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Asymmetric Transformations of Enolates and Azaenolates



Emma Alcock, B.Sc.

A thesis presented for the degree of
Doctor of Philosophy
to
National University of Ireland, Cork

School of Chemistry
University College Cork

Supervisor: Dr Gerard McGlacken
Head of School: Prof Anita Maguire

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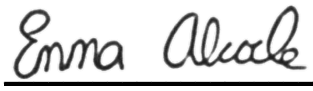
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Declaration

This is to certify that the work I am submitting is my own work and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly identified and acknowledged within the contents. I have read and understood the regulations of University College Cork regarding plagiarism and intellectual property.



Emma Alcock

27th April 2023

Date

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tough. I hope we'll remain firm friends long after the scars of PhD research have faded! To Amy, thank you for always seeing the funny side, especially in the things I couldn't! Mark - thank you for always saying exactly the wrong thing at exactly the right time, being a great friend over the years and for the many times we laughed until I cried! To Eimear - thank you for your IT expertise, being such a generous friend, the 'notions' chats and all the delicious treats. Most importantly, thank you for saving my lab books from the burning building... unlike two others I could mention! To Aidan - the honorary/wannabe GMG - thank you for always enthusiastically celebrating even the rubbish results with me and for the many terrible jokes - I promise I always laughed with you and never at you! Davy - thank you for all the ideas and help, and for getting me started in the world of research. For that I'm not sure yet whether to thank you or blame you! To everyone else who came after - Robyn, Dave Ryan, Conor, Si Lok, MC, Ella, Muireann and Emma F - I wish you all every success in your chemistry careers! It has been a privilege to share my time as a PhD student with many people on the 4th floor of the Kane Building and 2nd floor of the Pharmacy Building – thank you to all of you for listening to me give out on the worst of days and laughing with me on the best of days! To Dr Nuala Maguire, thank you for all the coffee, cake, chats and for all your help with the HPLC! To Louise, Lil, Kevin, Conor and Ryan - it was great sharing this whole experience with you all, you really are a great bunch! Special thanks to Thomas, Aaron, Dan, Aoife K, Michelle, Orla and Dara for making this PhD an enjoyable and memorable experience - it was great getting to know you all and I hope we'll be friends for years to come! To my cellmate, Edel, thank you for everything - the shenanigans, the chats, the endless laughs, and occasional tears, all of which I'm sure contributed to an extended final year for both of us. Your friendship is one of the most valuable results from this PhD!

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"If I have seen further, it is by standing on the shoulders of giants" - Isaac Newton

Dedication

I dedicate this thesis to the memory of those who inspired it -

Nan and Thomas.

Abstract

Chapter I - The asymmetric α-alkylation of a ketone represents one of the most fundamental reactions in organic chemistry. In 2014, a chiral ligand strategy to furnish enantioenriched α-alkylated ketones was published by the McGlacken group. The yields and enantioselectivities achieved for this transformation were modest. The first section of this thesis outlines efforts to further expand the scope of this methodology and improve the enantioselectivity of this chiral ligand protocol. Whilst a 10% *ee* was observed for the direct α-alkylation of a ketone, future optimisations focused on the use of *N*,*N*-dimethylhydrazones as ketone surrogates. A number of previously unexplored solvents, chiral ligands, hydrazones and electrophiles were examined. However, attempts to improve the enantioselectivity proved unsuccessful. The latter section of this chapter details a number of asymmetric transformations with 2-alkyl pyridines (azaenolate equivalents). Investigations were undertaken to develop new asymmetric aldol and Michael-type reactions for these substrates using chiral amines. Modest enantio- and diastereoselectivities were observed for the aldol reaction.

Chapter II - Outlines efforts to develop a continuous flow chemistry protocol for the α-alkylation of a range of simple ketone substrates. Extensive optimisation studies are detailed within this chapter. Continuous flow chemistry proved to be a superior alternative to traditional batch chemistry for this transformation. Advantages of the continuous approach include: **i)** significantly higher yields; **ii)** reduced reaction times; **iii)** increased product purity; **iv)** more scalable reaction temperatures and **v)** an increased safety profile associated with the use of hazardous alkyl lithium and alkylating agents.

Chapter III - Describes methodology for the synthesis of 3-amino-1,5-diol derivatives with concurrent introduction of up to five contiguous chiral centres in one-pot. Highly functionalised amino alcohol derivatives of challenging substrates such as butanone, 3-pentanone and cyclobutanone were synthesised *via* an aldol, aldol-Tishchenko reaction of (*S*)-*tert*-butanesulfinyl imine derivatives. Modest yields (up to 55%) and excellent diastereoselectivites (up to > 99:1) were achieved for this transformation. The synthetic utility of the compounds synthesised was examined by selective cleavage of the ester and sulfinyl moiety. Finally, the absolute stereochemistry of the major diastereomer was elucidated by X-ray crystallography and mechanistic insight is provided using DFT calculations, through collaboration with Prof Ken Houk.

Preface

This thesis contains work which has been published after peer-review, or which is in preparation. Publications arising from this thesis are provided in Appendix I.

Table of Abbreviations

$[\alpha]_D^T$	Specific rotation
^{13}C NMR	Carbon nuclear magnetic resonance
^{19}F NMR	Fluorine nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
Å	Angstrom
Ac	Acetyl
ACC	Amino cyclic carbamate
AcOH	Acetic acid
aq	Aqueous
BINAP	2,2'-Bis-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
Bn	Benzyl
BnBr	Benzyl bromide
Boc	Tert-butylc
BOX	Bisoxazoline
BPR	Back pressure regulator
bpy	2,2’-bypyridine
br s	Broad singlet
Bu	Butyl
BuLi	Butyl lithium
c	Concentration (for optical rotation)
	Centi (10^{-2})
°C	Degrees Celsius
ca	Circa, approximately
Calcd.	Calculated
cat.	Catalytic
CIS-D	Complex induced *syn*-deprotonation
COSY	Correlation spectroscopy
COD	1,5-Cyclooctadiene
Cy	Cyclohexyl
d	Doublet
DCM	Dichloromethane
Dd	Doublet of doublets
ddd	Doublet of doublet of doublets
DiPAMP	(*R*,*R*)-1,2-Bis[(2methoxyphenyl)(phenylphosphino)]ethane

DME	Dimethoxyethane
Deg	degree
DEPT	Distortionless enhancement by polarisation transfer
DFT	Density Functional Theory
DIBAL-H	Diisobutylaluminium hydride
DIPA	Diisopropylamine
DMH	Dimethylhydrazone
DMBQ	2,6-Dimethylbenzoquinone
e.g.	For example
dq	Doublet of quartets
dr	Diastereomeric ratio
dt	Doublet of triplets
E	Electrophile
EDG	Electron donating group
ee	Enantiomeric excess
Equiv.	Equivalents
er	Enantiomeric ratio
Et	Ethyl
EWG	Electron withdrawing group
g	Gram (s)
GC	Gas chromatography
h	Hour(s)
HIV	Human immunodeficiency virus
HCLA	Homo chiral lithium amide
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
Hz	Hertz
i	iso
i.e.	That is
IR	Infrared spectroscopy
J	Coupling constant
k	Rate
K	Kelvin
L	Litre

LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
Lit.	Literature
LRMS	Low resolution mass spectrometry
m	Meter
	Milli (10^{-3})
	Multiplet
	medium
M	Molarity
m/z	Mass-to-charge ratio
Max	Maximum
Me	Methyl
MFC	Mass flow contoller
mg	Milligram
MHz	Megahertz
Min	Minute(s)
mL	Millilitre
mmol	Millimole
mol%	Mole percent
Mp	Melting Point
MS	Mass Spectrometry
n.d.	not determined
NMR	Nuclear magnetic resonance
o	Ortho
o/n	Overnight
p	Para
Ph	Phenyl
PhD	Doctorate of Philosophy
PMB	4-methoxybenzyl
PPh_3	Triphenylphosphine
ppm	Parts per million
Pr	Propyl
Prof	Professor
p-TsOH	*p*-toluenesulfonic acid
q	Quartet
quin	Quintet

R	Rectus configuration
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
R_f	Retention factor
rt	Room temperature
s	Singlet
	Strong
S	Sinister configuration
SS	Steady state
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
sat.	Saturated
sept.	Septet
sext.	Sextet
SM	Starting material
sp	Sparteine
t	Triplet
t	Tert, Tertiary
T	Temperature
td	Triplet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
	Trimethylsilyl
t_R	Retention time
Ts	4-Toluenesulfonyl, tosyl
UV	Ultraviolet
α	Stereochemical descriptor
δ	Chemical shift
ν	Frequency of max absorption

I

Towards the Asymmetric α-Alkylation of Ketones and Related Nitrogen Analogues

“I haven’t failed, I have just found 10,000 ways that do not work”

Thomas Edison

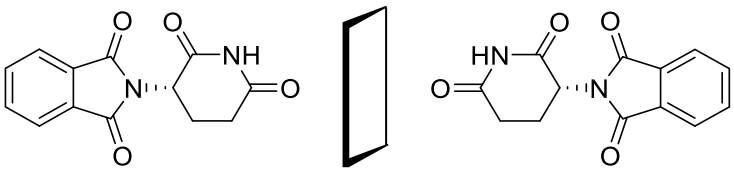
1 Introduction

1.1 Chirality

Chirality is an intriguing facet of nature. An object is described as chiral if it cannot be superimposed on its mirror image. Enantiomers, a term used by Pasteur to describe the two forms of a chiral molecule, exhibit identical chemical and physical properties in achiral environments. Although enantiomers have the same atomic connectivity, differing only in spatial arrangement, this difference can lead to dramatic consequences in chiral environments.

Biological systems represent one of the most important chiral environments, demonstrating selectivity in terms of chirality. Most naturally occurring molecules, amino acids and proteins, for example, exist predominantly as single enantiomers.

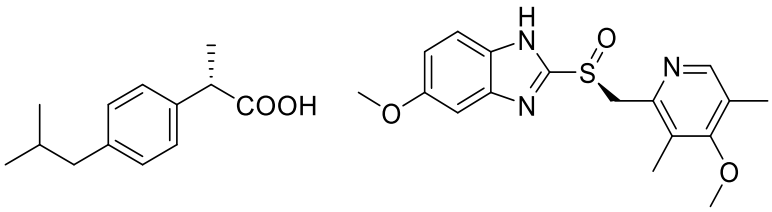
The importance of chirality, or stereochemistry, within drug design became fully understood in the 20th century. The pharmacological impact of drug molecules is significantly impacted by the stereochemistry of that compound. Probably the most infamous example of the effect of the stereochemistry of a compound was the therapeutic agent Thalidomide **(Figure 1.1)**. This drug was administered to alleviate the symptoms of morning sickness experienced by pregnant women. Marketed as a racemate, it was later discovered that the (*S*)-enantiomer behaved as a potent teratogen, while the (*R*)-enantiomer elicited the desired therapeutic effect.[1]



(*S*)-Thalidomide (*R*)-Thalidomide

Figure 1.1 Thalidomide

Consequently, strict regulations are in place regarding the marketing of active pharmaceutical agents (APIs) as racemates within the pharmaceutical industry. Many drugs, initially sold as a racemate, are now marketed as single enantiomers (**Figure 1.2**), in a strategy known as 'chiral switching'.[2] Chiral switching is a term used to describe the formulation of single enantiomer drugs from those previously synthesised and marketed as racemates. The well-known non-steroidal anti-inflammatory drug (NSAID) ibuprofen was the first in class to undergo this change.[3] It was found the (*S*)-enantiomer was 100 times more potent as an NSAID than the corresponding (*R*)-enantiomer.[4]



(*S*)-Ibuprofen (*S*)-Esomeprazole

Figure 1.2. APIs marketed in enantiopure form

As well as increased potency, an additional advantage of chiral switching is an increased safety profile, due to the reduced propensity for drug-drug interactions. This strategy can also be used within the pharmaceutical sector to extend a patent. This was the case for Omeprazole. Initially Omeprazole was marketed as a racemate for the treatment of gastric disorders. However, in 2000 AstraZeneca began to market only the single enantiomer drug (*S*)-esomeprazole.[5] Although it offered little clinical advantage to the racemic formulation, it prevented any generic competitors from selling the drug.

With an ever-increasing demand for enantiopure compounds, especially within the pharmaceutical sector, the importance of novel methodology to synthesise these compounds is paramount.[6]

1.2 Methods for accessing enantiomerically pure compounds

To achieve a stereoselective synthesis, at least one component of the reaction must be chiral. With an element of chirality present, stereoselectivity may be induced in a reaction, resulting in the synthesis of enantio- or diastereomerically enriched compounds. Traditionally used methods to achieve enantiomerically pure compounds include the chiral pool approach and chiral resolution. The most sophisticated and sought-after method for synthesising compounds enantioselectively is undoubtedly using an asymmetric synthesis **(Figure 1.3)**.

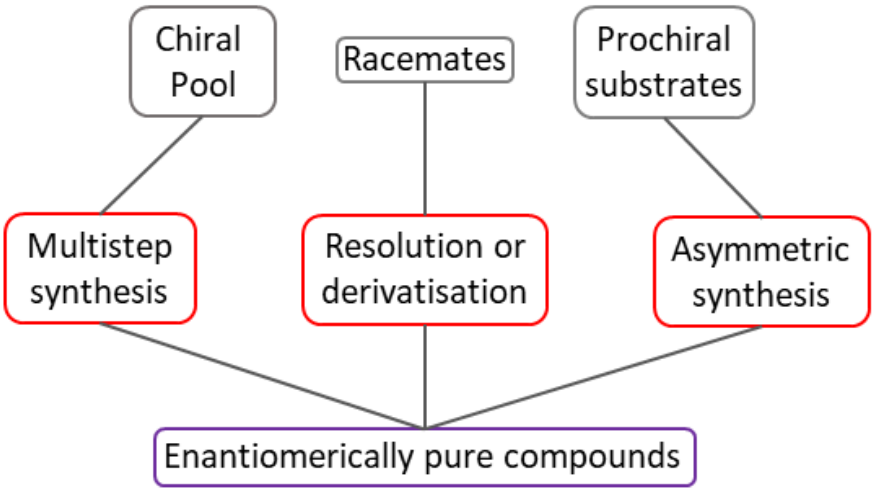


Figure 1.3. Methods to furnish enantiopure compounds

The chiral pool approach seeks to utilise the chirality ubiquitous in nature, using naturally occurring chiral molecules as precursors in the synthesis of more complex chiral compounds. Examples of these precursors include amino acids, carbohydrates and alkaloids. These readily available compounds, which occur naturally as single enantiomers, can then be coupled with a range of achiral molecules through a successive reaction sequence to obtain the desired chiral compound.[7]

Within the pharmaceutical sector, the most widely used method to synthesise enantiopure compounds is through the resolution of racemates.[8] Resolution of a racemate can be divided into four categories: kinetic resolution, dynamic kinetic resolution, crystallisation and chromatography. Kinetic resolution relies on differing reaction rates of enantiomers with a chiral reagent or catalyst, for example, an enzyme. One enantiomer is readily transformed to product, whereas the second reacts at a slower rate or not at all, ultimately leading to an enantiomeric excess. One major disadvantage however, is the maximum theoretical yield of the desired product is 50%.[9] A dynamic kinetic resolution (DKR) involves the rapid racemisation of the unreactive isomer to the reactive isomer and subsequent reaction of this isomer with the chiral reagent. For this to be possible, the rate of racemisation must be greater than the rate of reaction of the undesired isomer with the chiral reagent. Theoretically, this allows for complete consumption and conversion of both isomers.[10]

Both crystallisation and chromatographic methods require the formation of diastereomers through interaction with a chiral derivatising agent. The first reported example of diastereomeric separation by crystallographic methods is the separation of tartaric acid by Louis Pasteur.[11]

Undoubtedly, the optimum method for furnishing chiral compounds is by means of asymmetric synthesis, although these methods can be difficult to establish. Methods for the conversion of a prochiral precursor to a chiral product use a variety of strategies including chiral auxiliaries, chiral ligands and chiral catalysts. Such methods offer efficient pathways to accessing chiral compounds but are oftentimes negated by the cost of chiral reagents.

An asymmetric synthesis can be divided into two categories: enantioselective reactions and diastereoselective reactions. In an enantioselective reaction, a chiral reagent or catalyst can differentiate between the enantiotopic groups or faces of a chiral molecule, preferentially forming one enantiomer **(Figure 1.4)**.

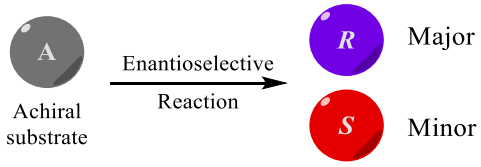


Figure 1.4. Enantioselective synthesis

A diastereoselective reaction, used to produce an enantiomeric product, typically requires four steps and the use of a chiral auxiliary: **i)** addition of the chiral auxiliary to a prochiral precursor; **ii)** reaction of the chiral compound to form diastereoisomers; **iii)** separation of the resulting diastereomers, if required and **iv)** removal of the auxiliary **(Figure 1.5)**. Similar to a protecting group strategy, this approach requires the use of two additional steps and limits the overall atom-economy of a synthetic route. In some incidences, these limitations can be overcome if a protocol for recycling the chiral auxiliary can be established.

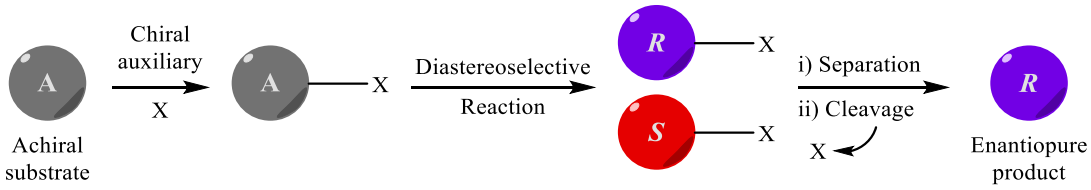
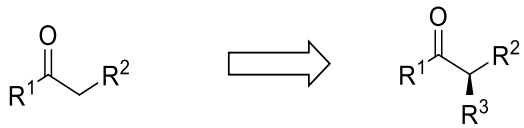


Figure 1.5. Diastereoselective synthesis

1.3 Asymmetric α-alkylation of ketones

The formation of a new carbon-carbon bond alpha (α) to a carbonyl group is one of the most fundamental transformations in organic chemistry. Of particular importance is the α-alkylation of ketones. This transformation often leads to the formation of a new stereogenic centre. Enantiomerically enriched α-alkylated ketones are important scaffolds in natural product synthesis **(Figure 1.6)**.[12-15] A large number of optically active drugs contain α-functionalised ketones, or simple derivatives thereof.[16] Although frequently regarded as a facile reaction, a

widely applicable direct method for the asymmetric α-alkylation of ketones remains an insurmountable challenge for organic chemists.[17]



>10^5 commercially available substrates **Valuable motif**

Figure 1.6. Asymmetric α-alkylation of a ketone

The obvious choice for the α-alkylation of ketones is through electrophilic addition to ketone enolates. However, this approach is fraught with numerous reactivity issues inherent to ketone enolates. The propensity of these nucleophilic species to undergo over-alkylation, self-condensation type and other side reactions often renders this approach ineffective **(Figure 1.7)**.

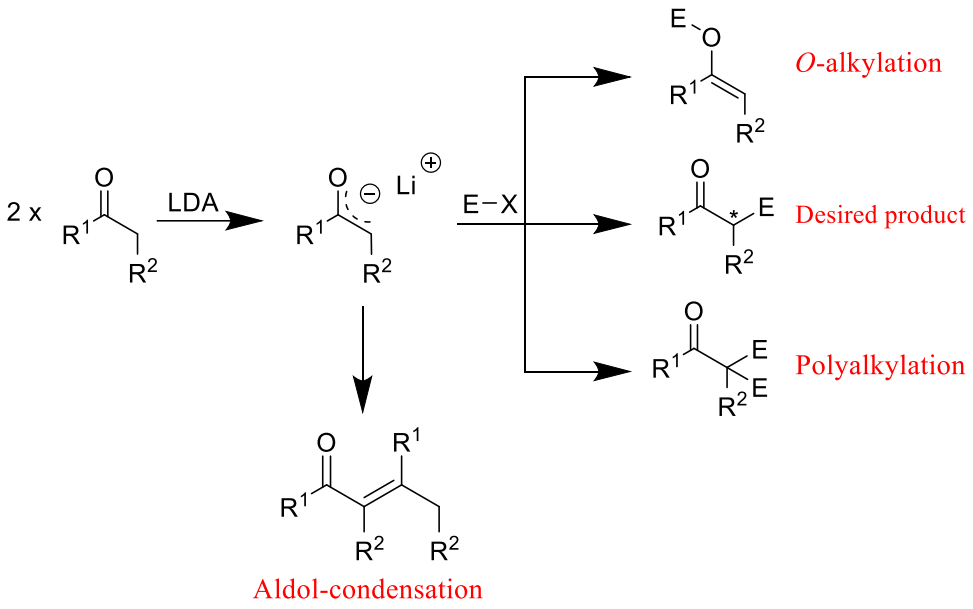


Figure 1.7. Inherent reactivity issues of ketone enolates

Additionally, the geometry around the C=C bond of the ketone enolate and the facial approach of the electrophile must be carefully considered, as both have an impact on the stereochemical outcome of this transformation **(Figure 1.8).**[18] The alkylation of non-symmetric ketones, which possess two possible sites for deprotonation, adds further complexity. To date, many indirect methods for the asymmetric α-alkylation of ketones have been developed. However, a direct method still remains elusive.[17]

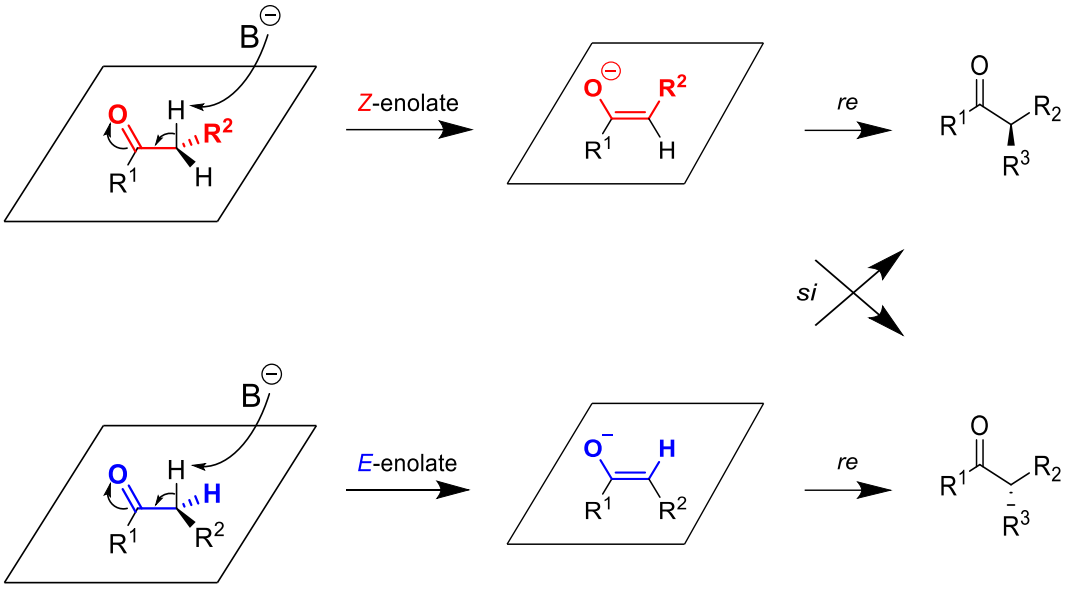
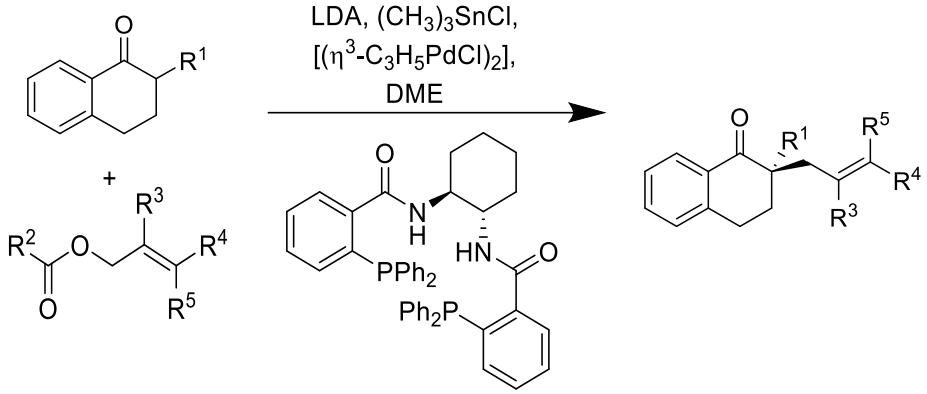


Figure 1.8. Stereochemical outcome of asymmetric α-alkylation of ketones

1.4 Methodologies for the asymmetric α-alkylation of ketones

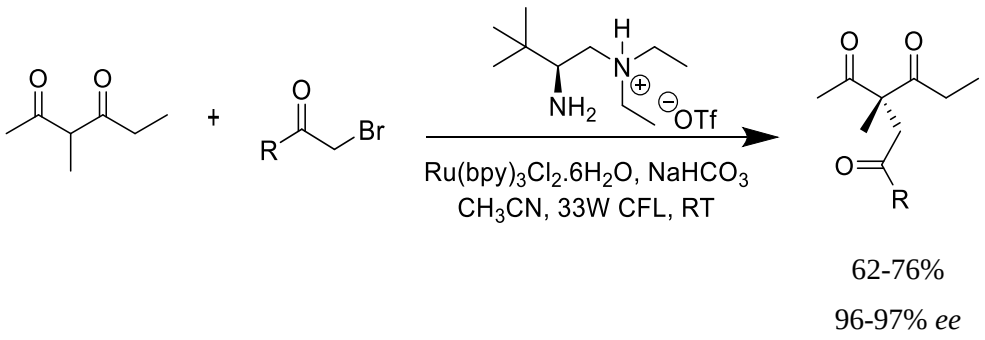
Although no direct method exists for the general asymmetric α-alkylation of ketones, catalytic and photochemical methods have had limited success in the area. Trost *et al*. reported one of the first intermolecular palladium-catalysed asymmetric α-allylation reactions of prochiral ketones **(Scheme 1.2)**.[19] The combined action of a Pd complex and a chiral ligand allowed access to chiral α-allylated ketones. However, the scope of this reaction was narrow, including only six membered rings and 1-tetralones.



Scheme 1.2. Pd catalysed asymmetric alkylation

The emerging area of photocatalysis has also proven successful for asymmetric α-alkylation reactions. Through combination of photocatalyst and a chiral primary amine, Zhu *et al*.[20] reported the photo-α-alkylation of β-ketocarbonyls. This strategy has allowed for the

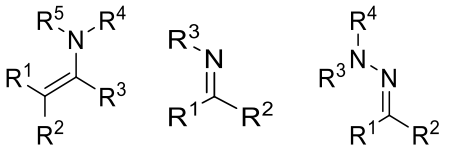
formation of compounds with all-carbon stereocentres, in good yield and excellent enantioselectivity **(Scheme 1.3)**.



Scheme 1.3. α-Photoalkylation of β-ketocarbonyls

1.5 Nitrogen analogues of carbonyl compounds

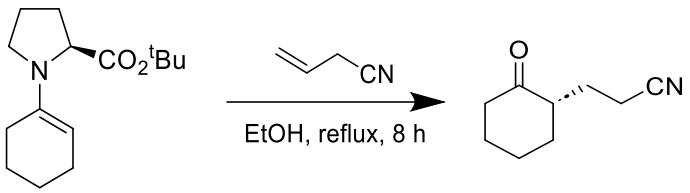
Oftentimes, in order to obviate the reactivity issues associated with highly energetic ketone enolates, nitrogen-containing analogues such as enamines, imines and hydrazones are used as synthetic equivalents to carbonyl compounds **(Figure 1.9)**.[21] The asymmetric α-alkylation of aldehydes and ketones *via* their corresponding azaenolates has proven to be the most effective route in terms of reactivity, selectivity and yield. This is most commonly achieved through the use of nitrogen based chiral auxiliaries.



Enamines *Imines* *Hydrazones*

Figure 1.9. Examples of nitrogen-containing ketone analogues

The use of chiral auxiliaries to achieve asymmetric transformations represents one of the major advancements in asymmetric synthesis.[22-23] One of the first asymmetric α-alkylation of carbonyl compounds was based on enamine chemistry, reported by Yamada *et al.* in 1969.[24] Using an L-proline derived enamine and Michael acceptors acrylonitrile or methyl acrylate, α-alkylated cyclohexanones were obtained in moderate yields and enantioselectivities **(Scheme 1.4)**.



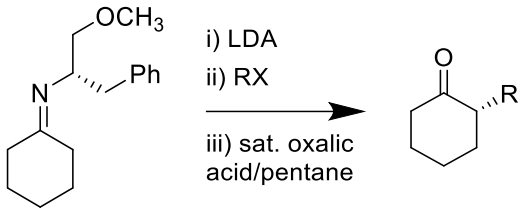
55%

43% *ee*

Scheme 1.4. Synthesis of α-alkylated cyclohexanones

In 1976, Meyers *et al.* reported the asymmetric α-alkylation of imines *via* the use of amino acid derived auxiliaries **(Scheme 1.5a)**.[23] Although initially this methodology was limited to rigid cyclic ketones, a subsequent publication in 1981 detailed the expansion of this methodology to include acyclic ketones **(Scheme 1.5b)**.[25] Moderate to excellent enantioselectivity and yields were achieved for simple imines, however enantioselectivity was significantly reduced when more sterically incumbered imines were examined.

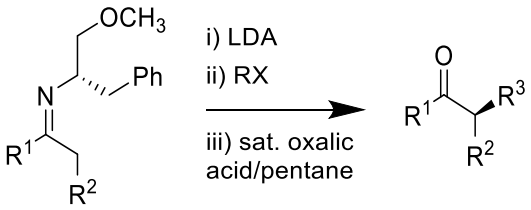
a)



50-80%

82-95% *ee*

b)



60-88%

19-97% *ee*

Scheme 1.5. Meyers asymmetric α-alkylation of a) cyclic and b) acyclic imines

Although these early developments marked a major advancement in the area, significant limitations reduced the synthetic utility of these reactions. Oftentimes this methodology only tolerated symmetric, cyclic ketones. Additionally, imines and enamines are difficult to form quantitatively and are hydrolytically unstable.[26]

1.5.1 *N,N*-Dialkylhydrazones

N,N-Dialkylhydrazones are highly valuable synthetic equivalents for aldehydes and ketones **(Figure 1.10)**. The enhanced reactivity profile of hydrazone-derived azaenolates, particularly organolithium azaenolates, make *N,N*-dialkylhydrazones incredibly useful building blocks in asymmetric synthesis.[21] Advantages include: **i)** the deprotonation of hydrazones proceeds with a high degree of regioselectivity, usually occurring at the least sterically hindered site. Reaction at the more sterically encumbered position is also possible when an anion stabilising group is present;[27] **ii)** the decreased acidity of the α-hydrogen of a hydrazone is sufficient to prevent racemisation of the newly formed stereogenic centre; **iii)** the presence of the dialkylamino group offers an additional coordination site, leading to a more stable metalated azaenolate intermediate; **iv)** unlike the corresponding ketone analogues, which have a propensity to overreact, hydrazones undergo only monoalkylation at the α-position. In contrast to aldehydes and ketones, competing heteroatom-alkylation is not observed when hydrazones are employed; **v)** hydrolytic, oxidative and reductive cleavage of the C=N bond allows for restoration of the parent carbonyl compound, whilst access to a range of primary amines is also possible *via* reductive cleavage of the N-N bond.[21]

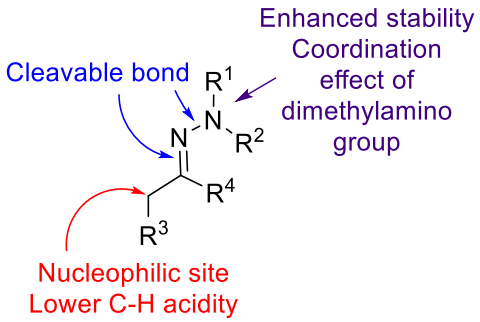


Figure 1.10. *N,N*-dialkylhydrazones

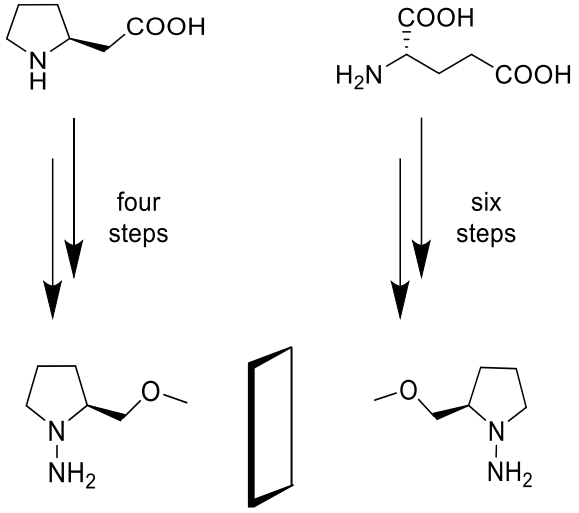
N,N-dialkylhydrazones are easily prepared, often quantitatively, *via* a condensation reaction between the parent carbonyl compound and the *N,N*-dialkylhydrazine. For more demanding substrates, occasionally an acid catalyst is required.[28] A variety of synthetically useful transformations are possible with this moiety, including α-alkylation, Michael, aldol and Claisen-type reactions.[28-31] Afterwards, liberation of the parent carbonyl compound is also a facile transformation, with numerous methods available.[32]

Pioneering work in the latter part of the 20th century demonstrated that *N,N*-dialkylhydrazones could serve as important intermediates in the stereoselective formation of C-C bonds. Weaver and co-workers, Stork *et al*. and Corey all published work using metalated *N,N*-dialkylhydrazones as carbonyl equivalents.[21, 33-34] However, the breakthrough discovery was

made by Enders when he reported a powerful method for the formation of enantiomerically enriched α-substituted carbonyl compounds.[35-36]

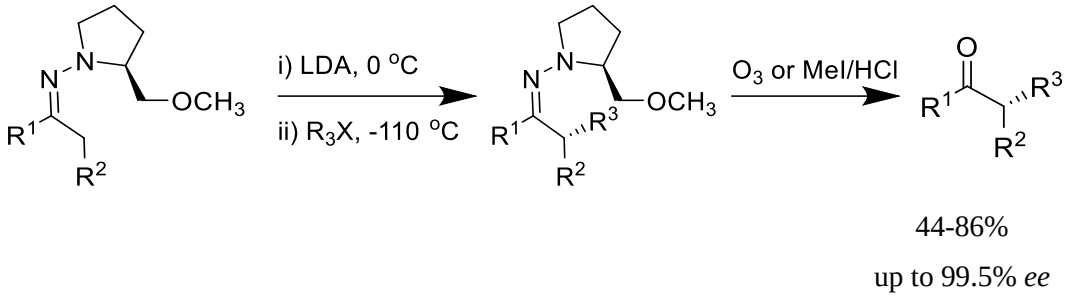
1.5.2 SAMP/RAMP hydrazones in asymmetric synthesis

Enders and co-workers reported a highly robust method for furnishing α-alkylated carbonyl compounds, which nowadays is still regarded as the landmark discovery in the asymmetric α-alkylation of ketones.[37] Using the chiral auxiliaries (*S*)-amino-2-methoxymethylpyrrolidine (SAMP) and (*R*)-amino-2-methoxymethylpyrrolidinone (RAMP), α-alkylated carbonyl compounds could be synthesised in good to excellent yield and enantioselectivity of up to 99%. SAMP can be prepared in four steps from (*S*)-proline in approximately 50% yield.[38] Due to difficulty accessing (*R*)-proline, RAMP is prepared over six steps, beginning with (*R*)-glutamic acid, in 35% yield **(Scheme 1.6)**. [39]



Scheme 1.6. Synthesis of SAMP & RAMP

Chiral hydrazones are easily prepared *via* a condensation reaction between either the aldehyde or ketone and enantiomerically pure SAMP/RAMP hydrazine. Often these reactions proceed quantitatively without the need for purification of the resulting hydrazones. For less electrophilic or more sterically challenging carbonyl compounds, reflux conditions or the addition of an acid catalyst may be required for the reaction to proceed. Treatment of the resulting hydrazone with LDA results in the formation of a metalated azaenolate intermediate, which can subsequently be trapped with a range of electrophiles to furnish diastereomerically enriched α-alkylated hydrazones. Racemisation free cleavage of the hydrazone moiety can be achieved using various methods including acid hydrolysis or ozonolysis, to afford enantiomerically enriched α-alkylated aldehydes or ketones, in yields of up to 86% and >99% *ee* **(Scheme 1.7)**.



Scheme 1.7. Ender's SAMP chiral auxiliary methodology

The stereochemical outcome of these reactions can be rationalised by considering the geometry of the azaenolate intermediate and subsequent reaction of this species with an electrophile. Extensive investigations have been conducted to ascertain the exact geometry of the azaenolate intermediate. Trapping experiments, spectroscopic investigations and X-ray crystallography confirmed that in both cyclic and acyclic systems, only the $E_{CC}Z_{CN}$ isomer is formed.[35, 40-41] This presumed-rigid intermediate ensures reaction with an electrophile proceeds with a high degree of diastereoselectivity. The stereochemistry of this alkylation step can be explained by the preferential approach of the electrophilic reagent from the least sterically hindered face **(Figure 1.11)**. Based on this mechanistic insight, enantioselectivity can be predetermined through selection of either SAMP or RAMP hydrazone when designing a synthetic route.

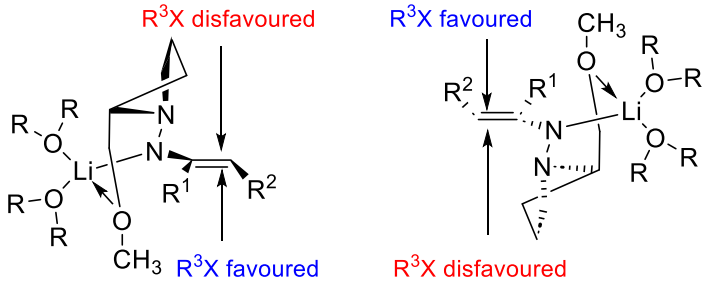


Figure 1.11. Stereochemical outcome of SAMP/RAMP protocol

A wide range of carbonyl compounds and electrophiles can be successfully tolerated within this methodology, leading to widespread uptake of this methodology in organic synthesis and natural product synthesis.[16] A variety of C-C bond forming reactions are possible, including α-alkylation, aldol, Michael and Claisen-type reactions.[21]

Although the SAMP/RAMP protocol remains a highly useful synthetic methodology for the asymmetric α-alkylation of carbonyl compounds, some inherent limitations exist. For example, this methodology proves problematic on scale-up due to the necessity for cryogenic reaction conditions. Additionally, the cost of the chiral auxiliary makes it unattractive as an industrial method to furnish α-alkylated ketones.

1.5.3 *N*-Amino cyclic carbamate hydrazones in asymmetric synthesis

In 2008, an alternative method for the asymmetric α-alkylation of acyclic ketones was reported, when Coltart and co-workers examined the use of *N*-amino cyclic carbamates (ACC) as chiral auxiliaries.[42] Some of the issues inherent to the SAMP/RAMP methodology, such as those mentioned previously, were alleviated. Various ACC auxiliaries have been synthesised from the corresponding oxazolidinones. Preliminary investigations into the stereoselectivity demonstrated that increasing steric bulk near the amino functionality resulted in better selectivity, with the camphor-base auxiliary proving the most successful **(Figure 1.12)**.

