(%) ^a	Purified Ratio ^a			
1	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph	18	~80–90%	76	Crude Ratio:	5		95
			20				Purified Ratio:	3		97 (13% ee)
										(3S, 4R)
2	В	$Cu(CH_3CN)_4PF_6/\Delta$	(4 <i>R</i>)-Ph	1	>90%	69	Crude Ratio:	15		85
			20				Purified Ratio:	12		88 (0% ee)
										(3S, 4R)
3	В	$CuCl_2/\Delta$	(3S, 8R)-	16	>90%	58	Crude Ratio:	<10		>90
			Ind 44				Purified Ratio:	1		99 (61% ee)
										(3R, 4S)
4	В	$CuCl_2/\Delta$	(4 <i>S</i>)- <i>t</i> -Bu	40	>90%	66	Crude Ratio:	<10		>90
			138				Purified Ratio:	3		97 (67% ee) ^{c,d}
										(3R, 4S)
5	В	$CuCl_2/\Delta$	(4R, 5S)-	30	>90%	67	Crude Ratio:	15		85
			di-Ph 137				Purified Ratio:	10		90 (4% ee)
										(3S, 4R)
6	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Bn	31	_ ^e	65	Crude Ratio:	_ ^e		_e
			43				Purified Ratio:	1		99 (48% ee) ^f
										(3S, 4R)
7	F	Rh ₂ (S-PTTL) ₄	-	4	~80–90% ^g	74	Crude Ratio:	10		90
		0 °C–rt					Purified Ratio:	5		95 (51% ee) ^h
										(3R, 4S)
8	Ε	$Rh_2(OAc)_4/\Delta$	-	2	~80–90% ⁱ	57	Crude Ratio:	12		88
		``´´					Purified Ratio:	10 (0% ee)		90 (0% ee)

Table 6.14 Copper and rhodium catalysed C–H insertion reactions of α -diazo- β -oxo sulfone **50**
- a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for NCH₂CH₂CH₂CH₃, *cis* γ-lactam, **210a**, δ_H 0.95 (3H, t, *J* 7.4, NCH₂CH₂CH₃); *trans* γ-lactam, **210b**, δ_H 0.92 (3H, t, *J* 7.4, NCH₂CH₂CH₃). 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 ¹H NMR spectra of the purified product, these signals were not observed in the ¹H NMR spectra of the crude product and may be due to external contamination; $\delta_H 3.79-3.81$ (m), 4.15-4.22 (m).
- d. Rotation value measured on this sample; $[\alpha]_{D}^{20}$ +47.27 (*c* 0.11, CH₂Cl₂).
- e. Data not available
- f. Rotation value measured on this sample; $\left[\alpha\right]_{D}^{20}$ -11.48 (*c* 0.0915, CH₂Cl₂).
- g. Additional peaks observed in the ¹H NMR spectra of the crude product; δ_H 4.21 (s), 5.12 (s), 9.05 (s).
- h. Additional peak observed in the ¹H NMR spectra of the crude product; δ_H 9.05 (s).
- i. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 2.41$ (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 ¹H 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,Ndipropylacetamide **46** (100 mg, 0.27 mmol) in distilled dichloromethane was added dropwise over 5 min to a refluxing solution of Rh₂(OAc)₄ (~1 mg) in distilled

dichloromethane (40 mL), stirred while heating under reflux for 6 h, in accordance to Method E. ¹H 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**; v_{max}/cm⁻¹ (film): 2965, 2934, 2875 (CH), 1691 (CO), 1453, 1298, 1138 (SO₂), 748, 701 (CS); δ_H (CDCl₃, 400 MHz): 0.92 (3H, t, J 7.4, NCH₂CH₂CH₃), 1.30 [3H, d, J 7.0, CH₃-C(4)], 1.49–1.63 (2H, m, NCH₂CH₂CH₃), 1.74–1.86 [2H, m, C(3')H₂], 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, NCH₂CH₂CH₃), 3.39-3.47 [3H, m, contains C(1')H₂, and C(3)H] 3.73 [1H, dd, J 9.6, 7.9, one of C(5)H₂], 7.13–7.23 (3H, m, ArH), 7.24–7.33 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 11.1 (CH₃, NCH₂CH₂CH₃), 20.3 (CH₂, NCH₂CH₂CH₃), 20.8 [CH₃, CH₃-C(4)], 25.9 [CH₂, C(2')H₂ or C(3')H₂], 25.9 [CH, *C*(4)H], 30.2 [CH₂, *C*(2')H₂ or *C*(3')H₂], 35.3 [CH₂, *C*(4')H₂], 44.8 (CH₂, NCH₂CH₂CH₃), 52.2 [CH₂, C(1')H₂], 53.1 [CH₂, C(5)H₂], 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 ¹H NMR spectra of the majority of the crude products resulting from the cyclisations of 2-diazo-2-[(4phenylbutyl)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 ¹H NMR spectra. All signals for *cis* **209a** overlap to some extent with

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those of *trans* **209b**, one signal has been tentatively assigned to *cis* **209a**; $\delta_{\rm H}$ (CDCl₃, 400 MHz) 0.93 (3H, t, *J* 7.4, NCH₂CH₂CH₃). A second set of signals were

observed in the ¹³C NMR of *trans* **209b** and are tentatively assigned to *cis* **209a**; δ_C (CDCl₃, 150.9 MHz): 13.8 (CH or CH₃), 20.5 (CH₂), 21.4 (CH₂), 31.9 (CH or CH₃), 53.3 (CH₂), 54.0 (CH₂), 65.6 (CH or CH₃), 125.9 (CH, aromatic *C*H), 141.5 (C, aromatic *C*), 166.8 (C, *C*O).

Entry	Method	Metal	Ligand	Time	Crude	Yield	Crude Ratio ^a	cis ^{a,b}	:	trans (% ee) ^a
				(h)	Efficiency ^a	(%) ^a	Purified Ratio ^a			
1	E	Rh ₂ (OAc) ₄	-	6	>90%	60	Crude Ratio:	8		92
							Purified Ratio:	5		95 (0% ee)
2	В	CuCl ₂	(4 <i>R</i>)-Ph 20	21	>90%	49	Crude Ratio:	3		97
							Purified Ratio:	3		97 (12% ee)
										(3S, 4R)
3	В	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)-Ind	21	>90%	61	Crude Ratio:	2		98
			44				Purified Ratio:	2		98 (54% ee)
										(3 <i>R</i> ,4 <i>S</i>)
4	В	CuCl ₂	(4 <i>S</i>)- <i>t</i> -Bu	50	>90%	60	Crude Ratio:	3		97
			138				Purified Ratio:	3		97 (62% ee)
										(3 <i>R</i> ,4 <i>S</i>)
5	В	CuCl ₂	(4 <i>S</i> ,5 <i>R</i>)-di-	21	>90%	49	Crude Ratio:	5		95
			Ph 137				Purified Ratio:	5		95 (3% ee)
										(3S, 4R)
6	В	CuCl ₂	(4 <i>R</i>)-Bn 43	21	>90%	51	Crude Ratio:	5		95
							Purified Ratio:	0		100 (45% ee)
										$[\alpha]_{\rm D}^{20}$ -11.36
										$(c 0.11 \text{ in CH}_2\text{Cl}_2)$
										(3S, 4R)
7	В	Cu(CH ₃ CN) ₄ PF ₆	(3 <i>S</i> ,8 <i>R</i>)-Ind	21	>90%	60	Crude Ratio:	5		95
			44				Purified Ratio:	2		98 (67% ee)

Table 6.15 *Rhodium acetate and asymmetric copper catalysed* C–H *insertion reactions of* α -*diazo*- β -*oxo sulfone* **46**

									(3R, 4S)
8	В	Cu(CH ₃ CN) ₄ PF ₆	(4 <i>S</i>)- <i>t</i> -Bu	21	>90%	52	Crude Ratio:	8	92
			138				Purified Ratio:	6	94 (72% ee)
									(3R, 4S)

a. Efficiency and relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(3)*H*, *cis* γ -lactam **209a**, $\delta_{\rm H}$ 0.93 (3H, t, *J* 7.4, NCH₂CH₂CH₃); *trans* γ -lactam, **209b**, $\delta_{\rm H}$ 0.92 (3H, t, *J* 7.4, NCH₂CH₂CH₃). 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), CuCl₂ (4.1 mg, 30.5 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (32.0 mg, 36.6 µmol) and bisoxazoline ligand (4R)-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**. ¹H 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 (10:90-20:80-30:70-40:60-60:40)acetate-hexane as eluent, *N*,*N*-diethyl-3phenyltetrahydrothiophene-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**; v_{max}/cm⁻¹ (neat, ATR) (for mixture of *cis* **218a** and *trans* **218b**): 2961, 2929 (CH), 1639 (CO), 1457, 1303, 1106 (SO₂), 764, 707 (CS); δ_H (CDCl₃, 600 MHz): 0.91 (3H, t, J 6.2, one of NCH₂CH₃), 0.95 (3H, t, J 6.2, one of NCH₂CH₃), 2.38–2.55 [1H, m, one of C(4)H₂], 2.95 (2H, q, J 7.2, one of NCH₂CH₃) 3.02-3.12 (1H, m, one of NCH₂CH₃), 3.13–3.26 [1H, m, one of C(4)H₂], 3.27–3.36 [1H, m, one of C(5)H₂], 3.37– 3.51 (1H, m, one of NCH₂CH₃), 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 (CDCl₃, 150.9 MHz): 12.6 (CH₃, one of NCH₂CH₃), 14.4 (CH₃, one of NCH₂CH₃), 26.0 [CH₂, C(4)H₂], 41.0 (CH₂, one of NCH₂CH₃), 42.4 (CH₂, one of NCH₂CH₃), 45.1 [CH₂, C(3)H], 51.7 [CH₂, $C(5)H_2$, 65.2 [CH₂, C(2)H], 128.0 (CH, aromatic CH), 128.3 (CH, 2 × aromatic CH), 128.8 (CH, 2 × aromatic CH), 136.8 (C, aromatic C), 163.7 (C, CO).



218a $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.02 (3H, t, *J* 7.2, NCH₂C*H*₃), 1.14 (3H, t, *J* 7.1, NCH₂C*H*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*]; $\delta_{\rm C}$ (CDCl₃, 150.9 MHz) 12.8 (CH₃, one of

NCH₂CH₃), 14.5 (CH₃, one of NCH₂CH₃), 28.0 (CH₂), 41.5 (CH₂), 42.3 (CH₂), 45.7 (CH), 53.1 (CH₂), 69.0 (CH), 127.1 (CH), 127.8 (CH), 128.8 (CH), 140.0 (C), 162.7 (C, CO).

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), CuCl₂ (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 γ -lactam product **216** [isolated as three fractions; fraction 1, (16.2 mg, 9%) (47% ee determined by chiral HPLC) (90% γ -lactam **216**, 10% unknown); fraction 2, (21.6 mg, 12%) (39% ee determined by chiral HPLC), (containing 94% γ -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



 v_{max}/cm^{-1} (neat, ATR): 2975, 2932 (CH), 1754 (CO), 1454, 1408, 1308, 1139, 1124 (SO₂), 750, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.22 (3H, t, *J* 7.3 one of NCH₂CH₃), 1.48 [3H, d, *J* 6.2, CH₃-C(4)], 2.17–2.30 [2H, m, C(2')H₂], 2.75–2.85

[2H, m, C(3')*H*₂], 3.09–3.16 (1H, sym m, one of NC*H*₂CH₃), 3.17–3.25 [2H, m, C(1')*H*₂], 3.39–3.48 (1H, m, one of NC*H*₂CH₃), 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 (CDCl₃, 150.9 MHz): 13.0 (CH₃, NCH₂CH₃), 18.0 [CH₃, *C*H₃-C(4)], 22.8 [CH₂, *C*(2')H₂], 34.3 [CH₂, *C*(3')H₂], 36.0 (CH₂, NCH₂CH₃), 47.7 [CH, *C*(4)H], 52.5 [CH₂, *C*(1')H₂], 72.4 [CH, *C*(3)H], 126.5 (CH, aromatic *C*H), 128.5 (CH, 2 × aromatic *C*H), 128.6 (CH, 2 × aromatic *C*H), 139.9 (C, aromatic *C*), 158.0 (C, *CO*); HRMS (ESI+): Exact mass calculated for C₁₅H₂₂NO₃S [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), Rh₂(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



 v_{max}/cm^{-1} (neat): 2936 (CH), 1683 (CO), 1455, 1435, 1305, 1281, 1122 (SO₂), 750, 700 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz) 1.16 (3H, t, *J* 7.3, NCH₂CH₃), 2.17–2.28 [2H, m, C(2')H₂], 2.36–2.45 [1H, m, one of C(4)H₂], 2.71–2.78 [1H, m, one of C(4)H₂], 2.78–2.83 [2H, m,

C(3')*H*₂], 3.32–3.47 [5H, m, C(1')*H*₂, NC*H*₂CH₃ 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*); $\delta_{\rm C}$ (CDCl₃, 150.9 MHz) 12.2 (CH₃, NCH₂CH₃), 17.5 [CH₂, *C*(4)H₂], 23.3 [CH₂, *C*(2')H₂], 34.4 [CH₂, *C*(3')H₂], 38.0 [CH₂, NCH₂CH₃], 45.0 [CH₂, *C*(5)H₂], 51.5 [CH₂, *C*(1')H₂], 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 C₁₅H₂₂NO₃S [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.

Entry	Method	М	Ligand	Time (h)	Crude Efficiency (%) ^a	Crude Ratio Purified Yield % Overall Yield (%)		<u>Products</u>	
							<i>trans</i> sulfolane ^b Least polar	β-lactam ^b Mid polarity	γ-lactam Most polar
1	В	CuCl₂/∆	(4 <i>R</i>)- Ph 20	21	80–90°	Crude Ratio Purified Yield (%) Overall Yield (%)	2 0.8% ^d 0.68%	37 _ ^e _ ^e	61 27% ^f (46% ee) 26%
2	В	CuCl₂/∆	(4 <i>R</i>)- Ph 20	21	80–90	Crude Ratio Purified Yield (%)	2 0.7% ^g	38 12% ^h	$ \begin{array}{c} 60 \\ 9\%^{i} (47\% \text{ ee}) \\ + 12\%^{j} (32\% \text{ ee}) \\ + 5\%^{k} (39\% \text{ ee}) \end{array} $
						Overall Yield (%)	0.65%	12%	21% (45% ee)

Table 6.16 *Rhodium acetate and asymmetric copper catalysed* C–H *insertion reactions of* α -*diazo-\beta-oxo sulfone* **51**

3	E	Rh₂(OAc)₄/∆ No NaBARF	-	4	80–90 ¹	Crude Ratio Yield (purified)% Overall Yield (%)	2 - 0.18%	7 3% ^m 2.6%	91 45% (0% ee) 45%
4	В	Cu(CH ₃ CN)PF ₆ /Δ No NaBARF	(4 <i>R</i>)- Ph 20	2	60–70 ⁿ	Crude Ratio Purified Yield (%) Overall Yield (%)	2 1.5%° 1.3%	23 8% ^p 4%	75 28% (69% ee) 28%

a. Efficiency and relative ratios calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *trans* sulfolane **218b**, $\delta_{\rm H}$ 4.38 [1H, d, *J* 5.3, C(2)*H*]; β -lactam **217b**, $\delta_{\rm H}$ 4.24 [1H, apparent qd, *J* 6.1, 1.6, C(4)*H*] and γ -lactam **216**, $\delta_{\rm H}$ 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 γ -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 ¹H 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; $\delta_{\rm H}$ 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% y-lactam **216**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H NMR spectra; $\delta_H 2.59-2.68$ (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% y-lactam **216**. Additional peaks present in the ¹H 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 ¹H NMR spectra; $\delta_H 3.10-3.16$ (m), 4.64–4.72 (m), 5.20–5.28 (m).
- k. Fraction contains 94% y-lactam **216**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 3.07–3.14 (m), 4.64–4.72 (m), 5.21–5.28 (m).
- 1. Additional peaks may be present in the ¹H 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; $\delta_{\rm H}$ 4.80–4.82 (m), 4.96–5.01 (m), 5.08 (s), 5.52 (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 ¹H NMR spectra; $\delta_H 4.67-4.75$ (m), 6.99 (s), 7.47-7.54 (m), 7.60-7.64 (m).

- n. Additional peaks may be present in the ¹H 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; $\delta_{\rm H}$ 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, SO₂CH₂CO). Additional peaks present in the ¹H 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-1propylpyrrolidin-2-one **208b** using 2-diazo-*N*,*N*-diethyl-2-[(4-

phenylbutyl)sulfonyl]acetamide 47 (90 mg, 0.26 mmol), CuCl₂ (1.8 mg, 13.3 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (14.2 mg, 16.0 µmol) and bisoxazoline ligand (3S,8R)-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**. ¹H 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, (2R,3R)-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, CH₂Cl₂) 92% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (neat, ATR): 2971, 2918 (CH), 1631 (CO), 1443, 1309, 1294, 1145, 1116 (SO₂), 853, 763, 708 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 0.82 (3H, t, J 7.2 one of NCH₂CH₃), 0.99 (3H, t, J 7.2 one of NCH₂CH₃), 1.74 [1H, apparent dq, J 13.7, 3.2, one of C(4)H₂], 2.15–2.31 [2H, m, C(5)H₂], 2.59–2.67 (1H, m, one of NCH₂CH₃), 2.68–2.76 (1H, m, one of NCH₂CH₃), 2.88 [1H, apparent qd, J 13.4, 3.9 one of C(4)H₂], 2.94–3.06 [2H, m, one of C(6)H₂ and one of NCH₂CH₃], 3.53 (1H, sym m, one of NCH₂CH₃), 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)H₂], 4.12 [1H, dd, J 4.5, 2.4, C(2)H], 7.23–7.33 (5H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 12.3 (CH₃, one of NCH₂CH₃), 13.8 (CH₃, one of NCH₂CH₃), 23.3 [CH₂, C(5)H₂], 24.2 [CH₂, C(4)H₂], 41.2 (CH₂ one of NCH₂CH₃), 42.3 (CH₂ one of NCH₂CH₃), 45.7 [CH, C(3)H], 48.3 [CH₂, C(6)H₂], 65.6 [CH, C(2)H], 127.77 (CH, 2 × aromatic CH), 127.84 (CH, aromatic CH), 128.9 (CH, 2 × aromatic CH), 140.0 (C, aromatic C), 164.3 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₆H₂₄NO₃S [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 γ -lactam **219** [recovered as three fractions; [fraction 1, (3.2 mg, 4%), containing 85% γ -lactam **219**, 15% unknown; fraction 2, (9.6 mg, 12%), containing 86% γ -lactam **219**, 14% unknown; fraction 3 (4 mg, 5%) containing 83% γ -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), CuCl₂ (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% γ-lactam **219**, 5% sulfone **118**, 10 % unknown; fraction 3 (2.4 mg, 3%) containing 62% γ-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



 v_{max}/cm^{-1} (neat): 2932 (CH), 1760 (CO), 1455, 1409, 1306, 1140 (SO₂), 748, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 600 MHz): 1.23 (3H, t, *J* 7.3 one of NCH₂CH₃), 1.48 [3H, d, *J* 6.3, CH₃-C(4)], 1.76–1.85 [2H, m, C(2')H₂ or C(3')H₂], 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 NC H_2 CH₃), 3.22 [2H, t, J 7.9, C(1') H_2], 3.40–3.48 (1H, m, one of NC H_2 CH₃), 4.02 [1H, br s, C(3)H], 4.25 [1H, q, J 6.1, C(4)H], 7.14–7.22 (3H, m, ArH), 7.25–7.32 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 13.0 (CH₃, NCH₂CH₃), 18.0 [CH₃, CH₃-C(4)], 20.9 [CH₂, C(2')H₂ or C(3')H₂], 30.1 [CH₂, C(2')H₂ or C(3')H₂], 35.3 [CH₂, C(4')H₂], 36.0 (CH₂, NCH₂CH₃), 47.7 [CH, C(4)H], 53.1 [CH₂, C(1')H₂], 72.2 [CH, C(3)H], 126.1 (CH, aromatic CH), 128.4 (CH, 2 × aromatic CH), 128.5 (CH, 2 × aromatic CH), 141.2 (C,

aromatic *C*), 158.1 (C, *CO*); 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 ¹H 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, SO₂C*H*₂CO).

The most polar fraction recovered from **Table 6.17**, entry 2 was γ -lactam **219** isolated as three fractions; [fraction 1, (9.6 mg, 12%) (54% ee determined by chiral HPLC), containing >99% γ -lactam **219**; fraction 2, (6.4 mg, 8%), (51% ee determined by chiral HPLC), containing >99% γ -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



 v_{max}/cm^{-1} (neat): 2936, 2872 (CH), 1684 (CO), 1495, 1436, 1455, 1282, 1135 (SO₂), 748, 701 (CS) ; δ_{H} (CDCl₃, 600 MHz): 1.16 (3H, t, *J* 7.3, NCH₂CH₃), 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 , NC H_2 CH₃ 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, ArH), 7.25– 7.31 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 12.2 (CH₃, NCH₂CH₃), 17.5 [CH₂, *C*(4)H₂], 21.3 [CH₂, *C*(2')H₂], 30.2 [CH₂, *C*(3')H₂], 35.4 [CH₂, *C*(4')H₂], 38.0 [CH₂, NCH₂CH₃], 45.0 [CH₂, *C*(5)H₂], 52.0 [CH₂, *C*(1')H₂], 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 C₁₆H₂₄NO₃S [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.

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency	Crude Ratio ^a		Products	
					(%) ^a	Purified Yield (%) ^a (%			
						ee) ^a	cis :	β :	Y
							thiopyran ^a	lactam ^{a,b}	lactam ^a
							least polar 1	nore polar r	nost polar
1	В	$CuCl_2/\Delta$	(3S, 8R)-	48	$70 - 80^{\circ}$	Crude Ratio	32	29	40
			Ind 44						
						<u>Purified Yield (%)</u>	10% (90% ee)	$8\%^{d} + 5\%^{e}$	$4\%^{g} + 12\%^{h}$
							(2R, 3R) +	+ 6% ^f	+ 5% ⁱ
							9% (94% ee)		
							(2R, 3R)		
						Overall Yield (%)	<u>20% (92% ee)</u>	<u>11%</u>	<u>18%</u>
								+	
							$[\alpha]_{p}^{20}$ -67.0	<u>5.8%</u>	
								total	
							(C = 0.05, C =	estimated for	
							CH_2CI_2)	sulfone 118	

Table 6.17 Asymmetric copper catalysed C–H insertion reactions of α -diazo- β -oxo sulfone 47

2	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph	21	70–80 ^j	Crude Ratio	17	20	63
			20						
						<u>Purified Yield (%)</u>	4% (>99% ee)	$2\% + 7\%^{k} +$	12% ^m (54% ee)
							(2S, 3S) +	3% ¹	$+8\%^{n}(51\% \text{ ee})$
							6% (96% ee)		+ 6% (49% ee)
							(2S, 3S)		
						Overall Yield (%)	<u>10% (97% ee)</u>	<u>10%</u>	
							$[\alpha]_{D}^{20} + 74.0$	<u>0.77%</u>	<u>26% (52% ee)</u>
							(c 0.05)	total	
							(C = 0.05), $CH_2CI_2)$	estimated for	
								sulfone 118	
3	D	$CuCl_2/\Delta$	(3S, 8R)-	21	70–80	Crude Ratio	38	30	32
			Ind 44					1000	1.697 0.09
			and			Purified Yield (%)	15% (0% ee)	12% (0% ee)	$16\%^{p}(0\% \text{ ee})$
			(3R, 8S)-				1507 (0.07 as)	001 (001 ac)	1407(007 ac)
			Ind 161			Overall Yield (%)	<u>15% (0 % ee)</u>	<u>9% (0% ee)</u>	<u>14% (0% ee)</u>
			(1:1)					<u>0.90%</u> total	
								estimated for	
								sulfone 118	

a. Efficiency and relative ratios calculated using ¹H 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 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 of which are in **Appendix I**.

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 ¹H 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, SO₂CH₂CO). Additional peaks may be present in the ¹H 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, SO₂CH₂CO). Additional peaks present in the ¹H 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, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; δ_H 2.77–2.84 (m).
- g. Fraction contains 85% γ -lactam 219. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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% γ -lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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% γ -lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H 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, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; δ_H 2.76–2.84 (m), 4.47 (d, *J* 6.8). These peaks may indicate *trans* sulfolane **222b**.
- 1. Fraction contains 62% β -lactam 221b and 14% sulfone 118 δ_H 3.98 (2H, s, SO₂CH₂CO). Additional peaks present in the ¹H NMR spectra; δ_H 2.77–2.84 (m).
- m. Fraction contains >99% y-lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 3.19–3.34, 4.08–4.20 (m), 4.65–4.71 (m), 5.20–5.26 (m).
- n. Fraction contains >99% y-lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_H 3.20-3.25$, 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 ¹H NMR spectra; $\delta_H 2.76-2.89$ (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% γ -lactam **219**. Additional peaks present in the ¹H NMR spectra; $\delta_{\rm H}$ 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 $\delta_{\rm H}$ 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 γ -lactam **219** and/or β -lactam **221b**, **Table 6.17**, entries 1-3 are indicative of *trans* sulfolane **222b** formation.



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The presence of a singlet at 5.28 ppm is indicative of chloride abstraction **223** (**Table 6.17**, entries 1 and 2).

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]-4methyl-1-propylpyrrolidin-2-one **208b** using *N*,*N*dibenzyl-2-diazo-2-[(3-phenylpropyl)sulfonyl]acetamide

53 (100 mg, 0.22 mmol), CuCl₂ (1.5 mg, 11.2 µmol), sodium tetrakis[3,5bis(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**. ¹H 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-4phenyl-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, CH₂Cl₂); 55% ee (determined by chiral-HPLC); v_{max}/cm⁻¹ (film): 2919 (CH), 1768 (CO), 1497, 1456, 1402, 1316, 1144 (SO₂), 699 (CS); δ_H (CDCl₃, 600 MHz): 2.16–2.29 [2H, m, C(2')H₂], 2.74–2.85 [2H, m, C(3')H₂], 3.16– 3.27 [2H, m, C(1')H₂], 3.92 (1H, d, J 15.3, one of NCH₂Ar), 4.32 [1H, d, J 1.6, C(3)H], 4.92 (1H, d, J 15.3, one of NCH₂Ar), 4.96 [1H, d, J 1.5, C(4)H], 7.15–7.35 (12H, m, ArH), 7.36–7.40 (3H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 22.9 [CH₂, C(2')H₂], 34.2 [CH₂, C(3')H₂], 45.4 (CH₂, NCH₂Ar), 52.8 [CH₂, C(1')H₂], 54.0 [CH, C(4)H], 74.6 [CH, C(3)H], 126.5 (CH, aromatic CH), 126.7 (CH, 2 × aromatic CH), 128.2 (CH, aromatic CH), 128.3 (CH, 2 × aromatic CH), 128.5 (CH, 2 × aromatic CH), 128.7 (CH, 2 × aromatic CH), 128.9 (CH, 2 × aromatic CH), 129.4 (CH, 2 × aromatic CH), 129.5 (CH, aromatic CH), 133.6 (C, aromatic C), 134.5 (C, aromatic C), 139.7 (C, aromatic C), 159.2 (C, CO); HRMS (ESI+): Exact mass calculated for C₂₅H₂₆NO₃S [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 ¹H NMR was obtained of this sample, the spectral characteristics remained unchanged and are given below;

Ethyl 2-[(3-phenylpropyl)sulfonyl]acetate⁶³ 227

(oil) $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.28 (3H, t, *J* 7.2 OCH₂CH₃), 2.17–2.26 [2H, m, C(2')H₂], 2.80 [2H, t, *J* 7.4, C(3')H₂], 3.21–3.28 [2H, m, C(1')H₂], 3.92 (2H, s, SO₂CH₂CO), 4.24 (2H, q, *J* 7.2 OCH₂CH₃), 7.15–7.26 (3H, m, ArH), 7.29–7.35 (2H, ArH). 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-[(2ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using *N*,*N*-dibenzyl-2-diazo-2-[(3phenylpropyl)sulfonyl]acetamide **53** (100 mg, 0.22

sodium tetrakis[3,5mmol), CuCl₂ (1.5)mg, 11.2 μmol), bis(trifluoromethyl)phenyl]borate (NaBARF) (11.9 mg, 13.4 µmol) and bisoxazoline ligand (3S,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; $\delta_{\rm H}$ (CDCl₃, 400 MHz)1.08 (3H, t, J 7.0, OCH₂CH₃), 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 OCH₂CH₃), 3.78–3.88 (1H m, one of OCH₂CH₃), 4.30 (1H, d, J 15.0, one of NCH₂Ph), 4.53 (1H, d, J 17.7, one of NCH₂Ph), 4.88 (1H, d, J 17.8, one of NCH₂Ph), 4.99 (1H, s, SO₂CH), 5.17 (1H, d, J 15.0, one of NCH₂Ph), 7.11–7.41 (15H, ArH). 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; $\delta_{\rm H}$ (CDCl₃, 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).