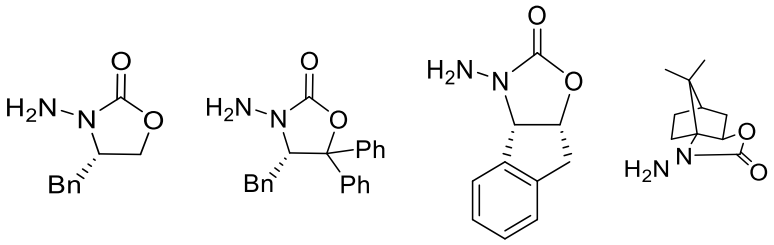
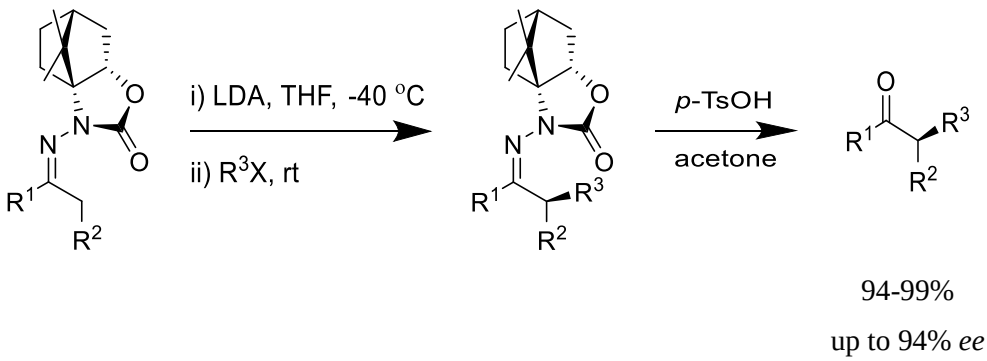


Figure 1.12. *N*-amino cyclic carbamates

The pivotal structural feature of ACC auxiliaries is the carbonyl moiety adjacent to the hydrazone functionality. This creates a so-called 'activated hydrazone'. The consequences of this carbonyl group are threefold: **i)** it increases the acidity of the α-proton, allowing for rapid deprotonation even at low temperatures; **ii)** upon lithiation, a highly stable, rigid five membered chelate results; and **iii)** it allows for regioselective deprotonation *via* complex-induced *syn*-deprotonation (CIS-D). CIS-D results in the reversal of the inherent preference of LDA to remove the most sterically accessible proton. Similar to the SAMP/RAMP methodology, installation of the ACC to form hydrazones is facile. LDA mediated deprotonation and subsequent alkylation with a range of alkyl halides affords diastereomerically enriched α-alkylated hydrazones. Cleavage under mild conditions allows for isolation of the desired enantioenriched α-alkylated ketone, in good to excellent yield and enantioselectivity **(Scheme 1.8)**.



Scheme 1.8. ACC chiral auxiliary protocol

The origin of stereoselectivity for this reaction has been rationalised using a similar approach to that reported by Enders.[43] Density functional theory (DFT) calculations revealed that the formation of the azaenolate intermediate is controlled by the orientation of the carbonyl group of the oxazolidinone ring. The preferred conformation of the ACC hydrazone is the one in which the steric interactions between the larger substituent (L) and R^2 are minimised **(Figure 1.13a)**. Coordination of the lithium ion of LDA to the carbonyl group results in a five membered chelate. This promotes '*syn*-directed' deprotonation and confers $E_{CC}Z_{CN}$ geometry on the resulting azaenolate. Alkylation occurs preferentially with the lower-energy-azaenolate, with addition of the electrophile occurring from the side opposite the bulky bicycloalkyl group **(Figure 1.13b)**.

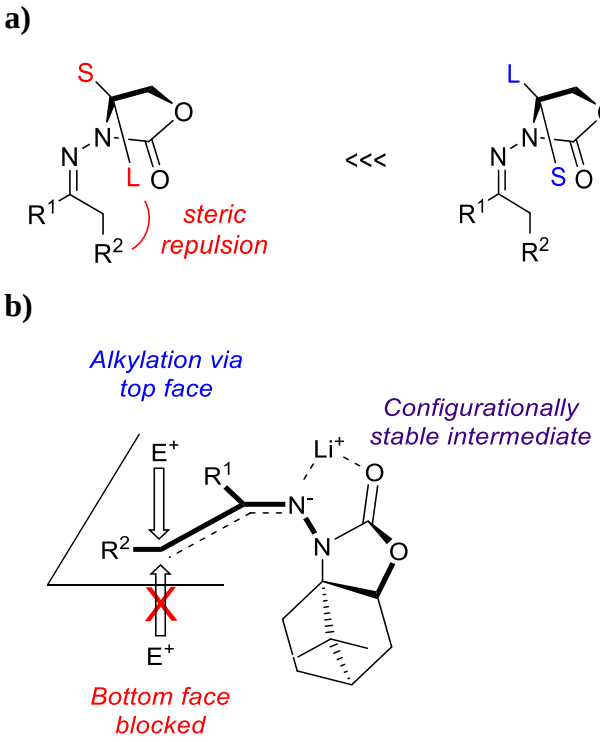
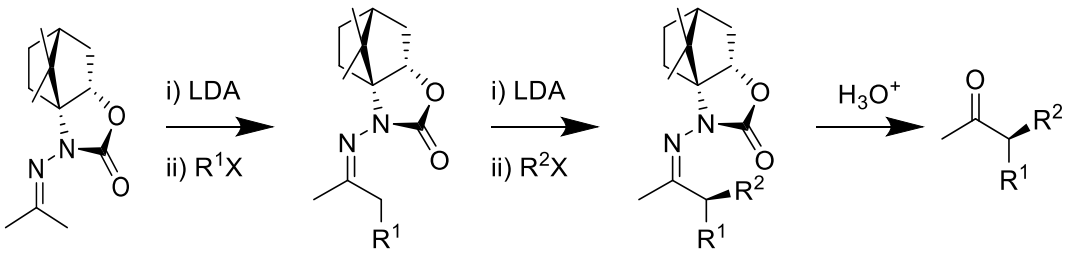


Figure 1.13. Origin of stereoselectivity of Coltart's ACC metodology

Perhaps the most synthetically useful application of this methodology is the fact that α,α-bisalkylation of ketones is possible, facilitated by CIS-D.[44] In general, LDA displays an inherent preference for the most sterically accessible proton in deprotonation reactions. However, CIS-D overrides this preference enabling α,α-bisalkylation of ketones, where both α-protons and α'-protons are available, as seen for the bisalkylation reaction of the acetone derivative **(Scheme 1.9)**. Additionally, the opposite enantiomer is accessible by simply reversing the order of the addition of alkylating agents.



Scheme 1.9. Asymmetric bis-alkylation using ACC chiral auxiliary

Although the use of chiral auxiliaries has proven a robust and reliable method for the asymmetric α-alkylation of carbonyl compounds, there are limitations inherent to this approach. These drawbacks include: **i)** the chiral auxiliary approach is often a costly approach, both financially and in terms of atom-economy; **ii)** two additional synthetic steps are required when using chiral auxiliaries; **iii)** stoichiometric amounts of chiral reagents are required for this approach, with no possibility for catalysis; **iv)** remarkably, the use of simple ketones such as 3-pentanone and propiophenone proves enormously challenging. Thus, the development of non-chiral auxiliary based strategies for the asymmetric α-alkylation of carbonyl compounds would represent a significant advancement in organic synthesis.

1.6 Chiral Ligands in asymmetric synthesis

Nowadays, chiral catalysis represents the gold standard in asymmetric synthesis, and is frequently achieved using a chiral ligand. Upon chelation to a metal, a chiral ligand can modify the reactivity and selectivity of a metal centre, inducing stereoselectivity in a reaction.[45] Many classes of chiral ligand are known, but only a small number have been labelled "privileged chiral ligands". This is a term reserved for chiral ligands which demonstrate a wide range of applicability and effectiveness across a variety of enantioselective transformations **(Figure 1.14)**.[46]

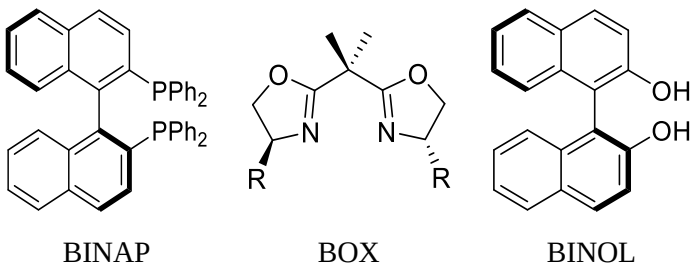
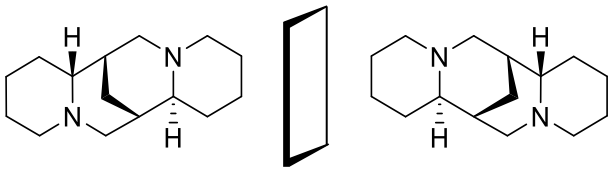


Figure 1.14. Privileged chiral ligands

1.6.1 Sparteine as a chiral ligand

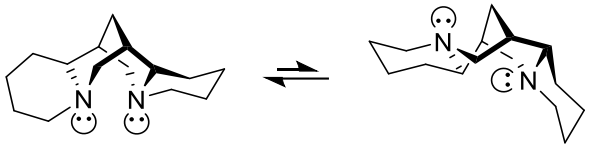
Although most privileged chiral ligands possess C_2-symmetry, a beneficial structural feature due to the reduced number of competing reaction pathways, the use of C_1-symmetric ligands in asymmetric transformations has become more frequent.[46] One such example is (±)-sparteine [(±)-sp], a naturally occurring lupin alkaloid, which acts as a highly effective chiral ligand across a number stereoselective reactions **(Figure 1.15)**.[47]



(-)-Sparteine (+)-Sparteine

Figure 1.15. Sparteine

In a review by Hoppe, (-)-sp is described as 'admirably suited as a chiral bidentate ligand, and its efficiency and breadth of application are so far unsurpassed'.[48] A semi-rigid bisquinolizidine, (-)-sp is predominantly combined with an alkyl lithium to form an effective chiral lithium base or nucleophile. The cisoid conformation is the preferred conformation, offering two attractive metal chelation sites **(Figure 1.16)**. Although predominantly combined with lithium, (-)-sp has also been reported as a metal chelate for magnesium, copper, zinc and palladium.[48]



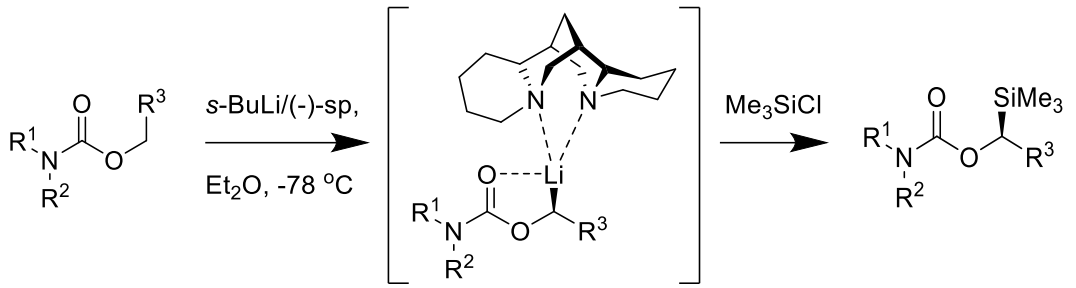
Cisoid *Transoid*

Figure 1.16. Possible conformations of sparteine

Organolithium reagents demonstrate a strong structure-activity relationship, which is entirely dependent on the extent of lithium aggregate formation.[49] It is accepted that a decrease in aggregate formation allows for increased reactivity. Hence, combining organolithium species with nitrogen ligands (resulting in a lower degree of aggregate formation) can have a large impact on the reactivity, regioselectivity and stereocontrol in these reactions. (±)-Sp has proven a hugely successful reagent for this reason, facilitating high levels of reactivity and selectivity in a range of transformations, including deprotonation, addition, rearrangement and carbolithiation reactions.[50-53]

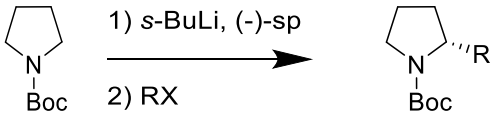
(-)-Sp has proven most successful as a chiral ligand when combined with *s*-BuLi, presumably due to effective disruption of aggregate formation. Initially, the use of this chiral adduct was

examined by Nozaki and co-workers in the 1960s when they furnished optically active allenes, albeit with limited success.[54] However, in 1990 Hoppe and co-workers reported an enantioselective silylation reaction of *O*-alkyl carbamates using s-BuLi/(-)-sp **(Scheme 1.10)**. Excellent yields and enantioselectivities were achieved, which were attributed to the formation of a configurationally stable lithium chelate intermediate.



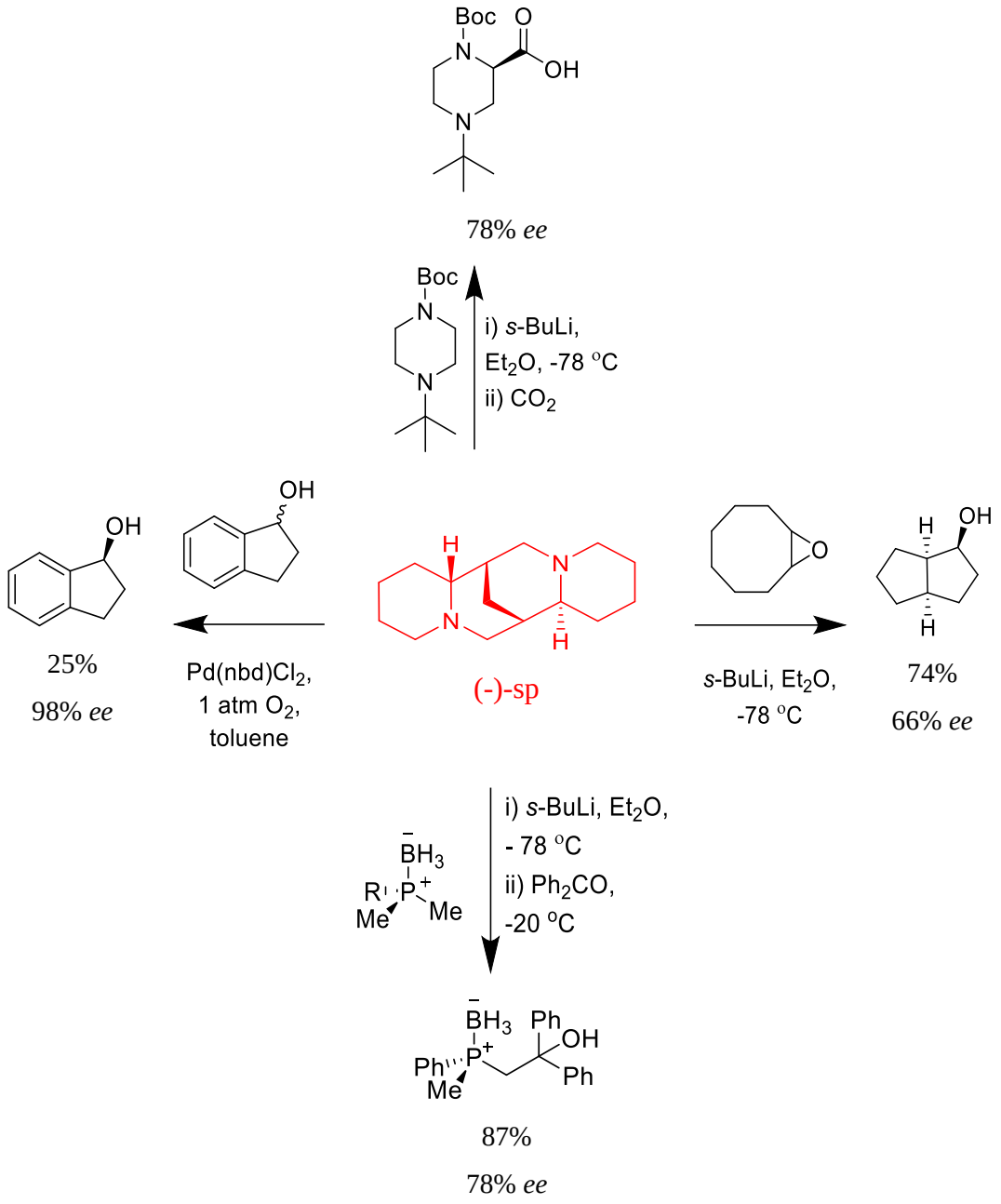
Scheme 1.10. Enantioselective silylation reaction of *O*-alkyl carbamates

Shortly thereafter, Beak *et al*. reported the (-)-sp induced asymmetric deprotonation-electrophilic substitution sequence of *N*-Boc pyrrolidines **(Scheme 1.11)**.[55] Since then, this work has been expanded to include other similar heterocycles, for example, piperidine[56] and piperazine.[57]



Scheme 1.11. Asymmetric alkylation of *N*-boc pyrollidines

Nowadays, the breadth of application of (-)-sp in asymmetric synthesis includes asymmetric deprotonations α- to nitrogen,[55] oxygen[50] and phosphorus,[58] asymmetric alkylations,[59] dynamic kinetic resolutions,[60] polymerisation reactions[61] and kinetic resolution of secondary alcohols **(Scheme 1.12)**.[62]



Scheme 1.12. Asymmetric transformations using (-)-sp

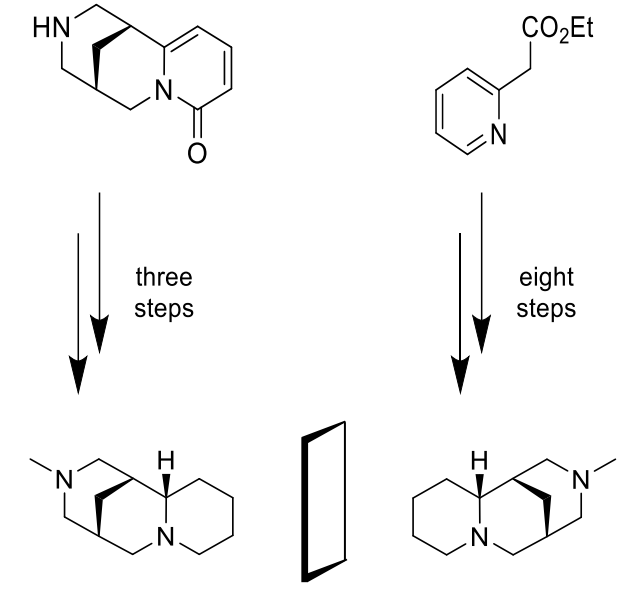
1.6.2 The sparteine surrogate in asymmetric synthesis

Initially, the use of sparteine as a chiral ligand was significantly hindered by the difficulty in accessing both enantiomeric forms. Both are naturally occurring, however (+)-sp is not readily available, and fluctuations in supply meant its widespread use was severely hampered. In 2002, Smith *et al*. reported the first total synthesis of (+)-sp.[63] Although an elegant synthesis**,** including an intramolecular Schmidt reaction and a novel variant of a photo-Beckmann rearrangement, only a 15% yield of (+)-sp was obtained after a fifteen step synthesis **(Scheme 1.13)**.



Scheme 1.13. Synthesis of (+)-sp

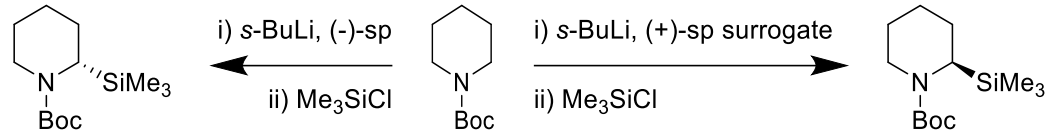
To overcome this, O'Brien and co-workers sought to prepare a sparteine surrogate which could be readily accessed in both enantiomeric forms. They postulated that the D-ring of (-)-sp had no impact on enantioselectivity when chelated to a lithium cation, due to being held too far away from the site of reaction. This led to the development of the sparteine surrogate, which lacks the D-ring and associated chiral centres of (-)-sp. This compound is easily accessed from (-)-cysteine in a three-step procedure in excellent yield and stereoselectivity.[64] However, accessing the (-)-enantiomer proved more difficult. It took a further sixteen years for the synthesis of the (-)-enantiomer to be reported, *via* an eight step procedure by O'Brien **(Scheme 1.14)**.[65]



(+)-sparteine surrogate (-)-sparteine surrogate

Scheme 1.14. Synthesis of sparteine surrogates

With a successful method to furnishing the (+)-sparteine surrogate in hand, O'Brien sought to examine the effectiveness of this ligand in comparison to (-)-sp. Interestingly, the surrogate proceeded with similar yields and enantioselectivities to (-)-sp across a range of reactions, including enantioselective rearrangements and kinetic resolution reactions.[64] In some instances however, the sparteine surrogate proved a more superior ligand to (-)-sp, for example, with less reactive substrates[66] **(Scheme 1.15)** and in catalytic asymmetric deprotonation reactions.[67]



8.5%
74% *ee*

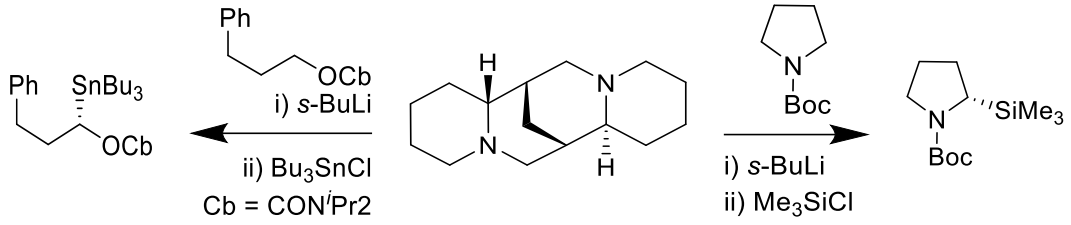
73%
72% *ee*

Scheme 1.15. Asymmetric silylation of *N*-Boc piperidines

1.6.3 Catalytic investigations of (-)-sp and the sparteine surrogate

The greatest advantage of asymmetric transformations using chiral ligands over analogous chiral auxiliary mediated transformations is the possibility for a catalytic route to be developed. Catalytic or sub-stoichiometric use of chiral reagents has the potential to lower costs and increase atom-economy, making for a greener approach to synthesis. Notably, a few examples of highly enantioselective transformations facilitated by sub-stoichiometric use of (-)-sp exist, including additions to imines,[68] carbolithiations,[69] conjugate additions to enolates[70] and Pd-mediated oxidation reactions.[71]

Since 2004, O'Brien and co-workers have been investigating the sub-stoichiometric use of (-)-sp or the (+)-sp surrogate for the asymmetric deprotonation and subsequent electrophilic trapping of *N*-Boc pyrrolidines and *O*-alkyl carbamates.[72] Initially, a significant reduction in enantioselectivity and yield were observed when a substoichiometric amount of chiral ligand was employed **(Scheme 1.16)**.



Stoichiometric = 73%, 98% *ee*
Catalytic = 17%, 70% *ee*

Stoichiometric = 87%, 90% *ee*
Catalytic = 34%, 50% *ee*

Scheme 1.16. Asymmetric deprotonation attempts using (-)-sp

This result suggested that the reactive *s*-BuLi/(-)-sparteine complex is not regenerated for recycling, as it fails to dissociate from the lithiated complex. This hindered any possible catalytic cycle. To overcome this issue and allow for a catalytic asymmetric deprotonation, a ligand exchange protocol was explored, where it was envisaged stoichiometric use of an achiral ligand would displace (-)-sp, allowing for the reactive *s*-BuLi/(-)-sp complex to be recycled. For this approach to work, several criteria needed to be met: **i)** ligand exchange must occur; **ii)** the organolithium must be configurationally stable during the ligand exchange; **iii)**

deprotonation of the substrate using *s*-BuLi/(-)-sp must occur at a faster rate than that using the achiral *s*-BuLi/diamine complex **(Figure 1.17)**.

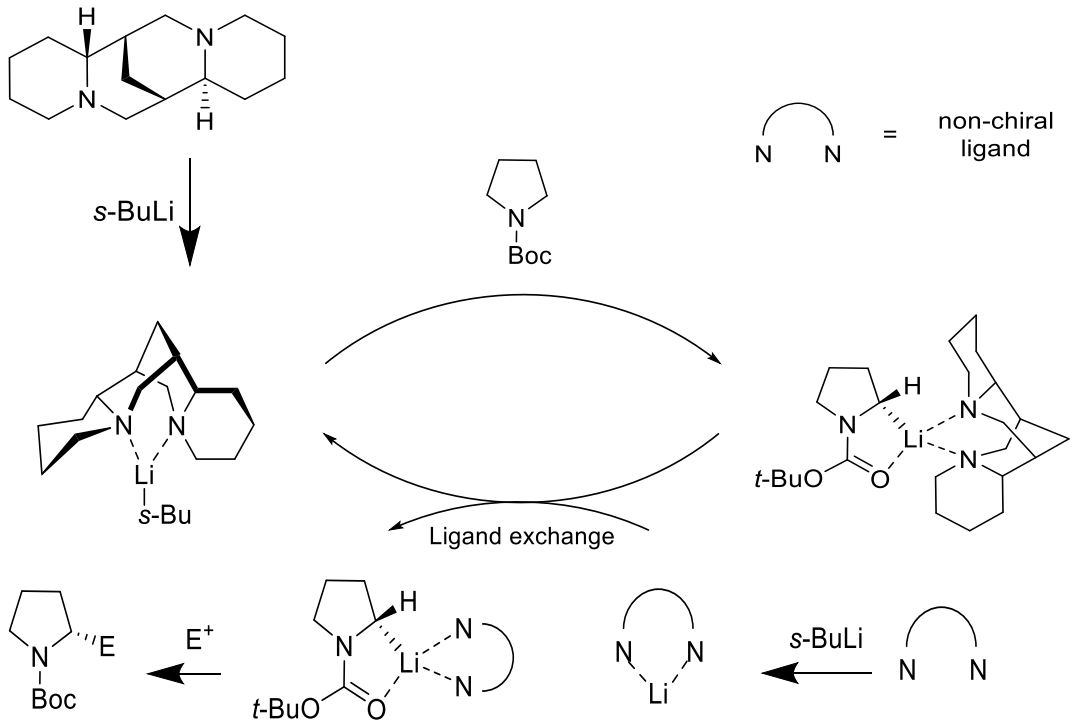
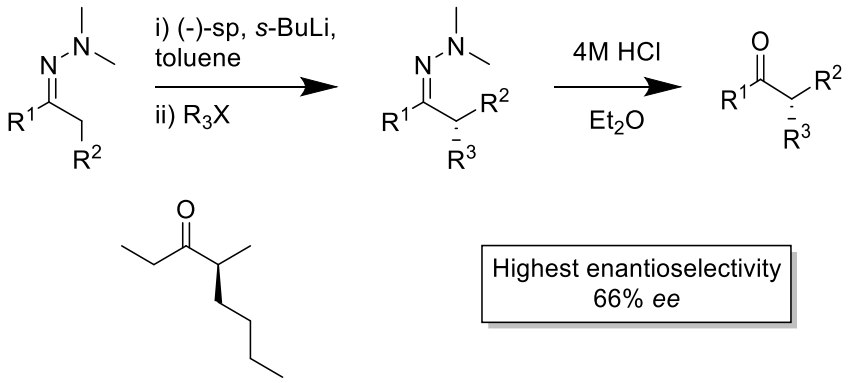


Figure 1.17. Ligand exchange protocol for catalytic asymmetric deprotonation

Using this ligand exchange protocol, O'Brien and co-workers successfully developed a method for catalytic asymmetric deprotonation and subsequent electrophilic trapping of *N*-Boc pyrrolidines, *O*-alkyl carbamates and phosphine boranes in excellent yield and enantioselectivity.[72-74] Both (-)-sp and the (+)-sparteine surrogate were successful, achieving almost identical if not slightly improved yields and levels of enantioselectivity to the analogous stoichiometric transformations.

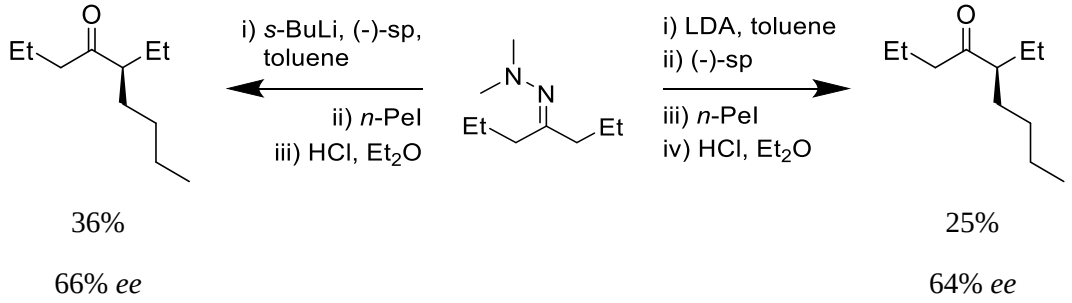
1.7 Asymmetric α-Alkylation of *N,N*-dimethylhydrazones using (-)-sp as a chiral ligand

In 2014, research within the McGlacken group reported a new strategy for the synthesis of enantioenriched α-alkylated ketones, in moderate to good yield and enantioselectivity **(Scheme 1.17)**.[75] This methodology employed non-chiral *N,N*-dimethylhydrazones (DMHs) as ketone surrogates. (-)-Sp was used as a chiral ligand, facilitating an intermolecular enantioselective transformation *via* the formation of a lithiated chiral diamine. Previous asymmetric transformations of this type are exclusively based on chiral auxiliary mediated methods. To date, the highest enantioselectivity achieved is 66% *ee*.



Scheme 1.17. Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones

Numerous optimisation reactions were conducted involving solvent, temperature, hydrazone moiety, reaction time and hydrazone cleavage method. Reactions to elucidate whether an asymmetric deprotonation or an asymmetric alkylation was operative in this reaction were also conducted. Deprotonation with lithium diisopropylamide (LDA) and subsequent addition of (-)-sp lead to only a minor decrease in enantioselectivity compared to pre-mixing *s*-BuLi and (-)-sp. This suggests an asymmetric alkylation rather than an asymmetric deprotonation is occurring **(Scheme 1.18)**.[75] Deprotonation of *N*,*N*-DMHs with *s*-BuLi/(-)-sp is presumed to lead to the formation of a highly structured azaenolate intermediate, with coordination of the lithium cation to the dimethylamino group expected to increase the conformational rigidity of the intermediate species **(Figure 1.18)**. This species is then expected to undergo facially selective reaction with an electrophile, furnishing an α-alkylated DMH. Previous work within the group was also conducted to establish the enantiostability of the α-alkylated DMHs synthesised. No evidence of racemisation of the newly installed stereocentre was observed when a variety of cleavage methods was investigated, including use of a biphasic mixture of 4M HCl in Et_2O or Amberlyst 15®. Additionally, exposure of the enantioenriched α-alkylated ketones synthesised to acidic conditions also resulted in no racemisation.[76]



Scheme 1.18. Asymmetric α-alkylayion of *N*,*N*-dimethylhydrazones

Extensive studies involving ^{1}H NMR spectroscopy and trapping experiments on *N*,*N*-dialkylhydrazones have revealed the most stable azaenolate configuration is $E_{CC}Z_{CN}$ for both cyclic and acyclic ketones, when LDA is used as a base.[41] Attempts to establish the origin of

stereoselectivity in these reactions proved futile. *In situ* NMR studies were conducted in collaboration with Prof David Collum of Cornell University. Results obtained from these studies revealed no formal azaenolate geometry predominated in solution, and instead a complex mixture of geometries and aggregates were present **(Figure 1.18)**.[76]

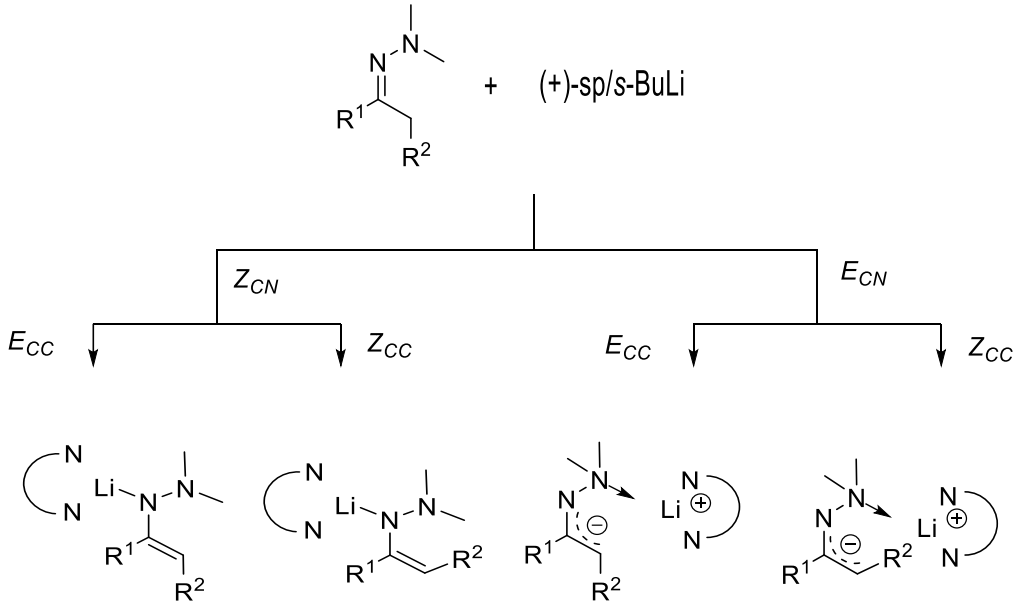
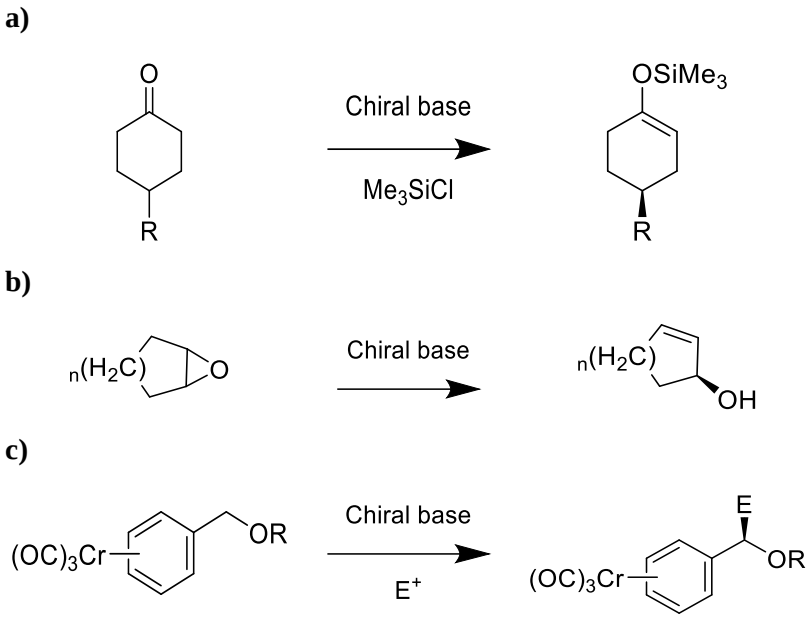


Figure 1.18. Possible azaenolate geometries

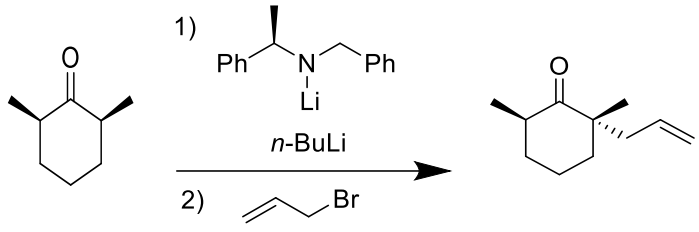
1.8 Chiral lithium amide bases

Chiral lithium amide bases are essentially chiral variants of LDA, formed *via* an *in-situ* reaction between an optically pure amine and *n*-butyllithium. Chiral lithium amide bases have been used successfully in three main types of asymmetric reactions: **i)** deprotonation reactions of conformationally locked prochiral cyclic ketones;[77-78] **ii)** rearrangements of epoxides to allylic alcohols[79] and **iii)** aromatic and benzylic functionalisations of tricarbonyl (η^6-arene)chromium complexes[80] **(Scheme 1.19)**. All three are examples of asymmetric desymmetrisation reactions in which the chiral base discriminates between two enantiotopic protons in a substrate possessing a plane of symmetry, producing an enantiomerically enriched chiral product.[81]



Scheme 1.19. Asymmetric reactions using chiral lithium amides

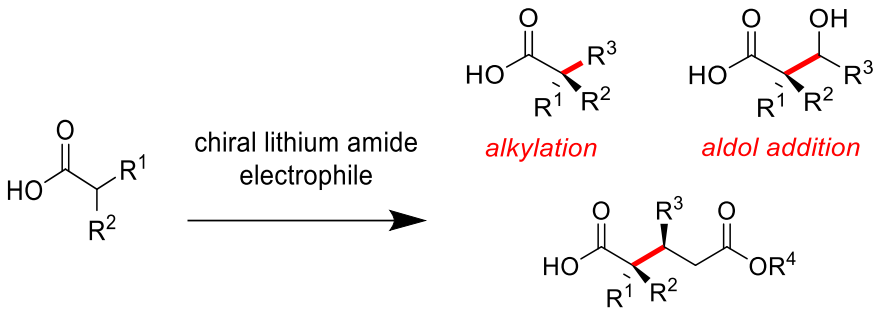
One of the first reported methodologies for the asymmetric α-alkylation of ketones involved chiral lithium amide bases. In 1990, Simpkins and co-workers reported the asymmetric allylation of substituted cyclohexanones, achieving poor to moderate levels of enantioselectivity **(Scheme 1.20)**.[77] The chiral lithium amide base demonstrated a stereoselective preference for axial protons in the rigid chair conformation, leading to enantiomerically enriched α-allylated cyclohexanones. However, a narrow range of substrates and low enantioselectivity led to poor uptake of this methodology, although this approach still deserves merit as it represents the only direct method for the asymmetric α-alkylation of ketones.