Entry	Method	Metal	Solvent	Purity of	Ligand	Т	Crude	Sulfone	Fraction	Purified	Yield	% ee ^a
				Solvent		(h)	Efficiency	227		Lactam:	(%) ^a	Lactam
							Lactam	(%)		Sulfone	Lactam,	
							(%) ^a	Crude ^a			Sulfone	
1	В	CuCl ₂ /Δ	CH ₂ Cl ₂	Doubly	(4 <i>R</i>)-Bn	30	50-60 ^b	-	Fr1	13%	13 ^c	55 % ee ^d
				distilled,	43					Lactam	Lactam	
				EtOH						only	only	
				absent								
2	В	CuCl ₂ /Δ	CH ₂ Cl ₂	Doubly	(4 <i>R</i>)-Ph	21	30-40 ^e	40–45	Fr 1	(38:62)	8	39% ee ^d
				distilled,	20				Fr 2	(50:50)	6 ^g	37% ee ^d
				trace					Fr 3	(70:30) ^f	2^{f}	-
				EtOH					<u>Overall</u>			
									<u>Yield</u>		(7.44%,	
											8.56%)	

Table 6.18 *Rhodium acetate and asymmetric copper catalysed* C–H *insertion reactions of* α -*diazo*- β -*oxo sulfone* **53**

3	В	$CuCl_2/\Delta$	CH ₂ Cl ₂	Doubly	(4 <i>R</i>)-Bn	24	30-40 ^h	40-45	Fr 1	(30:70)	4	59% ee ^d
				distilled,	43				Fr 2	(34:64)	6	56% ee ^d
				trace					Fr 3	$(58:42)^{i}$	5	56% ee ^d
				EtOH					Fr 4	$(69:31)^{i}$	7	57% ee ^d
									<u>Overall</u>		(11.51%	
									<u>Yield</u>		, 10.91%)	
4	В	$CuCl_2/\Delta$	CH ₂ Cl ₂	Doubly	(4 <i>R</i>)-di-	30	10–20 ^j	20–30	Fr1	(33:67)	8	52% ee ^d
				distilled,	Ph 137				Fr 2	(64 : 36)	10 ^k	56% ee ^d
				trace					<u>Overall</u>		(9.04%,	
				EtOH					<u>Yield</u>		8.96%)	
5	В	CuCl ₂ /Δ	CH ₂ Cl ₂	Doubly	(4 <i>S</i>)- <i>t</i> -Bu	50	$20-30^{1}$	35–45	Fr 1 ^{m,n}	(42:58)	5	53% ee ^p
				distilled,	138				Fr 2°	(35:65)	10	78% ee ^p
				trace					Fr 3°	(58:42)	9	48% ee ^p
				EtOH					<u>Overall</u>		(10.82%	
									<u>Yield</u>		, 13.18%)	
6	В	CuCl ₂ /Δ	CH ₂ Cl ₂	Doubly	(3S, 8R)-	21	30–40 ^q	30–40	Fr 1	(33:67)	2	84% ee ^p
				distilled,	Ind 44				Fr 2	(48:52)	9	82% ee ^p
									Fr 3	(61:39)	6	84% ee ^p

				trace					Fr 4	(68:32)	4	84% ee ^p
				EtOH					<u>Overall</u>		(11.36%	
									<u>Yield</u>		, 9.64%)	
7	В	CuCl ₂ /Δ	CH ₂ Cl ₂	Doubly	(3S, 8R)-	24	_ ^r	_ ^r	Fr1	(38:62)	5	85% ee ^p
				distilled,	Ind 44				Fr 2	(50:50)	9 ^s	81% ee ^p
				spiked					<u>Overall</u>		(6.4%,	
				with					<u>Yield</u>		7.6%)	
				EtOH								
8	В	CuCl ₂ /Δ	CH_2Cl_2	HPLC	(3S, 8R)-	30	30-40 ^t		Fr1	-	9	89% ee ^p
				grade, no	Ind 44				Fr2	-	12 ^u	77% ee ^{p,v}
				EtOH					<u>Overall</u>		21%	
									<u>Yield</u>			
9	Е	$Rh_2(OAc)_4/\Delta$	CH ₂ Cl ₂	Doubly	-	18	50-60 ^w		Fr1	$(37:63)^{x}$	6	0% ee
				distilled,					Fr2	$(67:33)^{x}$	10	
				trace					<u>Overall</u>		(8.92%,	
				EtOH					<u>Yield</u>		708%)	
			-									

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 OCH₂CH₃ for sulfone **227** δ_H 4.24 (2H, q, *J* 7.2 OCH₂CH₃). 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 ¹H 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 ¹H NMR spectra of the pure product; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ (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). $\delta_{\rm H}$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of Fr 3 (2 mg); $\delta_{\rm H}$ 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 ¹H NMR spectra; $\delta_{\rm H} 3.02-3.08$ (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; $\delta_{\rm H}$ (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). $\delta_{\rm H}$ (minor signals) 4.64–4.71 (m), 5.19–5.26 (m).
- h. Additional peaks observed in the ¹H 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 ¹H NMR spectra of the crude product; $\delta_H 3.04-3.13$ (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 ¹H NMR spectra; $\delta_{\rm H}$ 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; $\delta_{\rm H}$ 1.50–5.00 (series of overlapping signals), 5.43 (s), 6.99–7.43 (m)
- 1. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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; $\delta_{\rm H} 2.63-2.87$ (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 ¹H NMR spectra; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product showed that *approx* 5% of the starting material α -diazocarbonyl **53** was present. Additional signals observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 3.06–3.14 (m), 3.86 (s), 4.68 (s), 6.73 (br s).
- r. ¹H 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 ¹H NMR spectra of the crude product; $\delta_{H} 3.05-3.13$ (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 ¹H NMR spectra; $\delta_{\rm H}$ 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, CH₂Cl₂).
- w. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 4.59$ (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).
- 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 ¹H 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), CuCl₂ (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**. ¹H 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; v_{max}/cm^{-1} (neat, ATR): 2930, 2857 (CH), 1642 (CO), 1439, 1305, 1231, 1267, 1113 (SO₂), 762, 704 (CS); $\delta_{\rm H}$ (CDCl₃, 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 NC*H*₂ and OC*H*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 NC*H*₂), 3.27–3.36 (2H, sym m, morpholine OC*H*₂), 3.37–3.44 (1H, sym m, morpholine NC*H*₂), 3.55–3.62 (2H, sym m, morpholine NC*H*₂ and OC*H*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} (CDCl₃, 150.9 MHz): 23.2 [CH₂, *C*(5)H₂], 23.9 [CH₂, *C*(4)H₂], 42.2 (CH₂, morpholine NCH₂), 45.3 [CH, *C*(3)H], 46.6 (CH₂, morpholine NCH₂), 48.6 [CH₂, *C*(6)H₂], 65.0 [CH, *C*(2)H], 65.6 (CH₂, morpholine OCH₂), 66.2 (CH₂, morpholine OCH₂), 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 C₁₆H₂₂NO₄S [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 reactionsof α -diazo- β -oxo sulfone 48

Entry	Method	Metal	Ligand	Time	Crude	Fraction	Yield	ee (%)
				(h)	Efficiency		of 224a	
					(%) ^a		(%)	
1	D	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)- Ind 44 and (3 <i>R</i> ,8 <i>S</i>)- Ind 161 (1:1)	21	60–70 ^b	Fraction 1	20	0
2	В	CuCl ₂	(4 <i>R</i>)-Ph 20	21	40–50 ^c	Fraction	4 ^d	-
						1	15 ^d	98
						Fraction	~19%	(2 S ,3 S)
						2		$[\alpha]_{D}^{20} +$
						Overall		40.0
						yield (%)		(c = 0.05)
								$(C = 0.00)$, CH_2Cl_2
								/
3	В	CuCl ₂	(3S, 8R)-	21	40-50 ^e	Fraction	6 ^f	
			Ind 44			1	7	86
						Fraction	~13%	(2R, 3R)
						2		$\left[\alpha\right]_{\mathrm{D}}^{20}$ -
						Overall		57.0 (c
						yield (%)		0.1,
								CH ₂ Cl ₂)
						Overall yield (%)		[α] _D - 57.0 (<i>c</i> 0.1, CH ₂ Cl ₂)

- a. Efficiency calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **224a** $\delta_{\rm H}$ 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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H} 2.58-2.71$ (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 ¹H NMR spectrum; $\delta_H 2.59-2.72$ (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 ¹H NMR spectra; $\delta_H 1.74-1.85$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H} 2.62-2.71$ (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 ¹H 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-1propylpyrrolidin-2-one **208b** using 2- diazo-1-morpholino-2-[(3phenylpropyl)sulfonyl]ethanone **52** (70 mg, 0.21 mmol), CuCl₂ (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**. ¹H 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, CH₂Cl₂); 77% ee (determined by chiral-HPLC); mp 163–164 °C; v_{max}/cm⁻¹ (neat, ATR): 2963, 2872 (CH), 1651 (CO), 1449, 1300, 1260, 1114, 1032 (SO₂), 758, 701 (CS); $\delta_{\rm H}$ (CDCl₃, 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 NCH₂], 3.42–3.48 [2H, m, one of C(5)H₂ and morpholine NCH₂], 3.63–3.79 (5H, m, morpholine CH₂), 3.97–4.03 (1H, sym m, morpholine NCH₂), 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, ArH); δ_C (CDCl₃, 150.9 MHz): 28.2 [CH₂, C(4)H₂], 43.5 (CH₂, morpholine NCH₂), 45.0 [CH₂, C(3)H], 46.3 (CH₂, morpholine NCH₂), 53.2 [CH₂, C(5)H₂], 66.5 (CH₂, morpholine OCH₂), 66.6 (CH₂, morpholine OCH₂), 68.9 [CH₂, C(2)H], 127.3 (CH, 2 × aromatic CH), 127.9 (CH, aromatic CH), 129.2 (CH, 2 × aromatic CH), 139.6 (C, aromatic C), 161.6 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₅H₂₀NO₄S [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 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one for 208b using 2-diazo-1-morpholino-2-[(3-

mg, 10.4 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.0 mg, 12.4 µmol) and bisoxazoline ligand (4R)-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**. ¹H 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. [(2S,3R)-1,1-dioxido-3-phenyltetrahydrothiophen-2yl](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**; v_{max}/cm^{-1} (neat, ATR): 2920, 2850 (CH), 1618 (CO), 1470, 1439, 1315, 1140, 1104, 1027 (SO₂), 757, 699 (CS); δ_H (CDCl₃, 600 MHz): 2.44–2.52 [1H, m, one of C(4)H₂], 2.53–2.59 (1H, sym m, morpholine OCH₂), 2.76–2.83 (1H, sym m, morpholine NCH₂), 3.12 [1H, apparent qd, J 12.2, 12.2, 12.2, 6.8 one of C(4)H₂], 3.28 (1H, ddd, J 13.0, 7.9, 3.1, morpholine NCH₂), 3.26–3.31 (1H, m,

morpholine OCH₂), 3.31-3.37 [2H, m, one of C(5)H₂ and morpholine NCH₂], 3.40-3.45(1H, m, morpholine OCH₂), 3.57–3.62 (1H, sym m, morpholine OCH₂), 3.63–3.69 (1H, sym m, morpholine NCH₂), 3.75–3.81 [1H, m, one of C(5)H₂], 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 (CDCl₃, 150.9 MHz): 25.7 [CH₂, C(4)H₂], 42.1 (CH₂, morpholine NCH₂), 45.0 [CH₂, C(3)H], 46.5 (CH₂, morpholine NCH₂), 51.8 [CH₂, C(5)H₂], 64.7 [CH₂, C(2)H], 65.8 (CH₂, morpholine OCH₂), 66.2 (CH₂, morpholine OCH₂), 128.3 (CH, 2 × aromatic CH), 128.5 (CH, aromatic CH), 129.1 (CH, 2 × aromatic CH), 136.5 (C, aromatic C), 163.0 (C, CO).