Scheme 1.20. Asymmetric allylation of substituted cyclohexanones

More recently, Zakarian and co-workers have reported the use of chiral lithium amides for the enantioselective alkylation,[82-83] aldol addition[84] and Michael addition[85] reactions of carboxylic acids **(Scheme 1.21)**. A detailed analysis of the origin of stereoselectivity for these reactions was given by DFT calculations, NMR spectroscopic analysis and X-ray crystallography,

which revealed the extent of lithium aggregate formation is responsible for the observed stereoselectivity in these reactions.[86]

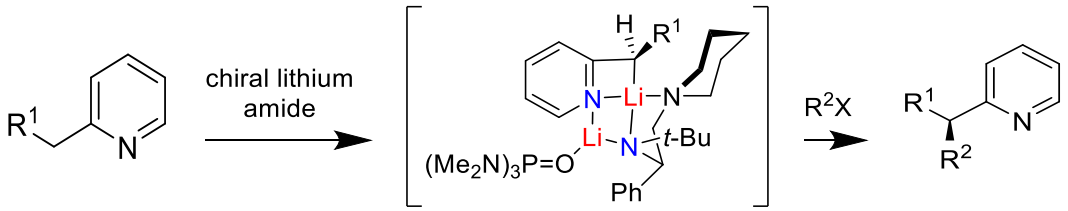


up to 89%

77-98% *ee*

Scheme 1.21. Enantioselective reactions of carboxylic acids using chiral lithium amides

In 2019, Zakarian and co-workers expanded this methodology to include the enantioselective alkylation of 2-alkylpyridines **(Scheme 1.22)**.[87] Pyridines represent the 2nd most common nitrogen-containing heterocycle in the pharmaceuticals,[88] however, no direct alkylation reaction of this class of compounds had previously been reported. Herein, the authors detail the use of chiral lithium amide bases in an operationally simple procedure for the asymmetric alkylation of 2-alkylpyridines. Insights into the mechanism of enantiocontrol are revealed by X-ray crystallography of the reaction intermediate.



up to 86%

up to 98% *ee*

Scheme 1.22. Enantioselective alkylation of 2-alkylpyridines

Results & Discussion

1.9 Aims and objectives

The aim of this chapter was to expand and further develop a strategy for the asymmetric α-alkylation of carbonyl containing compounds, particularly that of ketones. This transformation represents one of the most fundamental reactions in organic chemistry, and hence we believed further efforts in this area were warranted. The first section of this chapter describes an expansion of the work previously reported by the McGlacken research group. Our aims were:

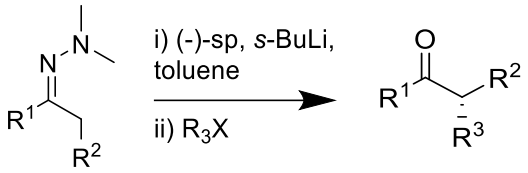
- To develop a direct method for the α-alkylation of ketones using the chiral ligand (+)-sp
- To investigate the use of alternative reaction solvents and the effect on enantioselectivity
- To conduct α-alkylation reactions of a prochiral ACC hydrazone, and examine if any enantioselectivity resulted when this substrate was used in combination with (+)-sp
- To synthesise a range of C_2-symmetric chiral ligands and to examine their effectiveness in an asymmetric α-alkylation reaction of ketones and prochiral hydrazones
- To investigate the use of chiral lithium amide bases in an asymmetric α-alkylation reaction of ketones and *N*,*N*-DMHs

2-Alkyl pyridines represent a prevalent scaffold in medicinal and natural product chemistry. When combined with alkyl lithium reagents this class of compound demonstrates analogous reactivity to carbonyl compounds. The latter part of this chapter describes transformations conducted using 2-alkyl pyridine substrates with the following aim:

- To develop an enantio- and diastereoselective aldol and Michael reaction of 2-alkyl pyridines using chiral lithium amide bases

1.10 Project background

To the best of our knowledge, at present the McGlacken chiral ligand methodology represents the only example of an asymmetric α-alkylation reaction of a prochiral hydrazone **(Scheme 1.23)**.[75] In contrast to previous publications, such as work by Enders[16] and Coltart,[89] in this reaction the enantioselectivity obtained results from an intermolecular transfer of chiral information from the chiral ligand to the prochiral hydrazone. Previous work within the group involved the design of an optimised set of reaction conditions. Several reaction parameters were examined and the optimised conditions applied to various substrates including symmetric and unsymmetric, cyclic and acyclic ketone surrogates. Electrophiles tolerated within this reaction included alkyl-, allyl and benzyl halides.

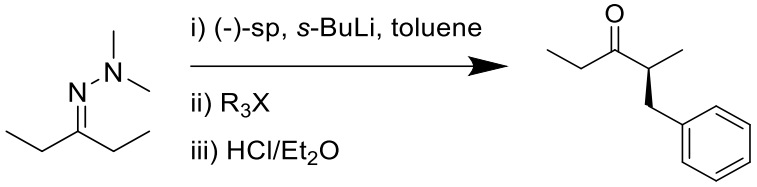


Up to 62%

Up to 66% *ee*

Scheme 1.23. Asymmetric α-alkylation of N,N-dimethylhydrazones using (-)-sp

Detailed mechanistic studies for this reaction were also conducted prior to the commencement of this project **(Scheme 1.24)**.[76, 90] Little variation in the enantioselectivity of this reaction was observed when the chiral ligand was added prior or post deprotonation. Therefore, it is suggested the reaction proceeds *via* an asymmetric substitution mechanism as opposed to an asymmetric deprotonation.



(-)-sp added prior to deprotonation: 54% *ee*

(-)-sp added post deprotonation: 53% *ee*

Scheme 1.24. Previous mechanistic studies

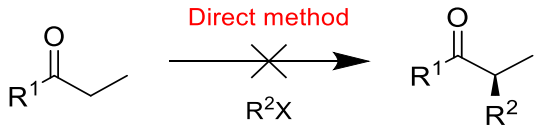
1.11 Synthesis of racemic α-alkylated ketones

The initial aim of this project was to expand the scope of previous work within the McGlacken group to include a direct method for the α-alkylation of ketones using the chiral ligand (+)-sp. Previous work within the group utilised both enantiomers, depending on the commercial availability at that time. Prior to attempting to synthesise their enantioenriched counterparts,

most compounds were first prepared as racemic mixtures. These compounds were fully characterised *via* ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy and mass spectrometry. GC conditions for the separation of enantiomers were also developed using the racemic mixtures. Subsequently, these same conditions were used to determine any enantioselectivity in later reactions.

A series of α-alkylated ketones were alkylated using the parent ketones to prepare racemic samples. In order to limit any potential side reactions, the formation of ketone enolates was conducted at -78 °C *via* deprotonation of the parent ketone. Suitable alkylating agents, including alkyl- and benzyl halides, were then added and the reaction mixture was warmed to room temperature (rt) to generate the desired α-alkylated ketones. These compounds were purified using column chromatography.

Our attention was focused on 3-pentanone **1** and propiophenone **2** as examples of symmetric and asymmetric ketones. As previously discussed, most reported methods to access enantioenriched α-alkylated ketones bypassed these simple yet important ketones **(Scheme 1.25)**. For this reason, these substrates were the focus of many of our investigations into developing a procedure for the direct asymmetric α-alkylation of simple ketones.

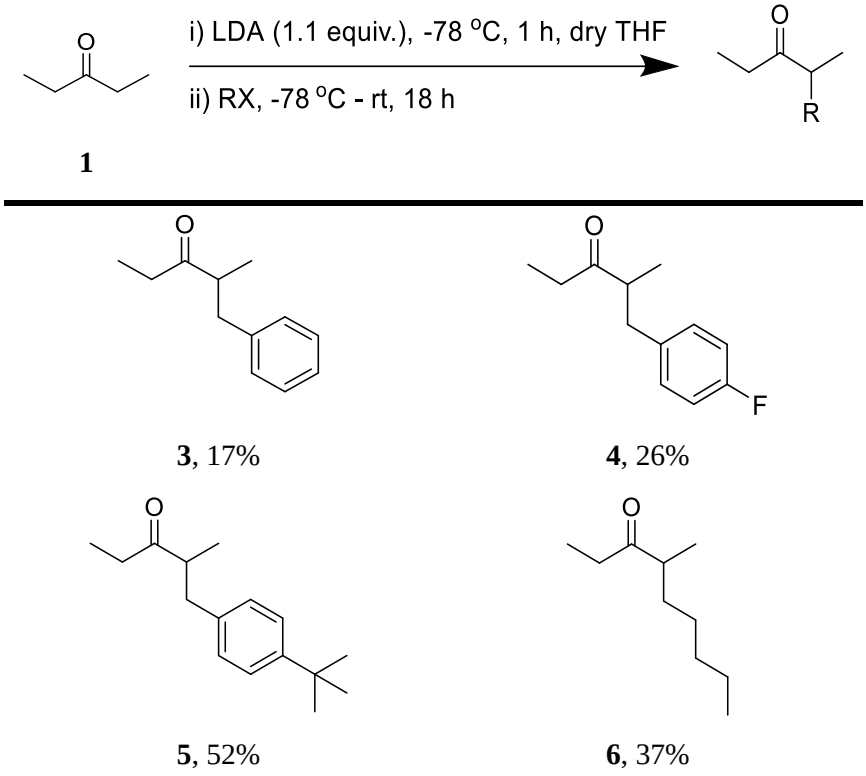


1, R^1 = Et

2, R^2 = Ph

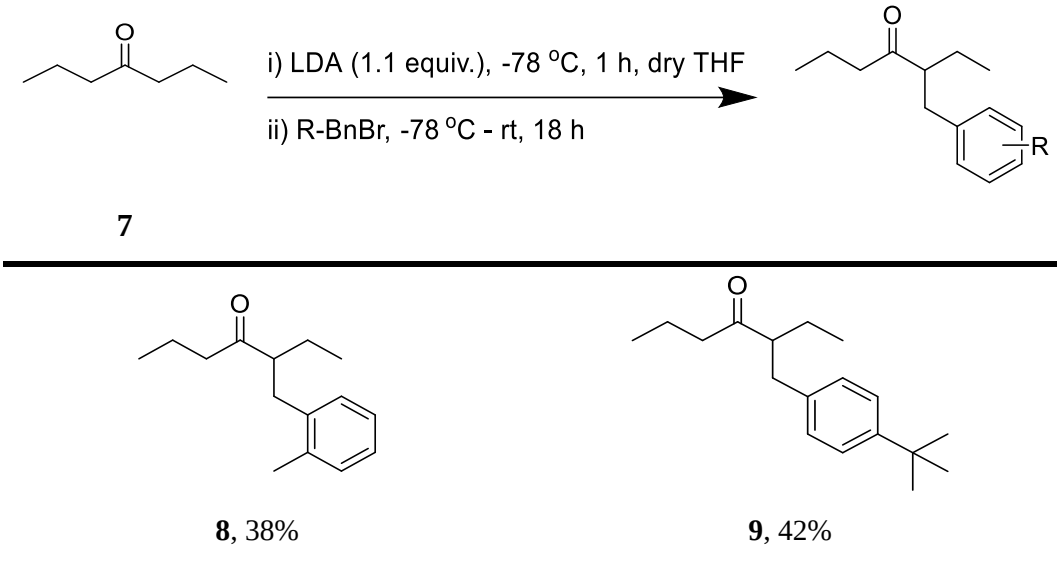
Scheme 1.25. Direct enantioselective α-alkylation reaction of simple ketones

Initially, a number of α-alkylated derivatives of 3-pentanone were prepared (**Scheme 1.26**). Benzyl bromide, and *p*-substituted derivatives thereof, were first examined as electrophiles. These compounds are known to display enhanced S_N2 reactivity, however, the yields obtained in these initial reactions were poor, with only a 17% and 24% yield obtained of **3** and **4**, respectively. We suspected the low yields obtained in these reactions were due to the volatility of the resulting α-alkylated product. To overcome this issue, we next employed 4-*tert*-butylbenzyl bromide as an electrophile. We hoped use of an electrophile of increased molecular weight would circumvent any issues associated with volatility and product loss. Pleasingly, an improved yield of 52% was obtained of **5**. Additionally we prepared the α-alkylated substrate **6**. Previous work within the group achieved the greatest level of enantioselectivity with this substrate, and so it would serve as a comparative α-alkylation reaction going forward.



Scheme 1.26. α-alkylated derivatives of **1**

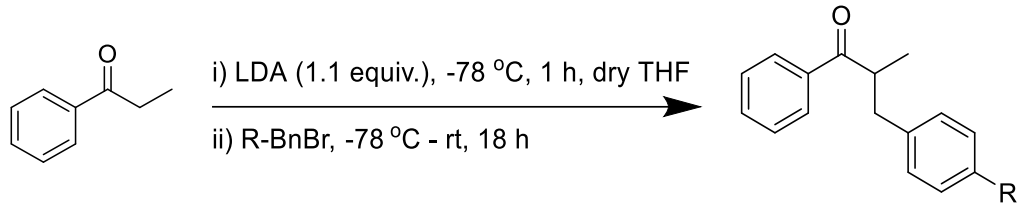
Additionally, in order to avoid issues associated with product volatility, and as an alternative symmetric ketone, α-alkylated derivatives of 4-heptanone **7** were also prepared. These compounds were prepared in moderate yields from the parent ketone and corresponding benzyl bromide reagents **(Scheme 1.27)**.



Scheme 1.27. α-alkylated derivatives of **7**

Racemic α-alkylated derivatives of propiophenone **2** were also prepared **(Scheme 1.28)**. This substrate proved less reactive than the alkyl ketones outlined above. Evidence of starting

material was present in the ^{1}H NMR spectrum of the crude reaction mixture after the reaction time elapsed. In addition, difficulties were also experienced when attempting to purify one of these substrates. The starting material and the benzylated product had similar R_f values, and so purification by column chromatography resulted in a significant loss of benzylated product. A poor yield of 26% was obtained of **10** after multiple purification attempts. An increased yield of **11** was obtained when 4-fluorobenzaldehyde was used. This is likely due to the fact this is a more reactive benzyl halide and issues associated with purification of the benzylated product were not experienced with this substrate.



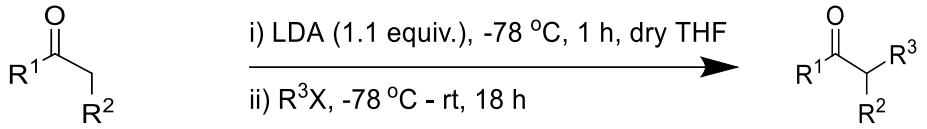
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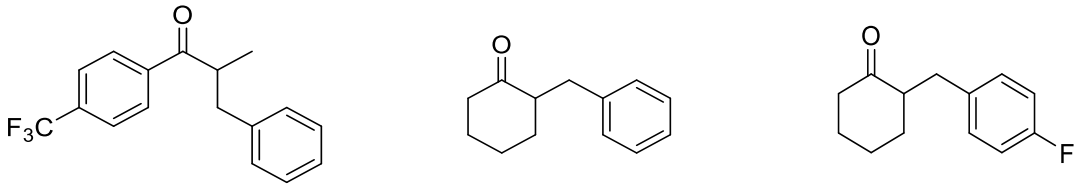


10, 26% **11**, 48%

Scheme 1.28. α-alkylated derivatives of **2**

At a later stage in this project, a small number of additional α-alkylated ketones were prepared **(Scheme 1.29)**. These substrates were synthesised as standards for use in Chapter II.





12, 52% **13**, 57% **14**, 49%

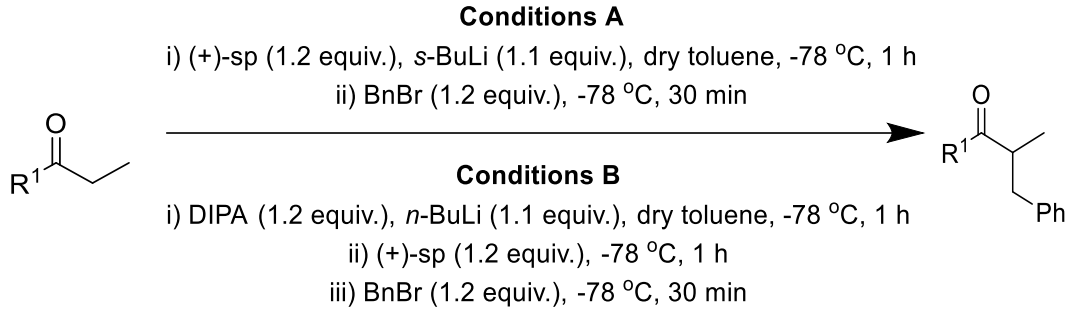
Scheme 1.29. Additional α-alkylated ketone substrates

1.12 Investigations into the direct asymmetric α-alkylation reaction of ketones using (+)-sp as a chiral ligand

With the racemic compounds in hand, and having optimised GC separation conditions for various substrates, our focus turned towards expanding upon work conducted by previous members of the McGlacken research group. Extensive work had been conducted to this point using *N*,*N*-DMHs as ketone surrogates. Combined with the chiral ligand (+)-sp, moderate levels of enantioselectivity had been achieved in the synthesis of α-alkylated ketones.[75] However, at the outset of this project, we were interested in expanding the scope of this methodology and developing an asymmetric α-alkylation reaction protocol using (+)-sp and the parent ketone directly.

Under the guidance of Dr Pamela Mackey, a number of reactions were conducted using both ketones **1** and **2**. For our study, the α-benzylation reaction of these substrates was chosen as a suitable model reaction. Due to the increased electrophilicity of ketones, it was decided to examine the use of the sterically encumbered LDA as a base in addition to the previously optimised *s*-BuLi. As mentioned, previous work also established that (+)-sp could be added either pre- or post the deprotonation step with no effect on the level of enantioselectivity observed. Toluene was used as the reaction solvent, and anhydrous, oxygen free reaction conditions were employed. Disappointingly, no enantioselectivity was observed for either ketone substrate using the reaction conditions described in **Table 1.1** and only trace amounts of α-benzylated products were obtained in each case.

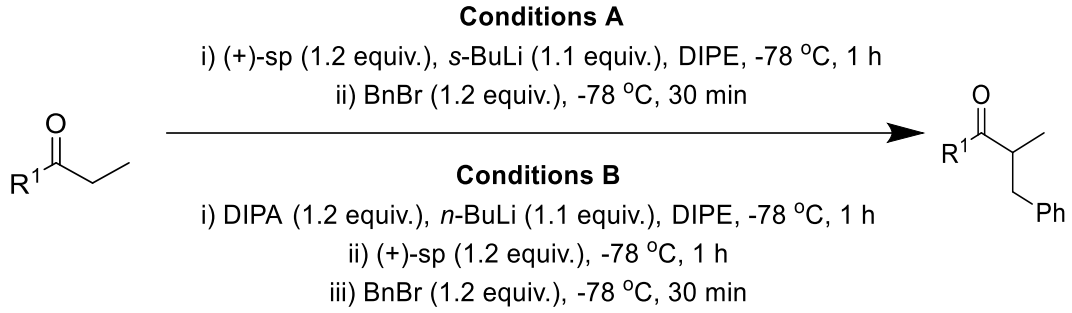
Table 1.1. Direct asymmetric α-alkylation of ketones using (+)-sp



Entry	Ketone, R^1	Conditions	Result
1	Et	A	Trace, racemic
2	Ph	A	Trace, racemic
3	Et	B	Trace, racemic
4	Ph	B	Trace, racemic

Solvents play a crucial role in the structure and reactivity of organolithium reagents, particularly on the extent of aggregate formation.[91] Many asymmetric reactions are conducted in ethereal solvents. For example Enders SAMP/RAMP protocol utilises Et_2O. However, previous work within our group detailed how the use of such solvents resulted in a decrease in the level of enantioselectivity recorded in these reactions. It is suggested that coordinating solvents, such as Et_2O and THF, compete with coordination of the chiral ligand at the reactive site in these reactions, hence nullifying any potential stereoselective effect of the chiral ligand. Despite extensive solvent screens conducted within our group, the use of diisopropyl ether (DIPE) as a reaction solvent had not been evaluated to date. We envisaged that the isopropyl groups might provide sufficient steric bulk to impede this solvent acting as a competitor to the chiral ligand in this reaction. Again, the direct α-alkylation of both ketone substrates was investigated using (+)-sp as a chiral ligand in diisopropyl ether solvent **(Table 1.2).**

Table 1.2. Direct asymmetric α-alkylation of ketones using (+)-sp in DIPE solvent



Entry	Ketone	Conditions	Result
1	Et	A	Trace, 10% *ee*
2	Ph	A	Trace, racemic
3	Et	B	Trace, racemic
4	Ph	B	Trace, racemic

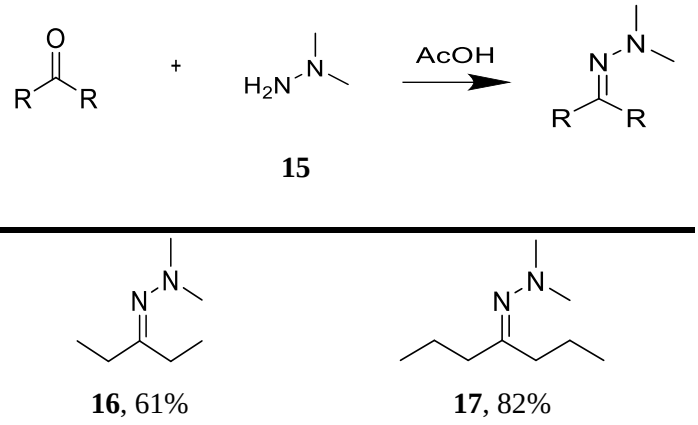
Encouragingly, a 10% *ee* was recorded for the reaction of **1** under the conditions described **(Table 1.2, entry 1)**. However, only a trace of the α-benzylated product was obtained using these conditions. Additionally, no enantioselectivity resulted in the corresponding reaction of **2 (Table 1.2, entry 2)**. Similarly, when LDA was employed as a base, neither ketone substrate was subjected to an enantioselective reaction and only a trace of the corresponding racemic α-benzylated product was evident **(Table 1.2, entries 3 & 4)**. Whilst a 10% *ee* was observed, for future work we decided to revert to using *N,N*-DMHs as ketone surrogates. However, it should be noted that if this small 10% *ee* could be improved, it would represent an enormous advance in enolate chemistry.

1.13 Synthesis and reactivity of *N,N*-DMHs as ketone surrogates

As previously described, *N,N*-dialkylhydrazones have proven to be effective ketone synthetic equivalents in various reactions, demonstrating improved yields, reduced reactivity and increased selectivity.[90, 23] Within the McGlacken research group, *N,N*-DMHs have proven to be effective ketone surrogates in alkylation reactions, particularly in transformations where issues surrounding regioselectivity proved troublesome.

1.13.1 Synthesis of *N,N*-DMHs

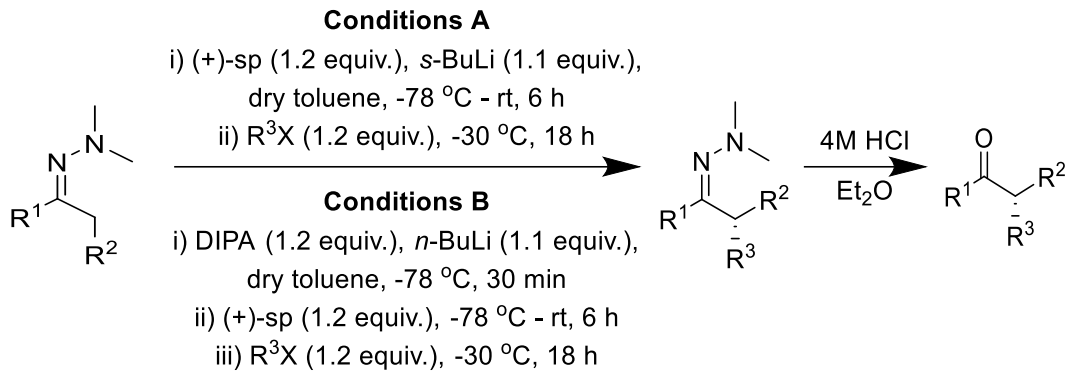
Preparation of *N,N*-DMHs is readily achieved *via* a condensation reaction between *N,N*-dimethylhydrazine **15** and the corresponding carbonyl compound. In the reaction of ketones, an acid catalyst is commonly employed to increase the electrophilicity of the carbonyl compound. For this project, two *N,N*-DMH substrates **16** and **17** were prepared and used throughout our investigations **(Scheme 1.30)**. Both substrates were purified *via* Kugelrohr distillation. However after purification, a lower yield of **16** was obtained, presumably due to the volatility of this *N,N*-DMH.

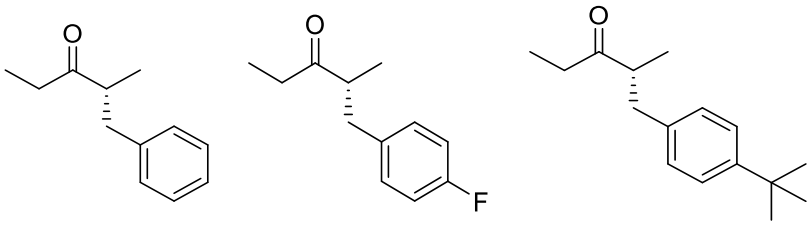


Scheme 1.30. Synthesis of *N,N*-DMHs

1.13.2 Reactivity of N,N-DMHs as ketone surrogates

To begin, three α-alkylated derivatives of **16** were prepared following previously optimised reaction conditions. Treatment of (+)-sp with *s*-BuLi at -78 °C resulted in the formation of a vivid yellow solution, evidence for the formation of the s-BuLi/(+)-sp complex. Dropwise addition of **16**, followed by slow warming of the resulting solution to rt over 6 h facilitated deprotonation. Finally, the solution was cooled to -30 °C and the alkylating agent was added dropwise to this solution. The temperature was maintained at -30 °C for a further 18 h. The resulting α-alkylated *N,N*-DMH derivatives were then hydrolysed to restore the original carbonyl moiety using a biphasic mixture of HCl and Et_2O. Purification of these substrates using column chromatography afforded enantioenriched α-alkylated ketones **(*R*)-3**, **(*R*)-4** and **(*R*)-5** in moderate yields and enantioselectivities **(Scheme 1.31)**. Next, two α-alkylated derivatives of the *N,N*-DMH **17** were prepared following a slightly altered reaction procedure. In this case, deprotonation was achieved using LDA generated *in situ* and (+)-sp was added post the deprotonation step. Once again, moderate yields and enantioselectivities were achieved in the preparation of enantioenriched α-alkylated ketones **(*R*)-8** and **(*R*)-9**.

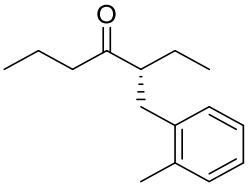




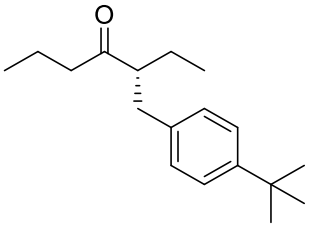
(*R*)-3
Conditions A
38%, 51% *ee*

(*R*)-4
Conditions A
61%, 44% *ee*

(*R*)-5
Conditions A
42%, 42% *ee*



(*R*)-8
Conditions B
45%, 52% *ee*

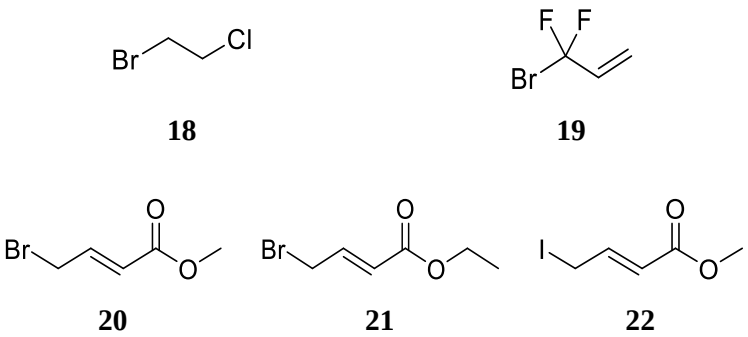


(*R*)-9
Conditions B
39%, 40% *ee*

Scheme 1.31. Synthesis of enantioenriched α-alkylated ketones *via N,N*-DMHs

1.13.3 Examination of challenging electrophiles

Subsequently, we sought to expand the range of electrophiles used in our *N,N*-DMH/(+)-sp chiral ligand methodology. A small number of compounds bearing alternative functional groups in addition to the electrophilic alkyl halide functionality were examined **(Figure 1.19)**.

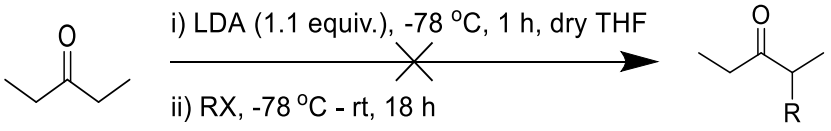


18 **19** **20** **21** **22**

Figure 1.19. Alternative electrophiles

In the case of compounds **18** and **19**, we hoped the carbon-bromine bonds in each would be suitably electrophilic to undergo reaction with the ketone enolate and result in the formation of α-alkylated ketones bearing an additional functionality, allowing for further derivatisation. For compounds **20** and **21** we were interested to establish whether an alkylation type reaction would be preferred over a Michael type reaction. Disappointingly, attempts to prepare racemic α-alkylated ketones using these compounds failed. In all instances, only a complex mixture containing starting materials and unidentified side products was obtained. As a final attempt, we synthesised the iodo-compound **22**. We hoped this compound would display increased reactivity and undergo the desired α-alkylation reaction more readily than the brominated analogue. Again however, no evidence for the formation of an α-alkylated ketone was observed in this reaction. For this reason we decided not to investigate the use of these reagents in our *N,N*-DMH/(+)-sp methodology.

Table 1.3. Attempted α-alkylation reactions using alternative electrophiles

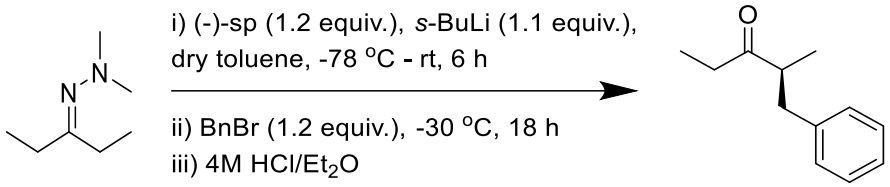


1

Entry	RX	Result
1	**18**	Complex mixture
2	**19**	Complex mixture
3	**20**	Complex mixture
4	**21**	Complex mixture
5	**22**	Complex mixture

1.13.4 Alternative reaction solvents for the α-alkylation of *N*,*N*-DMHs using (+)-sp

Beak and co-workers have previously described the impact of reaction solvent on the enantioselectivity observed in reactions using *s*-BuLi/(+)-sp.[56] Indeed, the enantioselectivity of our system was also shown to be highly solvent specific. As mentioned, previous work within the group involved an extensive screen of various solvents for the α-alkylation of *N*,*N*-DMHs using our chiral ligand strategy.[75] A wide range of solvents, including ethereal solvents such as THF and MTBE, and hydrocarbon solvents, including benzene and cyclohexane, were examined. Toluene was found to be the prime solvent for these reactions, resulting in the greatest level of enantioenrichment when the α-benzylation of **16** was examined **(Scheme 1.32)**.



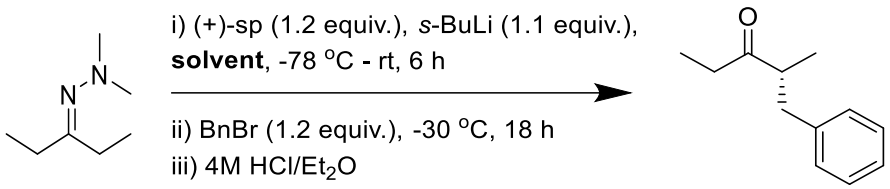
16 **(*S*)-3**

57%, 52% *ee*

Scheme 1.32. Asymmetric α-benzylation of **16**

Next we sought to expand upon this work and examine a range of solvents that had not previously been evaluated as potential reaction solvents in the above transformation **(Table 1.4)**. Note, (-)-sp had been used in previous solvent investigations due to availability. However, due to commercial availability (+)-sp was used for the duration of this project.

Table 1.4. Solvent investigations for the enantioselective α-benzylation of **16**



16 **(*R*)-3**

Entry	Solvent	*ee*	Yield
1	Toluene	51%	53%
2	Ethylbenzene	55%	35%
3	Fluorobenzene	-[a]	-
4	Chlorobenzene	-[a]	-
5	*m*-Xylene	-[a]	-
6	Mesitylene	-[a]	-
7	Diethyl ether	33%	-[b]
8	*i*-Pr_2O	40%	-[b]
9	CPME	0%	-[b]

[a] No evidence of desired α-alkylated ketone

[b] Not isolated

As toluene proved to be the optimal reaction solvent to date in terms of enantioselectivity, a number of similar hydrocarbon solvents was investigated. When ethylbenzene was employed as the reaction solvent, a slight increase in enantioselectivity was recorded **(Table 1.4, entry 2)**. However, a decreased yield of **(*R*)-3** was obtained for this reaction. We suspect this is due to the volatility of **(*R*)-3**, and product loss occurring during the solvent removal step. A complex mixture resulted when halogenated solvents were used. No evidence for the formation of **(*R*)-3** was present in the ^{1}H NMR spectrum of the crude reaction mixtures **(Table 1.4, entries 3 & 4)**. In each case, a complex mixture of unidentified products was noted. Similarly, when aromatic solvents *m*-xylene and mesitylene were employed as reaction solvents, no evidence to support the formation of **(*R*)-3** was observed **(Table 1.4, entries 5 & 6)**.

Previously when examined, the use of THF as reaction solvent afforded a racemic mixture, presumably due to competing coordination between the THF and (-)-sp.[75] The use of Et_2O as a reaction solvent had resulted in varied levels of enantioselectivity and issues associated with reproducibility had been experienced.[76, 90] When examined in the course of these reactions,

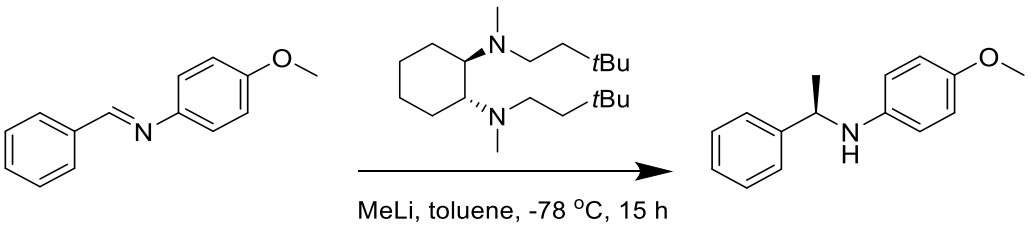
the use of Et_2O as a reaction solvent resulted in a decreased level of enantioselectivity being recorded, compared to toluene **(Table 1.4, entry 7)**.

It is well documented that the use of coordinating solvents can have an impact on the reactivity of organolithium reagents, and the extent to which these species form aggregates.[63, 65, 92] As a rule, if the extent of aggregate formation can be minimised in reactions of this type, then an increase in reactivity of the organolithium species is observed. It was recently stated by Collum and co-workers *"the control of aggregate structure appears to accompany and possibly be a prerequisite for high stereocontrol"*.[86] We were interested to know if sterically encumbered ethereal solvents would be suitable reaction solvents for the above transformation. We wondered if increasing the steric bulk of the ether substituents might impede it acting as a competive ligand to (+)-sp in our reaction system, whilst also reducing the extent of aggregate formation of the organolithium species in this reaction, and thus promoting an enantioselective reaction. For this reason, we examined the use of both *i*-Pr_2O and CPME. Disappointingly, in the case of *i*-Pr_2O, only a 40% *ee* was recorded **(Table 1.4, entry 8)**. Furthermore, only a racemic mixture resulted when CPME was used **(Table 1.4, entry 9)**.

1.14 Synthesis and reactivity of a range of C_2 symmetric chiral diamine ligands

Seminal work by the groups of Hoppe,[48, 50] Beak[56, 59-60, 93-94] and O'Brien[72] have highlighted the importance and effectiveness of (-)-sp as chiral ligand across numerous transformations. The naturally occurring lupin alkaloid is widely regarded as unrivalled in its utility as a chiral ligand. However, one issue inherent to the use of (-)-sp is the fluctuation in the availability of both enantiomeric forms. Given the continued research into (-)-sp mediated asymmetric transformations, and the fact both enantiomers are rarely commercially available simultaneously, the development of a chiral ligand that behaves as effectively as (-)-sp in asymmetric transformations is of paramount importance.

In 2003, Alexakis and co-workers reported the design and synthesis of C_2 symmetric diamines as "conceptually new" chiral ligands.[95] Diamines were chosen as the focus of this work for a number of reasons: **i)** a wide range of these scaffolds are readily available in both enantiomerically pure forms and **ii)** many structural varieties are possible with easy modification of the nitrogen substituents. Preliminary work published in this report detailed the use of a chiral cyclohexyldiamine ligand **(*R,R*)-29** for the enantioselective addition of methyllithium to an imine **(Scheme 1.33)**.[95]

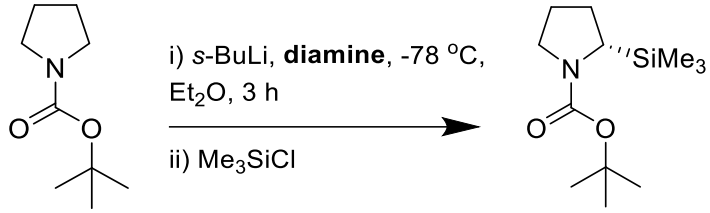


23 **(*R*)-24**

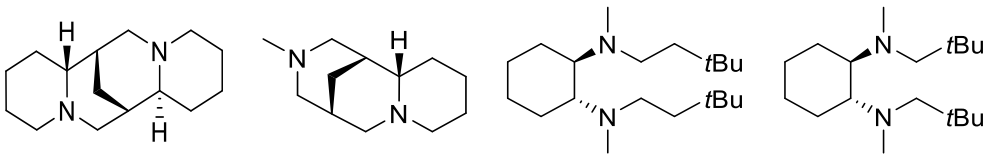
98%, 67% *ee*

Scheme 1.33. Enantioselective addition of MeLi to **23**

Work conducted by O'Brien and co-workers, focused on designing an alternative chiral ligand to (-)-sp (-)-**27**, led to the development of the (+)-sp surrogate (+)-**28**.[64] Notwithstanding the success of ligand **(+)-28** in numerous asymmetric transformations, it is only a pseudo-enantiomer of (-)-sp, and as such, the reactivity of this compound does not strictly mirror that of (-)-sp. Additionally, issues also arose accessing the (-)-sp surrogate.[65] Expanding upon the work of Alexakis, in 2008, O'Brien and co-workers detailed the use of the same ligand as a (-)-sp alternative in the asymmetric deprotonation of *N*-Boc pyrrolidine **(Scheme 1.34)**.[96]



25 **(*S*)-26**



(-)-27 **(+)-28** **(*R*,*R*)-29** **(*R*,*R*)-30**

85%, 90% *ee* 84%, 90% *ee* 72%, 90% *ee* 4%, racemic

Scheme 1.34. Enantioselective silylation reaction of **25**

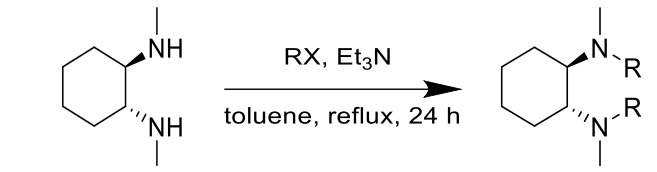
Further expanding on this, previous work within the McGlacken research group focused on synthesising and examining a range of chiral diamine ligands, both known and novel, in a range of asymmetric transformations.[47] Unfortunately, all ligands examined failed to promote a comparable level of enantioselectivity to (-)-sp in the transformations investigated.

1.14.1 Ligand Synthesis

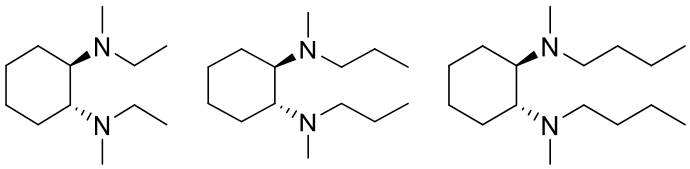
Not deterred by this result, we next decided to further expand the scope of the chiral diamines synthesised. The work reported by O'Brien highlights the sensitive nature of asymmetric

synthesis and how subtle changes to the structure of the chiral ligand can have dramatic effects on the reactivity of such ligands in asymmetric transformations **(Scheme 1.36)**. We believed if a ligand could be found which displayed comparable reactivity to (-)-sp, it might be advantageous for a number of reasons: **i)** these compounds are easy to prepare in multi-gram quantities in one pot from commercially available starting materials; **ii)** they can be readily accessed in both enantiomeric forms and **iii)** they are easily modified and tuned, depending on the nitrogen substituents.

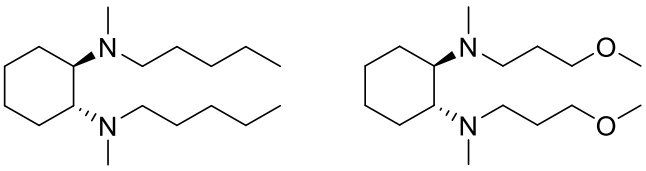
We initiated this work by synthesising a range of alkyl derivatives of (*R*,*R*)-dimethylcyclohexane-1,2-diamine **(Scheme 1.35)**. In total, five derivatives were prepared in one pot procedures where **(*R*,*R*)-31** and the corresponding alkyl halide reagent were heated at reflux for 24 h in the presence of Et_3N.[97] Purification by Kugelrohr distillation yielded the desired diamines in moderate to good yields (41 - 73%).



(*R*,*R*)-31



(*R*,*R*)-32, 46% **(*R*,*R*)-33**, 64% **(*R*,*R*)-34**, 60%

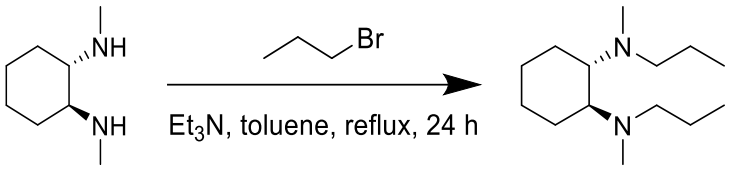


(*R*,*R*)-35, 41% **(*R*,*R*)-36**, 73%

Scheme 1.35. Synthesis of alkyl derivatives of **31**

Whilst more compounds were prepared successfully from the corresponding alkyl bromide reagent, synthesis of the lowest yielding pentyl-derivative **(*R*,*R*)-35** required the use of the more reactive alkyl iodide reagent. Using the same method, it was also possible to synthesis the methoxy-derivative **(*R*,*R*)-36** in excellent yield.

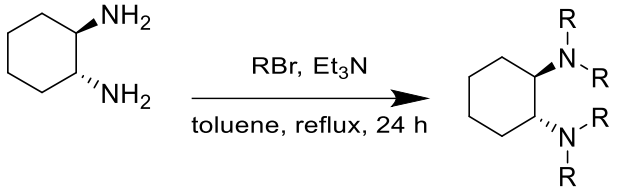
Additionally, for a later comparative study, one derivative of the opposite enantiomer **(*S,S*)-33** was also synthesised **(Scheme 1.36)**. Following the same procedure as that outlined above, an identical yield of the opposite enantiomer was isolated.



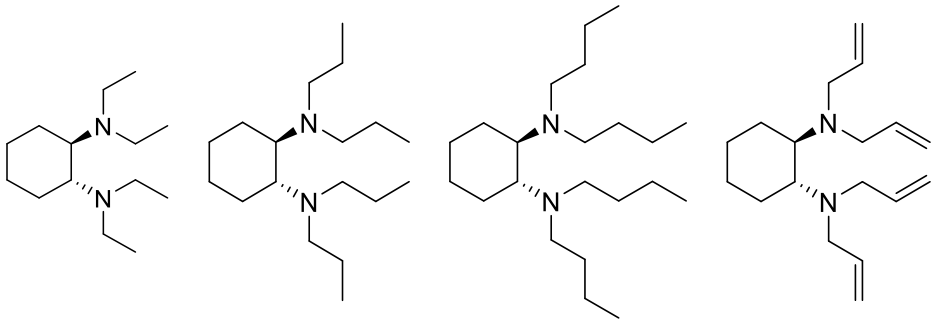
(*S,S*)-31 **(*S,S*)-33**, 64%

Scheme 1.36. Synthesis of **(*S,S*)-33**

Finally, following a similar procedure, a number of (*R,R*)-cyclohexane-1,2-diamine derivatives were prepared **(Scheme 1.37)**. However, lower yields of these compounds were obtained (22 - 45%), with an increase in yield observed as the alkyl chain length increased. It was also possible to synthesis the allyl derivative **(*R,R*)-41** in a moderate yield of 40% using the same method.



(*R,R*)-37



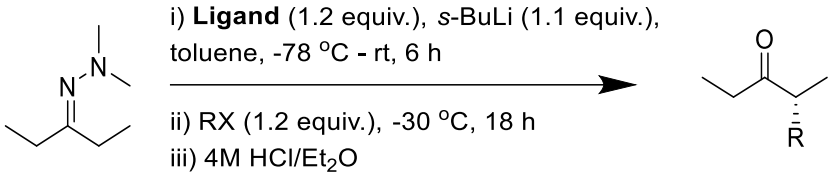
(*R,R*)-38, 22% **(*R,R*)-39**, 38% **(*R,R*)-40**, 45% **(*R,R*)-41**, 40%

Scheme 1.37. Synthesis of alkyl derivatives of **(*R,R*)-37**

1.14.2 Evaluation of the ligands in an asymmetric α-alkylation reaction of *N,N*-DMHs

With the chiral ligands in hand, our focus next turned to examining these ligands in an asymmetric α-alkylation reaction. We hoped that these ligands would demonstrate a comparable, if not an improved, level of enantioselectivity when exposed to our previously optimised chiral ligand protocol. For these investigations, we again chose the α-benzylation reaction of **16**.

Table 1.5. Asymmetric α-alkylation of **16** using *trans*-1,2-cyclohexyldiamine derived chiral ligands



Entry	Ligand	Electrophile	Yield	*ee*
1	**(+)-27**	BnBr	38%[b]	51%
2	**(*R,R*)-32**	BnBr	23%[a]	0%
3	**(*R,R*)-33**	BnBr	26%[b]	55%
4	**(*R,R*)-34**	BnBr	27% [a]	0%
5	**(*R,R*)-38**	BnBr	21% [a]	0%
6	**(*R,R*)-36**	BnBr	15% [a]	0%
7	**(+)-27**	4-*t*-butylBnBr	42%	42%
8	**(*R,R*)-35**	4-*t*-butylBnBr	32% [a]	0%
9	**(*R,R*)-39**	4-*t*-butylBnBr	24% [a]	0%
10	**(*R,R*)-40**	4-*t*-butylBnBr	54% [a]	34%
11	**(*R,R*)-41**	4-*t*-butylBnBr	0%	-[c]
12	**(*R,R*)-32**	1-iodopentane	16%[b]	0%

[a] Yield determined over two steps *via* ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard

[b] Isolated yield

[c] No evidence of desired α-alkylated ketone

Initial reactions were conducted using BnBr as an alkylating agent **(Table 1.5, entries 2 - 6)**. Disappointingly, in all cases the α-alkylated product **3** was obtained in a significantly lower yield than the reaction using (+)-sp **(+)-27.** Additionally, almost all the ligands investigated failed to promote any enantioselectivity. The exception to this was when **(*R,R*)-33** was used **(Table 1.5, entry 3)**. In this case, a slightly improved enantioselectivity was recorded compared to the reaction using (+)-sp **(+)-27**, however a lower yield of **(*S*)-3** was obtained. Discouragingly, the lowest yield, and no enantioselectivity, was obtained when ligand **(*R,R*)-36** was employed **(Table 1.5, entry 6)**. We were hopeful use of this ligand would result in an enantioselectivity being induced in the reaction due to the additional chelation points of the ether moiety, however this was not the case. In an attempt to improve the yields obtained, 4-*tert*-butylbenzyl bromide was used as an electrophile in subsequent screening reactions, as it was hoped this would result in a less volatile product. Unfortunately, although slight

improvements in yield were recorded in most cases, again no enantioselectivity was induced in these reactions by the chiral ligands employed **(Table 1.5, entries 8 - 9)**. When ligand **(*R,R*)-40** was used in the above transformation, an *ee* of 34% was achieved, a considerably lower level of enantioselectivity compared to when (+)-sp **(+)-27** was used for the same transformation **(Table 1.5, entry 10)**. Similarly to the case of **(*R,R*)-36**, we were again hopeful the use of allyl derivative **(*R,R*)-41** would result in the formation of a more structured lithium chelate during this reaction, and hence promote facial discrimination of the electrophile resulting a high level of enantioselectivity in the reaction. This was not the case however, and no evidence for the formation of α-alkylated ketone was present in the ^{1}H NMR spectrum of the crude reaction mixture in this case **(Table 1.5, entry 11)**. Finally, as use of iodopentane as an electrophile in combination with (-)-sp **(-)-27** had previously resulted in the greatest level of enantioselectivity for the α-alkylation of *N,N*-DMH **16**, we subjected our best performing diamine ligand **(*R,R*)-33** to these reaction conditions. Disappointingly however, only a low yield of racemic α-alkylated product **6** was obtained **(Table 1.5, entry 12)**.

Although for the most part these results proved disappointing, they did highlight the extremely sensitive and complex nature of reactions employing chiral ligands. Even the slightest modification of the chiral ligand structure, such as the addition or removal of a simple methylene group, was enough to cause drastic differences on the reaction results obtained. It is strongly believed and supported throughout the literature that the resulting enantioselectivity from reactions of this type is not exclusively influenced by the chiral ligand but instead is influenced by numerous complex factors, including aggregate formation and azaenolate geometry.

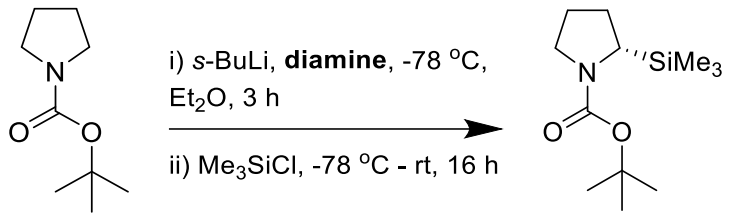
Numerous reports have described the aggregation state of simple lithiated-DMHs using ^{6}Li NMR spectroscopy,[98-99] X-ray crystallography and IR spectroscopy.[100] Studies by Collum and co-workers suggest the reactive species in these reactions are solvated monomers, however aggregates as complex as tetramers exist, and the possibility of trisolvated cyclic trimers and solvated dimers cannot be excluded.[99] Expanding on from this, previous work conducted in the group on the *N,N*-DMH/(-)-sp reaction system in collaboration with Prof Collum also revealed a complex mixture of azaenolate geometries also exist in this reaction system. Described by Prof Collum as an "*observable mess*",[101] these studies were further evidence to support the complexity of the reaction system described.[75-76, 90]

1.14.3 Synthesis of enantioenriched *N*-Boc pyrrolidines using C_2 symmetric chiral ligands

Encouraged by the result obtained when **(*R,R*)-33** was used in the α-alkylation reaction of **16**, we next sought to examine if this ligand could match or improve the enantioselectivity in other (-)-sp mediated asymmetric transformations. As previously discussed, the use of (-)-sp is marred by numerous issues and we believed our ligand had the potential to be a more attractive choice, due in the main, to the ease in accessing both enantiomeric forms in large quantities.

The asymmetric alkylation of *N*-Boc pyrrolidines was a reaction pioneered by Beak and co-workers,[60, 94, 102] and since then the products of this reaction have proven to be important precursors in the synthesis of various APIs.[96] Using *s*-BuLi/(-)-sp **(-)-27** complex, this transformation proved to be very successful in terms of yield and enantioselectivity. O'Brien and co-workers described further success with this transformation using cyclohexane derived ligand **(*R,R*)-29 (Scheme 1.36)**.[96] Thus, we sought to examine if any of the cyclohexane derived ligands (see **Scheme 1.37** and **Scheme 1.39** for ligand structures) synthesised during this project displayed similar, or improved levels of enantioselectivity in this transformation. As ligand **(*R,R*)-33** had proven most successful, we initiated our studies using this ligand. We also proceeded to examine if the varying the length of the substituent alkyl chain had any effect on the enantioselectivity in this reaction **(Table 1.6)**.

Table 1.6. Asymmetric alkylation of *N*-Boc-pyrrolidine using trans-1,2-cyclohexyldiamine derived chiral ligands



25 **(*S*)-26**

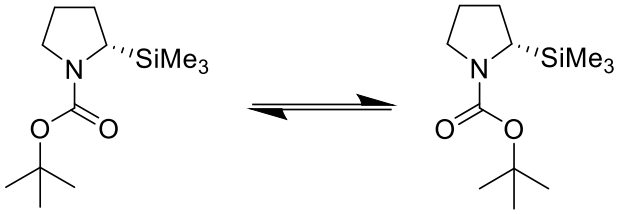
Entry	Ligand	Specific rotation of (*S*)-26 (10^{-1} deg cm^2 g^{-1})	Yield	*ee*[a]
1[96]	**(*R,R*)-29**	+76.7	72%	90%
2	**(*R,R*)-32**	+ 41.0	58%	48%
3	**(*R,R*)-33**	+ 49.2	68%	58%
4	**(*R,R*)-34**	+ 53.9	71%	63%
5	**(*R,R*)-35**	+ 45.6	72%	54%
6	**(*S,S*)-33**	-24.0	62%	28%[b]

[a] Enantiomeric excess values were estimated based on specific rotation values measured experimentally.

[b] Opposite enantioselectivity

Disappointingly, when ligands **(*R,R*)-32** and **(*R,R*)-33** were used in the above transformation, both a decreased yield and decreased level of stereoselectivity resulted compared to O'Brien's transformation **(Table 1.6, entries 1 - 3)**. However, it was noticed that increasing the length of the alkyl substituent did increase the extent of enantioselectivity in the above reaction. Additionally, a comparable yield to that obtained by O'Brien resulted from the use of ligands **(*R,R*)-34** and **(*R,R*)-35** was observed, although a lower degree of enantioselectivity was achieved in both cases **(Table 1.6, entries 4 & 5)**. It was also noted the degree of enantioselectivity in this case decreased once again once the alkyl chain length of the nitrogen substituent had surpassed that of **(*R,R*)-34**. For comparison, the opposite enantiomer of one diamine **(*S,S*)-33** was also examined in the above transformation **(Table 1.6, entry 6)**. Although comparable yields were achieved, a decrease in enantioselectivity was observed in this reaction. This further supports the suggestion that the chiral ligand is not the only discriminatory factor in reactions of this type, and for example, the variable nature of aggregate formation and reactivity.

Both ^{1}H NMR and ^{13}C NMR spectra were obtained upon purification of **(*S*)-26** and an interesting observation was made. **(*S*)-26** exists as a mixture of *syn*- and *anti*- rotamers due to the dynamic nature of the C-N bond of the carbamate **(Figure 1.20)**.



anti-**(*S*)-26** *cis*-**(*S*)-26**

Figure 1.20. Rotamers of **(*S*)-26**

The rate of interconversion between the rotamers is sufficiently rapid that the resonances for both species appeared as averaged signals in the ^{1}H and ^{13}C NMR spectra of this compound leading to signal broadening in some cases. To enable observation of these individual resonances, NMR experiments were run on a spectrometer with a higher field magnet (500 MHz) where the enhanced signal-to-noise ratio allowed us to obtain satisfactory spectra for this compound. Additionally, it was observed that two signals appeared in the region of 156-158 ppm in the ^{13}C NMR spectrum of this compound; these were attributed to distinct carbonyl signals for each of the rotameric species. **(Figure 1.21)**.

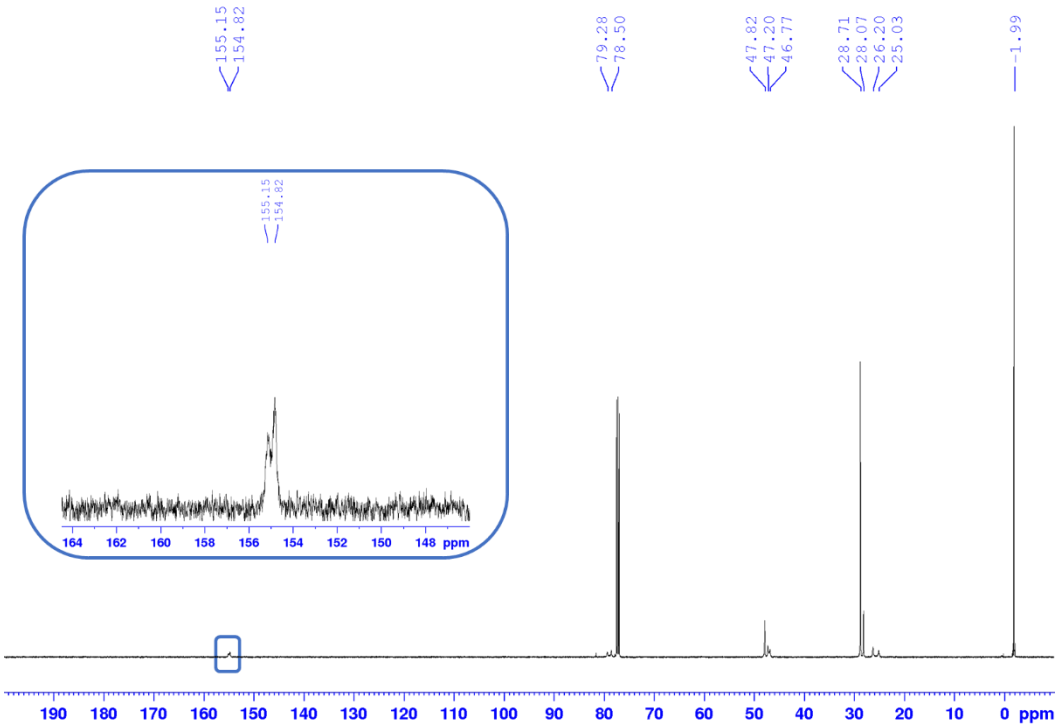


Figure 1.21. ^{13}C NMR spectrum of **(*S*)-26**

1.15 Synthesis and reactivity of a prochiral amino cyclic carbamate hydrazone

Previous work within the group investigated the use of various *N*,*N*-dialkylhydrazones in the chiral ligand protocol, however limited success was achieved.[90] As discussed previously, in 2008 Coltart and co-workers reported the use chiral ACC auxiliaries as an alternative method for the synthesis of enantioenriched α-alkylated ketones.[42-44, 89, 103] Inspired by this, we wondered if combining an ACC hydrazone as a ketone surrogate with (+)-sp **27** would lead to a novel method to access enantioenriched α-alkylated ketones.

We envisaged the use of a so called "activated hydrazone" derivative in combination with (+)-sp **(+)-27** would result in a highly structured reaction intermediate, and that in turn would result in a highly enantioselective transformation taking place. Upon deprotonation, we postulated a highly favourable five-membered chelate would be formed, similar to that reported by Coltart, in addition to coordination of the lithium cation to (+)-sp **(+)-27 (Figure 1.22)**. If formation of this rigid, highly structured azaenolate species was to occur, we hoped this would result in facial discrimination by the electrophile employed and would ultimately allow access to a range of enantioenriched α-alkylated ketones.

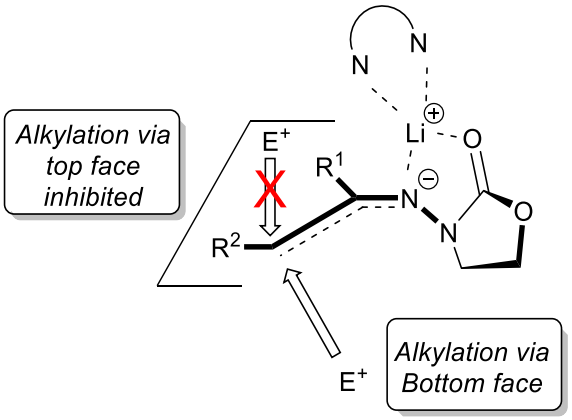
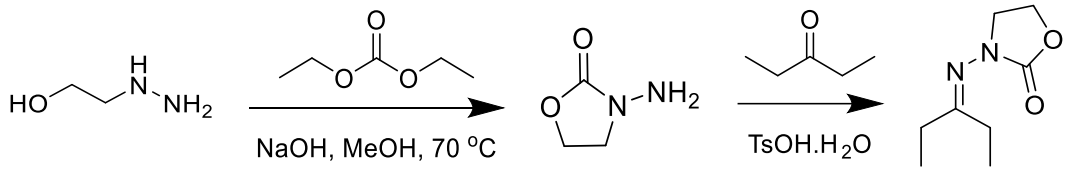


Figure 1.22. Predicted azaenolate intermediate

Hydrazone **44** was prepared over two steps in a moderate yield of 66%, following a known literature procedure **(Scheme 1.38)**.[89, 104] It is worth noting during the synthesis of intermediate **43**, reaction took place exclusively at the internal nitrogen atom of **42**. The α-effect, a term created by Pearson and Edwards to explain the unexpected enhanced reactivity of nucleophiles which bear an unshared pair of electrons at the atom adjacent to the nucleophilic centre, can be used to explain the regioselectivity observed in this reaction.[105-106] In a publication by Mayr and co-workers describing a similar observation, they suggested reaction at the less substituted site occurs under conditions of thermodynamic product control whereas more rapid reaction at the more substituted nitrogen atom takes place under kinetic reaction conditions.[107-108] Subsequent condensation of this species with **1** yielded hydrazone **44**.

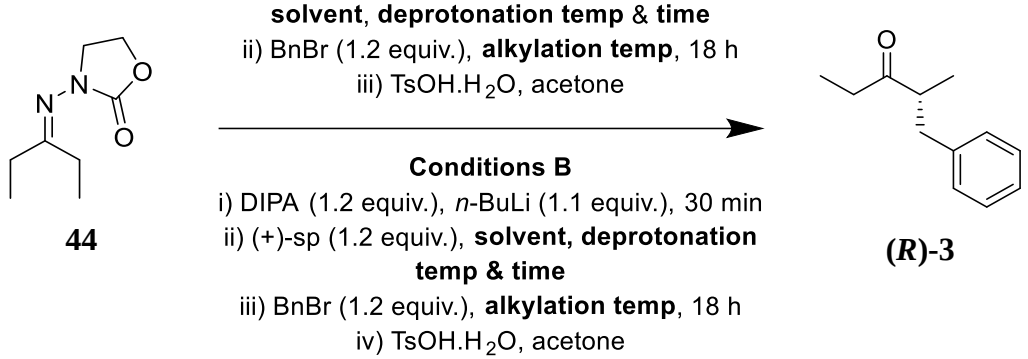


42 **43** **44**, 66%

Scheme 1.38. Synthesis of **44**

With hydrazone **44** in hand we next sought to evaluate the reactivity of this species in an asymmetric α-alkylation reaction using our chiral ligand protocol. We chose the α-benzylation of **44** as a suitable test reaction **(Table 1.7)**.

Table 1.7. Asymmetric α-alkylation of **44** using (+)-sp as a chiral ligand



44 **(*R*)-3**

Entry	Conditions	Deprotonation time (h)	Deprotonation temperature (°C)	Alkylation temperature (°C)	Solvent	*ee*
1	A	6 h	-78 °C - rt	-30 °C	Toluene	0%
2	B	6 h	-78 °C - rt	-30 °C	Toluene	0%
3	B	1 h	-78 °C	-78 °C	Toluene	-[a]
4	B	1 h	-78 °C	-78 °C	THF	-[a]
5	A	1 h	-78 °C - 0 °C	-78 °C - rt	Toluene	0%
6	A	1 h	-78 °C - 0 °C	-78 °C - rt	THF	8%

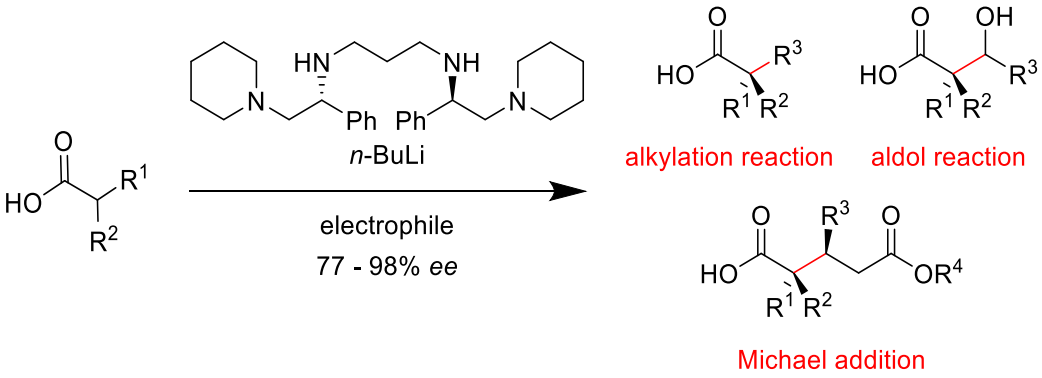
[a] No evidence of desired α-alkylated ketone

Initially, we subjected hydrazone **44** to the conditions previously optimised for *N*,*N*-DMHs. Unfortunately, only racemic α-benzylated products were obtained when either *s*-BuLi or LDA were used to conduct the above transformation **(Table 1.7, entries 1 & 2)**. In the original report by Coltart and co-workers, the authors describe how the use of such "activated hydrazones" in these reactions facilitate the reaction being conducted at - 78 °C.[42] With this is mind, next we investigated maintaining a decreased reaction temperature of - 78 °C throughout the duration of the reaction in the hope this would result in an enantioselective transformation

(Table 1.7, entry 3). We also conducted the reaction using THF as a reaction solvent, as reported by Coltart (**Table 1.7, entry 4).** Unfortunately, neither reaction resulted in the formation of any α-alkylated product. Finally, we employed slightly altered reaction conditions, utilising a combination of reaction temperatures in both toluene and THF solvent. Pleasingly, both reactions resulted in the formation of α-alkylated product **(*R*)-3 (Table 1.7, entries 5 & 6)**. However, the greatest level of enantioselectivity achieved was a disappointing 8% *ee*. For this reason, we no longer pursued this avenue of research.

1.16 Synthesis and reactivity of Koga's chiral bases

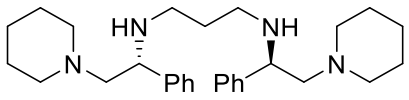
At this stage in the project, we felt the next logical step was to investigate the use of alternative chiral reagents. Of particular interest to us was a group of compounds commonly referred to as Koga's bases. These amines are typically combined with alkyl lithium reagents to form chiral lithium amide (CLA) bases. This class of compounds has achieved notable success in a range of enantioselective transformations over the years.[109-110] Additionally, they are easy to prepare and can be readily modified. Publications we felt noteworthy at this stage were those which had emerged from the research group of Prof Armen Zakarian.[82-83, 85-86] In 2017, this group reported several enantioselective transformations of carboxylic acids using an alternative approach to the use of traditional covalently attached chiral auxiliaries. They detailed how the use of CLAs resulted in the formation of discrete, well-defined aggregates with lithium enolates and effectively provided a chiral environment conducive to asymmetric bond formation for several transformations **(Scheme 1.39)**.[84]



Scheme 1.39. Enantioselective formation of tetrasubstituted carbon centres using CLAs

Although the formation of enediolates was a critical step in the above asymmetric transformations, and this would not be possible for our ketone or *N*,*N*-DMH system, we remained curious to know whether similar levels of enantioselectivity could be achieved using CLAs in our asymmetric α-alkylation reaction. We were further encouraged by a subsequent publication in 2019 detailing the enantioselective α-alkylation of a range of 2-alkyl pyridines using a similar reaction protocol to earlier publications.[87] Herein, CLAs derived from amines

were shown to produce mixed aggregates with a broad range of organolithium reagents with a remarkably defined three-dimensional architecture. Such ordered aggregation allowed the CLAs to direct the stereochemistry for monoanionic carbanions and obviate the need for covalently bound chiral auxiliaries. We wondered if *N*,*N*-DMHs would behave similarly to the azaenolates formed upon deprotonation of the pyridine substrates. As a starting point for these investigations, gratifyingly, Prof Armen Zakarian supplied us with a multigram sample of **(*R*,*R*)-45 (Figure 1.23)**.

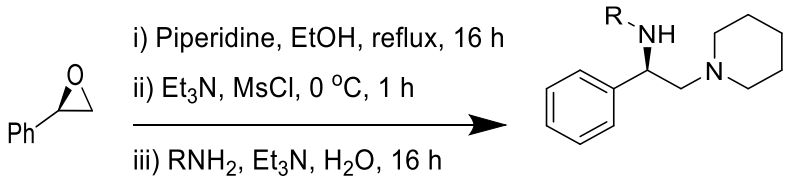


(*R*,*R*)-45

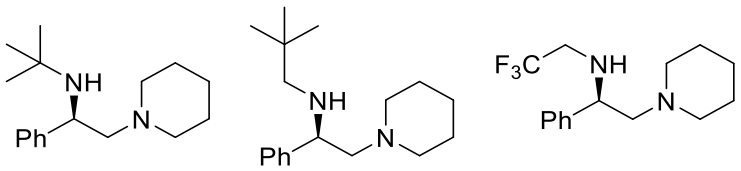
Figure 1.23. Chiral tetramine supplied by Prof Armen Zakarian

1.16.1 Synthesis of chiral diamines

Initially, we synthesised a range of additional chiral diamines using a known literature procedure **(Scheme 1.40)**.[111]



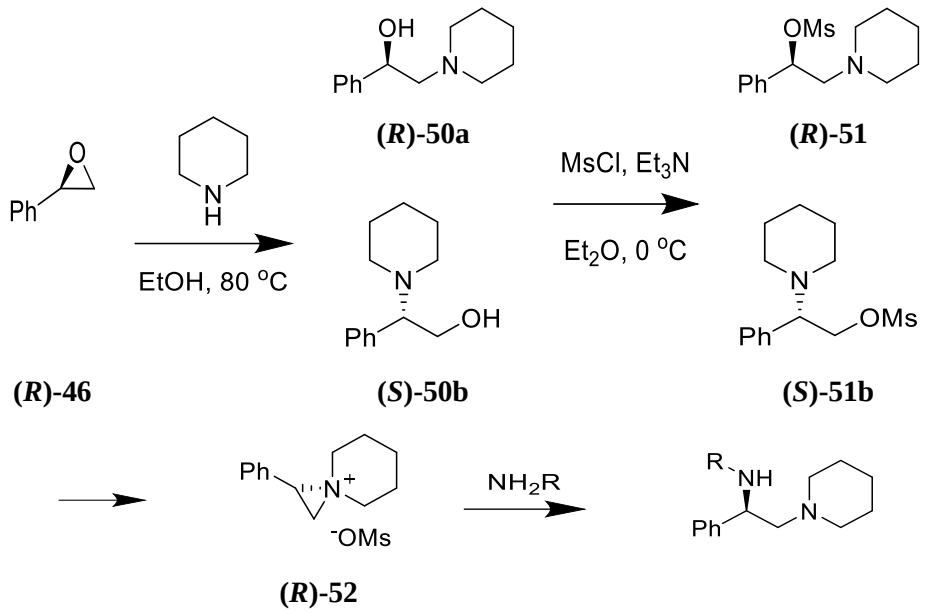
(*R*)-46



(*R*)-47, 78% **(*R*)-48**, 77% **(*R*)-49**, 65%

Scheme 1.40. Synthesis of chiral amines

These compounds were synthesised over three steps from the commercially available chiral epoxide **(*R*)-46**. Initially, piperidine mediated ring opening of the chiral epoxide **(*R*)-46** resulted in the formation of amino alcohols **(*R*)-50a** and **(*S*)-50b**. Mesylation of these alcohols and subsequent nucleophilic displacement of this mesylate resulted in the formation of aziridinium ion **(*R*)-52**. This species was subsequently trapped using a range of substituted amines to yield the desired compounds in moderate to good yields **(Scheme 1.41)**.

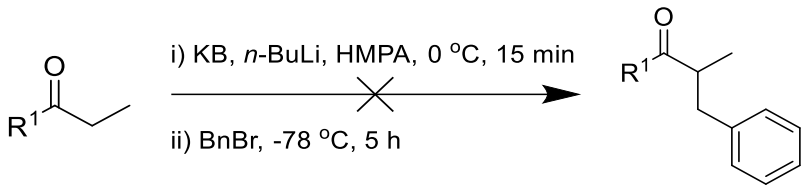


Scheme 1.41. Formation of chiral amines

1.16.2 Asymmetric α-alkylation reactions of ketones and *N,N*-DMHs using Koga's bases

With the chiral diamines and tetramine in hand, we sought to investigate if we could achieve similar levels of enantioselectivity using ketone substrates. Initially, we exposed both 3-pentanone **1** and propiophenone **2** to the conditions previously optimised by Zakarian. Within their publications, the Zakarian group detailed that the relative stoichiometry of the chiral amine and alkyl lithium reagent is a crucial reaction parameter to achieve high levels of asymmetric induction in these reactions. For this reason, immediately prior to all reactions, the concentration of *n*-BuLi was determined by titration against diphenylacetic acid. Unfortunately, all our reaction attempts failed to generate any conversion to α-alkylated product **(Table 1.8)**.

Table 1.8. Evaluation of Koga's Bases in asymmetric α-alkylation of ketones



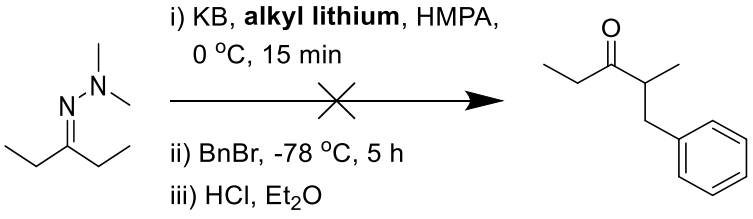
1, R^1 = Et
2, R^1 = Ph

3, R^1 = Et
10, R^1 = Ph

Entry	Ketone	Koga Base (1.2 equivs)
1	**1**	**(*R*,*R*)-45**
2	**1**	**(*R*)-47**
3	**1**	**(*R*)-48**
4	**1**	**(*R*)-49**
5	**2**	**(*R*,*R*)-45**
6	**2**	**(*R*)-47**
7	**2**	**(*R*)-48**
8	**2**	**(*R*)-49**

Following this, we next investigated the above transformation using *N*,*N*-DMHs **(Table 1.9)**. Disappointingly, none of the reactions described resulted in the formation of α-alkylated product. Failure of these reactions may be due a number of additional complicating factors present in our system, for example the number of possible azaenolate geometries. Additionally, unlike the well defined reactive chiral aggregate described by Zakarian, the precise structure of the reactive aggregate in our system is unknown.

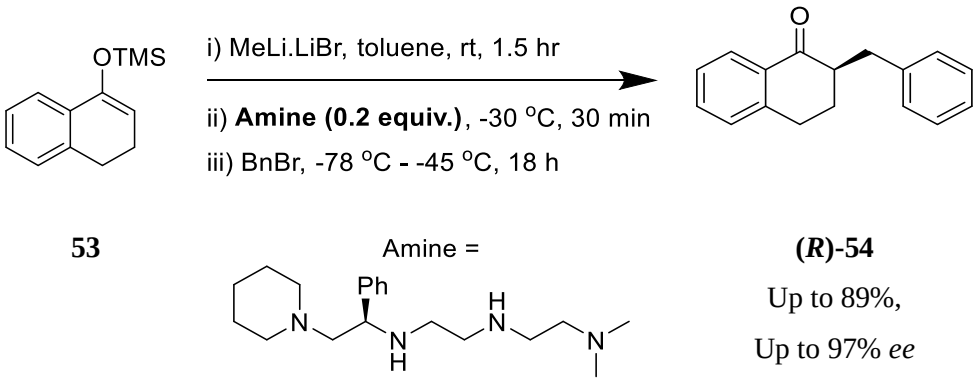
Table 1.9. Evaluation of Koga's Bases in asymmetric α-alkylation of *N,N*-DMHs



16 **3**

Entry	Alkyl lithium	Koga Base
1	*n*-BuLi	**(*R,R*)-45**
2	*n*-BuLi	**(*R*)-47**
3	*n*-BuLi	**(*R*)-48**
4	*n*-BuLi	**(*R*)-49**
5	*s*-BuLi	**(*R,R*)-45**
6	*s*-BuLi	**(*R*)-47**
7	*s*-BuLi	**(*R*)-48**
8	*s*-BuLi	**(*R*)-49**

Not discouraged by the above results, our final attempt to establish an asymmetric α-alkylation reaction of a ketone focused on the use of silyl enol ethers as protected ketones. Publications by Koga and co-workers described the construction of chiral quaternary carbon centres using achiral enolates derived from TMS enol ethers and chiral tetradentate ligands.[78, 112-114] Using this strategy, asymmetric alkylation,[114] aldol[115] and Michael[116] reactions were achieved in excellent stereoselectivity and yield. In some cases, it was possible to conduct these transformations using sub-stoichiometric amounts of chiral amine **(Scheme 1.42)**.[117]



53 **(*R*)-54**

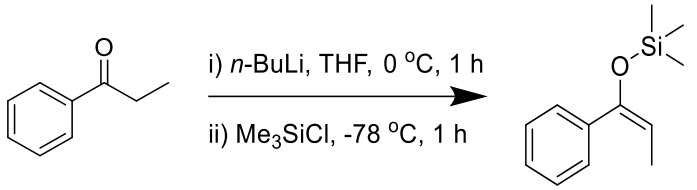
Up to 89%,

Up to 97% *ee*

Scheme 1.42. Asymmetric α-benzyaltion of **53** by Koga

We wondered if it would be possible to expand this methodology to include an asymmetric α-alkylation reaction of an acyclic ketone. Once again, we chose the TMS enol ether of both 3-

pentanone **1** and propiophenone **2** to conduct these studies. Synthesis of both compounds was conducted following a known procedure **(Scheme 1.43)**. However, it was not possible to isolate the TMS enol ether of 3-pentanone due to degradation of this compound during purification.

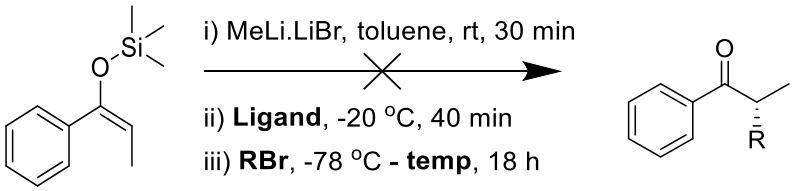


2 **55**, 73%

Scheme 1.43. Synthesis of **55**

Disappointingly, exposure of **55** to reaction conditions similar to that described by Koga did not produce any promising results, with no evidence of α-alkylated products resulting from any of reaction conditions attempted **(Table 1.10)**. Altering the Koga base employed **(Table 1.10, entries 1 & 2)**, the alkylating agent **(Table 1.10, entries 3 & 4)** or warming the reaction to 0 °C proved unsuccessful **(Table 1.10, entries 5 & 6)**.

Table 1.10. Attempted asymmetric α-alkylation of TMS enol ether



55 **(*R*)-10**, R = Bn

(*R*)-56, R = allyl

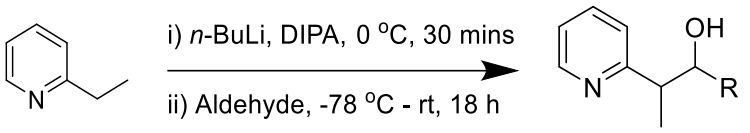
Entry	Ligand	RBr	Temperature (°C)
1	**(*R,R*)-45**	BnBr	-45
2	**(*R*)-47**	BnBr	-45
3	**(*R,R*)-45**	AllylBr	-45
4	**(*R*)-47**	AllylBr	-45
5	**(*R,R*)-45**	BnBr	0
6	**(*R*)-47**	BnBr	0
7	**(+)-27**	BnBr	0
8	**(*R,R*)-33**	BnBr	0

Additionally, we also investigated the use of (+)-sp **(+)-27** and diamine ***(R,R)*-33** as alternative diamines in the above transformation **(Table 1.10, entries 7 & 8)**. Once again, no α-alkylated product was obtained from these reactions.