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-[(3phenylpropyl)sulfonyl]ethanone 52 (70 mg, 0.21 mmol), CuCl₂ (1.4 mg, 10.4 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (11.0 mg, 12.4 µmol) and bisoxazoline ligand (3S,8R)-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



 $\delta_{\rm H}$ (CDCl₃, 400 MHz): 3.57-3.63 (2H, m, CH₂) morpholine), 3.69 (4H, br s, CH2 morpholine), 3.73-3.77 (2H, m, CH₂ morpholine), 4.06 (2H, s, SO₂CH₂CO), 4.13 [2H, d, J 7.6, C(1')H₂], 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, ArH), 7.40–7.46 (2H, m, ArH).

Assignment of the above compound 231a and 231b was made with the aid of 2D NMR experiments namely HSQC, HMBC and NOESY.

Entry	Method	Metal	Ligand	Time (h)	Crude Efficiency	Crude Ratio ^a Purified Vield (%) ^a	Products	
						(% ee) ^a	cis : sulfolane 231a more polar	<i>trans</i> sulfolane 231b less polar
1	В	$CuCl_2/\Delta$	(4 <i>S</i>)- <i>t</i> -Bu 138	48	60–70 ^b	Crude Ratio	20	80
			100			Purified Yield (%)	8°	22 ^d (77% ee) ^e
						<u>Overall Yield (%)</u>	7	$\begin{array}{c} \frac{23}{D} \\ \left[\alpha\right]_{D}^{20} -22.78 \ (c) \\ 0.09, \ CH_{2}Cl_{2} \end{array}$
2	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Bn 43	60	60–70 ^f	Crude Ratio	20	80
						Purified Yield (%)	5%	$8^{g} (45\% \text{ ee})^{h}$ $[\alpha]_{D}^{20} +1.961 (c)$ $(\alpha)_{D} +1.961 (c)$ $(\alpha)_{D} +1.961 (c)$ $(\alpha)_{D} +1.961 (c)$ $(\alpha)_{D}^{20} +7.692 (c)$ $(\alpha)_{D} +7.692 (c)$ $(\alpha)_{D} +7.692 (c)$ $(\alpha)_{D} +1.969 (c)$ $(\alpha)_{D} +1.969$

Table 6.20 Rhodium acetate and asymmetric copper catalysed C–H insertion reactions of α -diazo- β -oxo sulfone 52

						Overall Yield (%)	<u>5%</u>	$\frac{28\% (42\% \text{ ee})^{i}}{28\% (42\% \text{ ee})^{i}}$
3	В	$CuCl_2/\Delta$	(3S, 8R)- Ind 44	21	60–70% ^j	Crude Ratio	30	70
						Purified Yield (%)	-	17% ^k (47% ee) ^e
								$ [\alpha]_{D}^{20} -9.542 (c) 0.105, CH_2Cl_2) $
4	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph 20	21	60-70%1	Crude Ratio	70	30
						Purified Yield (%)	18% ^m	6% ⁿ
5	В	$CuCl_2/\Delta$	(4 <i>R</i> ,5 <i>S</i>)-di- Ph 137	21	60–70%°	Crude Ratio	60	40
						Purified Yield (%)	15% ^m	8% ⁿ
6	Е	$\frac{Rh_2(OAc)}{4/\Delta}$		6	50-60% ^p	Crude Ratio	60	40
		· -				Purified Yield (%)	-	14% ^q

a. Efficiency and relative ratios were calculated using ¹H 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra were observed; $\delta_H 2.15-2.29$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra were observed; $\delta_H 2.15-2.28$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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.
- 1. Additional peaks observed in the ¹H 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 ¹H NMR spectra of the crude product; $\delta_H 4.71$ (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 ¹H 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 ¹H NMR; $\delta_{\rm H} 2.76-2.85$ (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 Rh₂(OAc)₄ (~1 mg) in distilled dichloromethane (20 mL), stirred while heating

under reflux for 21 h, in accordance with Method E. ¹H 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; v_{max}/cm⁻¹ (film): 2971, 2930, 2862 (CH), 1652 (CO), 1447, 1305, 1278, 1248, 1175, 1156, 1133, 1114, 1065, 1037 (SO₂), 761 (CS); δ_H (CDCl₃, 400 MHz): 1.51 [3H, d, *J* 7.0, C(1')H₃], 3.41 (1H, ddd, J13.1, 8.6, 3.4, morpholine CH₂), 3.56–3.65 (1H, m, morpholine CH₂), 3.66–3.74 (1H, m, morpholine CH₂), 3.77–3.81 (1H, m, morpholine CH₂), 3.82– 3.88 (2H, m, morpholine CH_2), 3.95–4.05 (1H, sym m, morpholine CH_2), 4.07–4.14 (1H, sym m, morpholine CH₂), 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, ArH), 7.61–7.71 (2H, m, ArH); δ_C (CDCl₃, 75.5 MHz): 18.9 [CH₃, C(1')H₃], 36.6 [CH, C(3)H], 43.6 (CH₂, morpholine NCH₂), 46.7 (CH₂, morpholine NCH₂), 66.7 (CH₂, morpholine OCH₂), 66.9 (CH₂, morpholine OCH₂), 69.7 [CH, C(2)H], 121.5 (CH, aromatic CH), 125.5 (CH, aromatic CH), 128.9 (CH, aromatic CH), 134.2 (CH, aromatic CH), 136.9 (C, aromatic C), 141.5 (C, aromatic C), 160.7 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₄H₁₈NO₄S [M+H]⁺, 296.0957. Found 296.0950. m/z (ESI+): 296.2 [M+H]+.



¹H NMR spectral characteristics of *cis* were determined from the spectra of the crude product **233a**; $\delta_{\rm H}$ (CDCl₃, 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.
Entry	Method	Μ	Ligand	Time	Crude	Sulfone	Yield		Prod	lucts ratios	
				(n)	of C–H insertion (%) ^a	(%Crude) ^b	(%)		trans 233b c	is 233a	(S) 117
1	Ε	$Rh_2(OAc)_4/\Delta$	-	21	>90%	-	160	Crude ratio	96	4	-
2	В	CuCl ₂ /Δ	(3 <i>S</i> ,8 <i>R</i>)- Ind 44	24	50–60%°	10–15%	46% Fr1 5% Fr2 8% Total	Purified ratio Crude ratio Purified ratio Fr1 Fr2	99 (0% ee) 44 80 (10% ee) ^{d,e} 66 (14% ee) ^{d,e} 9.28%	1 44 10 (60% ee) ^f 12 (67% ee) ^f 1.46 %	12 10 22 2.26 %
3	В	CuCl₂/∆	(4 <i>R</i> ,5 <i>S</i>)- 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

Table 6.21 *Rhodium acetate and Asymmetric copper catalysed* C-H *insertion reactions of* α -*diazo*- β -*oxo sulfone* **58**

							Total		9.48%		1.52%
4	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Ph	6	50–55% ¹	~8%		Crude ratio	20	68	12
			20					Purified ratio ⁿ			
							Fr1		only $(90\% \text{ ee})^{j,o}$	-	-
							1% ^m				
										-	-
							Fr2				
							3%		only $(70\% \text{ ee})^{1}$		
							E-2		an ln (6007 an)i	-	-
							ГГЭ 20%		omy (00% ee)		
							Z70 Total		6%		
5	D	CC1 /A	(AD) Dr	21	50 600 p	501	<u>10tai</u>	Canada natio	670	20	2
5	Б	$CuCl_2/\Delta$	(4K)-DII 13	21	30-00% ^r	~3%		Crude ratio	08	50	Z
			43					I ul illeu l'auo			
							Fr1		78 (43% ee) ^{e,r}	$2.2^{s,t}$	-
							4% ^q		/ 0 (10 / 0 00)	$27^{s,t}$	-
							Fr2		73 (37% ee) ^{e,r}	$22^{s,t}$	2
							6% ^q				
							Fr3		74 (32% ee) ^{e,r}		
							4% ^q				
							<u>Total</u>		<u>10.46%</u>	<u>3.38%</u>	0.08%
6	В	$CuCl_2/\Delta$	(4S)-t-Bu	30	50-60	~5%		Crude ratio	74	22	4
			138					Purified ratio			
							E-1		77 (0 (0/)i)	$22(700) - 1^{\circ}$	-
									// (86% ee) ^{,,u}	$23(70\% \text{ ee})^{4}$	-
							2%0°				-
							Er2		81 (70% ee) j,u	$10(70\% e^{1})^{f}$	
							4%q			17 (1010 00)	

							Fr3 3% ^q		82 (78% ee) ^{j,u}	8 (70% ee) ^f	
							<u>Total</u>		7.24%	1.76%	
7	В	CuCl ₂ /Δ	(4 <i>R</i>)-Bn 43	24	50-60	~1%		Crude ratio Purified ratio	72	27	1
							Fr1		only (37% ee) ^e	-	-
							Fr2		only (33% ee) ^e	-	-
							7% ^v Total		13%		
8	В	CuCl ₂ /Δ	(4 <i>S</i>)- <i>t</i> -Bu 138	48	50-60 ^w	~1%	<u>10tai</u>	Crude ratio Purified ratio	80	19	1
							Fr1 9%		only (60% ee) ^{j,x}		
							Fr2 6%		98 (50% ee) ^j	2 ^y	
							<u>Total</u>		14.88%	0.12%	

a. Efficiency and relative ratios calculated using ¹H NMR using the following signals: $\delta_{\rm H}$ 4.67 [1H, d, *J* 6.0, C(2)*H*] for *cis* sulfolane **233a**; $\delta_{\rm H}$ 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 using¹H NMR using the following signals: $\delta_H 4.27$ (2H, s, SO₂CH₂CO). Additional signals were observed for sulfone **117**; $\delta_H 1.35$ (3H, t, *J* 7.5, ArCH₂CH₃), 3.10 (2H, q, *J* 7.5, ArCH₂CH₃).

c. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_{\rm H} 5.17$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 5.17 (s), 5.59 (s).
- h. Impure fraction. Additional peaks present in the ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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.
- 1. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 5.17 (s), 5.60 (s), 9.41 (s).
- m. Impure fraction. Additional peaks present in the ¹H NMR spectra of the purified product; $\delta_H 3.77-3.99$ (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 ¹H 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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 4.20–4.25 (m overlapping), 4.30 (d, J 5.4).
- w. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_H 4.91$ (s), 5.59 (s), 6.54–6.61 (m).
- x. Contains ~5% additional compound that contains the following peaks in the ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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-1propylpyrrolidin-2-one **208b**, using 2-diazo-2-(dodecylsulfonyl)-1-

morpholinoethanone **49** (80 mg, 0.22 mmol), CuCl₂ (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**. ¹H 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; v_{max}/cm^{-1} (film): 2923, 2854 (CH), 1644 (CO), 1315, 1115 (SO₂); Characteristic signals are seen at $\delta_{\rm H}$ (CDCl₃, 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(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*]; $\delta_{\rm C}$ (CDCl₃, 100.6 MHz): 164.2 (C, *CO*) HRMS (ESI+): Exact mass calculated for C₁₈H₃₄NO₄S [M+H]⁺, 360.2209. Found 360.2211. m/z (ESI+): 360.3 [M+H]⁺.

Additional signals observed in the ¹H NMR spectra of the purified spectra $\delta_{\rm H}$ (CDCl₃, 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 2diazo-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.

Entry	Method	Μ	Ligand	Time	Crude	Yield
				(h)	Efficiency	(%)
					(%) ^a	
1	В	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)- Ind 44	72	10–20 ^b	c
2	В	CuCl ₂	(4 <i>R</i>)-Ph 20	96	10–20 ^d	_e
3	D	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)-Ind 44 and (3 <i>R</i> ,8 <i>S</i>)-Ind 161 (1:1)	75	10–20 ^f	_e

Table 6.22 Asymmetric copper catalysed C–H insertion reactions of α -diazo- β -oxo

sulfone **49**

a. Efficiency calculated using ¹H NMR spectra of the crude product using signals for C(2)*H*, *cis* thiopyran **229a** $\delta_{\rm H}$ 4.10 [1H, dd, *J* 4.0, 2.1, C(2)*H*].

b. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 1.64-1.99$ (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 ¹H NMR spectra of the crude product and are listed above.

d. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 1.64-1.99$ (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 $\delta_H 5.95$ (s) signal in the ¹H NMR spectra when compared to reactions reported in entries 1 and 3.

- e. Not purified.
- f. Additional peaks observed in the ¹H 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 ¹H 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, <math>3R,4S) (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 $(3 \times 20 \text{ mL})$. The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate (3×20 mL), brine (50 mL), dried with MgSO₄, 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, CH₂Cl₂); v_{max}/cm^{-1} (neat): 2962, 2930 (CH), 1682 (CO), 1267; δ_H (CDCl₃, 600 MHz): 0.90 (3H, t, J 7.4, NCH₂CH₂CH₃), 1.12 [3H, d, J 6.8, CH₃-C(4)], 1.54 (2H, apparent sextet, J 7.4, NCH₂CH₂CH₃), 2.05 [1H, dd, J 16.4, 6.6, one of C(3)H₂], 2.38–2.48 [1H, m, C(4)H], 2.57 [1H, dd, J 16.5, 8.6, one of C(3)H₂], 2.95 [1H, dd, J 9.6, 5.8 one of C(5)H₂], 3.14–3.31 (2H, sym m, NCH₂CH₂CH₃), 3.49 [1H, dd, J 9.6, 7.7, one of C(5)H₂]; δ_C (CDCl₃, 150.9 MHz): 11.3 (CH₃, NCH₂CH₂CH₃), 19.9 [CH₃, CH₃-C(4)], 20.5 (CH₂, NCH₂CH₂CH₃), 26.4 [CH, C(4)H], 39.5 [CH₂, C(3)H₂], 44.1 (CH₂, NCH₂CH₂CH₃), 54.5 [CH₂, C(5)H₂], 174.7 (C, CO); HRMS (ESI+): Exact mass calculated for C₈H₁₆NO (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 αdiazo-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}



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}



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}





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





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 interand intramolecular cyclopropanation reactions.^{42–48} Monteiro and McKervey were the first to report the use of these substrates for this transformation, with McKervey and coworkers achieving 12% ee for the rhodium mandelate catalysed cyclopropanation reaction of an α -diazosulfone substrate, as illustrated in **Scheme 7.7**.^{49,50}



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 -oxosulfones45



Entry	R	R ¹	R ²	R ³	Starting	Product	\mathbf{L}^{*}	Temp.	Time	Yield	ee (%)
					Material	Material			(h)	(%)	
1	Ph	Н	Н	Н	239	240	241	rt	2	91	65
							(X1)				(1 <i>R</i> ,5 <i>R</i>)
2	Ph	Н	Н	Н	239	240	242	rt	2	67	75
							(X2)				(1 <i>R</i> ,5 <i>R</i>)
3	Ph	Н	Н	Н	239	240	243	rt	2	67	72
							(X4)				(1 <i>R</i> ,5 <i>R</i>)
4	Ph	Н	Н	Н	239	240	244	rt	5.5	61	73
							(X5)				(1 <i>R</i> ,5 <i>R</i>)
5	Ph	Н	Н	Н	239	240	138	50 °C	5.5	61	32
							(X3)				(1R, 5R)
6	Mes	Н	Н	Н	245	246	241	50 °C	1.5	93	83
							(X1)				(1R, 5R)
7	Mes	Н	Н	Н	245	246	243	rt, 50	2,2	89	90
							(X4)	°C			(1 <i>R</i> ,5 <i>R</i>)
8	Mes	Н	Н	Η	245	246	244	rt, 50	2,2.5	87	93
							(X5)	°C			(1 <i>R</i> ,5 <i>R</i>)

9	Mes	Η	Η	Me	247	248	244	50 °C	2	90	98
							(X5)				(1 <i>R</i> ,5 <i>R</i>)
10	Mes	Me	Me	Η	249	250	244	rt	5	84	92
							(X5)				(1 <i>R</i> ,5 <i>R</i>)
11	Mes	Η	Η	Br	251	252	244	50 °C	2.5	63	98
							(X5)				(1 <i>S</i> ,5 <i>S</i>)

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 (4S)-Bn ligand 242 giving the best enantioselectivity of 75% ee (Table 7.1, entry 2). Enantioselectivities remained high for the (4S)-i-Pr 243 and (4S)-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 (4S)-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 (4S)-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 NaBARF⁵⁶



Entry	\mathbf{L}^{*}	Time (h)	Yield (%)	ee (%)
1	(4 <i>R</i>)-Bn 43	2	81	7 (1 <i>S</i> ,5 <i>S</i>)
2	(4 <i>R</i>)-Ph 20	4	93	8 (1 <i>R</i> ,5 <i>R</i>)
3	(4 <i>R</i> ,5 <i>S</i>)-di-Ph	2	93	17 (1 <i>R</i> ,5 <i>R</i>)
	137			
4	(4 <i>S</i>)- <i>t</i> -Bu 138	4	87	26 (1 <i>S</i> ,5 <i>S</i>)
5	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	2	82	9 (1 <i>S</i> ,5 <i>S</i>)

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.



Scheme 7.8^{45,56}

Interestingly, a significant decrease in enantioselectivity was observed for reaction of CuCl₂-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 CuCl₂-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 CuCl₂-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 <i>S</i>)-Bn 242	67	75
2	Slattery, Δ	(4 <i>R</i>)-Bn 43	81	7
3 ^a	Nakada, 50 °C	(4 <i>S</i>)- <i>t</i> -Bu 138	61	32
4	Slattery, Δ	(4 <i>S</i>)- <i>t</i> -Bu 138	87	26

a. Reaction was heated to 50 $^{\circ}$ 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



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 sulfones⁵⁸

	SO ₂ Mes ligan	uOTf 0 mol%) d 15 mol% bluene	H SO ₂ Me		$H + C_2 Mes = 0$	-H 60 ₂ Mes
	5		а	b	С	
253			254	256	255	
Entry	Ligand	Time (h)	Yield (%)	Yield (%)	% ee	
			b and c	а	а	
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 thiopyrans⁵³ 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 v_{max} 2126 cm⁻¹ (C=N₂) had occurred within 21 hours, at which time the reaction was deemed complete.



Scheme 7.14

Examination of the ¹H 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 ¹H 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 ¹H NMR, ¹³C NMR and IR spectroscopy and high resolution mass spectrometry. There are a number of key distinctive signals

present in the ¹H 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 ¹H NMR spectrum is the presence of two distinct signals for the inequivalent protons at C(7) H_2 at $\delta_H 1.64$ [1H, dd, J 8.3, 6.4, one of C(7) H_2] and at $\delta_H 1.70$ [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 $v_{max}/cm^{-1} 1732$ (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 ¹H NMR, employing [(+)-Eu(hfc)₃] as a chiral shift reagent, which proved successful as can be seen in **Figure 7.3**.



Figure 7.3 ¹H NMR spectra recorded in (CDCl₃, 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 $\delta_{\rm H}$ 5.16–5.85 for the terminal alkene protons and a 1H multiplet at $\delta_{\rm H}$ 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 $\delta_{\rm H}$ 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% CuCl₂, 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**

		1e —	CuCl ₂ (5 mol%) NaBARF (6 mol%) L*(6 mol%) CH ₂ Cl ₂ , Δ efficiency 80–90%	O O O S OMe +	O O O S OMe
	59			257a	258b
Entry	L	Time (h)	Crude ratios ^a Purified Yields (%) ^a ee (%) ^a	Produ	icts
				thiopyran	trans sulfolane
				(cyclopropanation)	(C-H insertion)
				More polar	Less polar
				257a	258b
1	(4 <i>R</i>)-Ph 20	21	Crude ratio	90	10
			Purified Yield (%)	70%	-
			ee (%)	67% ee (1 <i>S</i> ,6 <i>R</i>) (72%ee) ^b	
2	(4 <i>R</i> ,5 <i>S</i>)-di-	21	Crude ratio	90	10
	Ph 137		Purified Yield (%)	66%	-
			ee (%)	61% ee (1 <i>S</i> ,6 <i>R</i>)	-
3	$(3\overline{S},8R)$ -Ind	21	Crude ratio	92	8
	44		Purified Yield (%)	59%	-
			ee (%)	08% ee (1 K ,03)	

4	(4 <i>R</i>)-Bn 43	21	Crude ratio Purified Yield (%) ee (%)	95 63% 38% ee ^c (1 <i>S</i> ,6 <i>R</i>)	5 -
5	(4 <i>S</i>)- <i>t</i> -Bu 138	48	Crude ratio Purified Yield (%) ee (%)	98 61% 61% ee (1 <i>R</i> ,6 <i>S</i>)	2

- a. Crude efficiency and relative ratios calculated using ¹H NMR spectra of the crude product using signals for *cis* thiopyran **257a**; $\delta_{\rm H}$ 1.64 (1H, dd, *J* 8.3, 6.4, one of methylene *CH*₂), 1.70 (1H, dd, *J* 9.6, 6.4, one of methylene *CH*₂) and signals for *trans* sulfolane **258b**; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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 (4R)-Ph 20, (4R,5S)-di-Ph 137 (cyclopropane 257a : C-H insertion product 258b, 90 : 10) (Table 7.5, entries 1 and 2) and (3S,8R)-Ind 44 (cyclopropane 257a: C-H insertion product 258b, 92 : 8). Slightly lower amounts were observed for use of (4R)-Bn 43 (cyclopropane 257a: C-H insertion product 258b, 95 : 5) (Table 7.5, entry 4) and (4S)-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 CuCl₂-NaBARFbisoxazoline catalyst system, with 68% ee being the highest value attained in this study for reaction with (3S, 8R)-Ind ligand **44** (**Table 7.5**, entry 3). Similar enantioselectivities were obtained for the use of (4R)-Ph ligand **20** (67% ee, **Table 7.5**, entry 1) with slightly lower values observed for (4R,5S)-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 -sulforyl 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 (4S)-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 (4R)-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 (4S)-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 (3S,8R)-Ind **44** as a ligand, was determined to be (1R,6S) and the rotation of this sample was positive $[\alpha]_D^{20}$ +36.5 (*c* 0.1, CH₂Cl₂) (Figure 7.15). In comparison with the methyl ester series **257a**, a positive rotation was also obtained when (4S)-*t*-Bu **138** was employed as a ligand and a negative rotation was obtained through use of (4R)-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**.



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 ¹H 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).





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 [Rh₂(*S*-PTTL)₄, Rh₂(*S*-PTPA)₄, Rh₂(*S*-DOSP)₄, Rh₂(*S*-mand)₄] and one rhodium carboxamidate [Rh₂(*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 [Rh₂(*S*-PTTL)₄, Rh₂(*S*-PTPA)₄ and Rh₂(*S*-mand)₄], each of the reactions was complete within 30 h at room temperature (**Table 7.7**, entries 1,3,5). With Rh₂(*S*-DOSP)₄ and Rh₂(*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 Rh₂(*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**



Entry	Metal	Time	Crude	Crude ratio ^a	Produ	ıcts
		(h)	Efficiency	Purified Yield		
			(%) ^a	(%) ^a	thiopyran	trans sulfolane
				% ee ^a	(cyclopropanation)	(C–H insertion)
					More polar	Less polar
					257a	258b
1	Rh ₂ (S- PTTL) ₄ 0 °C-rt	6 rt	80–90%	Crude ratio Purified Yield (%) % ee	88 67% 34% ee (1 <i>R</i> ,6S)	12 3%
2	$ \begin{array}{c} \text{Rh}_2(S-\\ \text{DOSP})\\ ^4\\ 0 \ ^\circ\text{C-rt-}\\ \Delta \end{array} $	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 <i>R</i> ,6 <i>S</i>)	17 4%
4	$\begin{array}{c} \operatorname{Rh}_2(S-\\ \operatorname{MEPY}) \\ {}^4\\ 0 \ {}^\circ\mathrm{C}\text{-rt-} \\ \Delta \end{array}$	30 rt +120∆	-	-	Starting material only recovered	-
5	Rh ₂ (S- mand) ₄ 0 °C-rt	21 rt	80–90%	Crude ratio Purified Yield (%) % ee	91 54% (contains ~10% <i>trans</i> sulfolane 258b) ~12% ee ^b (1 <i>S</i> ,6 <i>R</i>)	9
				Total	49%	5%

a. Crude efficiency and relative ratios calculated using ¹H NMR spectra of the crude product using signals for *cis* thiopyran **257a**; $\delta_{\rm H}$ 1.64 (1H, dd, *J* 8.3, 6.4, one of methylene *CH*₂), 1.70 (1H, dd, *J* 9.6, 6.4, one of methylene *CH*₂) and signals for *trans* sulfolane **258b**; $\delta_{\rm H}$ 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 ¹H 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 Rh₂(*S*-DOSP)₄ (cyclopropanation : C–H insertion, 82 : 18) (**Table 7.7**, entry 2) and Rh₂(*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**.





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**). Rh₂(*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 Rh₂(*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**.



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 ¹H 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 ¹H 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 ¹H NMR spectra of the crude reaction material of the cyclisation of methyl ester **59** using Rh₂(*S*-PTTL)₄ as a catalyst is included in **Figure 7.7**.



Figure 7.7 ¹H NMR spectra recorded in (CDCl₃, 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 ¹H NMR, ¹³C 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% CuCl₂, 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

Entry	L*	Crude Ratio ^{a-d}		Prod	ucts	
		Purified Yield (%) ^e % ee ^f	<i>cis</i> thiopyran 259a ^a	<i>trans</i> sulfolane 260b ^b	sulfone 131 ^c	X–H Insertion 261 ^d
1	(3 <i>S</i> ,8 <i>R</i>)- Ind 44	Crude (%) Purified Yield (%) % ee	72% 56 % 80% ee (1 <i>R</i> ,6 <i>S</i>)	4%	3% % ^g : 50	5% 0.6%
2	(4 <i>R</i> ,5 <i>S</i>)- di-Ph 137	Crude (%) Purified Yield (%) % ee	84% 45% 73% ee (1 <i>S</i> ,6 <i>R</i>)	2% 1% 0 %ee	0% -	2%
3		Crude (%)	70%	2%	2%	1%

	(4 <i>R</i>)-Ph 20	Purified Yield (%)	49%	-	29 83	% ^g :17	
		% ее	75% ee (1 <i>S</i> ,6 <i>R</i>)		-		
4	(4 <i>R</i>)-Bn 43	Crude (%) Purified Yield (%)	70% 52%	-	1%	2%	3%
		% ее	75% e (1 <i>S</i> ,6 <i>R</i>)	ee	_h		
5	(4 <i>S</i>)- <i>t</i> -Bu 138	Crude (%) Purified Yield (%) % ee	83% 58 80% e (1 <i>R</i> ,6 <i>S</i>)	ee	6% 2 _ ^h	0%	0%

a. Relative ratios of reaction products calculated using ¹H NMR spectra of the crude product using signals for C(6)*H*; $\delta_{\rm H}$ 2.36–2.42 [1H, m, C(6)*H*] for *cis* thiopyran **259a**

b. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(3)*H*; $\delta_{\rm H}$ 3.70–3.78 [1H, m, C(3)*H*] for *trans* sulfolane **260b**

c. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for reduction product **131**; δ_{H} 4.57 (2H, s, SO₂CH₂CO).

d. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for X–H insertion product **261**; $\delta_{\rm H}$ 6.02 (2H, s, SO₂CHXCO).

- 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 ¹H 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*)-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 CuCl₂-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 (3S, 8R)-Ind 44 or the (4S)-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 (4R)-Ph 20 and (4R)-Bn 43 (Table 7.8, entries 3 and 4) with 73% ee being the lowest enantioselectivity obtained in this study, for the use of (4R)-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 enantioselectivity 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 (4R)-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.