1.16.3 Enantio- and diastereoselective aldol and Michael reactions of 2-alkyl pyridines using Koga's bases

Concurrent to the work described above, we also sought to expand upon the asymmetric transformations of 2-alkyl pyridines first published by Zakarian.[87] We sought to investigate two important classes of enolate reactions: **i)** an asymmetric aldol reaction and **ii)** an asymmetric conjugate addition reaction. Initially, we concentrated our efforts on the aldol reaction. We chose pyridine substrate 2-ethyl pyridine **57** as a suitable starting point. Initial reactions focused on determining a suitable aldol acceptor **(Table 1.11)**.

Table 1.11. Aldol reaction of 2-ethyl pyridine

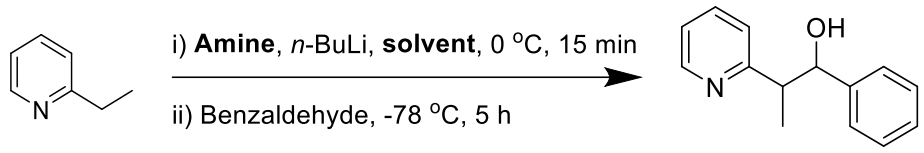


57 **58**, R = Ph, 54%

Entry	Aldehyde	Product
1	Benzaldehyde	**58**, 54%
2	Pivaldehyde	Starting material

Pleasingly, the reaction between **57** and benzaldehyde resulted in alcohol product **58**, albeit in modest yield of 54% **(Table 1.11, entry 1)**. Unfortunately, only starting material was recovered from the corresponding reaction with pivaldehyde **(Table 1.11, entry 2)**. Next, we focused on identifying the optimal reaction conditions for the asymmetric aldol reaction of **57**. We evaluated the diastereoselectivity of the reaction employing various amines in both THF and toluene solvent **(Table 1.12)**.

Table 1.12. Optimal reaction conditions for the aldol reaction of **57**



57 **58**

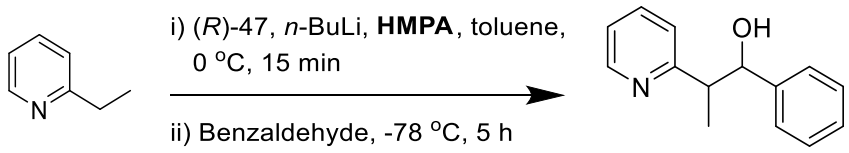
Entry	Amine	THF		Toluene	
		Yield	*dr*	Yield	*dr*
1	**(*R*,*R*)-45**	15%	56:44	24%	73:27
2	**(*R*)-47**	20%	57:43	28%	73:27
3	**(*R*)-48**	23%	58:42	32%	59:41
4	**(*R*)-49**	-[a]	-[a]	12%	47:53

[a] No evidence of desired aldol product.

Comparably low yields and disappointing diastereoselectivites were achieved for the reactions conducted using THF as the reaction solvent **(Table 1.12, entries 1, 2 & 3)**. When chiral diamine **(*R*)-49** was used, no evidence for the formation of aldol product was present in the ^{1}H NMR spectrum of the crude reaction mixture **(Table 1.12, entry 4)**. However, both the yields obtained and the levels of diastereoselectivity achieved in these reactions were higher when toluene was used as the reaction solvent. Similar yields and identical diastereoselectivites resulted from the use of tetramine **(*R*,*R*)-45** and diamine **(*R*)-47 (Table 1.12, entries 1 & 2)**. Although a marginal increase in yield was observed when **(*R*)-48** was used, this corresponded with a decrease in diastereoselectivity **(Table 1.12, entry 3)**. Finally, once again diamine **(*R*)-49** faired poorest in this reaction in toluene and resulted in the lowest diastereoselectivity achieved **(Table 1.12, entry 4)**.

Our final attempt to improve the stereoselectivity of this reaction focused on the use of hexamethylphosphoramide (HMPA) as an additive. HMPA is commonly used as an additive for alkyl lithium reagents because of the effect it has on the aggregation states of these compounds. It often results in an increase in reactivity and selectivity in alkyl lithium mediated transformations. Zakarian and co-workers again noted the importance of the relative stoichiometry of the chiral amine and additive and the impact slight modifications had on the observed enantioselectivity of the alkylation reactions detailed.[87] For this reason, we screened a range of HMPA equivalents in combination with diamine **(*R*)-47** in our reaction **(Table 1.13)**.

Table 1.13. HMPA equivalents screen for the aldol reaction of **57**



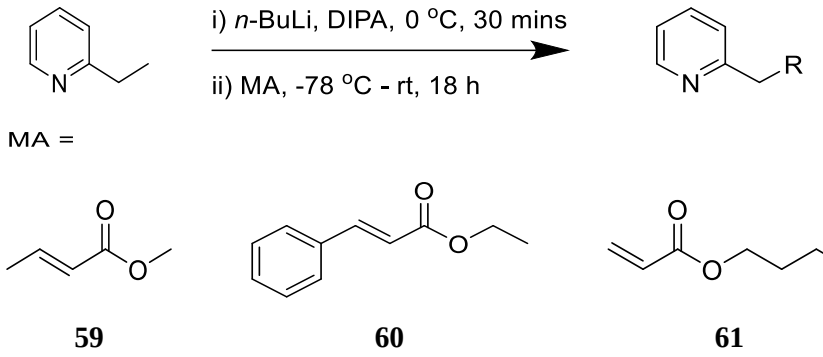
57 **58**

Entry	HMPA equivalents	Yield	*dr*	*ee* (Major)	*ee* (Minor)
1	0	28%	73:27	58%	0%
2	0.25	20%	57:43	50%	32%
3	0.5	36%	55:45	35%	10%
4	0.75	43%	58:42	56%	10%
5	1	60%	58:42	58%	10%
6	1.25	62%	61:39	62%	16%
7	1.5	51%	65:35	30%	14%

Pleasingly, an improvement in yield was observed with increasing equivalents of HMPA up to a maximum yield of 62% when 1.25 equivalents was used **(Table 1.13, entries 1 - 6)**. Use of 1.25 equivalents of HMPA also represented the greatest level of enantioselectivity observed in this reaction **(Table 1.13, entry 6)**. After this, further increasing the equivalents of HMPA to 1.5 equivalents led to a decrease in the yield and enantioselectivity obtained **(Table 1.13, entry 7)**. More importantly however, the addition of HMPA to our reaction system resulted in a decrease in the diastereoselectivity of the aldol reaction of **57**, compared to the corresponding reaction without the additive. The greatest *dr* observed was when 1.5 equivalents of HMPA was used, however this was still a decreased selectivity compared to the HMPA-free reaction **(Table 1.13, entries 1 & 7**). Collectively, the stereoselectivity observed in these reactions was disappointing. No obvious trends with respect to increasing *ee* and *dr* could be extrapolated from these reactions. This result is suggestive that unlike the corresponding asymmetric alkylation reaction, no single highly structured three-dimensional reaction intermediate, conducive to a stereoselective transformation, is present in this reaction.

Due to the disappointing results described above, we turned our attention towards the second important class of reactions and focused on attempts to develop an asymmetric Michael reaction of 2-alkyl pyridines. We initially screened a range of Michael acceptors (MAs) to determine if they would undergo an α,β-addition reaction with 2-ethyl pyridine **(Table 1.14).**

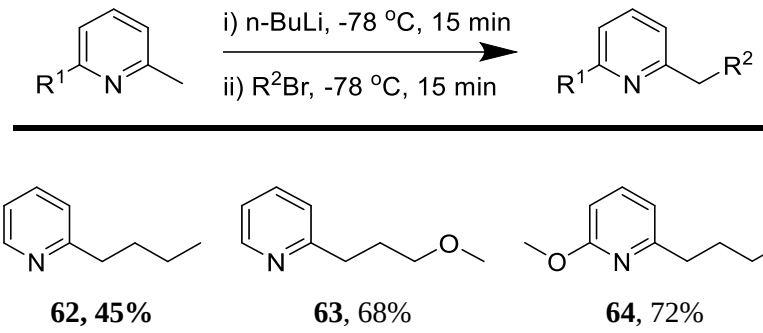
Table 1.14. Attempted Michael reactions of 2-alkyl pyridines



59 **60** **61**

Entry	MA	Result
1	**59**	Complex mixture
2	**60**	Complex mixture
3	**61**	Complex mixture

In all cases, the reaction resulted in a complex mixture of unidentified products. No evidence for the formation of the desired Michael addition product was present in the ^{1}H NMR spectrum of each reaction. For this reason, we decided to alter the 2-alkyl pyridine employed. We chose the substrates which resulted in the greatest levels of enantioselectivity for the α-alkylation reaction of 2-alkyl pyridines described by Zakarian and co-workers.[87] These substrates were synthesised according to a known literature procedure from the corresponding 2-methyl pyridines **(Scheme 1.45)**.



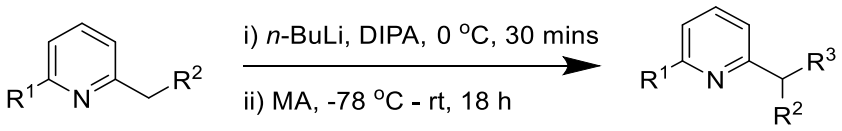
62, 45% **63**, 68% **64**, 72%

Scheme 1.44. Synthesis of 2-alkyl pyridines

We were interested to examine the reactivity of compounds **63** and **64** in a conjugate addition reaction as we wondered whether the additional functionality of the pyridine would impact its reactivity. The additional chelation points of these substrates had resulted in high levels of enantioselectivity for the α-alkylation reaction. Once again, we screened these 2-alkyl

pyridines in a Michael addition reaction with the various Michael acceptors used previously **(Table 1.15)**.

Table 1.15. Attempted Michael reactions of 2-alkyl pyridine substrates

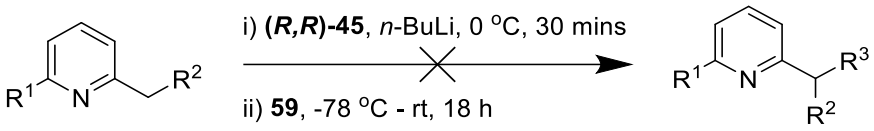


Entry	2-alkyl pyridine	MA	Result
1	**62**	**59**	Complex mixture
2	**63**	**59**	Complex mixture
3	**64**	**59**	Complex mixture

In all cases, the reaction resulted in a complex mixture of unidentified products **(Table 1.15, entries 1, 2 & 3)**. No evidence for the formation of the desired Michael addition product was present in the ^{1}H NMR spectrum of each reaction mixture.

In a final attempt to establish a protocol for an asymmetric Michael reaction of 2-alkyl pyridines we conducted a reaction using chiral tetramine **(*R,R*)-45**. We wondered if the addition of a chiral ligand would sufficiently alter the reactivity compared to the LDA mediated reaction and promote a Michael reaction **(Table 1.16)**.

Table 1.16. Attempted asymmetric Michael reaction attempts



Entry	2-alkyl pyridine	Result
1	**62**	Complex mixture
3	**64**	Complex mixture

Once again, both reactions resulted in a complex mixture of products with no evidence for the formation of the desired Michael addition product in each case **(Table 1.16, entries 1 & 2)**. Due to these disappointing results, we decided to no longer pursue this avenue of research.

1.17 Conclusions & Future Work

In summary, a range of asymmetric transformations for ketone enolates and related azaenolates were examined in this chapter. Racemic and enantioenriched α-alkylated ketones were synthesised throughout. Efforts to develop a direct asymmetric α-alkylation reaction (in useful *ee*) of a ketone using a chiral ligand strategy proved unsuccessful.

A number of reaction parameters were investigated in an effort to improve the enantioselectivity of the chiral ligand protocol previously developed within the McGlacken group. The use of challenging electrophiles bearing additional functionality was examined in addition to the evaluation of a range of previously unexplored reaction solvents. Attempts to utilise a prochiral ACC hydrazone in place of *N*,*N*-DMHs were also undertaken.

A series of chiral ligands were synthesised and examined as alternative chiral ligands to (+)-sp in a series of organolithium mediated transformations. Whilst one ligand yielded comparable results to (+)-sp for an α-alkylation reaction of an *N*,*N*-DMH, its breadth of applicability was less than (+)-sp.

An investigation into the use of chiral lithium amides for an asymmetric α-alkylation reaction of an acyclic ketone was also undertaken. A method for an asymmetric aldol reaction of 2-alkyl pyridines was developed, although the overall levels of stereoselectivity observed in this transformation were modest. Finally, attempts were made to develop an asymmetric Michael addition reaction for a series of 2-alkyl pyridines.

Future work in this area of research is expected to focus on the direct asymmetric α-alkylation of ketones. Pleasingly, during this work we achieved a 10% *ee* for the direct asymmetric α-alkylation of 3-pentanone using BnBr. Although the level of enantioenrichment that resulted from this reaction was low, this remains a promising result. Future work will focus on further investigating this. One avenue of interest which will be pursued is the addition of additives to the reaction in order to improve the level of enantioselectivity.

It is expected the use of silyl enol ethers as ketone synthetic equivalents will be further investigated. For example, it would be interesting to examine the E/Z selectivity of a variety of 3-pentanone and propiophenone derived silyl enol ethers, and the effect of the enolate geometry on the resulting stereoselectivity of asymmetric transformations employing these substrates.

Future work will also consist of examining alternative classes of chiral ligand to affect a direct asymmetric α-alkylation reaction of a range of acyclic ketones. Previous work within the group determined that the use of bisoxazoline (BOX) ligands in combination with lithium proved ineffective in an asymmetric α-alkylation of *N*,*N*-DMHs.[118] However, the use of these ligands in combination with other metals, Mg for example, remains unexplored in this context **(Figure 1.24)**.

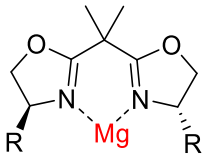
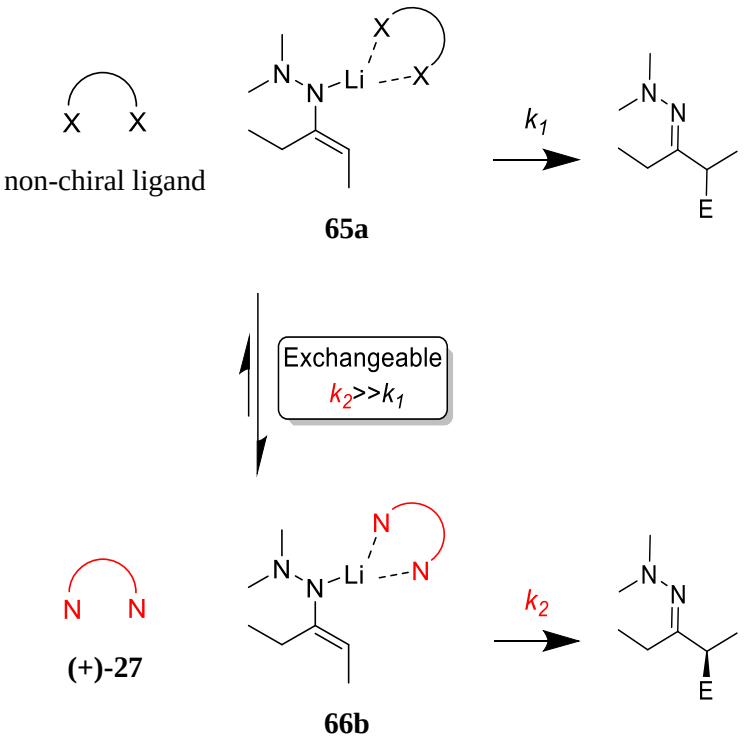


Figure 1.24. Mg/BOX complexes

The overarching aim of this project remains the development of a catalytic chiral ligand protocol for the asymmetric α-alkylation of *N*,*N*-DMHs **(Scheme 1.45).** Future work will be directed to achieving this aim.



Scheme 1.45. Catalytic ligand exchange approach

For this approach to be possible, certain criteria must be met: **i)** the chiral ligand must be exchangeable with a non-chiral ligand and **ii)** the rate of alkylation of the azaenolate **66b** must be more rapid than the rate of alkylation of azaenolate **65a**. If k_2 is greater than k_1, the resulting equilibrium will funnel through azaenolate **66b** and the chiral alkylated hydrazone would be formed preferentially.

Additional future work will focus on the use of continuous flow chemistry for the development of a protocol for an asymmetric α-alkylation reaction of a ketone and will be discussed further in Chapter II.

Experimental

1.18 General procedures

Solvents and reagents employed were dried prior to use as follows: THF and toluene were distilled from sodium/benzophenone ketyl[119] and stored over 3Å molecular sieves (20% w/v) in a Young's flask. Diisopropylamine was distilled from calcium hydride. The concentration of *n*-BuLi in hexanes and *s*-BuLi in hexanes were determined by titration with diphenylacetic acid.[120] All other reagents were purchased from Sigma Aldrich, Fluorochem, Alfa Aesar and Fisher Scientific and used without further purification, unless otherwise noted. All non-aqueous experiments were carried out under an oxygen-free nitrogen atmosphere, using flame-dried glassware and Schlenk set-up.

Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin Layer Chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV light and potassium permanganate staining.
Melting points (m.p.) were recorded on a Thomas Hoover Capillary Melting Point apparatus or an Electrothermal IA9300 Digital Melting Point apparatus.

Infrared spectra were recorded on a Perkin-Elmer FTIR UATR2 spectrophotometer as neat samples or on a Perkin-Elmer FTIR Paragon 1000 spectrophotometer. For the latter, liquid samples were examined neat as a thin film on an NaCl plate. Solid samples were dissolved in DCM and dispersed on an NaCl plate as a thin film. The DCM was allowed to evaporate before any measurement was recorded.

NMR spectra were run in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard at 300 K, unless otherwise stated. ^{1}H NMR (600 MHz) spectra, ^{1}H NMR (500 MHz) spectra, ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively. ^{13}C NMR (150 MHz) spectra, ^{13}C NMR (125 MHz) spectra, ^{13}C NMR (100 MHz) spectra and ^{13}C NMR (75.5 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively in proton decoupled mode. All spectra were recorded at University College Cork. Chemical shifts δ_H and δ_C are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz) as observed and are uncorrected. Splitting patterns in ^{1}H NMR spectra are designated as a singlet (s), doublet (d), doublet of

doublets (dd), doublet of quartets (dq), triplet (t), triplet of doublets (dt), quartet (q), quintet (quin), sextet (sext) and multiplet (m). For ^{13}C NMR spectra the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. ^{1}H–^{1}H COSY, HSQC and HMBC experiments were performed to aid the NMR assignment of novel chemical structures. An arbitrary numbering system was employed to aid the assignment of ^{1}H NMR and ^{13}C NMR spectra.

LRMS were recorded on a Waters Quattro Micro Triple Quadrupole instrument in ESI mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. Samples were made up in acetonitrile. HRMS were recorded on a Waters LCT Premier ToF LC-MS instrument in ESI mode using 50% acetonitrile-water with 0.1% formic acid as eluent. HRMS were also recorded on a Waters Vion IMS instrument (SAA055K) with Waters Acquity I-class UPLC in electrospray ionization (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent and Leucine Enkephalin as reference solution. Samples were prepared in acetonitrile to a concentration of *ca.* 1 mg/mL.

Optical rotations were measured on an Autopol V Plus Automatic 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 expressed in units of 10^{-1} deg cm^2 g^{-1}. Specific rotations were employed to indicate the direction of enantioselection and optically active samples are given the prefix of (+) or (-).

Gas chromatography analysis was carried out on an Agilent Technologies 7820A GC System using a G4513A Series Injector and Astec Chiraldex™ G-TA fused silica capillary column, 20 m × 0.25 mm × 0.12 μm, purchased from Sigma Aldrich Supelco. Conditions for separation were determined using the following operating conditions as standard: flow rate equal to 1 mL/min, injection volume of 0.2 μL, split ratio of 10:1, front inlet temperature equal to 150 °C, detector temperature equal to 155 °C. Representative samples were prepared for GC analysis by flushing a solution of analyte in Et_2O (concentration of ca 2 mg/mL) through a silica plug. Due to the shortening length of the GC column over time, slight alterations to the analytical methods for known compounds were required.

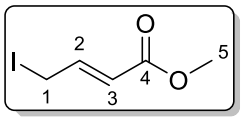
High performance liquid chromatography was performed using an Agilent 1200 Series HPLC system and a CHIRACEL® OD-3 column, 250 mm × 4.6 mm × 3.0 μm, purchased from Parc d'Innovation. Representative samples were prepared for HPLC analysis in hexane;IPA (90:10 to a concentration of ca 2 mg/mL). Samples were filtered using PTFE filters (13 mm diameter, 0.2 μm pore size) before analysis.

A Julabo FT902 cryocooler was used for low temperature reactions performed in batch.

1.18.1 Analysis of known and novel compounds

^{1}H NMR spectra, ^{13}C NMR spectra, IR and LRMS analyses were recorded for all previously reported compounds. For novel compounds, in addition to the aforementioned analyses, HRMS was also obtained. Optical rotations were used to assign absolute stereochemistry for known chiral compounds.

1.19 Synthesis of methyl 4-iodocrotonate, 22



To a stirred solution of 4-bromocrotonate (0.48 mL, 4 mmol) in acetone (10 mL) was added sodium iodide (1.20 g, 8 mmol) and the solution stirred at 55 ºC for 18 h. The reaction was cooled to rt and diluted with DCM (10 mL). The resulting suspension was washed with 10% $Na_2S_2O_4$ (10 mL), H_2O (10 mL), sat. NH_4Cl (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography (10:1, hexane: Et_2O) on silica gel yielded the title compound as a pale yellow oil (0.61 g, 67%). Spectroscopic characteristics were consistent with previously reported data.[121]

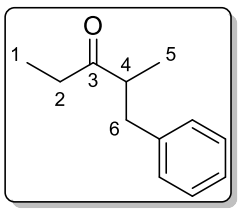
IR (NaCl) ν_{max}: 1731 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 3.74 (3H, s, H-5), 3.94 (2H, dd, *J* = 8.3, 0.9 Hz, H-1), 5.95 (1H, dt, *J* = 15.4, 1.2 Hz, H-3), 7.01 (1H, dt, *J* = 15.5, 7.0 Hz, H-2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 0.8 (C-1), 51.8 (C-5), 122.8 (C-3), 143.8 (C-2), 166.0 (C-4) ppm. MS (ESI) *m/z*: 227 $[M+H]^+$.

1.20 Synthesis of racemic α-alkylated ketones

General procedure for the synthesis of racemic α-alkylated ketones

To a Schlenk tube under N_2 atmosphere containing anhydrous THF and commercially available LDA (1.1 equiv.) at -78 ºC was added ketone (1 equiv.), dropwise. This solution was stirred at -78 ºC for 1 h before dropwise addition of electrophile (1.2 equiv.). The resulting mixture was allowed to warm to rt over 16 h. The reaction was quenched with H_2O (2 mL) and diluted with Et_2O (10 mL). The resulting solution was washed with H_2O (3 x 10 mL), the organic layer dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography on silica gel yielded the racemic alkylated ketone.

2-Methyl-1-phenylpentan-3-one, 1

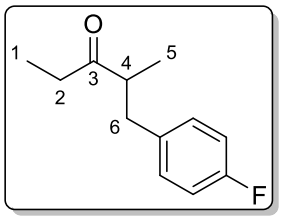


Prepared according to the general procedure outlined above using 3-pentanone (0.11 mL, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). Purification by column chromatography (10:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.030 g, 17%). Spectroscopic characteristics were consistent with previously reported data.[75]

IR (ATR) ν_{max}: 3086, 2877 (C-H stretch), 1713 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.3 Hz, H-1), 1.08 (3H, d, *J* = 6.8 Hz, H-5), 2.25 (1H, dq, *J* = 16.9,

7.3 Hz, one of H-2), 2.43 (1H, dq, *J* = 16.9, 7.3 Hz, one of H-2), 2.56 (1H, dd, *J* = 13.2, 7.3 Hz, one of H-6), 2.83 (1H, sext, *J* = 6.9 Hz, H-4), 2.97 (1H, dd, *J* = 13.2, 7.3 Hz, one of H-6), 7.07-7.32 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.6 (C-1), 16.6 (C-5), 35.2 (C-2), 39.3 (C-6), 47.9 (C-4), 126.2 (Ar-CH), 128.4 (2 × Ar-CH), 128.9 (2 × Ar-CH), 139.9 (Ar-C), 214.7 (C-3) ppm. MS (ESI) *m/z*: 177 $[M+H]^+$.

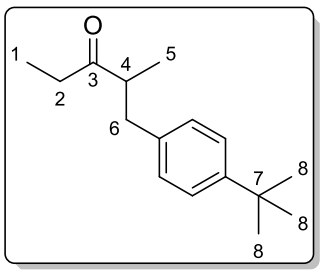
1-(4-Fluorophenyl)-2-methylpentan-3-one, 4



Prepared according to the general procedure outlined above using 3-pentanone (0.11 mL, 1 mmol) and 4-fluorobenzyl bromide (0.15 mL, 1.2 mmol). Purification by column chromatography (10:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.109 g, 26%). Spectroscopic characteristics were consistent with previously reported data.[122]

IR (ATR) ν_{max}: 3961, 2874 (C-H stretch), 1712 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.2 Hz, H-1), 1.07 (3H, d, *J* = 7.0 Hz, H-5), 2.37 (1H, dq, *J* = 17.9, 7.2 Hz, one of H-2), 2.43 (1H, dq, *J* = 17.8, 7.3 Hz, one of H-2), 2.54 (1H, dd, *J* = 13.3, 6.9 Hz, one of H-6), 2.81 (1H, sext, *J* = 7.0 Hz, H-4), 2.94 (1H, dd, *J* = 13.4, 7.4 Hz, one of H-6), 6.90-6.98 (2H, m, Ar-H), 7.06-7.12 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.5 (C-1), 16.7 (C-5), 35.2 (C-2), 38.4 (C-6), 47.9 (C-4), 115.1 (d, $^2J_{C\text{-}F}$ = 20.8 Hz, 2 × Ar-CH), 130.3 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, 2 × Ar-CH), 135.5 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, Ar-C), 161.5 (d, $^1J_{C\text{-}F}$ = 243.9 Hz, Ar-C), 214.5 (C-3) ppm. MS (ESI) *m/z*: 195 $[M+H]^+$.

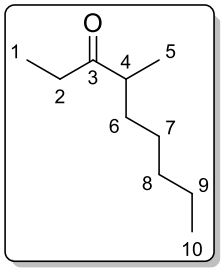
1-(4-(*Tert*-butyl)phenyl)-2-methylpentan-3-one, 5



Prepared according to the general procedure outlined above using 3-pentanone (0.11 mL, 1 mmol) and 4-*tert*-butylbenzyl bromide (0.22 mL, 1.2 mmol). Purification by column chromatography (15:1, hexane:Et_2O) yielded the title compound as a colourless oil (0.122 g, 52%). Spectroscopic characteristics were consistent with previously reported data.[123]

IR (NaCl) ν_{max}: 2965, 2873 (C-H stretch), 1714 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.2 Hz, H-1), 1.08 (3H, d, *J* = 6.8 Hz, H-5), 1.30 (9H, s, H-8), 2.30 (1H, dq, *J* = 17.7, 7.4 Hz, one of H-2), 2.44 (1H, dq, *J* = 17.7, 7.3 Hz, one of H-2), 2.53 (1H, dd, *J* = 13.3, 7.3 Hz, one of H-6), 2.82 (1H, sext, *J* = 6.8 Hz, H-4), 2.95 (1H, dd, *J* = 13.2, 6.9 Hz, one of H-6), 7.05-7.08 (2H, m, Ar-H), 7.24-7.30 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.6 (C-1), 16.6 (C-5), 31.4 (C-8), 34.4 (C-7), 35.0 (C-2), 38.7 (C-6), 47.9 (C-4), 125.2 (2 × Ar-CH), 128.6 (2 × Ar-CH), 136.7 (Ar-C), 149.0 (Ar-C), 214.9 (C-3) ppm. MS (ESI) *m/z*: 233 $[M+H]^+$.

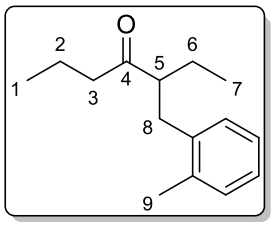
4-Methylnonan-3-one, 6



Prepared according to the general procedure outlined above using 3-pentanone (0.11 mL, 1 mmol) and 1-iodopentane (0.16 mL, 1.2 mmol). Purification by column chromatography (10:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.058 g, 37%). Spectroscopic characteristics were consistent with previously reported data.[75]

IR (NaCl) ν_{max}: 2961, 2874 (C-H stretch), 1715 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, *J* = 6.9 Hz, H-10), 1.04 (3H, t, *J* = 7.3 Hz, H-1), 1.05 (3H, t, *J* = 6.9 Hz, H-8), 1.19-1.35 (7H, m, one of H-6, H-7, H-8 and H-9), 1.58-1.68 (1H, m, one of H-6), 2.38-2.58 (3H, m, H-2 and H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.8 (C-1), 14.0 (C-10), 16.4 (C-5), 22.5, 27.0, 31.9 (C-7, C-8 and C-9), 33.1 (C-6), 34.2 (C-2), 46.1 (C-4), 215.5 (C-3) ppm. MS (ESI) *m/z*: 157 $[M+H]^+$.

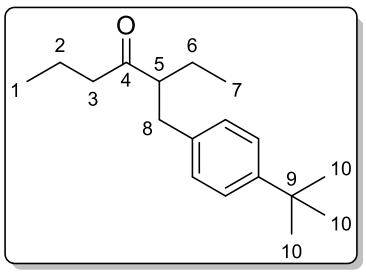
3-(2-Methylbenzyl)heptan-4-one, 8



Prepared according to the general procedure outlined above using 4-heptanone (0.14 mL, 1 mmol) and 2-methylbenzyl bromide (0.16 mL, 1.2 mmol). Purification by column chromatography (15:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.099 g, 38%). Spectroscopic characteristics were consistent with previously reported data.[90]

IR (NaCl) ν_{max}: 2975, 2878 (C-H stretch), 1713 (C=O stretch, m) cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.79, 0.88 (2 × 3H, t, *J* = 7.4 Hz, H-1, H-7), 1.35-1.78 (4H, m, H-2 and H-6), 2.08 (1H, dt, *J* = 17.4 Hz, 7.4 Hz, one of H-3), 2.19-2.25 (1H, m, one of H-3), 2.31 (3H, s, H-9), 2.63-2.92 (3H, m, H-5 and H-8), 6.99-7.24 (4H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9, 13.7 (C-1 and C-7), 16.6 (C-2), 19.4 (C-9), 24.9 (C-6), 35.1 (C-8), 45.9 (C-3), 53.9 (C-5), 125.9 (Ar-CH), 126.3 (Ar-CH), 129.7 (Ar-CH), 130.4 (Ar-CH), 136.0 (Ar-C), 138.0 (Ar-C), 214.4 (C-4) ppm. MS (ESI) *m/z*: 218 $[M+H]^+$.

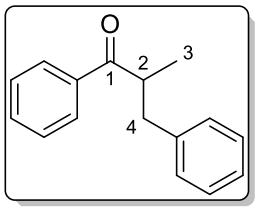
3-(4-(*Tert*-butyl)benzyl)heptan-4-one, 9



Prepared according to the general procedure outlined above using 4-heptanone (0.14 mL, 1 mmol) and 4-*tert*-butylbenzyl bromide (0.18 mL, 1.2 mmol). Purification by column chromatography (15:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.109 g, 42%). Spectroscopic characteristics were consistent with previously reported data.[90]

IR (NaCl) ν_{max}: 2962, 2933, 2874 (C-H stretch), 1713 (C=O stretch, m) cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.78, 0.87 (2 × 3H, t, *J* = 7.4 Hz, H-1 and H-7), 1.29 (9H, s, H-10), 1.39-1.69 (4H, m, H-2 and H-6), 2.13 (1H, dt, *J* = 17.1, 7.1 Hz, one of H-3), 2.28 (1H, dt, *J* = 17.1, 7.1 Hz, one of H-3), 2.62 (1H, dd, *J* = 12.5, 6.0 Hz, one of H-8), 2.66-2.77 (1H, m, H-3), 2.83 (1H, dd, *J* = 12.3, 7.5 Hz, one of H-8), 7.04-7.08 (2H, m, Ar-H), 7.26-7.30 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.8, 13.7 (C-1 and C-7), 16.6 (C-2), 24.2 (C-6), 31.4 (C-10), 34.4 (C-9), 37.2 (C-8), 45.5 (C-3), 55.5 (C-5), 125.2 (2 × Ar-CH), 128.5 (2 ×Ar-CH), 136.8 (Ar-C), 149.0 (Ar-C), 214.5 (C-4) ppm. MS (ESI) *m/z*: 261 $[M+H]^+$.

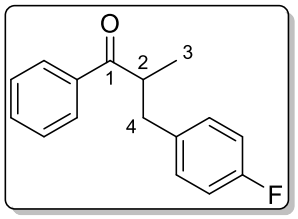
2-Methyl-1,3-diphenylpropan-1-one, 10



Prepared according to the general procedure outlined above using propiophenone (0.13 mL, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). Purification by column chromatography (20:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.058 g, 26%). Spectroscopic characteristics were consistent with previously reported data.[124]

IR (NaCl) ν_{max}: 3085, 2931 (C-H stretch), 1681 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, d, *J* = 6.8 Hz, H-3), 2.69 (1H, dd, *J* = 13.7, 7.7 Hz, one of H-4), 3.17 (1H, dd, *J* = 13.7, 6.2 Hz, one of H-4), 3.74 (1H, sext, *J* = 7.1 Hz, H-2), 7.10-7.32 (5H, m, Ar-H), 7.41-7.46 (2H, m, Ar-H), 7.51-7.56 (1H, m, Ar-H), 7.90-7.93 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.4 (C-3), 39.4 (C-4), 42.8 (C-2), 126.2 (Ar-CH), 128.3 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.1 (2 × Ar-CH), 132.9 (Ar-CH), 136.5 (Ar-C), 140.0 (Ar-C), 203.7 (C-1) ppm. MS (ESI) *m/z*: 225 $[M+H]^+$.

3-(4-Fluorophenyl)-2-methyl-1-phenylpropan-1-one, 11

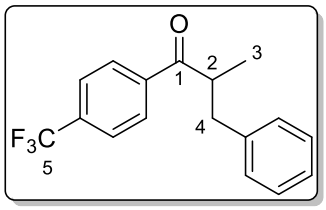


Prepared according to the general procedure outlined above using propiophenone (0.13 mL, 1 mmol) and 4-fluorobenzyl bromide (0.15 mL, 1.2 mmol). Purification by column chromatography (20:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.116 g, 48%). Spectroscopic characteristics were consistent with previously reported data.[125]

IR (NaCl) ν_{max}: 2966, 2925, 2853 (C-H stretch), 1681 (C=O stretch) cm^{-1}.^{1}H NMR (600 MHz, $CDCl_3$): δ 1.20 (3H, d, *J* = 7.0 Hz, H-3), 2.68 (1H, dd, *J* = 13.9, 7.5 Hz, one of H-4), 3.13 (1H, dd, *J* = 13.7, 6.6 Hz, one of H-4), 3.71 (1H, sext, *J* = 7.1 Hz, H-2), 6.92-6.96 (2H, m, Ar-H), 7.13-7.17 (2H, m, Ar-H), 7.42-7.46 (2H, m, Ar-H), 7.52-7.56 (1H, m, Ar-H), 7.87-7.92 (2H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6 (C-3), 38.5 (C-4), 42.9 (C-2), 115.1 (d, $^{2}J_{C\text{-}F}$ = 21.1 Hz, 2 × Ar-CH), 128.3 (2 × Ar-CH), 128.7 (2 × Ar-CH), 130.5 (d, $^{3}J_{C\text{-}F}$ = 7.8 Hz,

2 × Ar-CH), 133.0 (Ar-CH), 135.6 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 136.4 (Ar-C), 161.5 (d, $^{1}J_{C\text{-}F}$ = 244.8 Hz, Ar-C), 203.6 (C-1) ppm. MS (ESI) *m/z*: 243 $[M+H]^{+}$.

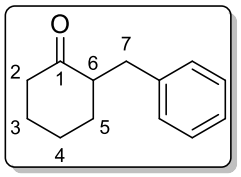
2-Methyl-3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-one, 12



Prepared according to the general procedure outlined above using 4-trifluoromethylpropiophenone (0.202 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). Purification by column chromatography (20:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.150 g, 52%). Spectroscopic characteristics were consistent with previously reported data.[126]

IR (NaCl) ν_{max}: 2973, 2935, 2863 (C-H stretch), 1688 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.9 Hz, H-3), 2.71 (1H, dd, *J* = 13.5, 7.3 Hz, one of H-4), 3.16 (1H, dd, *J* = 13.7, 6.7 Hz, one of H-4), 3.73 (1H, sext, *J* = 7.1 Hz, H-2), 7.14-7.28 (5H, m, Ar-H), 7.68 (2H, d, *J* = 8.3 Hz, Ar-H), 7.97 (2H, d, *J* = 8.0 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.3 (C-3), 39.4 (C-4), 43.3 (C-2), 123.7 (q, $^{1}J_{C\text{-}F}$ = 272.4 Hz, C-5), 125.7 (q, $^{3}J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-CH), 126.4 (Ar-CH), 128.5 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.0 (2 × Ar-CH), 134.2 (q, $^{2}J_{C\text{-}F}$ = 32.7 Hz, Ar-C), 139.3 (Ar-C), 139.6 (Ar-C), 202.8 (C-1) ppm. HRMS (ESI) *m/z* calcd for $C_{17}H_{16}F_3O[M+H]^{+}$: 293.1148, found 293.1138.

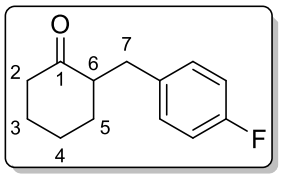
2-Benzylcyclohexan-1-one, 13



Prepared according to the general procedure outlined above using cyclohexanone (0.10 mL, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). Purification by column chromatography (15:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.107 g, 57%). Spectroscopic characteristics were consistent with previously reported data.[127]

IR (ATR) ν_{max}: 2934, 2860 (C-H stretch), 1708 (C=O stretch) cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (1H, dq, *J* = 12.2, 3.5 Hz, one of H-5), 1.50-1.88 (3H, m, one of H-3, H-4), 1.96 - 2.10 (2H, m, one of H-3, one of H-5), 2.27-2.47 (3H, m, H-2, one of H-7), 2.50-2.59 (1H, m, H-6), 3.23 (1H, dd, *J* = 13.7, 4.7 Hz, one of H-7), 7.12-7.22 (3H, m, Ar-H), 7.24-7.29 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (C-4), 28.1 (C-3), 33.4 (C-5), 35.5 (C-7), 42.2 (C-2), 52.5 (C-6), 126.0 (Ar-CH), 128.3 (2 × Ar-CH), 129.2 (2 × Ar-CH), 140.4 (Ar-C), 212.6 (C-1) ppm. MS (ESI) *m/z*: 189 $[M+H]^{+}$.