R



R Figure 7.8

The absolute stereochemistry of the cyclopropane products was determined from a crystal structure obtained from a reaction employing CuCl₂-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 (1R,6S), 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**).



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-\beta-oxo sulfone* **61**



Entry	Catalyst	Time (h)	Crude (%) Purified Yield (%)	<i>cis</i> ^a 263a	trans ^a 263b	unknown ^a 264
1	Rh ₂ (OAc) ₄ (1 mol%)	24	Crude (%) ^b Purified Yield (%)	60% -	20% 43%	-
			% ee	-	6% ee ^c	
2	CuCl ₂ (5 mol%)	24	Crude (%) ^d Purified Yield (%) ^b	8%	72%	12%
	(3 <i>S</i> ,8 <i>R</i>)-Ind 44 (6 mol%)		% ee	-	10 (17 g	
	NaBARF		Fr 1e		12 (47% ee) ^{c,r}	
	(6 mol%)		Fr 2 ^g		20 (47% ee) ^{c,f}	
			Fr 3		7 (47% ee) ^{c,f}	
			<u>Total</u>		<u>39% (47% ee)</u>	

3	$CuCl_2$ (5 mol%)	24	Crude (%) ^h	4%	79%	12%
	(4 <i>R</i>)-Bn 43 (6 mol%)		Purified Yield(%) %ee			
	NaBARF		Fr 1 ⁱ	-	16% (44% ee) ^j	
			Fr 2	-	21% (41% ee) ^j	
			Total		<u>37% (42% ee)</u>	
4	CuCl ₂ (5 mol%)	48	Crude (%) ^k Purified Yield(%)	2%	78% 37% ¹	20%
	(4 <i>S</i>)- <i>t</i> -Bu 138 (6 mol%)		% ee	-	$53\% ee^{f}$	
	NaBARF (6 mol%)					
5	CuCl ₂ (5 mol%) (4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	21	Crude(%) Purified Yield(%)	36%	54% 32%	-
	(6 mol%)		% ее	-	38% ee ^f	
	(6 mol%)					
6	$CuCl_2$ (5 mol%)	21	Crude (%) Purified Yield (%)	26%	61% 40%	2%
	(4 <i>R</i>)-Ph 20 (6 mol%)		% ee	-	43% ee ^f	
	NaBARF					

(6 mol%)			

- a. Quantities of products in crude mixtures are calculated from the ¹H NMR spectra using the following signals; $\delta_{\rm H}$ 3.96–4.04 [1H, m, C(3)*H*] for *trans* sulfolane **263b** and $\delta_{\rm H}$ 4.91 (d, *J* 6.90) for *cis* sulfolane **263b**; $\delta_{\rm H}$ 6.16 (1H, d, *J* 2.6) for unknown **264**.
- b. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 9.67$ (s).
- c. HPLC trace not clean.
- d. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{H} 6.01$ (s), 6.19 (s).
- e. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_H 5.41-5.48$ (m), 5.50-5.11 (m), 6.18 (s). ~10%
- h. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H} 6.01$ (s), 6.19 (s).
- i. Contains impurity ~15%; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 5.49–5.51 (m), 5.52–5.75 (m), 6.19 (s)
- 1. Additional peaks observed in the ¹H 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 ¹H 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 $Rh_2(5S-MEPY)_4$ 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 Rh₂(5S-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.



Scheme 7.18

Work subsequently began on the asymmetric copper-bisoxazoline catalysed reactions of α -diazo- β -oxo sulfone **61**. Examination of the ¹H 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 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 (4R,5S)-di-Ph 137 and (4R)-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; (3S,8R)-Ind 44, (4R)-Bn 43 and (4*S*)-*t*-Bu 138, far smaller amounts of the *cis* isomer were observed in the ${}^{1}\text{H}$ 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 (4S)-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 (4R,5S)-di-Ph 137 was employed (Table 7.9, entry 5). The remaining

ligands (3S,8R)-Ind **44**, (4R)-Bn **43**, and (4R)-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 (3R,8S)-Ind **44** and (4R)-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 (4R)-Ph 20, (4R,5S)-di-Ph 137 and (4R)-Bn 43 ligands, are expected to lead to the opposite enantiomeric outcome to the use of (3S,8R)-Ind 44 and (4S)-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 (3S,8R)-Ind **44**, (4R)-Bn **43** and (4S)-*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 (4R,5S)-di-Ph **137** was used. It was also only present at 2% in the reaction employing (4R)-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 ¹H NMR spectrum. The presence of signals at $\delta_{\rm H}$ 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 $\delta_{\rm H}$ 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 [$\delta_{\rm H}$ 6.16 (1H, d, *J* 2.6), may also be two singlets $\delta_{\rm H}$ 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 CuCl₂-NaBARF-(4*R*)-Ph **20** and CuCl₂-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** 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



3	CuCl ₂	50		Crude ratio	53	47		
	(5 mol%)		43%	Purified yield (%)	48	52	98 ^d	90 ^d
	138 (6							
	mol%)							
	NaBARF							
	(6 mol%)							
4	CuCl2	18		Crude ratio	83	17		
	(5 mol%)	10			00	17		
	(AD 5S) = 1		39%	Purified yield (%)	85	15	37 ^e	57 ^e
	$(4\pi, 55)$ -di- Ph 137 (6							
	mol%)							
	NaBARE							
	(6 mol%)							
5	C ₂ C ¹	10		Course la sus d'a	00	10		
5	(5 mol%)	18		Crude ratio	90	10		
			40%	Purified Yield (%)	90	10	58 ^d	87 ^d
	(3S,8R)-							
	(6 mol%)							
	NDADE							
	(6 mol%)							
6	CuCl ₂	30		Crude ratio	60	40		
	(5 mol%)		2501	Durified Viold (07)	61	26	f	f
	(4 <i>R</i>)-Ph 20		23%	rui illeu xielu (%)	04	50	-	-
	(6 mol%)							
	NaBARF							

- 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 ¹H NMR spectra of the crude product using signals for OCH₃; δ_H 3.88 (3H, s, OCH₃) for *trans* sulfolane **270a**, and δ_H 3.90 (3H, s, OCH₃) for byproduct **271**.
- c. Several attempts were made to calculate the enantiopurity of *trans* sulfolane 270a. The use of a chiral shift reagent in ¹H 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 ¹H 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; $\delta_{\rm H} 2.33$ (3H, br s), 3.31-3.36 (2H, m), 3.91 (3H, s, OCH₃). 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 ¹H NMR shift reagent was also not possible due to the presence of byproduct 271 in the purified ¹H 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 CuCl₂ (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 adiazo- 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; (4R)-Ph 20, (4R,5S)-di-Ph 137, (4R)-Bn 43, (4S)-t-Bu 138 and (3S,8R)-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 (4S)-t-Bu 138 and (4R)-Ph 20 ligands, nearly equal amounts of both products were seen in the ¹H NMR spectra of the crude mixtures (Table 7.10, entries 3 and 6). The use of (4R,5S)-di-Ph 137 and (3S,8R)-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 (4R)-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 (¹H 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 (4S)-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 (4R)-Bn 43 and (3S,8R)-Ind 44 ligands are employed (Table 7.10, entries 2 and 5), with (4R,5S)-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 CuCl₂-NaBARF-bisoxazoline system, which had been developed for C–H insertion processes, can be generalised to enantioselective cyclopropanation.

7.4 Experimental

(1S,6R)-Methyl 2-thiabicyclo[4.1.0]heptane-1-carboxylate 2,2-dioxide 257a



The title compound was prepared according to the procedure described for (3S,4R) 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-OMe 2-one 208b using methyl 2-diazo-2-(pent-4-en-1-ylsulfonyl)acetate 59 0.43 mmol), CuCl₂ (2.8 mg, 21.2 µmol), sodium tetrakis[3,5-(100)mg, 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. ¹H 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 acetatehexane (10:90–20:80–30:70) as eluent, (1S,6R)-methyl 2-thiabicyclo[4.1.0]heptane-1carboxylate 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 ¹H NMR sample of the purified product indicated that the product had 67% ee; v_{max}/cm^{-1} (film): 2955 (CH), 1732 (CO), 1438, 1315, 1298, 1274, 1162, 1120 (SO₂); δ_H (CDCl₃, 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)H₂], 3.86 (3H, s, OCH₃); $\delta_{\rm C}$ (CDCl₃, 150.9 MHz): 19.6 [CH₂, C(4)H₂ or C(5)H₂], 20.1 [CH₂, C(7)H₂], 20.8 [CH₂, C(4)H₂ or C(5)H₂], 25.9 [CH, C(6)H], 45.3 [C, C(1)], 51.2 [CH₂, C(3)H₂], 53.5 (CH₃, OCH₃) 167.0 (C, CO); HRMS (ESI+): Exact mass calculated for C₈H₁₃O₄S [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 HSOC 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;



C(2')*H*₂], 5.69–5.85 [1H, sym m, C(1')*H*], δ_C (CDCl₃, 150.9 MHz): 26.5 [*C*(4)H₂], 43.2 [CH, *C*(3)H], 52.6, 53.5 [*C*(5)H₂ and OCH₃], 69.8 [CH, *C*(2)H], 118.1 [*C*(2')H₂], 135.5 [CH, *C*(1')H], 175.3 (CO).

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.

							Pro	oducts
E (Ţ	Time	Crude	Crude ratio ^a	<i>cis</i> thiopyran (cyclopropanation)	<i>trans</i> sulfolane (C–H insertion)
Entry	Method	Metai	L	(h)	(%) ^a	% ee ^a	257a	258b
					80–90	Crude ratio	90	10
1	В	CuCl ₂ /Δ	(4 <i>R</i>)-Ph 20	21		Purified yield (%)	70%	-
						% ee	67% ee (1 <i>S</i> ,6 <i>R</i>) (72% ee) ^b	
					80–90	Crude ratio	90	10
2	В	CuCl ₂ / Δ	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	21		Purified yield (%)	66%	-
						% ee	61% ee (1 <i>S</i> ,6 <i>R</i>)	-
3	В	$CuCl_2/\Delta$	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	21	80–90	Crude ratio	92	8

Table 7.11 *Copper and rhodium catalysed cyclopropanation reactions of* α *-diazo-\beta-oxo sulfone* **59**

						Purified yield (%)	59%	-
						% ee	68% ee (1 <i>R</i> ,6 <i>S</i>)	-
					80–90	Crude ratio	95	5
						Purified yield (%)	63%	-
4	В	$CuCl_2/\Delta$	(4 <i>R</i>)-Bn 43	21		% ee	38% ee (1S.6R)	
							$[\alpha]_{D}^{20} -13.0$	
							$(c \ 0.1, CH_2Cl_2)$	
					80–90	Crude ratio	98	2
-	D			40		Purified yield (%)	61%	-
5	В	$CuCl_2/\Delta$	(4 <i>S</i>)- <i>t</i> -Bu 138	48		% ee	61% ee (1 <i>R</i> ,6 <i>S</i>)	-
							$\begin{bmatrix} \alpha \end{bmatrix}_{D}^{20} +15.7 (c 0.1, \\ CH_2Cl_2) \end{bmatrix}$	
					80–90	Crude ratio	88	12
6	F	Rh ₂ (S-PTTL) ₄ 0 °C-rt	-	6		Purified yield (%)	67%	3%
						% ee	34% ee (1 <i>R</i> ,6S)	
		$Rh_2(S-DOSP)_4$			80–90	Crude ratio	82	18
7	G	0 °C-rt-Δ 24h, 24h	-	48		Purified yield (%)	58%	4%

						% ee	11% ee	
8	F	Rh ₂ (S-PTPA) ₄ 0 °C-rt	-	8	80–90	Crude ratio Purified yield (%)	83 67%	17 4%
9	G	$\frac{\text{Rh}_2(S-\text{MEPY})_4}{0 \text{ °C-rt- }\Delta}$	-	150	-	% ee -	8% ee (1R,6S)Starting material only recovered	-
10	F	Rh ₂ (<i>S</i> -mand) ₄ 0 °C-rt	-	21	80–90	Crude ratio Purified yield (%)	91 54% (contains ~10% <i>trans</i> sulfolane 258b)	9
11	В	CuCl ₂ /Δ ^c	CN-(4 <i>S</i>)-Ph 158	-	-	% ee	 ~12% ee^e (15,6K) Starting material only recovered 	-
12	В	CuCl ₂ / Δ^{c}	Py-(4 <i>R</i>)-Ph 159	-	-	-	Starting material only recovered	-
13	В	CuCl ₂ / Δ^{c}	Py-(4 <i>S</i>)- <i>i</i> -Pr 160		-	-	Mainly starting material ~10% cyclopropanation	-
14	Е	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 ¹H NMR spectra of the crude product using signals for *cis* thiopyran **257a**; $\delta_{\rm H}$ 1.64 (1H, dd, *J* 8.3, 6.4, one of methylene *CH*₂), 1.70 (1H, dd, *J* 9.6, 6.4, one of methylene *CH*₂) and signals for *trans* sulfolane **258b**; $\delta_{\rm H}$ 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 ¹H 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 ¹H 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.

[(1R,6S)-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 (3S,4R) 3-[(2-ethylphenyl)sulfonyl]-4-methyl-1-propylpyrrolidin-2-one **208b** using 2-diazo-2-(pent-4-en-1-ylsulfonyl)-1-phenylethanone **60**

(80)0.29 mmol), CuCl₂ (1.9 mg, 14.3 μ mol), sodium tetrakis[3,5mg, bis(trifluoromethyl)phenyl]borate (NaBARF) (15.2 mg, 17.2 µmol) and bisoxazoline ligand (3S,8R)-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. ¹H 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, [(1R,6S)-2,2dioxido-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; $\left[\alpha\right]_{D}^{20}$ +36.5 (*c* 0.1, CH₂Cl₂); 80% ee (determined by chiral-HPLC); mp 128–130 °C v_{max}/cm^{-1} (neat): 2950, 2927 (CH), 1677 (CO), 1598 (C=C), 1450, 1308, 1294, 1274, 1123, (SO₂), 766, 686, 658 (CS); δ_H (CDCl₃, 600 MHz): 1.57 [1H, dd, J 9.6, 6.4, one of C(7)H₂], 1.90 [1H, dd, J 8.4, 6.5, one of C(7)H₂], 1.93–2.02 [1H, m, one of C(4)H₂], 2.06–2.13 [1H, m, one of C(4)H₂], 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)H₂], 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 (CDCl₃, 150.9 MHz): 18.1 [CH₂, C(7)H₂], 18.2 [CH₂, C(4)H₂], 21.5 [CH₂, C(5)H₂], 22.1 [CH, C(6)H], 50.7 [C, C(1)], 53.0 [CH₂, C(3)H₂], 128.7 (2 × CH, aromatic CH_{meta}), 129.7 (2 × CH, aromatic CH_{ortho}), 134.0 (CH, aromatic CH_{para}), 136.1 (C, aromatic C), 190.8 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₃H₁₅O₃S [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) Å³, F(000) = 528, μ (Cu K α) = 2.340 mm⁻¹, R(F_o) = 0.032, for 1845 observed reflections with I > 2 σ (I), wR_2 (F²) = 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 K α radiation, $\lambda = 1.54178$ Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F² 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**. $\delta_{\rm H}$ (CDCl₃, 400 MHz): 1.97–2.08 [2H, m, C(2')H₂ or C(3')H₂], 2.20–2.31 [2H, m, C(2')H₂ or C(3')H₂], 3.27–3.39 [1H, m, one of C(1')H₂], 3.45–3.56 [1H, m, one of C(1')H₂], 5.05–5.16 [2H, m, C(5')H₂], 5.70–5.84 [1H, m, C(4')H], 6.02 (2H, s, SO₂CHXHCO), 7.50–7.58 (2H, m, ArH), 7.65–7.72 (1H, m, ArH), 7.98–8.05 (2H, m, ArH).

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), CuCl₂ (1.9 mg, 14.3 µmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (15.2 mg, 17.2 µmol) and bisoxazoline ligand (4R,5S)-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 v_{max}/cm^{-1} (neat, ATR): 2954 (CH), 1683 (CO), 1597 (C=C), 1449, 1312, 1273, 1122, (SO₂), 753 (CS); $\delta_{\rm H}$ (CDCl₃, 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*); $\delta_{\rm C}$ (CDCl₃, 150.9 MHz): 25.4 [CH₂, *C*(4)H₂], 41.9 [CH₂, *C*(3)H], 52.4 [CH₂, *C*(5)H₂], 69.7 [CH₂, *C*(2)H], 116.9 [CH₂, *C*(2')H₂], 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 C₁₃H₁₅O₃S [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.

Entry	Method	Method	L*	Time		Products			
				(h)	Crude (%) ^{a-d}	cis thiopyran ^a	trans	sulfolane ^c 131	Х–Н
						259a	sulfolane ^b		insertion ^d 261
					Purified yields (%) ^e		260b		
						Most polar	Mid p	olarity	Least polar
					% ee ^f		_		
1	В	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	22	Crude (%)	72%	4%	3%	5%
									0.6%
					Purified yield (%)	56 %	ہے	<u></u>	
							1	% ^g	
							50	50	
							50	:50	
					% ee	80% ee	_h		
						(1R 6S)			
						(111,00)			
2	В	CuCl ₂	(4 <i>R</i> ,5 <i>S</i>)-di-Ph	22	Crude (%)	84%	2%	0%	2%
			137						
					Purified yield (%)	45%	1%	-	
					% ee	73% ee	0% ee		
						(1S, 6R)			

Table 7.12 Copper and rhodium catalysed cyclopropanation reactions of α -diazo- β -oxo sulfone 60

						$\begin{bmatrix} \alpha \end{bmatrix}_{D}^{20} -101.7$ (c 0.12, CH ₂ Cl ₂)			
3	В	CuCl ₂	(4 <i>R</i>)-Ph 20	22	Crude (%) Purified yield (%)	70% 49%	2% 83	2% % ^g :17	1%
					% ее	75% ee (1 <i>S</i> ,6 <i>R</i>)	h		
4	В	CuCl ₂	(4 <i>R</i>)-Bn 43	22	Crude ⁱ (%) Purified yield (%) % ee	70% 52% 75%ee (1 <i>S</i> ,6 <i>R</i>)	1% 19 - ^h	2% ^{%gj}	3%
5	В	CuCl ₂	(4 <i>S</i>)- <i>t</i> -Bu 138	48	Crude (%)	83%	6%	0%	0%
					Purified yield (%)	58	2^k		
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					% ee	80% ee (1 R ,6 S) [α] $^{20}_{D}$ +133.3 (c 0.21, CH ₂ Cl ₂)	_h		
6	Е	Rh ₂ (OAc) ₄	-	22	Crude ¹ (%)	60%	6%	1%	2%
					Purified yield (%)	41 ^m	3 ⁿ		
					% ee	$3\% ee^{h}$	0%ee		

a. Relative ratios of reaction products calculated using ¹H NMR spectra of the crude product using signals for C(6)*H*; $\delta_{\rm H}$ 2.36–2.42 [1H, m, C(6)*H*] for *cis* thiopyran **259a**.

b. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for C(3)H; $\delta_H 3.70-3.78$ [1H, m, C(3)H] for *trans* sulfolane **260b**.

c. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for reduction product 131; $\delta_{\rm H}$ 4.57 (2H, s, SO₂CH₂CO).

d. Relative ratios of isomers calculated using ¹H NMR spectra of the crude product using signals for X–H insertion product **261** $\delta_{\rm H}$ 6.02 (2H, s, SO₂CHXCO).

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 ¹H 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 ¹H NMR spectra of the crude product; $\delta_H 6.53$ (s), 6.99 (s).
- j. Additional peaks present in the ¹H NMR spectra of the purified product; $\delta_{\rm H} 6.34-6.41$ (m), 7.02 (s), 9.69 (s).
- k. Impure fraction. Additional peaks present in the ¹H NMR spectra of the purified product; $\delta_{\rm H} 2.79-3.98$ (m), 4.03-4.29 (m).
- 1. Additional peaks present in the ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR spectra of the crude product; $\delta_H 3.51-3.79$ (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 ¹H NMR spectra of the purified product; $\delta_{\rm H}$ 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. ¹H 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); v_{max}/cm^{-1} (neat, ATR): 2958 (CH), 1724 (CO), 1439, 1309, 1291, 1119 (SO₂); $\delta_{\rm H}$ (CDCl₃, 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, OC*H*₃), $\delta_{\rm C}$ (CDCl₃, 150.9 MHz): 18.4 [CH₂, *C*(6)H₂], 19.9 [CH₂, *C*(4)H₂], 27.0 [CH, *C*(5)H], 43.9[C, *C*(1)], 46.1 [CH₂, *C*(3)H₂], 53.5 (CH₃, OCH₃) 166.4 (C, CO); HRMS (ESI+): Exact mass calculated for C₇H₁₁O₄S [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 ¹H NMR spectra, with the following characteristic signals; $\delta_{\rm H}$ (CDCl₃, 400 MHz) 2.33 (3H, br s), 3.31-3.36 (2H, m), 3.91 (3H, s, OCH₃).

Entry	Method	Metal	Ligand	Time (h)	Yield ^a (%)	Product Ratio ^b	sulfolane 270a	ВР ^ь 271	% ee Sulfol	ane 270a ^c
							U		ee (%) ^c (UV detector)	ee (%) ^c (LSD detector)
1	Ε	Rh ₂ (OAc) ₄	-	18	41%	Crude ratio ^d Purified ratio	95 96	5 4	0	8°
2	В	CuCl ₂	(4 <i>R</i>)-Bn 43	18	33%	Crude ratio Purified ratio	77 77	23 23	_1	71 ^f
3	В	CuCl ₂	(4 <i>S</i>)- <i>t</i> -Bu 138	50	43%	Crude ratio Purified ratio	53 48	47 52	98°	90 ^e

Table 7.13 Copper and rhodium catalysed cyclopropanation reactions of α -diazo- β -oxo sulfone 63

4	В	CuCl ₂	(4 <i>R</i> ,5S)-di- Ph 137	18	39%	Crude ratio Purified ratio	83 85	17 15	37 ^f	57 ^f
5	В	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)-Ind 44	18	40%	Crude ratio ^g Purified ratio	90 90	10 10	58°	87°
6	В	CuCl ₂	(4 <i>R</i>)-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 ¹H NMR spectra of the crude product using signals for OCH₃; δ_H 3.88 (3H, s, OCH₃) for sulfolane 270a, and δ_H 3.90 (3H, s, OCH₃) 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 ¹H NMR of the spectra of the crude product; $\delta_{\rm H}$ 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 ¹H NMR of the spectra of the crude product; $\delta_{H} 2.61-2.80$ (m), 3.15-3.20 (m), 3.37-3.45.
- h. Additional peaks present in the ¹H NMR of the spectra of the crude product; $\delta_H 3.15 3.25$ (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 ¹H NMR of the spectra of the purified product; $\delta_{\rm H}$ 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**. ¹H 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**; v_{max}/cm^{-1} (neat, ATR): 2927, 2854 (CH), 1684 (CO), 1597 (C=C), 1449, 1312, 1279, 1126 (SO₂), 749 (CS); δ_H (CDCl₃, 600 MHz): 1.66 (3H, d, J 1.3, one of CH₃), 1.74 (3H, d, J 1.3, one of CH₃), 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)H₂], 3.38 [1H, ddd, J 12.8, 7.0, 1.5, one of C(5)H₂], 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, ArH), 7.61–7.66 (1H, m, ArH), 8.06–8.11 (2H, m, ArH); δ_C (CDCl₃, 150.9 MHz): 18.3 (CH₃, one of CH₃), 25.8 (CH₃, one of CH₃), 27.6 [CH₂, C(4)H₂], 39.0 [CH₂, 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 $(CH, 2 \times \text{aromatic } CH)$, 129.0 (CH, 2 × aromatic CH), 134.5 (CH, aromatic CH), 136.6 [C, aromatic C or C(2')], 137.0 [C, aromatic C or C(2')], 189.5 (C, CO); HRMS (ESI+): Exact mass calculated for C₁₅H₁₉O₃S [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 ¹H NMR of the crude products: δ_H (CDCl₃, 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 ¹H 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 ¹H NMR of the crude products; $\delta_{\rm H}$ (CDCl₃, 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)].

•

Entry	Method	Metal	L	Time (b)		cis ^a	trans ^a	unknown ^a
1	Е	Rh ₂ (OAc) ₄	-	24	Crude ratio (%) ^b	60	20	-
					Purified yield (%)	-	43%	
					% ee	-	(6% ee) ^c	
2	В	CuCl ₂	(3 <i>S</i> ,8 <i>R</i>)-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	В	CuCl ₂	(4 <i>R</i>)-Bn 43	24	Crude ratio ^h	4	79	12
					Purified yield (%) % ee			

Table 7.14 Copper and rhodium catalysed C–H insertion reactions of α -diazo- β -oxo sulfone **61**

					Fr 1 ⁱ Fr 2 <u>Total</u>	-	16% (44% ee) ^j 21% (41% ee) ^j <u>37% (42% ee)</u>	
4	В	CuCl ₂	(4 <i>S</i>)- <i>t</i> -Bu 138	48	Crude ratio ^k	2	78	20
					Purified yield (%)	-	37% 1	
					% ee		53% ee ^f	
5	В	CuCl ₂	(4 <i>R</i> ,5 <i>S</i>)-di-Ph 137	21	Crude ratio	36	54	-
					Purified yield (%) % ee	-	32% 38% ee ^f	
6	В	CuCl ₂	(4 <i>R</i>)-Ph 20	21	Crude ratio	26	61	2
					Purified yield (%)	-	40%	
					% ee		43% ee ^f	

- a. Quantities of products in crude mixtures are calculated from the ¹H NMR spectra using the following signals; $\delta_{\rm H}$ 3.96–4.04 [1H, m, C(3)*H*] for *trans* sulfolane **263b** and $\delta_{\rm H}$ 4.91 (d, *J* 6.90) for *cis* sulfolane **263b** and $\delta_{\rm H}$ 6.16 (1H, d, *J* 2.6) for unknown **264**.
- b. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 9.67$ (s).
- c. HPLC trace not clean.
- d. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{H} 6.01$ (s), 6.19 (s).
- e. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 5.41-5.48$ (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 ¹H NMR spectra of the crude product; $\delta_{\rm H}$ 5.41–5.48 (m), 5.50–5.11 (m), 6.18 (s). ~10%
- h. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_{\rm H} 6.01$ (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 ¹H NMR spectra of the crude product; δ_{H} 5.49–5.51 (m), 5.52–5.75 (m), 6.19 (s)
- 1. Additional peaks observed in the ¹H NMR spectra of the crude product; $\delta_H 5.41-5.48$ (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/γ - 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.**). While

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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**.



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 CH₂ 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 ¹H NMR; Determination of enantiopurity Appendix ii-Absolute stereochemistry determination Appendix iii-Representative ¹H NMR spectra Appendix iv-¹H NMR spectra of byproducts Appendix vi-Publications

Appendix I Chiral HPLC and Chiral shift ¹H 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.
- 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.