2-(4-Fluorobenzyl)cyclohexan-1-one, 14



Prepared according to the general procedure outlined above using cyclohexanone (0.10 mL, 1 mmol) and 4-fluorobenzyl bromide (0.15 mL, 1.2 mmol). Purification by column chromatography (4:1, hexane: Et_2O) yielded the title compound as a colourless oil (0.101 g, 49%). Spectroscopic characteristics were consistent with previously reported data.[128]

IR (ATR) ν_{max}: 2934, 2861 (C-H stretch), 1710 (C=O stretch) cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (1H, dq, *J* = 12.7, 3.1 Hz, one of H-5), 1.53-1.75 (2H, m, one of H-3, one of H-4), 1.78-1.89 (1H, m, one of H-4), 1.96-2.12 (2H, m, one of H-3, one of H-5), 2.25-2.56 (4H, m, H-2, H-6, one of H-7), 3.18 (1H, dd, *J* = 14.0, 4.0 Hz, one of H-7), 6.90-7.00 (2H, m, Ar-H), 7.09-7.13 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (C-4), 28.0 (C-3), 33.5 (C-5), 34.7 (C-7), 42.2 (C-2), 52.5 (C-6), 115.1 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, 2 × Ar-CH), 130.5 (d, $^2J_{C\text{-}F}$ = 7.6 Hz, 2 × Ar-CH), 136.0 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 161.4 (d, $^1J_{C\text{-}F}$ = 242.3, Hz, Ar-C), 212.4 (C-1) ppm. MS (ESI) *m/z*: 207 $[M+H]^+$.

1.21 Direct asymmetric α-alkylation of ketones

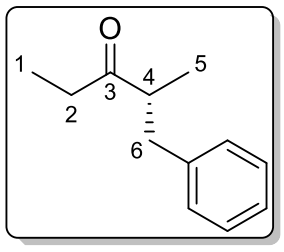
General procedure for attempts at the direct asymmetric α-alkylation of ketones using (+)-sparteine as a chiral ligand

To a Schlenk tube under a N_2 atmosphere containing anhydrous solvent (2 mL/mmol of ketone) was added (+)-sp (1.2 equiv.). Base was added at -78 °C and the resulting yellow solution allowed to stir for 15 min. Ketone (1.0 equiv.) was added dropwise at -78 °C and held at this temperature over 1 h. Electrophile (1.2 equiv.) was added dropwise and vigorously stirred for 30 min. Saturated NH_4Cl (0.5 mL) was added at -78 °C and the mixture allowed warm to rt. Et_2O (10 mL) was added and the mixture was washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude alkylated ketone.

Table 1.17. Direct asymmetric α-alkylation of ketones using (+)-sp

Entry	Ketone	Solvent	Base	*ee*
1	3-pentanone	toluene	*s*-BuLi	0%
2	3-pentanone	toluene	LDA	0%
3	3-pentanone	*i*-Pr_2O	*s*-BuLi	0%
4	3-pentanone	*i*-Pr_2O	LDA	0%
5	propiopheonone	toluene	s-BuLi	0%
6	propiopheonone	toluene	LDA	0%
7	propiopheonone	*i*-Pr_2O	*s*-BuLi	10%
8	propiopheonone	*i*-Pr_2O	LDA	0%

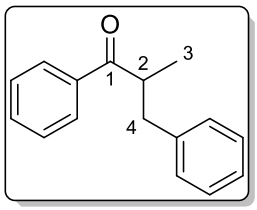
Methyl-1-phenylpentan-3-one, (*R*)-3



Prepared according to the general procedure outlined above 3-pentanone (0.21 mL, 2 mmol) and benzyl bromide (0.29 mL, 2.4 mmol). Purification by column chromatography (15:1, hexane: Et_2O) yielded title compound as a colourless oil (not isolated, 10% *ee*/racemic). Spectroscopic characteristics were consistent with previously reported for **3** and literature data.[75]

Enantioselectivity was determined by GC analysis: t_R = 23.0 (*R*-enantiomer) and 23.5 (*S*-enantiomer) (80 °C hold for 20 min, ramp 10 °C/min to 140 °C, hold for 5 min).

2-Methyl-1,3-diphenylpropan-1-one, 10



Prepared according to the general procedure above using propiophenone (0.27 mL, 2 mmol) and benzyl bromide (0.29 mL, 2.4 mmol). Purification by column chromatography (20:1, hexane: Et_2O) yielded the title compound as a colourless oil (not isolated, racemic). Spectroscopic characteristics were consistent with previously reported for **10** and literature data.[124]

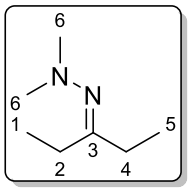
Enantioselectivity was determined by GC analysis: t_R = 73.0 (*R*-enantiomer) and 73.4 (*S*-enantiomer) (90 °C hold for 70 min, ramp 10 °C/min to 140 °C, hold for 5 min).

1.22 Synthesis of *N,N*-dimethylhydrazones

General procedure for the synthesis of *N,N*-dimethylhydrazones

Ketone (neat) was stirred with AcOH (few drops) and then treated with *N,N*-dimethylhydrazine (2 equiv.). The reaction was heated to reflux and reaction progress was monitored by TLC analysis. Upon completion, the reaction mixture was cooled to rt and water (10 mL) was added. The crude product was extracted with Et_2O (3 x 15 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude hydrazone, which was purified *via* Kugelrohr distillation at reduced pressure.

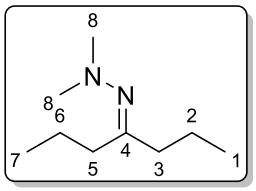
1,1–Dimethyl-2-(pentan-3-ylidene)hydrazine, 16



Prepared following the general procedure outlined above using 3-pentanone (4.91 g, 57 mmol) and *N,N*-dimethylhydrazine (6.85 g, 114 mmol). The crude hydrazone was purified by Kugelrohr distillation to yield the title compound as a colourless oil (4.44 g, 61%).[75]

IR (NaCl) ν_{max}: 2974, 2770 (C-H stretch), 1637 (C=N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (6H, t, *J* = 7.5 Hz, H-1 and H-5), 2.23 (2H, q, *J* = 7.5 Hz, H-2), 2.41 (6H, s, H-6), 2.44 (2H, q, *J* = 7.5 Hz, H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.0, 11.6 (C-1 and C-5), 22.6, 28.7 (C-2 and C-4), 47.5 (C-6), 174.3 (C-3) ppm. HRMS (ESI) *m/z* calcd for $C_7H_{17}N_2$ $[M+H]^+$:129.1392, found 129.1390.

2-(Heptan-4-ylidene)-1,1-dimethylhydrazine, 17



Prepared following the general procedure outlined above using 4-heptanone (2.50 g, 22 mmol) and *N*,*N*-dimethylhydrazine (2.64 g, 44 mmol). The crude hydrazone was purified by Kugelrohr distillation to yield the title compound as a yellow oil (2.81 g, 82%). Spectroscopic characteristics were consistent with previously reported data.[90]

IR (NaCl) ν_{max}: 2962, 2769 (C-H stretch), 1633 (C=N stretch) cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$): δ 0.89-0.99 (6H, m, H-1 and H-7), 1.45-1.64 (4H, m, H-2 and H-6), 2.15-2.20 (2H, m, H-3), 2.37-2.42 (8H, m, H-5 and H-8) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7, 14.3 (C-1 and C-7), 19.8, 20.5 (C-2 and C-6), 31.7, 37.9 (C-3 and C-5), 47.5 (C-8), 172.4 (C-4) ppm. MS (ESI) *m/z*: 157 $[M+H]^+$.

1.23 Asymmetric α-alkylation of *N,N*-dimethylhydrazones using (+)-sp

Procedure for the asymmetric α-alkylation of *N,N*-dimethylhydrazones using (+)-sparteine as a chiral ligand - *Procedure A*

To a Schlenk tube under N_2 atmosphere was added (+)-sp (1.2 equiv.) and anhydrous toluene (2 mL/mmol of hydrazone) and the resulting solution cooled to -78 °C. *s*-BuLi (1.1 equiv.) was added dropwise and the resulting yellow solution was stirred at this temperature for 30 mins. To this was added freshly distilled hydrazone (1 equiv.) dropwise and the reaction mixture was warmed to rt over 6 h. This solution was then cooled to -30 °C before dropwise addition of electrophile (1.2 equiv.), neat. The resulting solution was stirred for 18 h at this temperature before being quenched with NH_4Cl (2 mL). The reaction mixture was diluted with Et_2O (10 mL) and washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated *N,N*-dimethylhydrazone.

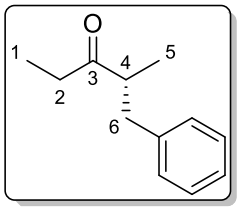
Procedure for the asymmetric α-alkylation of *N,N*-dimethylhydrazones using (+)-sparteine as a chiral ligand - *Procedure B*

To a Schlenk tube under N_2 atmosphere was added DIPA (1.2 equiv.) and anhydrous toluene (2 mL/mmol of hydrazone) and the resulting solution cooled to -78 °C. *n*-BuLi (1.1 equiv.) was added dropwise and the resulting solution was stirred at this temperature for 30 mins before (+)-sp was added dropwise at this temperature. After 30 mins, to this yellow solution was added freshly distilled hydrazone (1 equiv.) dropwise and the reaction mixture was warmed to rt over 6 h. This solution was then cooled to -30 °C before dropwise addition of electrophile (1.2 equiv.), neat. The resulting solution was stirred for 18 h at this temperature before being quenched with NH_4Cl (2 mL). The reaction mixture was diluted with Et_2O (10 mL) and washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated *N,N*-dimethylhydrazone.

Hydrolysis Procedure

To a stirred solution of crude α-alkylated *N,N*-dimethylhydrazone in Et_2O (5 mL/mmol) was added aq. HCl (0.5 mL/mmol, 4M). This biphasic mixture was vigorously stirred until TLC analysis showed complete consumption of crude hydrazone. The reaction was then diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated ketone. Purification by column chromatography on silica gel afforded pure α-alkylated ketone.

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-3

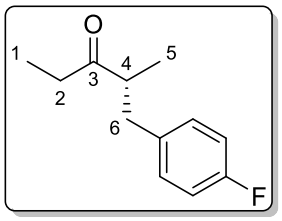


Prepared according to *Procedure A* outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). The hydrolysed product was purified by column chromatography (15:1, hexane: Et_2O) to yield the title compound as a colourless oil (0.067 g, 38% over two steps, 51% *ee*). Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[75]

$[\alpha]_D^{20}$ -29 (c 0.1, $CHCl_3$) (lit.[128] $[\alpha]_D^{23}$ +70.9 (c 1.1, $CHCl_3$, for 99% *ee*, *S* enantiomer).

Enantioselectivity was determined by GC analysis: t_R = 23.0 (*R*-enantiomer) and 23.5 (*S*-enantiomer) (80 ℃ hold for 20 min, ramp 10 ℃/min to 140 ℃, hold for 5 min).

(*R*)-1-(4-Fluorophenyl)-2-methylpentan-3-one, (*R*)-4

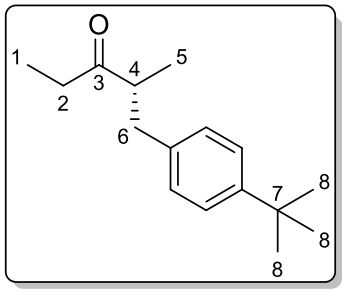


Prepared according to *Procedure A* outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and 4-fluorobenzyl bromide (0.15 mL, 1.2 mmol). The hydrolysed product was purified by column chromatography (15:1, hexane: Et_2O) to yield the title compound as a colourless oil (0.119 g, 61% over two steps, 44% *ee*). Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[75]

$[\alpha]_D^{20}$ -7.9 (c 0.1, $CHCl_3$) (lit.[75] $[\alpha]_D^{20}$ +7.3 (c 0.22, Et_2O, for 40% ee, *S* enantiomer).

Enantioselectivity was determined by GC analysis: t_R = 33.5 (*R*-enantiomer) and 34.2 (*S*-enantiomer) (80℃ hold for 30 min, ramp 10℃/min to 140℃, hold for 5 min).

(*R*)-1-(4-(*tert*-butyl)phenyl)-2-methylpentan-3-one, (*R*)-5

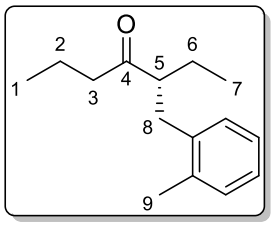


Prepared according to *Procedure A* outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and 4-*tert*-butylbenzyl bromide (0.18 mL, 1.2 mmol). The hydrolysed product was purified by column chromatography (15:1, hexane: Et_2O) to yield the title compound as a colourless oil (0.098 g, 42% over two steps, 42% *ee*). Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[75]

$[\alpha]_D^{20}$ -19.7 (c 0.1, $CHCl_3$) (lit.[76] $[\alpha]_D^{20}$ -25.1 (c 1.0, Et_2O, for 42% *ee*, *S* enantiomer).

Enantioselectivity was determined by GC analysis: t_R = 12.9 (*R*-enantiomer) and 13.4 (*S*-enantiomer) (140℃ hold for 30 min).

(*R*)-3-(2-Methylbenzyl)heptan-4-one, (*R*)-8

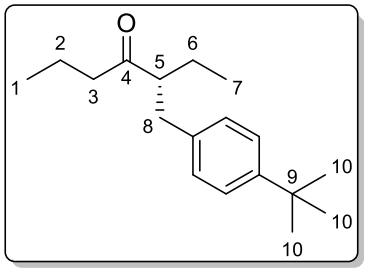


Prepared according to *Procedure B* outlined above using 2-(heptan-4-ylidene)-1,1-dimethylhydrazine (0.156 g, 1 mmol) and 2-methylbenzyl bromide (0.16 mL, 1.2 mmol). The hydrolysed product was purified by column chromatography (15:1, hexane: Et_2O) to yield the title compound as a colourless oil (0.118 g, 45% over two steps, 52% *ee*). Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[90]

$[\alpha]_D^{20}$ -26 (c 0.1, $CHCl_3$) (lit.[75] $[\alpha]_D^{20}$ -22.4 (c 0.5, CH_2Cl_2, for 32% *ee*, *R* enantiomer).

Enantioselectivity was determined by GC analysis: t_R = 22.3 (*R*-enantiomer) and 25.4 (*S*-enantiomer) (90 °C hold for 30 min, ramp 2 °C/min to 140 °C, hold for 5 min).

(*R*)-3-(4-(*Tert*-butyl)benzyl)heptan-4-one, (*R*)-9



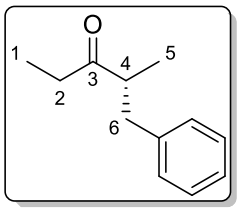
Prepared according to *Procedure B* outlined above using 2-(heptan-4-ylidene)-1,1-dimethylhydrazine (0.156 g, 1 mmol) and 4-*tert*-butylbenzyl bromide (0.18 mL, 1.2 mmol). The hydrolysed product was purified by column chromatography (15:1, hexane: Et_2O) to yield the title compound as a colourless oil (0.09 g, 39% over two steps, 40% *ee*). Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[90]

$[\alpha]_D^{20}$ -11.6 (c 0.1, $CHCl_3$) (lit.[75] $[\alpha]_D^{20}$ -13.9 (c 0.6, CH_2Cl_2, for 42% ee, *R* enantiomer).

Enantioselectivity was determined by GC analysis: t_R = 62.3 (*R*-enantiomer) and 62.8 (*S*-enantiomer) (90 °C hold for 30 min, ramp 2 °C/min to 140 °C, hold for 5 min).

1.24 Asymmetric α-alkylation of *N,N*-dimethylhydrazones using (+)-sp - *Solvent screen*

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-3



To a Schlenk tube under inert atmosphere was added (+)-sp (1.2 equiv.) and anhydrous solvent (2 mL/mmol of hydrazone) and the resulting solution cooled to -78 °C. *s*-BuLi (1.1 equiv.) was added dropwise and the resulting yellow solution was stirred at this temperature for 30 mins. To this was added freshly distilled 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) dropwise and the reaction mixture was warmed to rt over 6 h. This solution was then cooled to -30 °C before dropwise addition of benzyl bromide (0.14 mL, 1.2 mmol) neat. The resulting solution was stirred for 18 h at this temperature before being quenched with NH_4Cl (2 mL) and warmed to rt. The reaction mixture was diluted with

Et_2O (10 mL) and washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated *N*,*N*-dimethylhydrazone.

Hydrolysis Procedure

To a stirred solution of crude α-alkylated *N*,*N*-dimethylhydrazone in Et_2O (5 mL/mmol) was added aq. HCl (0.5 mL/mmol, 4M). This biphasic mixture was vigorously stirred until TLC analysis showed complete consumption of the crude hydrazone. The reaction was then diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated ketone.

Enantioselectivity was determined by GC analysis: t_R = 23.0 (*R*-enantiomer) and 23.5 (*S*-enantiomer) (80 °C hold for 20 min, ramp 10 °C/min to 140 °C, hold for 5 min).

Table 1.18. Solvent investigation

Entry	Solvent	*ee*[a]
1	Toluene	51%
2	Ethylbenzene	55%
3	Fluorobenzene	-[b]
4	Chlorobenzene	-[b]
5	*m*-Xylene	-[b]
6	Mesitylene	-[b]
7	Diethyl ether	33%
8	*i*-Pr_2O	40%
9	CPME	0%

[a] Due to the enantiomeric excess values observed in these reactions no compounds were isolated

[b] No evidence of desired α-alkylated ketone

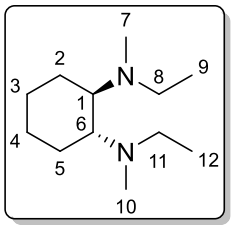
1.25 Synthesis of *trans*-1,2-cyclohexyldiamines

General procedure for the synthesis of (1*R*,2*R*)-dimethylcyclohexane-1,2-diamine derived ligands

To a stirred solution of dimethylcyclohexane-1,2-diamine (1 equiv.) in toluene (2 mL/mmol of diamine) was added triethylamine (2.2 equiv.) and alkyl bromide (2.5 equiv.). The resulting solution was stirred at reflux for 24 h. Upon cooling to rt, the solution was acidified to pH 1 with aq. HCl (1M). The aqueous layer was separated and the organic layer was washed with H_2O (2 x 10 mL). The combined aqueous layers were basified to pH 14 using aq. NaOH (10% (w/v)). The resulting cloudy suspension was extracted with Et_2O (3 x 15 mL). The combined

organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure.. Purification by Kugelrohr distillation afforded pure diamine.

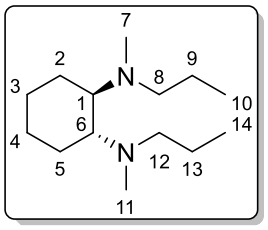
(1*R*,2*R*)-Diethyldimethylcyclohexane-1,2-diamine, (*R*,*R*)-32



Prepared according to the general procedure outlined above using (1*R*,2*R*)- dimethylcyclohexane-1,2-diamine (1.42 g, 10 mmol) and 1-bromoethane (1.9 mL, 25 mmol). Purification by Kugelrohr distillation yielded the title compound (0.91 g, 46%). Spectral characteristics were consistent with previously reported data.[97]

$[\alpha]_D^{25}$ - 36 (c 0.26, CH_2Cl_2). IR (NaCl) ν_{max}: 2955, 2791 (C-H stretch), 1168 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (6H, t, *J* = 7.2 Hz, H-9 and H-12), 1.11-1.28 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.69-1.80 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.24 (6H, s, H-7 and H-10), 2.49-2.65 (6H, m, H-1, H-6, H-8 and H-11) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.8 (C-9 and C-12), 25.1, 25.9 (C-2, C-3, C-4 and C-5), 36.3 (C-7 and C-10), 61.9 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_9H_{17}N$ $[M+H]^+$: 140.1434, found 140.1431.

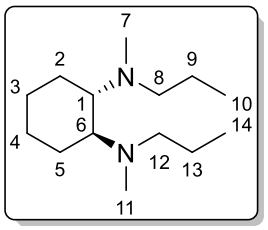
(1*R*,2*R*)-Dimethyldipropylcyclohexane-1,2-diamine, (*R*,*R*)-33



Prepared according to the general procedure outlined above using (1*R*,2*R*)- dimethylcyclohexane-1,2-diamine (0.71 g, 5 mmol) and 1-bromopropane (1.14 mL, 12.5 mmol). Purification by Kugelrohr distillation yielded the title compound (0.72 g, 64%). Spectral characteristics were consistent with previously reported data.[130]

$[\alpha]_D^{20}$ - 41 (c 0.1, $CHCl_3$). IR (NaCl) ν_{max}: 2957, 2790 (C-H stretch), 1166 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (6H, t, *J* = 7.4 Hz, H-10 and H-14), 0.98-1.28 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.38-1.53 (4H, m, H-9 and H-13), 1.62-1.82 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.23 (6H, s, H-7 and H-11), 2.34-2.58 (6H, m, H-1, H-6, H-7 and H-14) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.1 (C-10 and C-14), 21.6 (C-9 and C-13), 25.7, 25.9 (C-2, C-3, C-4 and C-5), 36.5 (C-7 and C-11), 56.6 (C-8 and C-12), 63.2 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{14}H_{31}N_2$ $[M+H]^+$: 227.2482, found 227.2480.

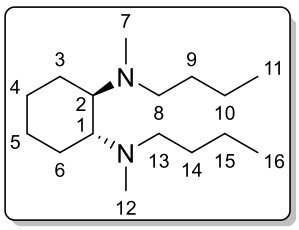
(1*S*,2*S*)-Dimethyldipropylcyclohexane-1,2-diamine, (*S*,*S*)-33



Prepared according to the general procedure outlined above using (1*S*,2*S*)- dimethylcyclohexane-1,2-diamine (0.71 g, 5 mmol) and 1-bromopropane (1.14 mL, 12.5 mmol). Purification by Kugelrohr distillation yielded the title compound (0.72 g, 64%). Spectral characteristics were consistent with previously reported data.[130]

$[\alpha]_D^{25}$ + 29.0 (c 0.57, CH_2Cl_2). IR (ATR) ν_{max}: 2956, 2789 (C-H stretch), 1166 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (6H, t, *J* = 7.4 Hz, H-10 and H-14), 0.98-1.28 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.38-1.53 (4H, m, H-9 and H-13), 1.62-1.82 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.23 (6H, s, H-7 and H-11), 2.34-2.58 (6H, m, H-1, H-6, H-7 and H-14) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.1 (C-10 and C-14), 21.6 (C-9 and C-13), 25.7, 25.9 (C-2, C-3, C-4 and C-5), 36.6 (C-7 and C-11), 56.6 (C-8 and C-12), 63.2 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{14}H_{31}N_2$ $[M+H]^+$: 227.2482, found 227.2478.

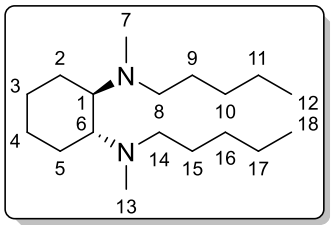
(1*R*,2*R*)-Dibutyldimethylcyclohexane-1,2-diamine, (*R*,*R*)-34



Prepared according to the general procedure outlined above using of (1*R*,2*R*)-dimethylcyclohexane-1,2-diamine (0.71 g, 5 mmol) and 1-bromobutane (1.14 mL, 12.5 mmol). Purification by Kugelrohr distillation yielded the title compound (0.76 g, 60%). Spectral characteristics were consistent with previously reported data.[130]

$[\alpha]_D^{20}$ - 9 (c 0.1, $CHCl_3$). IR (NaCl) ν_{max}: 2955, 2788 (C-H stretch), 1166 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (6H, t, *J* = 7.1 Hz, H-11 and H-16), 0.99-1.52 (12H, m, one of each of H-2, H-3, H-4 and H-5 and H-9, H-10, H-14 and H-15), 1.60-1.84 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.23 (6H, s, H-7 and H-12), 2.35-2.57 (6H, m, H-1, H-6, H-8 and H-13) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2 (C-11 and C-16), 20.8 (C-10 and C-15), 25.6, 25.9 (C-2, C-3, C-4 and C-5), 30.8 (C-9 and C-14), 36.6 (C-7 and C-12), 54.5 (C-8 and C-13), 63.0 (C-1 and C-2) ppm. HRMS (ESI) *m/z* calcd for $C_{16}H_{35}N_2$ $[M+H]^+$: 255.2789, found 255.2800.

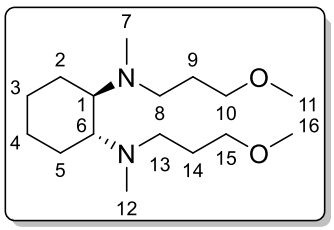
***(*1*R*,2*R*)-Dimethyldipentylcyclohexane-1,2-diamine, (*R*,*R*)-35**



Prepared according to the general procedure outlined above using (1*R*,2*R*)-dimethylcyclohexane-1,2-diamine (0.71 g, 5 mmol) and 1-iodopentane (1.63 mL, 12.5 mmol). Purification by Kugelrohr distillation yielded the title compound (0.58 g, 41%).

$[\alpha]_D^{20}$ - 24 (c 0.1, $CHCl_3$). IR (NaCl) ν_{max}: 2929, 2788 (C-H stretch), 1162 (C-N stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (6H, t, *J* = 7.0 Hz, H-12 and H-18), 1.02-1.53 (16H, m, one of each of H-2, H-3, H-4 and H-5 and H-9, H-10, H-11, H-15, H-16 and H-17), 1.62-1.85 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.23 (6H, s, H-7 and H-13), 2.34-2.56 (6H, m, H-1, H-6, H-8 and H-14) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1 (C-12 and C-18), 22.7 (C-11 and C-17), 25.6, 25.9 (C-2, C-3, C-4 and C-5), 28.3 (C-9 and C-15,), 29.9 (C-10 and C-16), 36.6 (C-7 and C-13), 54.5 (C-8 and C-14), 63.1 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{18}H_{39}N_2$ $[M+H]^+$: 283.3113, found 283.3100.

(1*R*,2*R*)-Bis(3-methoxypropyl)-dimethylcyclohexane-1,2-diamine, (*R*,*R*)-36



Prepared according to the general procedure outlined above using (1*R*,2*R*)-dimethylcyclohexane-1,2-diamine (0.71 g, 5 mmol) and 1-bromo-3-methoxypropane (1.68 mL, 15 mmol). Purification by Kugelrohr distillation yielded the title compound (1.05 g, 73%).

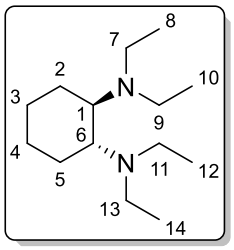
$[\alpha]_D^{20}$ - 33 (c 0.1, $CHCl_3$). IR (NaCl) ν_{max}: 2927, 2805 (C-H stretch), 1164 (C-N stretch), 1119 (C-O stretch) cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 0.99-1.24 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.60-1.83 (8H, m, one of each of H-2, H-3, H-4 and H-5 and H-9 and H-14), 2.23 (6H, s, H-7 and H-12), 2.42-2.63 (6H, m, H-1, H-6, H-8 and H-13), 3.33 (6H, s, H-11 and H-16), 3.37-3.48 (4H, m, H-10 and H-15) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 25.8 (C-2, C-3, C-4 and C-5), 28.5 (C-9 and C-14,), 36.4 (C-7 and C-12), 51.2 (C-8 and C-13), 58.5 (C-11 and C-16), 63.6 (C-1 and C-6), 71.4 (C-10 and C-15) ppm. HRMS (ESI) *m/z* calcd for $C_{16}H_{35}N_2O_2$ $[M+H]^+$: 287.2699, found 287.2692.

General procedure for the synthesis of (1*R*,2*R*)-cyclohexane-1,2-diamine derived ligands

To a stirred solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (1 equiv.) in toluene (2 mL/mmol of diamine) was added triethylamine (4.4 equiv.) and alkyl bromide (5 equiv.). The resulting solution was stirred at reflux for 24 h. Upon cooling to rt, the solution was acidified to pH 1 with aq. HCl (1M). The aqueous layer was separated, and the organic layer was washed with H_2O (2 x 10 mL). The combined aqueous layers were basified to pH 14 using aq. NaOH (10%

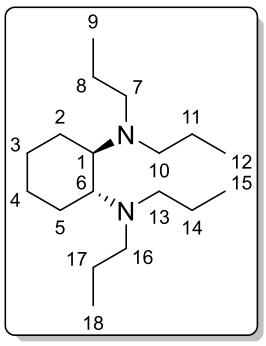
(w/v)). The resulting cloudy suspension was extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by Kugelrohr distillation afforded pure diamine.

(1*R*,2*R*)-Tetraethylcyclohexane-1,2-diamine, (*R*,*R*)-38



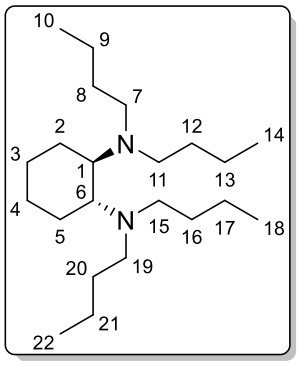
Prepared according to the general procedure outlined above using (1*R*,2*R*)-cyclohexane-1,2-diamine (0.57 g, 5 mmol) and 1-bromoethane (1.86 mL, 25 mmol). Purification by Kugelrohr distillation yielded the title compound as a pale yellow oil (0.24 g, 22%). Spectral characteristics were consistent with previously reported data.[131] $[\alpha]_D^{20}$ - 116 (c 0.1, $CHCl_3$) (lit. [131] $[\alpha]_D^{20}$ - 116 (c 1.17, EtOH, for *R*,*R*-enantiomer). IR (NaCl) ν_{max}: 2968, 2804 (C-H stretch), 1173 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (12H, t, *J* = 7.2 Hz, H-8, H-10, H-12 and H-14), 0.98-1.19 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.59-1.76 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.31-2.43 (4H, m, one of each of H-7, H-9, H-11 and H-13), 2.49-2.62 (6H, m, H-1, H-6, one of each of H-7, H-9, H-11 and H-13) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.9 (C-8, C-10, C-12 and C-14), 26.3 (C-3 and C-4), 27.6 (C-2 and C-5), 43.8 (C-7, C-9, C-11 and C-13), 60.7 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{14}H_{31}N_2$ $[M+H]^+$: 227.2487, found 227.2486.

(1*R*,2*R*)-Tetrapropylcyclohexane-1,2-diamine, (*R*,*R*)-39



Prepared according to the general procedure outlined above using (1*R*,2*R*)-cyclohexane-1,2-diamine (0.57 g, 5 mmol) and 1-bromopropane (2.27 mL, 25 mmol). Purification by Kugelrohr distillation yielded the title compound (0.64 g, 38%). Spectral characteristics were consistent with previously reported data.[133] $[\alpha]_D^{20}$ - 97 (c 0.1, $CHCl_3$). IR (NaCl) ν_{max}: 2957, 2805 (C-H stretch), 1160 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (12H, t, *J* = 7.4 Hz, H-9, H-12, H-15 and H-18), 1.01-1.19 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.33-1.49 (8H, m, H-8, H-11, H-14 and H-17), 1.66-1.84 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.27-2.52 (10H, m, H-1, H-6, H-7, H-10, H-13 and H-16) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 12.0 (C-9, C-12, C-15 and C-18), 22.7 (C-8, C-11, C-14 and C-17), 26.4 (C-3 and C-4), 27.6 (C-2 and C-5), 52.8 (C-7, C-10, C-13 and C-16), 61.6 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{18}H_{39}N_2$ $[M+H]^+$: 283.3113, found 283.3100.

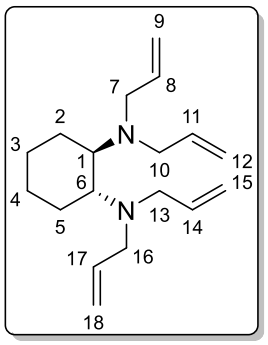
(1*R*,2*R*)-Tetrabutylcyclohexane-1,2-diamine, (*R*,*R*)-40



Prepared according to the general procedure outlined above using (1*R*,2*R*)-cyclohexane-1,2-diamine (0.57 g, 5 mmol) and 1-bromobutane (2.68 mL, 25 mmol). Purification by Kugelrohr distillation yielded the title compound (0.77 g, 45%).

$[\alpha]_D^{20}$ - 82 (c 0.1, $CHCl_3$). IR (NaCl) ν_{max}: 2956, 2806 (C-H stretch), 1158 (C-N stretch) cm^{-1}.^{1}H NMR (300MHz, $CDCl_3$): δ 0.89 (12H, t, *J* = 7.1 Hz, H-10, H-14, H-18 and H-22), 1.03-1.15 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.17-1.47 (16H, m, H-8, H-9, H-12, H-13, H-16, H-17, H20 and H-21), 1.66-1.82 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.31-2.56 (10H, m, H-1, H-6, H-7, H-11, H-15 and H-19) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.2 (C-10, C-14, C-18 and C-22), 20.9 (C-9, C-13, C-17 and C-21), 26.4 (C-3 and C-4), 27.7 (C-2 and C-5), 32.0 (C-8, C-12, C-16 and C-20), 50.6 (C-7, C-11, C-15 and C-19), 61.5 (C-1 and C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{22}H_{47}N_2$ $[M+H]^+$: 339.3739, found 339.3735.

(1*R*,2*R*)-Tetraallylcyclohexane-1,2-diamine, (*R*,*R*)-41



Prepared according to the general procedure outlined above using (1*R*,2*R*)-cyclohexane-1,2-diamine (0.57 g, 5 mmol) and allyl bromide (1.82 mL, 25 mmol). Purification by Kugelrohr distillation yielded the title compound (0.55 g, 40%). Spectral characteristics were consistent with previously reported data.[134]

$[\alpha]_D^{20}$ - 9 (c 0.1, $CHCl_3$) (lit.[133] $[\alpha]_D^{25}$ - 5.5 (c 3.18, $CHCl_3$, for *R*,*R*-enantiomer). IR (NaCl) ν_{max}: 2977, 2804 (C-H stretch), 1158 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97-1.12 (4H, m, one of each of H-2, H-3, H-4 and H-5), 1.59-1.78 (4H, m, one of each of H-2, H-3, H-4 and H-5), 2.55-2.58 (2H, m, H-1 and H-6), 2.86-2.93 (4H, m, one of each of H-7, H-10, H-13 and H-16), 3.19-3.26 (4H, m, one of each of H-7, H-10, H-13 and H-16), 4.94-5.10 (8H, m, H-9, H-12, H-15 and H-18), 5.70-5.83 (4H, m, H-8, H-11, H-14 and H-17) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 26.0 (C-3 and C-4), 26.8 (C-2 and C-5), 52.9 (C-7, C-10, C-13 and C-16), 59.5 (C-1 and C-6,), 115.6 (C-9, C-12, C-15 and C-18), 138.7 (C-8, C-11, C-14 and C-17) ppm. HRMS (ESI) *m/z* calcd for $C_{18}H_{31}N_2$ $[M+H]^+$: 275.2487, found 275.2475.

1.26 Asymmetric α-alkylation of *N,N*-dimethylhydrazones using *trans*-1,2-cyclohexyldiamine derived chiral ligands

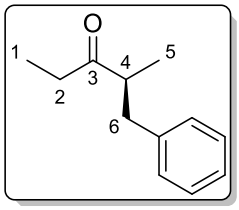
General procedure for the asymmetric α-alkylation of *N,N*-dimethylhydrazones using trans-1,2-cyclohexyldiamine derived chiral ligands

To a Schlenk tube under inert atmosphere was added ligand (1.2 equiv.) and anhydrous toluene (2 mL/mmol of hydrazone) and the resulting solution cooled to -78 °C. *s*-BuLi (1.1 equiv.) was added dropwise and the resulting yellow solution was stirred at this temperature for 30 mins. To this was added freshly distilled hydrazone (1 equiv.) dropwise and the reaction mixture was warmed to rt over 6 h. This solution was then cooled to -30 °C before dropwise addition of electrophile (1.2 equiv.) neat. The resulting solution was stirred for 18 h at this temperature before being quenched with NH_4Cl (2 mL). The reaction mixture was diluted with Et_2O (10 mL) and washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated *N,N*-dimethylhydrazone.

Hydrolysis Procedure

To a stirred solution of crude α-alkylated *N,N*-dimethylhydrazone in Et_2O (5 mL/mmol) was added aq. HCl (0.5 mL/mmol, 4M). This biphasic mixture was vigorously stirred until TLC analysis showed complete consumption of the crude hydrazone. The reaction was then diluted with H_2O (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated ketone. Purification by column chromatography on silica gel afforded pure α-alkylated ketone.

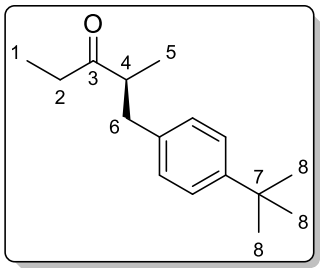
(*S*)-2-Methyl-1-phenylpentan-3-one, (*S*)-3



Prepared according to the general procedure outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). Purification by column chromatography (15:1, hexane: Et_2O) yielded the title compound as a colourless oil. Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[75]

Enantioselectivity was determined by GC analysis: t_R = 16.2 (*R*-enantiomer) and 16.7 (*S*-enantiomer) (140 °C hold for 20 min).

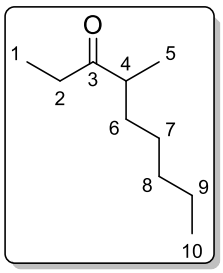
(*S*)-1-(4-(*T*ert-butyl)phenyl)-2-methylpentan-3-one, (*S*)-5



Prepared according to the general procedure outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and 4-*tert*-butylbenzyl bromide (0.22 mL, 1.2 mmol). Purification by column chromatography (15:1, hexane: Et_2O) yielded the title compound as a colourless oil. Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[123]

Enantioselectivity was determined by GC analysis: t_R = 16.3 (*R*-enantiomer) and 16.7 (*S*-enantiomer) (140 °C hold for 20 min).

4-Methylnonan-3-one, 6



Prepared according to the general procedure outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and 1-iodopentane (0.16 mL, 1.2 mmol). Purification by column chromatography (10:1, hexane: Et_2O) yielded the title compound as a colourless oil. Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[75]

Enantioselectivity was determined by GC analysis: t_R = 4.4 (*R*-enantiomer) and 4.7 (*S*-enantiomer) (105 °C hold for 15 min, ramp 10 °C/min to 140 °C, hold for 5 min).

Table 1.19. Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using *trans*-1,2-cyclohexyldiamine derived chiral ligands

Entry	Ligand	Electrophile	Yield	*ee*
1	**(+)-27**	BnBr	38%[b]	51%
2	**(*R*,*R*)-32**	BnBr	23%[a]	0%
3	**(*R*,*R*)-33**	BnBr	26%[b]	55%
4	**(*R*,*R*)-34**	BnBr	27% [a]	0%
5	**(*R*,*R*)-38**	BnBr	21% [a]	0%
6	**(*R*,*R*)-36**	BnBr	15% [a]	0%
7	**(+)-27**	4-*t*-butylBnBr	42%	42%
8	**(*R*,*R*)-35**	4-*t*-butylBnBr	32% [a]	0%
9	**(*R*,*R*)-39**	4-*t*-butylBnBr	24% [a]	0%
10	**(*R*,*R*)-40**	4-*t*-butylBnBr	54% [a]	34%
11	**(*R*,*R*)-41**	4-*t*-butylBnBr	0%	-[c]
12	**(*R*,*R*)-32**	1-iodopentane	16%[b]	0%

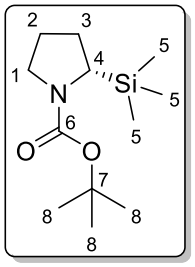
[a] Yield determined over two steps *via* ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard

[b] Isolated yield

[c] No evidence of desired α-alkylated ketone

1.27 Asymmetric alkylation of *N*-Boc-pyrrolidine using *trans*-1,2-cyclohexyldiamine chiral ligands

(*S*)-*tert*-butyl-2-(trimethylsilyl)pyrrolidine-1-carboxylate, (*S*)-26



To a stirred solution of diamine ligand (1.3 equiv.) in anhydrous Et_2O (3 mL) under N_2 atmosphere at -78 °C was added *s*-BuLi (1.4 M, 0.9 mL, 1.3 mmol) and the resulting solution stirred at this temperature for 10 min. To this solution was added *N*-Boc-pyrrolidine (0.18 mL, 1 mmol) as a solution in Et_2O (0.5 mL) and the resulting solution stirred at -78 °C for 6 h. Me_3SiCl (0.19 mL, 1.5 mmol) was added dropwise and the reaction was warmed to rt over 16 h. NH_4Cl (5 mL) was added and the reaction mixture was stirred for 20 min. The resulting mixture was then extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography (25:1 hexane:Et_2O) on silica gel afforded the title compound as a pale yellow oil (0.173 g, 71%). Spectral characteristics were consistent with previously reported data.[55]

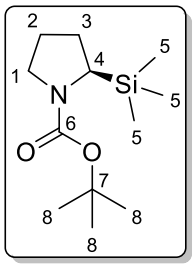
$[\alpha]_D^{20}$ + 53.9 (c 2.6, CH_2Cl_2) (lit.[96] $[\alpha]_D^{20}$ + 76.7 (c 1.0, CH_2Cl_2, for 90% *ee S*-enantiomer). IR (ATR) ν_{max}: 2966, 2874 (C-H stretch), 1689 (C=O stretch), 1246 (Si-C stretch), 1064 (C-O stretch) cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$, 50:50 mix of rotamers) δ 0.02 (9H, s, H-5), 1.43 (9H, s, H-8), 1.75-1.96 (4H, m, H-2 and H-3), 3.10-3.53 (3H, m, H-1 and H-4) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ -1.99 (C-5), 25.0, 26.2 (C-3), 28.1 (C-2), 28.7 (C-8), 46.8, 47.2, (C-1), 47.8 (C-4), 78.5, 79.3 (C-7), 154.8, 155.2 (C-6) ppm. MS (ESI) *m/z*: 244 $[M+H]^+$.

Table 1.20. Asymmetric alkylation of *N*-Boc-pyrrolidine using trans-1,2-cyclohexyldiamine derived chiral ligands

Entry	Ligand	Specific rotation (10^{-1} deg cm^2 g^{-1})	Yield	*ee*[a]
1	**(*R*,*R*)-32**	+ 41.0	58%	48%
2	**(*R*,*R*)-33**	+ 49.2	68%	58%
3	**(*R*,*R*)-34**	+ 53.9	71%	63%
4	**(R,R)-35**	+ 45.6	72%	54%

[a] Enantiomeric excess values were calculated based on specific rotation values measured experimentally.

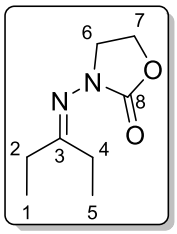
(*R*)-*Tert*-butyl-2-(trimethylsilyl)pyrrolidine-1-carboxylate, (*R*)-26



To a stirred solution of diamine ligand (1.3 equiv.) in anhydrous Et_2O (3 mL) under N_2 atmosphere at -78 °C was added *s*-BuLi (1.4 M, 0.9 mL, 1.3 mmol) and the resulting solution stirred at this temperature for 10 min. To this solution was added *N*-Boc-pyrrolidine (0.18 mL, 1 mmol) as a solution in Et_2O (0.5 mL) and the resulting solution stirred at -78 °C for 6 h. Me_3SiCl (0.19 mL, 1.5 mmol) was added dropwise and the reaction was warmed to rt over 16 h. NH_4Cl (5 mL) was added and the reaction mixture was stirred for 20 min. The resulting mixture was then extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (25:1 hexane:Et_2O) on silica gel afforded the title compound as a pale yellow oil (0.151 g, 62%, 28% *ee*). Spectral characteristics were consistent with previously reported data.[55]

$[\alpha]_D^{20}$ -24.0 (c 4.125, CH_2Cl_2) (lit.[96] $[\alpha]_D^{20}$ + 76.7 (c 1.0, CH_2Cl_2, for 90% *ee S*-enantiomer).

1.28 Synthesis of 3-(pentan-3-ylideneamino)oxazolidin-2-one, 44



Prepared over two steps using known procedures.[89, 104]

To a round bottom flask containing 2-hydrazinoethanol (2.05 mL, 30 mmol) and diethyl carbonate (4.8 mL, 40 mmol) was added NaOH (0.1 g, 2.5 mmol) in MeOH (1 mL) and the resulting solution was heated to 70 °C. After stirring for 24 h at this temperature, the resulting slurry was concentrated to dryness to afford 3-aminooxazolidin-2-one as a white solid (1.93 g, 63%), which was used in the next step without further purification.

3-Pentanone (0.25 g, 3.33 mmol) was dissolved in DCM (5 mL) and 3-aminooxazolidin-2-one (0.41 g, 4 mmol) was added. TsOH.H_2O (0.38 g, 20 mol%) was added and the reaction mixture was heated at reflux for 24 h. Upon completion, the reaction was cooled to rt and $NaHCO_3$ (5 mL) added. This was extracted with DCM (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to yield crude hydrazone. Purification by column chromatography (4:1, hexane:EtOAc) afforded the title compound as a colourless oil (0.37 g, 66%).

IR (NaCl) ν_{max}: 2976, 2915 (C-H stretch), 1761 (C=O stretch), 1633 (C=N stretch), 1424 (C-O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.12, 1.16 (2 × 3H, t, J = 7.6 Hz, H-1 and H-5), 2.41, 2.42 (2 × 2H, q, J = 7.6 Hz, H-2 and H-4), 3.76-3.81 (2H, m, H-6 or H-7), 4.37-4.42 (2H, m, H-6 or H-7) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 10.5, 10.8 (C-1 and C-5), 25.1, 28.8 (C-2 and C-4), 48.8 (C-6), 61.7 (C-7), 155.8 (C-3), 182.0 (C-8) ppm. MS (ESI) *m/z*: 171 $[M+H]^+$.

Note: Compound X is a novel compound. No HRMS data was obtained for this compound as no service was available at the time of synthesis.

1.29 Asymmetric α-alkylation of 3-(pentan-3-ylideneamino)oxazolidin-2-one using (+)-sp

General procedure for the asymmetric *α*-alkylation of 3-(pentan-3-ylideneamino)oxazolidin-2-one using (+)-sparteine as a chiral ligand - *s*-BuLi

To a Schlenk tube under inert atmosphere was added (+)-sp (1.2 equiv.) and *anhydrous solvent* (2 mL/mmol of hydrazone) and the resulting solution cooled to -78 °C. *s*-BuLi (1.1 equiv.) was added dropwise and the resulting yellow solution was stirred at this temperature for 30 mins. To this was added 3-(pentan-3-ylideneamino)oxazolidin-2-one (1 equiv.) dropwise and the reaction mixture was warmed to *deprotonation temperature* over *deprotonation time*. This solution was then cooled to *alkylation temperature* before dropwise addition of electrophile (1.2 equiv.), neat. The resulting solution was stirred for 18 h at this temperature before being

quenched with NH_4Cl (2 mL). The reaction mixture was diluted with Et_2O (10 mL) and washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated hydrazone.

General procedure for the asymmetric *α*-alkylation of 3-(pentan-3-ylideneamino)oxazolidin-2-one using (+)-sparteine as a chiral ligand - *LDA*

To a Schlenk tube under inert atmosphere was added diisopropyl amine (1.2 equiv.) and anhydrous solvent (2 mL/mmol of hydrazone) and the resulting solution cooled to 0 ℃. *n*-BuLi (1.1 equiv.) was added dropwise and the resulting solution was stirred at this temperature for 30 mins. This was then cooled to – 78 ℃ and (+)-sp (1.2 equiv.) added dropwise and the resulting yellow solution stirred at this temperature for a further 30 min. To this was added 3-(pentan-3-ylideneamino)oxazolidin-2-one (1 equiv.) dropwise and the reaction mixture was held at *deprotonation temperature* over *deprotonation time*. This solution was then adjusted to *alkylation temperature* before dropwise addition of electrophile (1.2 equiv.), neat. The resulting solution was stirred for 18 h at this temperature before being quenched with NH_4Cl (2 mL). The reaction mixture was diluted with Et_2O (10 mL) and washed with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated hydrazone.

Hydrolysis procedure

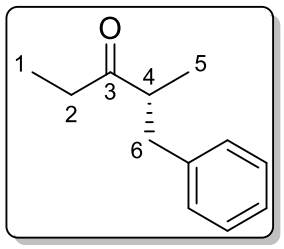
To a stirred solution of crude α-alkylated hydrazone in acetone (5 mL/mmol) was added $TsOH.H_2O$ (2 equiv.). This mixture was vigorously stirred until TLC analysis showed complete consumption of crude hydrazone. The reaction was then diluted with saturated aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated ketone.

Table 1.21. Asymmetric α-alkylation of 3-(pentan-3-ylideneamino)oxazolidin-2-one using (+)-sp as a chiral ligand

Entry	Base	Deprotonation time (h)	Deprotonation temperature (°C)	Alkylation temperature (°C)	Solvent	*ee*
1	*s*-BuLi	6 h	-78 °C - rt	-30 °C	Toluene	0%
2	LDA	6 h	-78 °C - rt	-30 °C	Toluene	0%
3	LDA	1 h	-78 °C	-78 °C	Toluene	-[a]
4	LDA	1 h	-78 °C	-78 °C	THF	-[a]
5	*s*-BuLi	1 h	-78 °C - 0 °C	-78 °C - rt	Toluene	0%
6	*s*-BuLi	1 h	-78 °C - 0 °C	-78 °C - rt	THF	8%

[a] No evidence of desired α-alkylated ketone

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-3



Prepared according to the general procedure outlined above using 1,1–dimethyl-2-(pentan-3-ylidene)hydrazine (0.128 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). Spectroscopic characteristics were consistent with previously reported data for the racemic compound and literature data.[75] Compound (racemic/8% *ee*) was not isolated.

Enantioselectivity was determined by GC analysis: t_R = 16.2 (*R*-enantiomer) and 16.7 (*S*-enantiomer) (140 °C hold for 20 min).

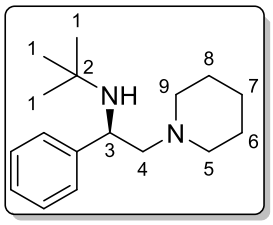
1.30 Synthesis of Koga's Chiral Bases

Prepared according to a known procedure.[111]

To a solution of (*R*)-2-phenyloxirane (1 equiv.) in EtOH (3 mL/mmol) was added piperidine (1.6 equiv.). The resulting solution was heated to reflux for 18 h. The solution was cooled to rt and concentrated under reduced pressure to afford a yellow solid which was used in the next step without further purification. Under N_2 atmosphere, this solid was dissolved in anhydrous Et_2O (100 mLs) and Et_3N (1.6 equiv.) was added. The resulting solution was then treated with MsCl (1.2 equiv.) and the resulting suspension vigorously stirred for 30 mins. Amine (various equiv.), Et_3N (2 equiv.) and H_2O (50 mLs) were added and the resulting biphasic mixture stirred at rt for 16 h. The layers were then separated and the aqueous layer extracted with Et_2O (3 x 30 mLs). The combined organic extracts were washed with $NaHCO_3$ (30 mLs) and H_2O (30 mLs), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure.

Purification by either Kugelrohr distillation or column chromatography yielded the desired Koga base.

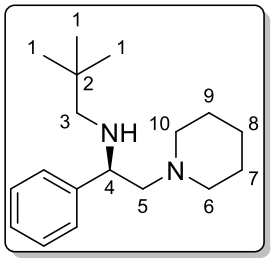
(*R*)-2-Methyl-*N*-(1-phenyl-2-(piperidin-1-yl)ethyl)propan-2-amine, (*R*)-47



Prepared according to the general procedure outlined above using (*R*)-2-phenyloxirane (2.9 mL, 25 mmol) and *t*-butylamine (28.9 mL, 275 mmol). Purification by Kugelrohr distillation gave the title compound as a pale yellow oil. (5.08 g, 78%). Spectral characteristics were consistent with previously reported data.[111]

$[\alpha]_D^{25}$ - 142 (c 0.2, CH_3OH) (lit.[111] $[\alpha]_D^{25}$ - 77 (c 1.0, $CHCl_3$). IR (NaCl) ν_{max}: 3291 (N-H stretch), 2935, 2755 (C-H stretch), 1230 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (9H, s, H-1), 1.34-1.69 (6H, m, H-6, H-7 and H-8), 2.11-2.31 (5H, m, N-H, H-4 and one of each of H-5 and H-9), 2.53-2.59 (2H, m, one of each of H-5 and H-9), 3.90 (1H, dd, *J* = 10.8, 3.9 Hz, H-3), 7.14-7.20 (1H, m, Ar-H), 7.24-7.29 (2H, m, Ar-H), 7.38-7.42 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.5 (C-7), 26.2 (C-6 and C-8), 30.2 (C-1), 50.9 (C-2), 54.3 (C-3), 54.4 (C-5 and C-9), 67.1 (C-4), 126.5 (Ar-CH), 127.4 (2 × Ar-CH), 128.0 (2 × Ar-CH), 146.7 (Ar-C) ppm. MS (ESI) *m/z*: 261 [M+H]+.

(*R*)-2,2-Dimethyl-*N*-(1-phenyl-2-(piperidin-1-yl)ethyl)propan-1-amine, (*R*)-48

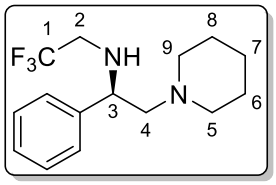


Prepared according to the general procedure outlined above using (*R*)-2-phenyloxirane (2.9 mL, 25 mmol) and 2,2-dimethylpropylamine (8.8 mL, 75 mmol). Purification by Kugelrohr distillation followed by column chromatograpghy (2:1 hexane:EtOAc) gave the title compound as a pale yellow oil. (5.26 g, 77%). Spectral characteristics were consistent with previously reported data.[112]

$[\alpha]_D^{25}$ - 105 (c 0.1, MeOH) (lit.[112] $[\alpha]_D^{25}$ - 113 (c 1.19, C_6H_6). IR (NaCl) ν_{max}: 3316 (N-H stretch), 2937, 2796 (C-H stretch), 1257 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (9H, s, H-1), 1.34-1.69 (6H, m, H-7, H-8 and H-9), 2.13-2.58 (9H, m, N-H, H-3, H-5, H-6 and H-10), 3.67 (1H, dd, *J* = 11.0, 3.9 Hz, H-4), 7.14-7.40 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.6 (C-8), 26.3 (C-7 and C-9), 27.9 (C-1), 31.6 (C-2), 54.4 (C-6 and C-10), 60.9 (C-4), 61.0 (C-3), 66.6 (C-5), 126.9 (Ar-CH), 127.4 (2 × Ar-CH), 128.2 (2 × Ar-CH), 144.0 (Ar-C) ppm. MS (ESI) *m/z*: 275 [M+H]+.

Note: Minor impurities remained after purification attempts due to an impurity present in the EtOAc used for column chromatography. Subsequent purification attempts failed to remove this contaminant.

(*R*)-2,2,2-Trifluoro-*N*-(1-phenyl-2-(piperidin-1-yl)ethyl)ethan-1-amine, (*R*)-49

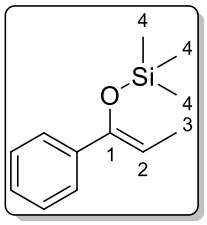


Prepared according to the general procedure outlined above using (*R*)-2-phenyloxirane (1.2 mL, 10 mmol) and trifluoroethylamine (0.94 mL, 12 mmol). Purification by Kugelrohr distillation followed by column chromatography (10:1 hexane:EtOAc) gave the title compound as a pale yellow oil. (1.10 g, 38%). Spectral characteristics were consistent with previously reported data.[113]

$[\alpha]_D^{25}$ - 75 (c 0.1, MeOH) (lit.[112] $[\alpha]_D^{25}$ - 82.7 (c 1.20, MeOH). IR (NaCl) ν_{max}: 3293 (N-H stretch), 2938, 2762 (C-H stretch), 1234 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40-1.68 (6H, m, H-6, H-7 and H-8), 2.25-2.48 (4H, m, H-4 and one of each of H-5 and H-9), 2.55-2.59 (2H, m, one of each of H-5 and H-9), 2.94-3.16 (3H, m, H-2 and N-H), 3.94 (1H, dd, J = 10.9, 3.3 Hz, H-3), 7.22-7.40 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 24.5 (C-7), 26.2 (C-6 and C-8), 47.8 (q, $^2J_{C\text{-}F}$ = 30.7 Hz, C-2), 54.5 (C-5 and C-9), 58.2 (C-3), 66.4 (C-4), 126.0 (q, $^1J_{C\text{-}F}$ = 276.7 Hz, C-1), 127.5 (3 × Ar-CH), 128.5 (2 × Ar-CH), 141.6 (Ar-C) ppm. MS (ESI) *m/z*: 287 [M+H]+.

1.31 Synthesis of trimethyl((1-phenylprop-1-en-1-yl)oxy)silane, 55

To a round bottom flask under N_2 atmosphere containing propiophenone (1 mL, 7.5 mmol) in anhydrous THF (20 mL) at 0 °C was added *n*-BuLi (9 mL, 1.25 M in hexanes, 11.25 mmol). The resulting solution was stirred at this temperature for 1h. To this solution was added Me_3SiCl (1.43 mL, 11.25 mmol) dropwise and the resulting solution stirred at this temperature for 1 h. The reaction was quenched with MeOH (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography (25:1 hexane:EtOAc) on silica gel yielded the title compound as a pale yellow oil (1.13 g, 73%).



Spectral characteristics were consistent with previously reported data.[135] IR (ATR) ν_{max}: 2959 (C-H stretch), 1251 (C-Si stretch), 1060 (C-O stretch) cm^{-1}.^{1}H NMR (600 MHz, $CDCl_3$): δ 0.15 (9H, s, H-4), 1.75 (3H, d, J = 6.9 Hz, H-3), 5.34 (1H, q, J = 6.9 Hz, H-2), 7.21-7.24 (1H, m, Ar-H), 7.27-7.30 (2H, m, Ar-H), 7.46-7.47 (2H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 0.01 (C-4), 11.1 (C-3), 104.8 (C-2), 124.6 (2 × ArCH), 126.7 (Ar-CH), 127.4 (2 × Ar-CH), 138.6 (Ar-C), 149.3 (C-1) ppm. MS (ESI) *m/z*: 207 $[M+H]^+$.

1.32 Aldol reactions of 2-ethyl pyridine

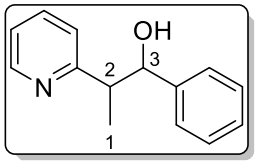
General Procedure – Koga base/solvent screen

To a Schlenk flask under N_2 atmosphere was added 2-ethyl pyridine (1 equiv), Koga base (1.03 equiv.) and anhydrous solvent (2 mL). The resulting solution was cooled to 0 ℃ and *n*-BuLi (1.23 M in hexanes, 2.03 equiv.) added dropwise. This solution was stirred at 0 ℃ for 15 mins, cooled to -78 ℃ and stirred for a further 15 mins. Aldehyde (2.5 equiv.) was added at -78 ℃ and the resulting solution stirred for 5 h. This was then quenched with MeOH (0.3 mL) and stirred for 15 mins before warming to rt. The reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. The crude extract was purified by column chromatography to yield aldol product.

General Procedure – HMPA equivalents

To a Schlenk flask under N_2 atmosphere was added 2-ethyl pyridine (1 equiv), **(*R*)-47** (1.03 equiv.), HMPA (various equiv.) and anhydrous toluene (2 mL). The resulting solution was cooled to 0 ℃ and *n*-BuLi (1.23 M in hexanes, 2.03 equiv.) added dropwise. This solution was stirred at 0 ℃ for 15 mins, cooled to -78 ℃ and stirred for a further 15 mins. Aldehyde (2.5 equiv.) was added at -78 ℃ and the resulting solution stirred for 5 h. This was then quenched with MeOH (0.3 mL) and stirred for 15 mins before warming to rt. The reaction was diluted with H_2O (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered free of the drying agent and concentrated under reduced pressure. The crude extract was purified by column chromatography to yield aldol product.

1-Phenyl-2-(pyridin-2-yl)propan-1-ol, 58



Prepared according to the general procedure outlined above using 2-ethylpyridine (0.05 mL, 0.44 mmol) and benzaldehyde (0.12 mL, 1.1 mmol). Purification by column chromatography (1:1 hexane:EtOAc) yielded the title compound as a pale yellow oil (0.058 g, 62%, 61:39 $_{dr}$, 62% *ee*). Spectral characteristics were consistent with previously reported data.[136]

Enantioselectivity (major diastereomer) was determined by HPLC analysis: t_R = 18.0 and 21.9 (90:10 hexane:IPA, 0.5 mL/min, 25 ℃, 254 nm, 60 mins).

Enantioselectivity (minor diastereomer) was determined by HPLC analysis: t_R = 13.8 and 28.4 (90:10 hexane:IPA, 0.5 mL/min, 25 ℃, 254 nm, 60 mins).

Note: The absolute stereochemistry of the major diastereomer could not be determined

Major diastereomer:

$[\alpha]_D^{25}$ - 73 (c 0.1, CH_2Cl_2,). IR (ATR) ν_{max}: 3225 (O-H stretch), 2965, 2924, 2854 (C-H stretch), 1671 (C=N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (3H, d, *J* = 7.1 Hz, H-1), 3.22 (1H, quin, *J* = 6.6 Hz, H-2), 4.92 (1H, d, *J* = 6.1 Hz, H-8), 7.03 (1H, dt, *J* = 7.8, 1.0 Hz, Ar-H), 7.14-7.27 (6H, m, Ar-H), 7.58 (1H, td, *J* = 7.7, 1.8 Hz, Ar-H), 8.54-8.55 (1H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 18.7 (C-1), 47.4 (C-2), 78.4 (C-3), 121.7 (Ar-CH), 123.4 (Ar-CH), 126.3 (2 × Ar-CH), 127.1 (Ar-CH), 128.1 (2 × Ar-CH), 137.1(Ar-CH), 143.8 (Ar-C), 148.2 (Ar-CH), 163.7 (Ar-C) ppm. MS (ESI) *m/z*: 214 $[M+H]^+$.

Table 1.22. Aldol reaction of 2-ethyl pyridine – Koga base screen

Entry	Amine	THF		Toluene	
		Yield	***dr***	**Yield**	***dr***
1	**(*R*,*R*)-45**	15%	56:44	24%	73:27
2	**(*R*)-47**	20%	57:43	28%	73:27
3	**(*R*)-48**	23%	58:42	32%	59:41
4	**(*R*)-49**	-[a]	-[a]	12%	47:53

[a] No evidence of desired aldol product.

Table 1.23. Aldol reaction of 2-ethyl pyridine – HMPA equivalents screen

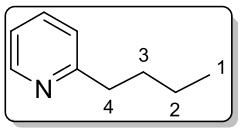
Entry	HMPA equivalents	Yield	*dr*	*ee* (Major)	*ee* (Minor)
1	0	28%	73:27	58%	0%
2	0.25	20%	57:43	50%	32%
3	0.5	36%	55:45	35%	10%
4	0.75	43%	58:42	56%	10%
5	1	60%	58:42	58%	10%
6	1.25	62%	61:39	62%	16%
7	1.5	51%	65:35	30%	14%

1.33 Synthesis of 2-alkyl pyridines

General procedure

To a solution of 2-alkylpyridine (1 equiv.) in anhydrous THF (2 mL/mmol) at -78 °C was added *n*-BuLi (1.05 equiv.) and the solution stirred for 15 mins. Alkyl bromide (1 equiv.) was added dropwise at -78 °C and the solution stirred for a further 30 mins at this temperature. The reaction was then quenched by addition of MeOH (2 mL) and allowed to warm to rt. The reaction mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford crude alkylated pyridine, which was subsequently purified by column chromatography on silica gel to afford pure alkylated 2-pyridine derivatives.

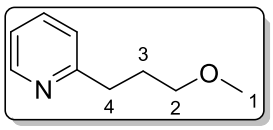
2-Butylpyridine, 62



Prepared according to the general procedure above using 2-methylpyridine (1.98 mL, 20 mmol) and 1-bromopropane (1.83 mL, 20 mmol). Purification by column chromatography (10:1 hexane:EtOAc) yielded the title compound as a colourless oil (1.22 g, 45%). Spectral characteristics were consistent with previously reported data.[87]

IR (ATR) ν_{max}: 2958, 2925, 2854 (C-H stretch), 1178 (C-N stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.5 Hz, H-1), 1.36 (2H, sext, *J* = 7.5 Hz, H-2), 1.64-1.74 (2H, m, H-3), 2.74-2.79 (2H, m, H-4), 7.03-7.12 (2H, m, Ar-H), 7.55 (1H, td, *J* = 7.7, 1.9 Hz, Ar-H), 8.48-8.50 (1H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.9 (C-1), 22.5 (C-2), 32.0 (C-3), 38.1 (C-4), 120.8 (Ar-CH), 122.6 (Ar-CH), 136.2 (Ar-CH), 149.2 (Ar-CH), 162.5 (Ar-C) ppm. MS (ESI) *m/z*: 136 $[M+H]^+$.

2-(3-Methoxypropyl)pyridine, 63

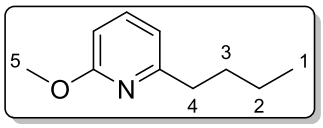


Prepared according to the general procedure above using 2-methylpyridine (1.0 mL, 10.7 mmol) and 2-bromo-1-methoxyethane (1.0 mL, 10.7 mmol). Purification by column chromatography (10:1 hexane:EtOAc) yielded the title compound as a colourless oil (1.10 g, 68%). Spectral characteristics were consistent with previously reported data.[87]

IR (ATR) ν_{max}: 2926, 2810 (C-H stretch), 1591 (C=N stretch), 1080 (C-O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97-2.06 (2H, m, H-3), 2.84-2.89 (2H, m, H-4), 3.34 (3H, s, H-1), 3.42 (2H, t, *J* = 6.5 Hz, H-2), 7.07-7.17 (2H, m, Ar-H), 7.58 (1H, td, *J* = 7.7, 1.8 Hz, Ar-H), 8.52-8.53 (1H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 29.5 (C-3), 34.8 (C-4),

58.5 (C-1), 72.0 (C-2), 121.0 (Ar-CH), 122.8 (Ar-CH), 136.2 (Ar-CH), 149.2 (Ar-CH), 161.7 (Ar-C) ppm. MS (ESI) *m/z*: 152 $[M+H]^+$.

2-Butyl-6-methoxypyridine, 64



Prepared according to the general procedure above using 2-methoxy-6-methylpyridine (1.22 mL, 10 mmol) and 1-bromopropane (0.91 mL, 10 mmol). Purification by column chromatography (10:1 hexane:EtOAc) yielded the title compound as a colourless oil (1.19 g, 72%). Spectral characteristics were consistent with previously reported data.[87]

IR (ATR) ν_{max}: 2955, 2859 (C-H stretch), 1579 (C=N stretch), 1035 (C-O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.3 Hz, H-1), 1.37 (2H, sext, *J* =7.6 Hz, H-2), 1.65-1.75 (2H, m, H-3), 2.65-2.70 (2H, m, H-4), 3.91 (3H, s, H-5), 6.51 (1H, d, *J* = 8.3 Hz, Ar-H), 6.68 (1H, d, *J* = 7.3 Hz, Ar-H), 7.43 (1H, dd, *J* = 8.3, 1.0 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.0 (C-1), 22.4 (C-2), 31.5 (C-3), 37.6 (C-4), 53.1 (C-5), 107.1 (Ar-CH), 115.0 (Ar-CH), 138.5 (Ar-CH), 160.4 (Ar-C), 163.7 (Ar-C) ppm. MS (ESI) *m/z*: 166 $[M+H]^+$.

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II

The α-Alkylation of Ketones by Continuous Flow

“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more so that we may fear less”

Marie Curie

2 Introduction

2.1 Continuous Flow Chemistry

Listed as one of IUPAC's top ten emerging technologies in chemistry for 2019, flow chemistry is a continually emerging and ever-evolving area of synthetic organic chemistry. It provides an orthogonal approach to traditional batch chemistry, and it is generally accepted that flow chemistry offers a valuable change to the process landscape.[1] The translation of a synthetic protocol from batch to continuous flow, along with the development of new continuous flow chemistry, can have a plethora of benefits, including the development of new reactivity patterns, improved reaction efficiency and enhanced scalability.[2] Additionally, flow chemistry forms an intrinsic part of modern day efforts to develop more resource conscious and sustainable synthetic routes. It currently satisfies eight of the twelve principles of green chemistry **(Figure 2.1)**.[3]



Figure 2.1. Principles of green chemistry

It is accepted that the most compelling advantage of continuous flow chemistry is the increased safety profile associated with reactions performed in this manner. Hazardous reagents, heat exchange and pressurised reactions, especially those involving hazardous gases, pose a high level of risk when performed at scale in batch. However, by design, flow chemistry can oftentimes alleviate, or significantly reduce these hazards. A review by Stevens and co-workers illustrates how many hazardous reagents such as diazo, diazonium, azide and organometallic species are successfully and, more importantly, safely used in continuous processing.[4]

The impact of the enclosed nature of a continuous flow system is twofold: **i)** it eliminates chemist exposure to hazardous reagents and **ii)** it allows for harmful intermediates to be immediately consumed, alleviating any issues associated with accumulation of these species. The high surface to volume ratio allows for superior temperature control, reducing the significance of any potential exotherms. In addition to the increased safety profile, advantages

of continuous flow chemistry also include: **i**) a greater reaction selectivity, facilitating minimal side-reactions due to reagents being continuously consumed, resulting in increased product quality; **ii)** reduced reaction times; **iii)** more effective and efficient cooling, resulting in superior control of potential exotherms; **iv)** possibility for precise reaction monitoring using in-line analytical techniques and **v)** reactions which are photo- or electrochemically driven are more amenable to flow chemistry over traditional batch chemistry. This is due to the smaller reactor dimensions facilitating more uniform irradiation or electrochemical distribution.[5]

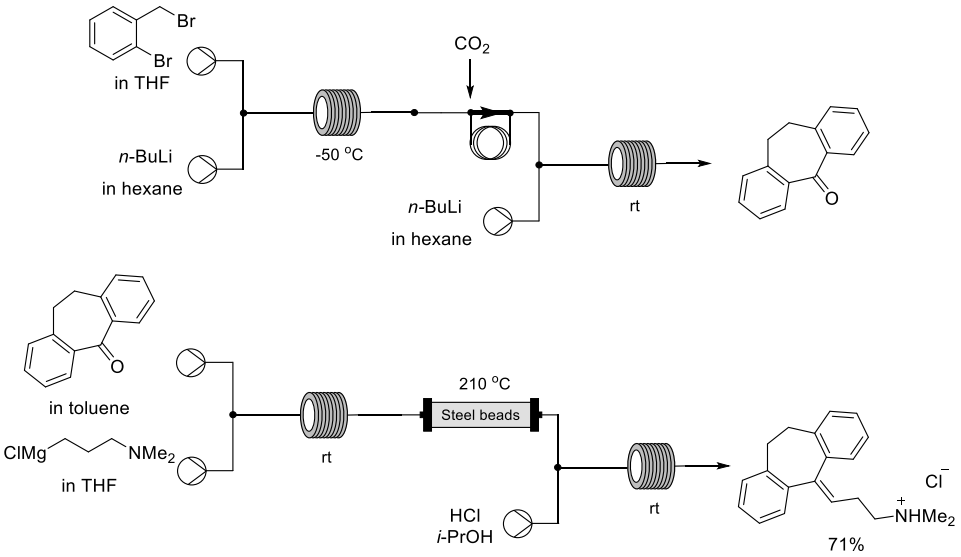
2.2 Organometallic reagents in continuous flow

Organometallic species such as organolithium and Grignard reagents are principal species in many organic transformations and represent highly valuable building blocks for the efficient synthesis of many pharmaceutical intermediates. Reactions involving these species are generally rapid and highly exothermic events. In traditional batch chemistry, slow addition of these reagents, high levels of dilution and cooling of the reaction mixture to cryogenic temperatures can result in an enhanced reaction selectivity and minimise any safety risk. Disadvantageously, use of these reagents on commercial scale is severely hindered by the highly energetic nature of the reaction intermediates and consequently, heat dissipation becomes a significant challenge.

Organolithium reagents are among the most reactive and arguably most important species in organic chemistry, utilised across numerous synthetic transformations. The polar C-Li bond allows the reagent to act as a strong base or nucleophile, allowing for the formation of new C-C bonds. However, despite the necessity and utility of organolithium species in organic synthesis, inherent safety issues obviate their use on scale. The heat dissipation required when using these reagents is difficult to achieve and has proven an onerous task. Additionally, large scale use of organolithium reagents results in the formation of aggregates or precipitates, presenting the additional challenge of solubility.[6] A continuous flow chemistry platform provides a viable alternative to traditional batch chemistry when considering these reactions. The high surface-to-volume ratio available in microreactors offers a means to circumvent these issues, allowing for much improved methods of heat dissipation, temperature control and energy transfer. Flow chemistry has enabled a safer regime for the employment of organolithium reagents. Reviews by Nagaki,[7] Luisi[8] and Piccardi[9] have showcased many examples of the safe and effective transfer of organometallic chemistry from flask to flow.

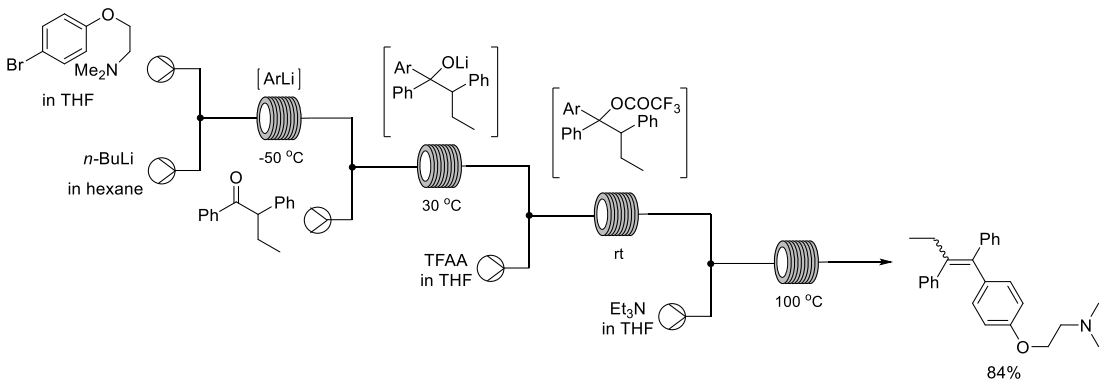
In 2013, Kirschning and co-workers reported the use of continuous flow chemistry to synthesise the tricyclic antidepressant Amitriptyline **(Scheme 2.1)**.[10] The process involved

low temperature as well as high temperature/high pressure transformations and included three lithium-halogen exchange reactions, the use of $CO_{2(g)}$ as an electrophile and a Grignard reaction, demonstrating the advantages and versatility of flow chemistry when handling hazardous reagents. The metalation steps could be conducted at high temperatures, therefore proceeding more efficiently than the corresponding batch reaction, generating 8.9 mg/min of amitriptyline.



Scheme 2.1. Multi-step continuous flow synthesis of amitriptyline

Similarly, in 2014 Ley and co-workers reported the use of a continuous flow set-up to synthesise the widely used medicine tamoxifen **(Scheme 2.2)**.[11] Tamoxifen is used as a first line treatment for breast cancer and it is estimated approximately 400,000 women are alive today due directly to this treatment.[12] Remarkably, the telescoped synthesis combines four chemically distinct transformations in one stream, including both air-sensitive and hazardous Grignard and Li-halogen exchange steps, makes use of five reactor pumps, pumping at three different flow rates, and allows for four different reaction temperatures to be achieved concomitantly. Using this approach, sufficient material for the therapeutic demand of 900 patients per day can be generated in just 80 minutes.



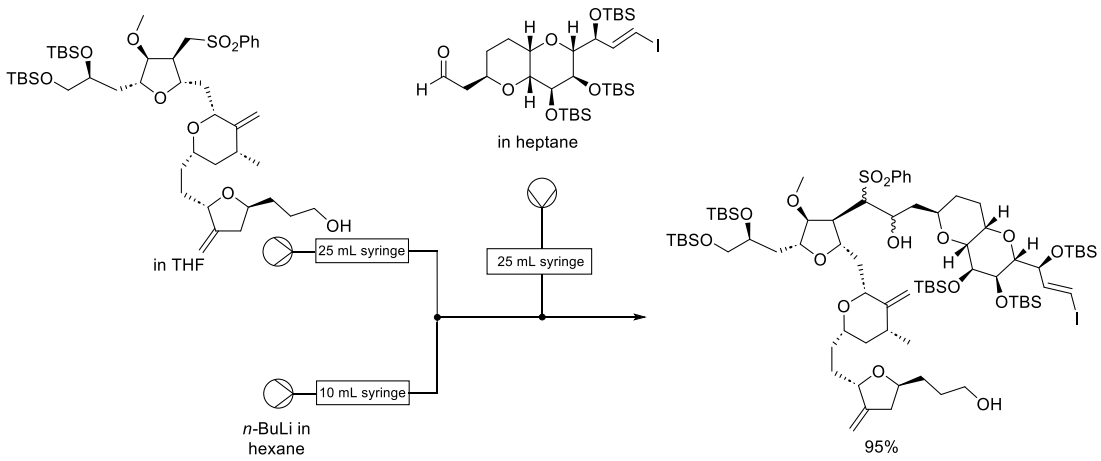
Scheme 2.2. Synthesis of tamoxifen by continuous flow

2.3 Organolithium mediated deprotonation reactions in continuous flow

Deprotonation chemistry using organolithium bases is critically important in organic chemistry. Highly efficient mass and heat transfer, precise control of reaction times and uniform mixing apparatus means flow chemistry has the potential to overcome many of the pitfalls associated with traditional batch chemistry using organolithium bases.[13]

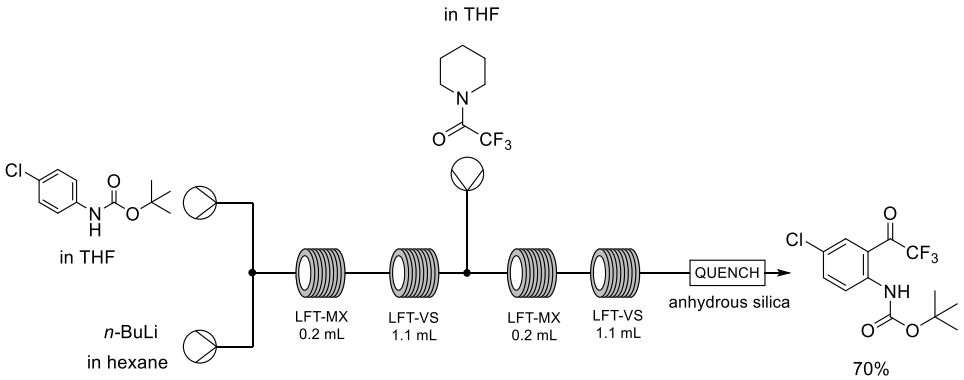
2.3.1 Alkyl lithium reagents

Alkyl lithium reagents, including *n*-BuLi and *s*-BuLi, are some of the most widely used reagents in organic synthesis. In recent years, use of these reagents in continuous flow has allowed for the design of more efficient, streamlined and safer synthetic routes to complex APIs. In 2015, Tagami and co-workers reported the use of continuous flow for two critical steps in the synthesis of eribulin mesylate.[14] Eribulin mesylate is a fully synthetic derivative of the structurally complex marine natural product halichondrin B, approved by the FDA in 2010 for the treatment of breast cancer.[15] Both a DIBAL-H reduction and a *n*-BuLi mediated coupling step could be run at higher temperatures than the corresponding batch reactions. The *n*-BuLi reaction could be run at 10 °C in flow, 80 °C higher than the corresponding batch reaction **(Scheme 2.3)**, generating the target molecule in 95% yield. These milder reaction conditions allowed for better conversion and considerable reduction of both the material and operational costs associated with the original synthetic route.