Chapter 4

Compound	Condition Set	Column	λ (cm ⁻ 1)	Flow Rate (mL/min)	Mobile Phase IPA:Hexane	Retention Time (min)	When to use
				, , ,			
0	1	AS-H	210	1	20:80	(+)-(2S,3S) 15 (-) (2P,2P) 20	For pure <i>cis</i>
						(-)-(2R,3R) 20	thiopyran 26a
	2	OJ-H	210	1	10:90-30:70	(-)-(2 <i>R</i> ,3 <i>R</i>) 31	When OH
Ph						(+)-(2S,3S) 36	insertion
26a							product 148 is
	2		210	1	Gradiant	(-) (2P 3P) 68	When OH
	5	OJ-H	210	1	2·98-4·96-	(-)-(2K,3K) 08 (+)-(2S,3S) 83	insertion
					6:94-8:92-	(1) (20,50) 05	product 148 is
					10:90-30:70-		present in
					10:90-98:2		addition to
							other
							impurities
O O O O O O O O O O O O O O O O O O O	1	AS-H	210	1	10:90	Two peaks 22, 26	
R ^O	2	OJ-H	21	1	10:90-30:70	Two peaks, 111, 189	-
148	3	OJ-H	209	1	Gradient: 2:98-4:96-	Two peaks, 140, 320	1
					6:94-8:92-		
					10:90-30:70-		
1			1		10:90-98:2	1	

		Chapter 4 cont	inued		
Compound	Column	λMax	Mobile Phase	Retention Tin	ne
			(nexane : IPA)	Enantiomer	min
0,00 S Ph 22a	Chiralpak OJ-H	212	90 : 10	(+)-(2 <i>S</i> ,3 <i>S</i>)	36
O O O O O O O O O O O O O O O O O O O				(–)-(2 <i>R</i> ,3 <i>R</i>)	41
O O O S Ph Ph 24a	Chiralpak AS-H	210	5 : 95	(+)-(2 <i>S</i> ,3 <i>S</i>)	51
O O O S Ph 24a				(-)-(2 <i>R</i> ,3 <i>R</i>)	59

O O O S OMe MC ₂ H ₅ 30a	Chiralpak AS-H	210	90 : 10	(+)-(2S,3R)	22
$\begin{array}{c} 0 & 0 & 0 \\ & & \\$				(–)-(2 <i>R</i> ,3 <i>S</i>)	25
0,00 S OMe 	Lux [™] Cellulose-2	210	80 : 20	_a	30
O O O S OME C ₂ H ₅ 30b				_a	37
O O O SV OMe				(+)-(2 <i>S</i> ,3 <i>S</i>)	18
Ph 28a	Chiralpak AS-H	210	80:20		



O, O S M OMe F 145a	Chiralpak AS-H	210	80 : 20	(+)-(2 <i>S</i> ,3 <i>S</i>)	22
O, O S OMe F 145a				(–)-(2 <i>R</i> ,3 <i>S</i>)	42
Ph 42b	Chiralpak AS-H	210	80 : 20	(+)-(2 <i>R</i> ,3 <i>S</i>)	30
Ph 42b				(–)-(2 <i>S</i> ,3 <i>R</i>)	41
O O O S OEt	Chiralpak AS-H	210	95.5	(+)-(2 <i>R</i> ,3 <i>S</i>)	72



a. Absolute stereochemistry for this series is unknown, therefore the assignment of an enantiomer to a HPLC peak is not made.

			Chapter 5		
Compound	Column	λ Max	Mobile Phase (hexane : IPA)	Retentio	n Time
				Enantiomer	min
O O OEt				(-)-(2 <i>R</i> ,3 <i>R</i>)	29
165b					
	Chiralpak AS-H	209	80 : 20	(+)-(2 <i>S</i> ,3 <i>S</i>)	21
165b					
O S OEt				(2 <i>S</i> ,3 <i>R</i>)	38
165a					
O S OEt				(2 <i>R</i> ,3 <i>S</i>)	46
165a					

				(-)-(2R,3R)	66
166b	Chiralpak OJ-H	209	95 : 5		
	-			(+)-(2S,3S)	113
166b					10
				(-)-(2R,3R)	40
166b	Lux TM Cellulose-2	209	95 : 5		
	-			(+)-(2S,3S)	37
166b					
				(-)-(2 <i>R</i> ,3 <i>R</i>)	42
167b	Chiralpak AS-H	209	80 : 20		

0 0 0 0 Ph 167b				(+)-(2 <i>S</i> ,3 <i>S</i>)	26
о 550 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0		200	80 - 20	(–)-(2 <i>R</i> ,3 <i>R</i>)	28
о	Спітаїрак АЗ-н	209	80:20	(+)-(2 <i>S</i> ,3 <i>S</i>)	20

Chapter 6									
Compound	Column	Flow mL/min	λ Max (min)	Mobile Phase (hexane : IPA)	Retention Time				
		,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	(1111)		Enantiomer	min			
			210	00.10	(-)-(3 <i>R</i> ,4 <i>S</i>)	40 (22)			
	Lux ^{1M} Cellulose- 4	1	210	90 : 10 (80 : 20)	(+)-(3 <i>S</i> ,4 <i>R</i>)	73 (45)			
	Lux [™] Cellulose-4	1	210	90 : 10 (80 : 20)	_a	23-25 (10)			
					_a	26-28 (12)			







Ph S ^{''''''} N 219	Chiralpak AS-H	1	210	80 : 20	_a	15
Ph S N 219					_a	23
$Ph \underbrace{O O O}_{S'_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_{i_$	Lux TM Cellulose-4	1	210	90 : 10	(+) ^a	40-55
Ph N Ph					(-) ^a	66-85
226b 0 0 0 Ph S 0 227					-	~34
0,00 S ¹ / ₁ / ₁ / ₁ / ₁ 224a	Chiralpak AS-H	1	210	90 : 10	(+)-(2 <i>S</i> ,3 <i>S</i>)	43
					(-)-(2R,3R)	39
-------	-------------------------------	---	-----	---------	------------------	----
Ph V						
N N					(+) ^a	33
Ph 0	Lux TM Cellulose-4	1	210	70:30		
	-					
S N					(-) ^a	44
Ph \O						
231b						
	Lux TM Cellulose-4	1	210	70 : 30	_a	53
Ph 0						
231a						
					_a	39
233b						



a. Absolute stereochemistry for this series is unknown, therefore the assignment of an enantiomer to a HPLC peak is not made.

Chapter 7					
Compound	Column	λ Max (min)	Mobile Phase	Retention Time	
			(hexane : IPA)	Enantiomer	min





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 ¹H 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 CDCl₃. 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 1¹H NMR spectra recorded in (CDCl₃, 400 MHz)



Figure 2¹H NMR spectra recorded in (CDCl₃, 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 (2S,3S). This crystal was subsequently dissolved in IPA and HPLC analysis was conducted. This confirmed that the (2S,3S) 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-(4R)-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}



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-(4R)-Ph **20** catalyst system. As this is consistent with results obtained by Flynn, the absolute stereochemistry of each of these was assigned as (2S,3S).



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}



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.



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.



Figure 7

As cyclisation of α -diazo- β -oxo sulfone **54** using CuCl₂-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**).





The absolute stereochemistry of the remaining *trans* sulfolanes **166b** and **167b** were assigned by analogy on the basis of optical rotations **Figure 9**.



7 : 93 *cis* : *trans*, 13 % ee *trans* $[\alpha]_{D}^{20}$ +16.0 (*c*, 0.1 CH₂Cl₂).

Figure 9

Chapter 6

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 γ -lactam **211b** and **208b**; employing (3*R*,8*S*)-Ind **161** results in γ -lactam **211b** having a negative specific rotation [α] $_{D}^{20}$ –9.5 (*c* 0.11, CHCl₃, 66% ee) and using (3*S*,8*R*)-Ind **44** leads to γ -lactam **208b** having a positive specific rotation [α] $_{D}^{20}$ +41.11 (*c* 0.09, CH₂Cl₂, 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**).







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 CuCl₂-NaBARF-(3*S*,8*R*)-Ind **44** as catalyst yielded **259a** with 80% ee (**Figure 12**).



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 (1R,6S), 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 (3S,8R)-Ind **44** as a ligand, was determined to be (1R,6S) and the rotation of this sample was positive [α] $_{D}^{20}$ +36.5 (*c* 0.1, CH₂Cl₂) (**Figure 14**). In comparison with the methyl ester series **257a**, a positive rotation was also obtained when (4S)-*t*-Bu **138** was employed as a ligand and a negative rotation was obtained through use of (4R)-Bn **43**.







259a

Determined using X-ray crystallography

 $[\alpha]_{D}^{20}$ +36.5 (*c* 0.1, CH₂Cl₂).



59





257a

$$[\alpha]_{\rm D}^{20}$$
 +15.7 (*c* 0.15, CH₂Cl₂).



59





257a

 $[\alpha]_{D}^{20}$ -13.0 (*c* 0.1, CH₂Cl₂).



Appendix iii *Representative* ¹*H NMR spectra*

Throughout the course of this work, a number of heterocycles and carbocycles were synthesised. These included, *cis* thiopyrans, *trans* sulfolanes, γ -lactams, β -lactams and cyclopropanes. The majority of these compounds were novel and were fully characterised. The ¹H NMR spectra of a selection of these compounds is given in this Appendix.

trans sulfolanes



Figure 15 ¹*H NMR spectrum of* **236b** *recorded in* (*CDCl*₃, 600 *MHz*)



Figure 16¹H NMR spectrum of 218b recorded in (CDCl₃, 600 MHz)



cis thiopyrans



Figure 18¹H NMR spectrum of 224a recorded in (CDCl₃, 600 MHz)



Figure 19¹H NMR spectrum of 220a recorded in (CDCl₃, 600 MHz)

y-lactams



Figure 20¹H NMR spectrum of 208b recorded in (CDCl₃, 600 MHz)



Figure 21¹H NMR spectrum of 219 recorded in (CDCl₃, 600 MHz)

β-lactams



Figure 22 ¹H NMR spectrum of 226b recorded in (CDCl₃, 600 MHz)



Figure 23¹H NMR spectrum of 257a recorded in (CDCl₃, 400 MHz)

Fused sulfolanes



Figure 24 ¹H NMR spectrum of 233b recorded in (CDCl₃, 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 ¹H 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 ¹H 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 ¹H 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 CuCl₂-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**.



Figure 25 Two dimensional NMR (COSY) of unidentified byproduct 148 (CDCl₃,500 MHz)

Chapter 6

In the CuCl₂-NaBARF-bisoxazoline and Rh₂(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 ¹H NMR spectra of the majority of the crude product mixtures. Herein, the ¹H NMR spectra of the crude product mixture of these cyclisations are presented.



CuCl₂-NaBARF- (3S,8R)-Ind 44, adventitious EtOH in DCM^a



Figure 26 ¹*H NMR spectra (CDCl₃, 400 MHz), (a of crude product, b of purified product)*



Figure 27 (*CDCl*₃, 400 *MHz*)

Chapter 7

In the CuCl₂-NaBARF-bisoxazoline and Rh₂(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 (CDCl₃, 400 MHz)

In the CuCl₂-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**.





Figure 29¹H NMR spectra (CDCl₃, 400 MHz)

Appendix V *Abbreviations*

Abbreviations	
<i>p</i> -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
DBU	1 8-diazabicycloundec-7-ene
DCC	N N'-dicyclohexylcarbodijmide
DCE	dichloroethane
DEPT	distortionless enhancement of polarisation transfer
	enantiomeric excess
equiv or eq	equivalents
Ether	diethyl ether
Etter FtOH	ethanol
EtOII Eu(hfe)	tris [2 Hantafluoronrony] hydroxymathylana (1) comphorato]
Eu(mc)	europium(III) derivative
F r	fraction
11 2	gram
g	bour
II UETCOD	Hoteronuclear chemical chift correlation
	Heteronuclear chemical sinit correlation
HMBC	Heleronuclear multiple-bond correlation spectroscopy
HKMS	High resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
HZ	
	isopropyl alconol
<i>l</i> -Pr	Isopropyl
	Infrared
Lit.	Interature
m	mutiplet
min	minute
mand	mandelate
меон	Methanol
Mg	Milligram
MHZ	Megahertz
ml	millitre
mmol	millimole
mol	Mole
m.p.	Melting point
NaBARF	sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate
<i>p</i> -NBSA	para nitrobenzenesulfonylazide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect Spectroscopy
UAc	Acetate
ptb	perfluorobutyrate
Ph	phenyl
q	quartet

r.t.	room temperature		
S	singlet		
sym	symmetrical		
t	triplet		
Т	Time		
<i>t</i> -Bu	<i>tert</i> -butyl		
THF	tetrahydrofuran		
TLC	thin layer chromatography		
TMS	tetramethylsilane		
Oct	octyl		
Rh ₂ (acam) ₄	rhodium acetamide		
$Rh_2(S-BSP)_4$	rhodium N-benzenesulfonylprolinate		
$Rh_2(4S,2'S$ -BSPIM) ₄	rhodium N-benzenesulfonylprolinoylimidazolidinone		
$Rh_2(cap)_4$	rhodium caprolactam		
Rh ₂ (S-DOSP) ₄	rhodium N-dodecylbenzenesulfonylprolinate		
Rh ₂ (OAc) ₄	rhodium acetate		
Rh ₂ (Ooct) ₄	rhodium octanoate		
$Rh_2(pfb)_4$	rhodium perfluorobutyrate		
$Rh_2(4S-MACIM)_4$	rhodium methylesteracetylimidazolidinone		
$Rh_2(S-mand)_4$	rhodium mandelate		
$Rh_2(4S,2'S,3'S-MCPIM)_4$	rhodium methylestercyclopropylimidazolidinone		
Rh ₂ (S-MEOX) ₄	rhodium methylesteroxazolidinone		
Rh ₂ (S-MEPY) ₄	rhodium methylesterpyrrolidinone		
Rh ₂ (S-MPPIM) ₄	rhodium methylesterphenylpropanoylimidazolidinone		
$Rh_2(S-PTPA)_4$	rhodium phthaloylphenylalanine		
$Rh_2(S-PTTL)_4$	rhodium phthaloyl-t-leucine		
Rh ₂ (S-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.*

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- Ring, A. PhD Thesis, National University of Ireland, Cork, thesis in progress, 2015.