Scheme 2.3. *n*-BuLi mediated coupling step in eribulin mesylate synthesis

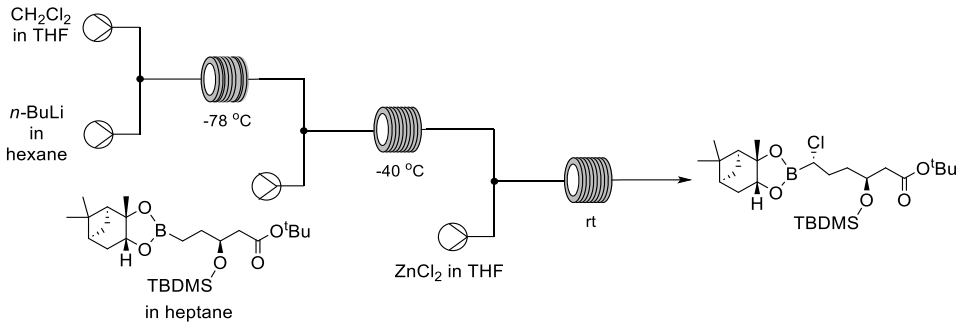
In 2017, Watts and co-workers described the continuous flow synthesis of an intermediate in the synthesis of Efavirenz **(Scheme 2.4)**, a potent non-nucleoside reverse transcriptase inhibitor (NNRTI).[16] This route offered significant advangtages over the traditional batch route. The batch synthesis commonly utilises *s*-BuLi or the significantly more hazardous *t*-BuLi to facilitate the deprotonation step.[17-18] Using continuous flow chemistry, *n*-BuLi can be used in place of these reagents offering a much less hazourdous synthetic route. A continuous process was designed whereby the substrate and organolithium base were reacted to form a lithiated intermediate, which advanced to meet the trifluoroacetylating agent, forming the product in up to 70% yield after an anhydrous silica quench. Additonally, the batch process requires TMEDA as an additive while continuous flow circumvents this requirement, consequently simplifying the purification process.



Scheme 2.4. Synthesis of Efavirenz intermediate

More recently, in 2019 Schuster and co-workers presented the design and scale-up of a process for the synthesis of a key intermediate towards the β-lactamase inhibitor vaborbactam,[19] a cyclic boronic acid used in the treatment of complicated urinary tract infections **(Scheme 2.5)**. One of the key steps in the synthetic route to this API is a diastereoselctive chain elongation of a boronic ester to an α-chloroboronic ester. Matteson conditions, requiring temperatures as

low as -100 °C in batch, are used to achieve this transformation, which includes generation of (dichloro-methyl)lithium, formation of a Lewis acid coordinated intermediate species and rearrngement of this species to yield the target molecule. The initial batch process proved unamenable to scale-up and a yield of only 30% and *dr* of 85:15 was achieved.[20] This was successfully translated into a continuous flow process by the authors, allowing for the industrial scale synthesis of this important pharmaceutical intermediate. Benefits of the flow protocol included a reduced ecological footprint and improved economics. The employment of continuous flow technology also allowed the temperature to be raised to more manageable -60 °C, and gave an increased *dr* of 95:5 and yield of 91%. Finally, the reproducibility of the synthesis in flow was far greater than the correpsonding reaction in batch.

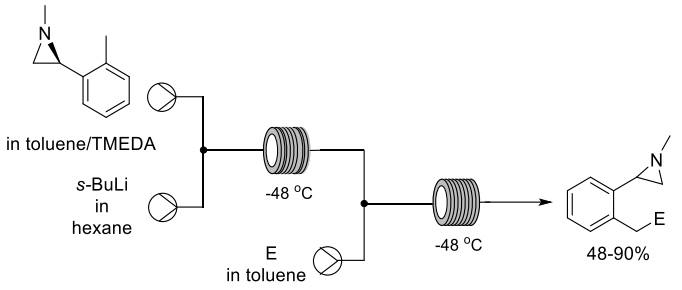


Scheme 2.5. Matteson reaction in the synthesis of vaborbactam

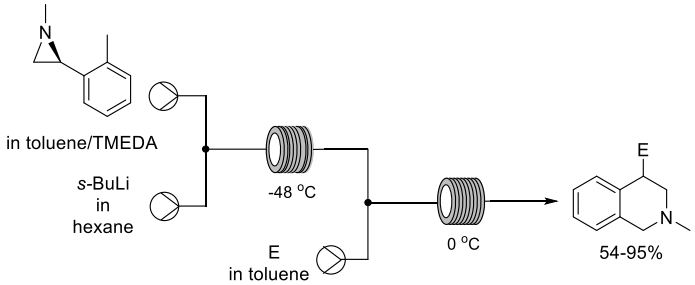
The use of *s*-BuLi has also been reported in continuous flow, allowing for a stronger, less nucleophilic base to be used whilst still alleviating some of the inherent safety issues associated with this reagent. Luisi and co-workers reported a new strategy for the synthesis of C-4 functionalised 1,2,3,4-tetrahydroisoquinolines (THIQs), which exploits the chemistry of lithiated aziridines and the advantages of flow chemistry.[21] Routes to these compounds are of high significance due to the biological activity associated with this strucural motif,[22] and in recent years, organometallic chemistry has emerged as a reliable method to furnishing such medicinal targets.[23-24] In the continuous flow synthesis described, the enantiopure substrate and *s*-BuLi are supplied independently to the system, furnishing the lithiated intermediate. Various electrophiles are then introduced to the system to yield the desired products. During optimisation studies, it became apparent to the authors that the reaction outcome was highly temperature dependent. Contingent upon the reaction temperature, two possible mechanistic pathways were possible. When the temperature was held at -48 °C for the duration of the reaction, production of a range of laterally substituted aziridines was observed, in yields of 48-90% **(Scheme 2.6a)**. If however, after deprotonation, the reaction temperature was increased to 0 °C C4-functionalised tetrahydroisoquinolines were generated in yields of 54-95% **(Scheme 2.6b)**. The continuous flow process allowed for comprehensive isomer control. Furthermore, it allowed direct synthesis of numerous THIQs, of which only two known

examples exist in batch.[13] Repetition of the above reaction in batch failed to generate the desired products, again illustrating the orthoganol reactivity of continuous flow chemistry to traditional batch chemistry.

a)



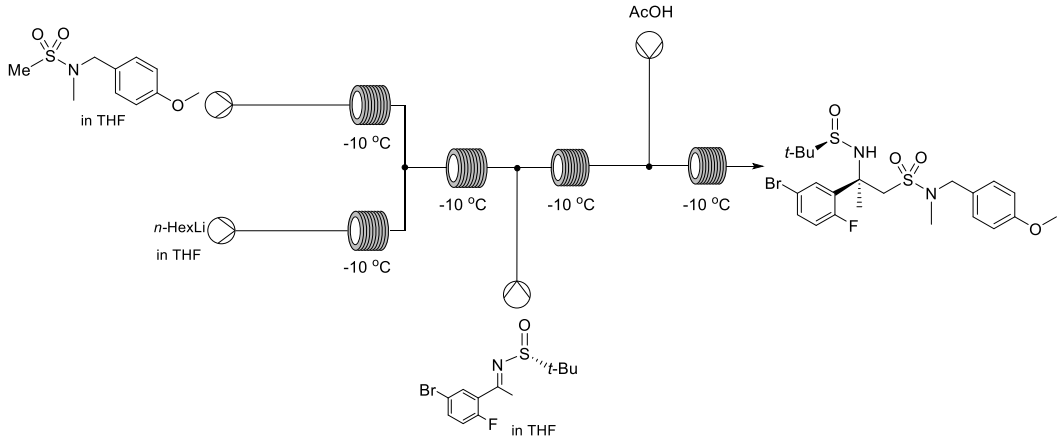
b)



Scheme 2.6. Continuous flow mediated thermal isomerisation of aziridines

Several reports of the use of phenyl- and hexyllithium in continuous flow have also been published.[25-29] Although the use of these reagents in a research setting or on small batch scale is infrequent, use of these reagents on an industrial scale in place of *n*-BuLi/*s*-BuLi is common.[30] Both alternatives offer an increased safety profile and, in general, liquid by-products are easier managed than the corresponding gaseous waste generated by their counterparts. Work by McMullen and co-workers reports the design of a continuous flow chemistry platform for the synthesis of Verubecestat, a drug which reached Phase III trials for Alzheimer's disease before being discontinued.[31] In batch, the synthesis of this drug candidate was problematic from the outset. The protocol proceeds *via* a Mannich-type addition of a methyl sulfonamide to a chiral Ellman-type sulfinyl ketimine. Excess sulfonamide and cryogenic reaction conditions were required for the batch procedure. It was found that both the nucleophile and lithium anion irreversibly deprotonate the electrophile, competing with the Mannich-type reaction, resulting in a significantly reduced yield in this step. The authors hypothesised a flow system would offer improved mixing and could alleviate this issue by limiting the exposure of the ketimine to the lithiated intermediate and thus preventing the problematic irreversible deprotonation step. Additionally, the flow system removed the requirement for cryogenic reaction conditions and reaction temperatures between -10 °C and

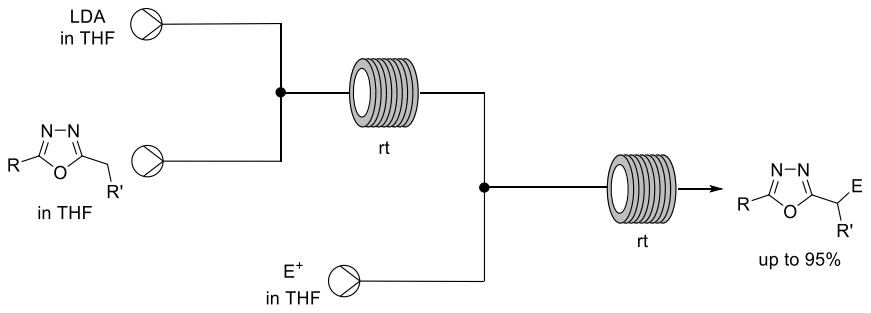
1 °C offered optimal results. Conversions of between 90-91% were consistently achieved after numerous reactions.



Scheme 2.7. Verubecestat synthesis Mannich reaction

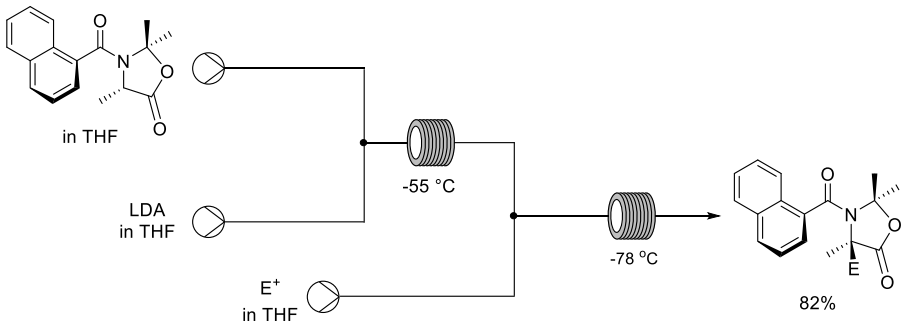
2.3.2 Lithium amides

Common to most organometallics, the use of lithium diisopropylamine (LDA) often requires cryogenic and carefully controlled reaction conditions. Continuous flow chemistry helps to alleviate issues associated with the use of LDA. In a publication by Barker and co-workers, the LDA mediated continuous flow lithiation reaction of 1,3,4-oxadiazoles is reported **(Scheme 2.8)**.[32] These 1,3,4-oxadiazoles are common motifs in bioactive compounds. Examples include raltegravir and zibotentan, medicines used in the treatment of HIV and prostate cancer, respectively. Under the continuous flow conditions reported, up to quantitative yields of these compounds were synthesised *via* room temperature metalation and subsequent electrophilic trapping reactions. The corresponding batch reaction requires much lower temperatures and lower yields are observed, attributed to ring decomposition, which is known to occur in batch. Continuous flow circumvents this issue due to superior mixing, allowing unstable intermediates to be intercepted by electrophilic trapping before decomposition can occur, even at temperatures as high as room temperature. Various electrophiles were well tolerated in this reaction, yielding highly functionalised oxadiazoles in yields previously unattainable in batch.



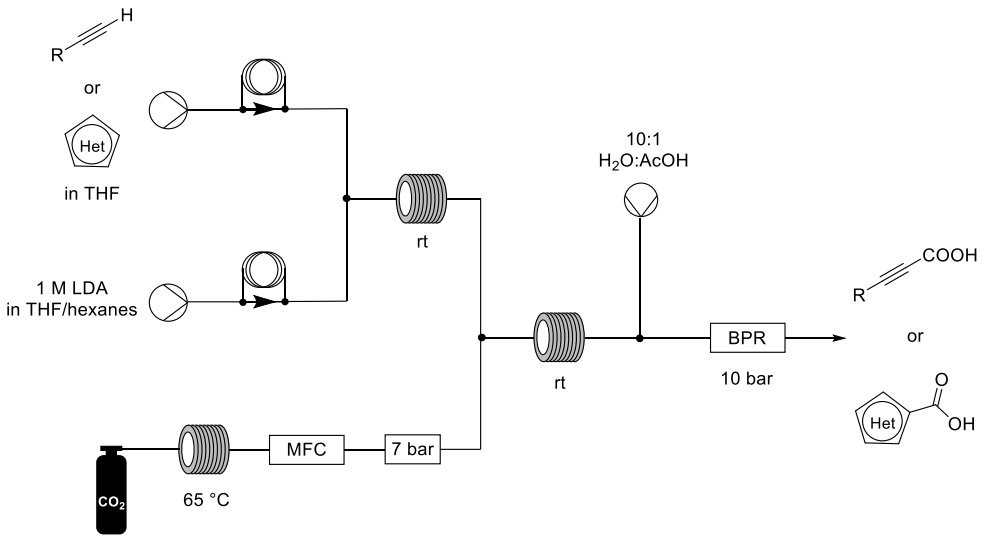
Scheme 2.8. Deprotonation and substitution of oxadiazoles

A publication by Alezra and co-workers outlined the synthesis of quaternary α-amino acids based on the concept of Memory of Chirality (MOC).[33] The synthesis involves the intermolecular alkylation of an enolate where the initial chirality of the starting α-amino acid is 'memorised' at low temperatures. Rotation of tertiary aromatic amides is inhibited at low temperatures, resulting in a stereoselective reaction. The strict temperature requirements meant that the reaction was extremely difficult to scale in batch, prompting the authors to develop a flow chemistry method for the synthesis **(Scheme 2.9)**.[34] Overall, the enantiomeric excess obtained using the flow system was slightly lower than that of batch. However, the flow system allowed for: **i)** a residence time of less than 3 minutes; **ii)** use of a more efficient temperature and **iii)** the reaction to be considered scalable. Yields of up to 99% and enantiomeric excesses of up to 89% were achieved using the continuous process.



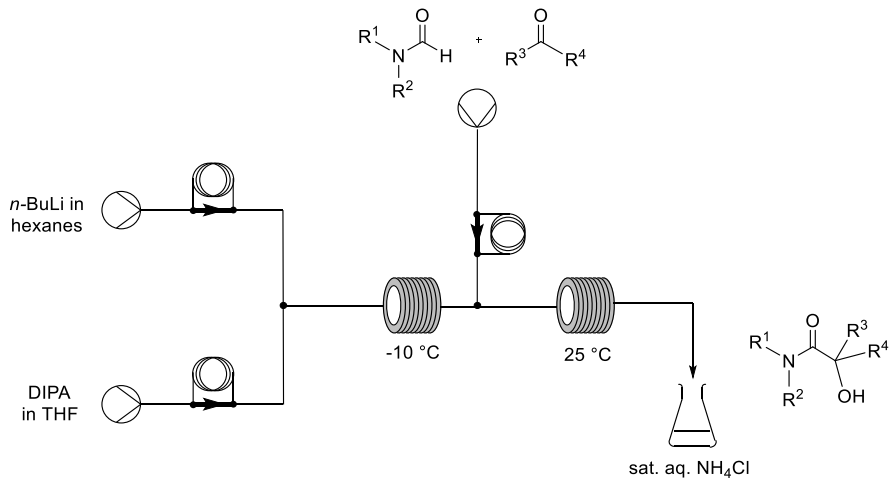
Scheme 2.9. 'Memory of Chirality' deprotonation and alkylation reaction

A continuous flow method for the LDA mediated direct lithiation of terminal alkynes and heterocycles, and subsequent electrophilic trapping with CO_2 was reported by Kappe and co-workers **(Scheme 2.10)**.[35] CO_2 is a highly attractive building block in organic synthesis as it is readily available, cheap, naturally abundant and is classified as an ideal renewable carbon source.[36] Combining CO_2 with organolithium reagents offers an effective strategy to overcome the low reactivity of CO_2. However, the highly exothermic nature of this reaction type severely hinders this approach. The authors exploited the advantages of continuous flow chemistry, namely, better heat and mass transfer. The decreased risk of thermal runaway, combustion and explosion enabled a flash synthesis of highly valuable carboxylic acid frameworks, in moderate to good yields, using $CO_{2(g)}$.



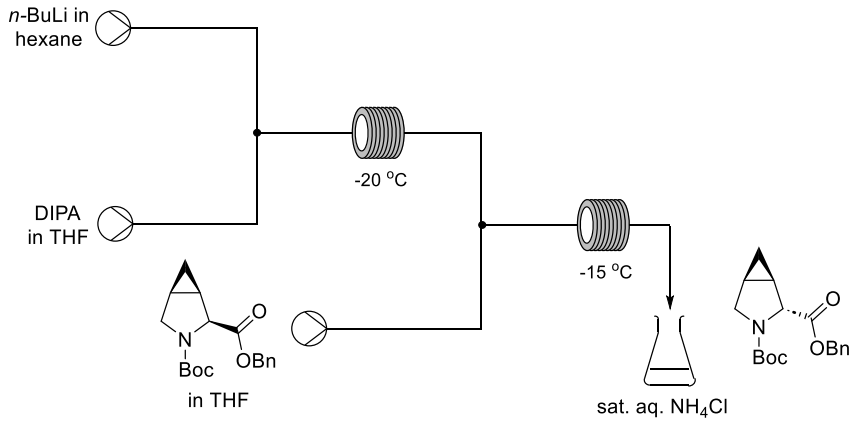
Scheme 2.10. LDA mediated carboxylation of heterocycles

Although LDA is commercially available as a solution in various solvents and concentrations, use of this reagent is not without limitations. These include fluctuations in quality and concentration, variability in supply and degradation issues inherent to the organometallic reagent. It is oftentimes advantageous to generate LDA immediately before use. This can be achieved through the reaction of *n*-BuLi with diisoproplamine. In 2017, Knochel and co-workers reported the *in situ* generation of LDA for the formation of α-hydroxy amides,[37] *via* an ambient temperature continous flow nucleophilic amidation or thioamidation reaction. The amide functionality, and analogous thioamide, are present in an extensive range of commercially available drugs. Hence, methods to generate these compounds have garnered significant interest in recent times. Of particular interest are methods involving carbamoyllithium intermediates. Knochel and co-workers described the formation of these species by LDA mediated deprotonation of the corresponding formamides. These intermediates were then be trapped by a range of electrophilic species, including ketones, allyl bromides and Weinreb and morpholino amides, generating a range of highly functionalised α-hydroxyamide or thioamides, in up 98% yields.Very little evidence of side-reactions or degradation issues are apparent in these reactions.



Scheme 2.11. Generation of α-hydroxy amides by continuous flow

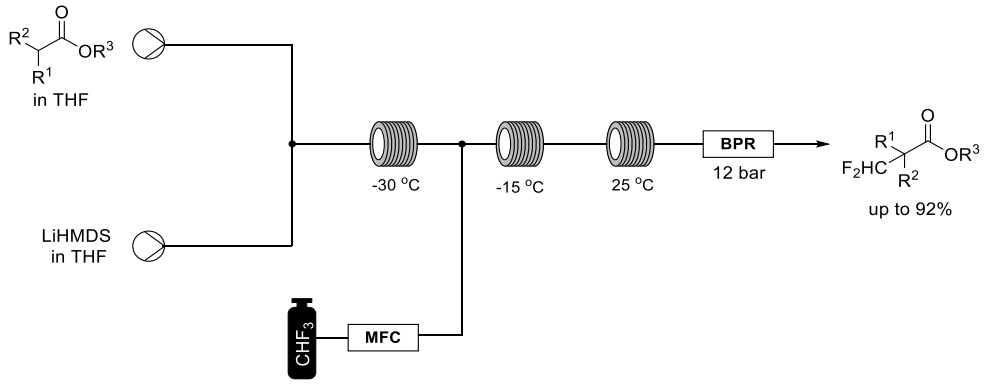
In similar work published by Ossola and co-workers, a continuous flow strategy was engineered to promote the epimerization of 3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid **(Scheme 2.12)**.[38] The continuous flow reaction significantly reduced the number of steps previously reported to access this unnatural amino acid. Unlike the batch method, the continuous approach was also amenable to scale up and eliminated the previous need for cryogenic reaction conditions.



Scheme 2.12. LDA mediated stereochemical inversion of *N*-Boc-piperidine esters

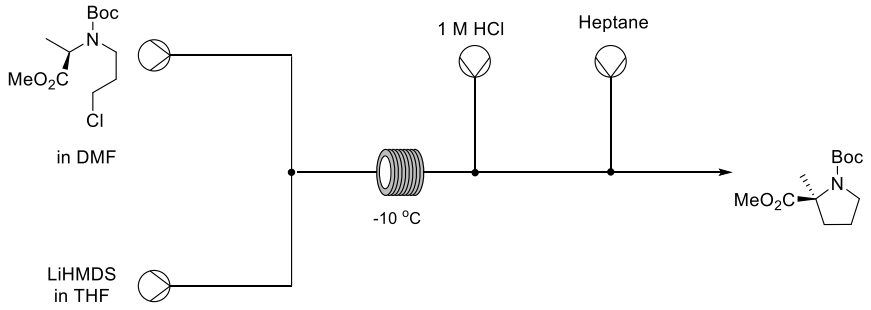
Lithium bis(trimethylsilyl)amide or lithium hexamethyldisilazide (LiHMDS), a lithiated organosilicon compound which is commonly used as a strong, non-nucleophilic base,[39] has also been used for deprotonation reactions in continuous flow. In 2018, Kappe and co-workers reported a continuous flow synthesis of difluoromethylated amino acids **(Scheme 13)**,[40] a class of compounds which exhibit a broad range of biological activities. Examples include antibacterial agents, antihypertensive medicines and anti-cancer drugs.[41] The mechanism of the difluoromethlation reaction is believed to proceed *via* a difluorocarbene intermediate, generated by treatment of gaseous fluoroform with LiHMDS and subsequent α-elimination of fluoride. This subsequently reacts with an ester-derived enolate to yield α-difluoromethyl

amino acids. The authors successfully extended this methodology to include the synthesis of eflornithine, an API currently used for the treatment bacterial infections associated AIDS. However, development of an industrial scale protocol was not achieved. Further work to scale up this process and incorporate a recycling or removal method for the fluoroform is currently underway.



Scheme 2.13. Continuous flow α-difluoromethylation of esters

Finally, Abele and co-workers described the intramolecular cyclisation of haloalkyl-substituted α-amino esters *via* memory of chirality, using LiHMDS as a base **(Scheme 14)**.[42] Cyclic amino acids with quaternary stereocenters are key structural motifs in many naturally occurring and bioactive compounds. Methods to furnish such compounds in an enantioselective fashion are highly sought after. The use of continuous flow chemistry in this instance allowed better control of the exotherm associated with this reaction and allowed for a more attainable reaction temperature to be used. A high level of enantioselectivity and full conversion of the reactive amino ester in a very short reaction time was reported.



Scheme 14. Asymmetric intramolecular cyclisation reaction to form chiral *N*-Boc piperidine

2.4 Outlook

Deprotonation chemistry using organolithium bases is a mainstay of organic synthesis. However, many organolithium reagents come with a challenging safety profile. Additionally, this chemistry typically requires cryogenic reaction conditions. These conditions are easily achieved on small scale. However, this can prove an insurmountable challenge when an

industrial scale is considered and often exclude this chemistry from industrial applications. Oftentimes, these efficient small-scale strategies are replaced by more convoluted ones upon scale-up.

Flow chemistry has the potential to avoid most of the pitfalls associated with organolithium chemistry in batch, through the use of highly efficient mass and heat transfer, precise control of residence times and sophisticated mixing apparatus. Advantages of continuous flow chemistry over traditional batch reactions in this context include: **i)** cryogenic conditions are easier to attain or in some instances can be eliminated entirely; **ii)** a reduction in the number of synthetic steps is often observed; **iii)** faster reaction times; **iv)** more selective reactions; **v)** higher conversions with reduced degradation or side-reactions observed and **vi)** improved safety profiles. Continuous flow chemistry has also allowed many unsuccessful or so-far-impossible batch reactions to be successfully performed.

All that said, it would be amiss to exclude the challenges still faced when using organolithium reagents in continuous flow. These include: **i)** issues associated with persistent formation of precipitates, leading to blockages in reaction systems; **ii)** the lack of any precedence for powerful asymmetric processes involving lithium (aza)enolates in flow[43-45] and **iii)** although a very useful reagent for many transformations, to the best of our knowledge, there is currently no literature precedence for the use of *t*-BuLi in continuous flow.[39]

Results & Discussion

2.5 Aims and objectives

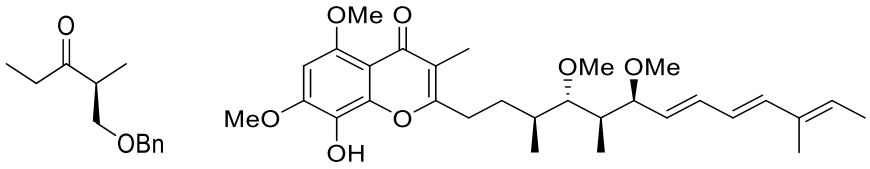
In this chapter, the α-alkylation of ketones *via* continuous flow chemistry is outlined and discussed. The primary aim of this work was to design a general methodology for the continuous flow deprotonation and alkylation of ketones, where a variety of both ketones and electrophiles would be tolerated.

The following is a brief outline of the aims discussed within this chapter:

- To configure a flow system capable of facilitating α-alkylation of ketones, avoiding very low reaction temperatures.
- To optimise key reaction parameters in the development of a continuous flow method for the α-alkylation of ketones.
- To expand the scope of this work to include a range of cyclic, acyclic, symmetric and asymmetric ketones and a variety of electrophiles.

2.6 Project background

As discussed in Chapter 1, the α-alkylation of ketones represents one of the most fundamental and important reactions in organic chemistry. Indeed, the α-alkylation of a ketone encompasses a full chapter of McMurry's Organic Chemistry.[46] A significant number of natural products and bioactive compounds contain α-alkylated ketones, or simple derivatives thereof.[47] For example, Paterson's ketone is an important scaffold in natural product synthesis and the synthesis of Stigmatellin A, a compound with antibacterial properties, involves a number of stereoselective α-alkylation reactions **(Figure 2.2)**.[48]



Paterson's ketone Stigmatellin A

Figure 2.2. Biologically important α-alkylated ketones and derivatives thereof

As previously discussed, it is widely known and accepted that although a powerful transformation, traditional methods used for the α-alkylation of ketones are belied by numerous reactivity issues **(Figure 2.3)**. Controlling the reactivity of enolates is an onerous task.

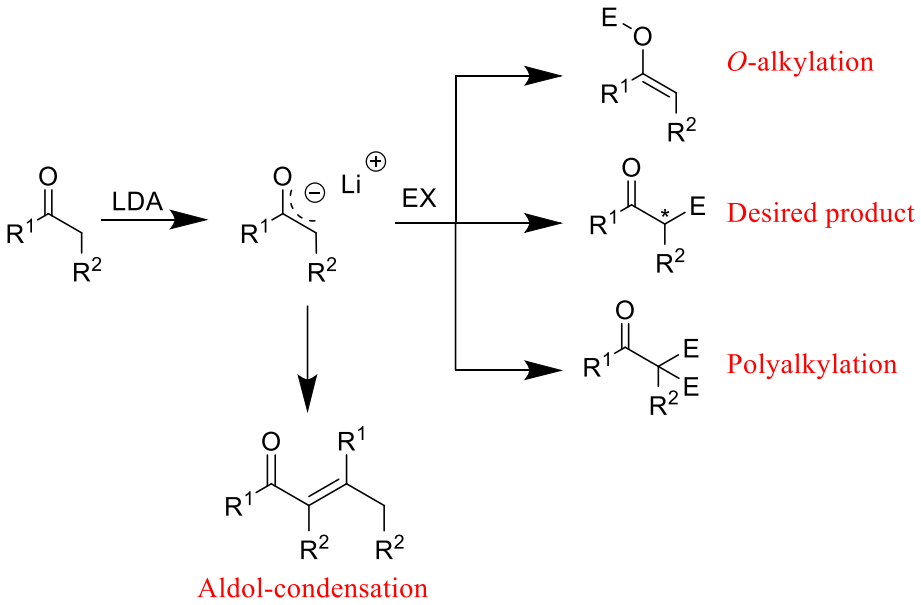
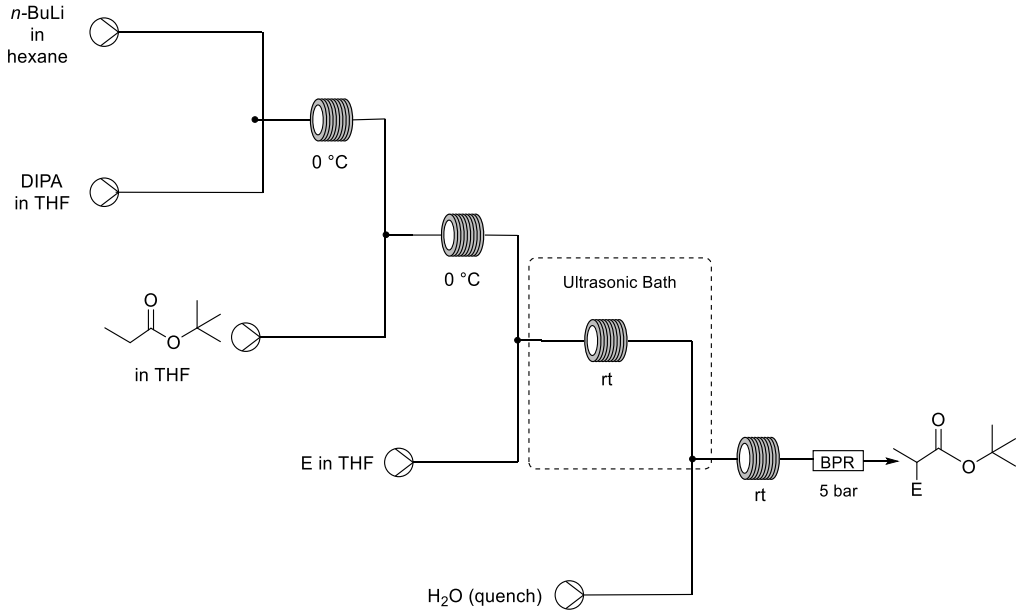


Figure 2.3. Inherent reactivity issues associated with ketone enolates

Due to inherent reactivity issues associated with lithium enolates, we believed reactions involving such species would be highly amenable to continuous flow chemistry and could alleviate many of the issues associated with this reaction in batch. Firstly, by design, continuous flow chemistry has the potential to obviate the occurrence of nuisance side

reactions. The occurrence of over alkylation is reduced due to the fact back mixing is limited. The immediate trapping of ketone enolate species by efficient mixing with an electrophile should, in theory, prevent self-condensation and side-reactions from taking place. Additionally, a continuous flow method for these reactions offers considerable improvements in terms of reaction efficiency. The high surface area to volume ratio should allow for better temperature control, meaning the necessity for cryogenic conditions may not be required for reactions of this kind performed in flow. We also expected reaction times of much shorter duration may be achievable in a continuous flow set-up, due to more efficient mixing and higher throughput of more concentrated reagents. And finally, we hoped design of a continuous flow method for the α-alkylation of ketones would offer a far superior safety profile over the traditional batch reaction. The enclosed nature of the flow system means exposure of the chemist to hazardous alkylating agents as well as the decreased exposure of alkyl lithium reagents to air should allow for a much safer process.

Encouragingly, in 2018, Kappe and co-workers reported on the α-alkylation of esters by continuous flow **(Scheme 2.15)**.[49] A series of α-alkylated esters were prepared in moderate to good yields *via* the *in situ* generation of LDA, subsequent enolate formation and finally trapping of these highly reactive species by a range of electrophiles.



Scheme 2.15. α-Alkylation of esters by continuous flow

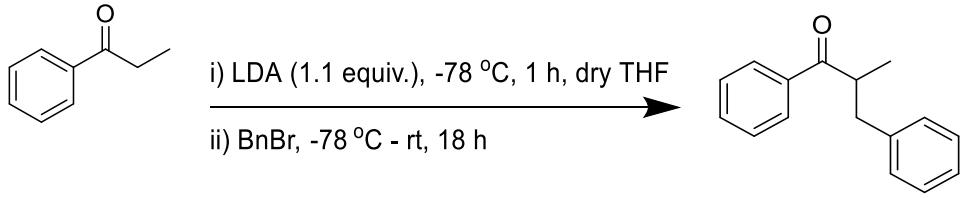
Although this report served as proof for the fact lithium enolates could successfully be alkylated in continuous flow, we remained cognisant of the additional challenges posed by ketone enolates over their ester counterparts. Enolates derived from ketones are known to be significantly more problematic than those derived from esters due to the increased

electrophilicity of these species. Consequently, it is harder to control the reactivity of these species and issues associated with the formation of unwanted side products become more pronounced.

2.7 Synthesis of α-alkylated ketones by continuous flow

2.7.1 Optimisation reactions

As a starting point for this project, the α-benzylation reaction of propiophenone was chosen as a representative reaction to conduct our optimisation studies **(Scheme 2.16)**. Although conceptually, this reaction appears straightforward, it represents a typical α-alkylation reaction which in batch proves problematic. Despite changing various reaction parameters, including time and reagent equivalents, it was only possible in our hands to isolate **10** in a disappointing yield of 26% in batch. In addition, purifying this compound using column chromatography proved challenging as both the starting material 2 and the desired product **10** display similar R_f values.



2 **10**, 26%

Scheme 2.16. α-Alkylation of **2** with BnBr

For several reasons, we envisaged designing a flow chemistry protocol for this reaction, and similar reactions, would help alleviate some of the issues associated with this batch reaction. Firstly, one of the key advantages of flow chemistry is the ability to operate the reactor at steady state **(Figure 2.4)**. If ideal 'plug-flow' behaviour is assumed, by definition, the concentration of a starting material and product in a reaction at steady state is invariant with time.[50] Thus ideally, at steady state the concentration of starting material will be minimal and the concentration of product is maximised. Contrastingly, in a batch reaction the starting material concentration is reduced over time, however it remains uniformly distributed throughout the flask. In theory, collecting only the fraction of a reaction deemed steady-state should help to alleviate, or significantly reduce, the issue of product loss due to contamination with unreacted starting material.[5] Also, we hoped it would allow for a safer, more efficient and industrially applicable route to α-alkylated ketones.

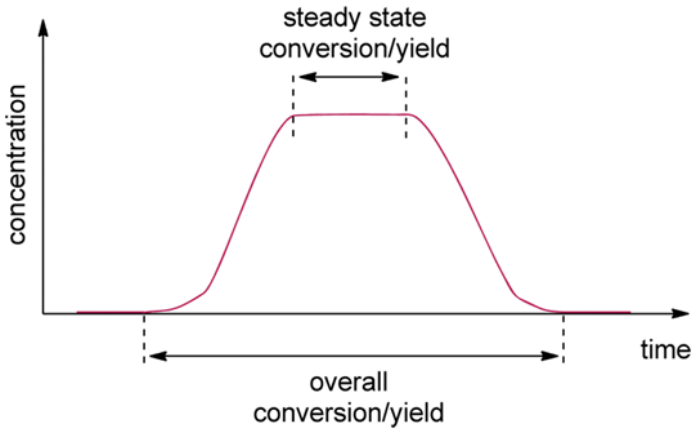
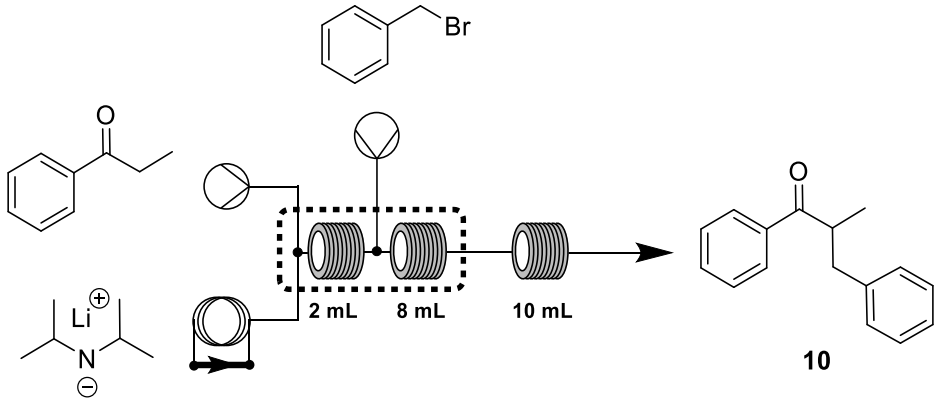


Figure 2.4. Steady state approximation[5]

2.7.1.1 Two reactor coil configuration

To begin our optimisation reactions for the α-alkylation of ketones in continuous flow, a flow set-up consisting of two reactor coils was chosen **(Scheme 2.17)**. This configuration consisted of a dual-core cooled reactor manifold, capable of facilitating reaction temperatures as low as -70 °C and a second heated reactor manifold, allowing for reaction temperatures from room temperature to 150 °C to be used. A dual-core cooled reactor manifold was used to facilitate enolate formation. For the first 2 mL of this reactor coil, only propiophenone **2** and LDA were supplied to the reactor, enabling formation of the reactive enolate species. Subsequently at the beginning of the 8 mL reactor coil, benzyl bromide was introduced to quench this species. The second reactor coil allowed for the reaction temperature to be increased in order to promote formation of benzylated propiophenone **10**. Reagent solutions were prepared under inert atmosphere, which was maintained throughout all experiments using an inert gas manifold. Solutions were added to the reactor either *via* syringe from stock bottles or injection through a sample loop. Various reaction parameters were investigated using this initial set-up, including reagent equivalents, temperature and residence time.

For reasons previously described, our optimisation focused on the conversion obtained when the reaction was deemed at steady state. For completeness however, the overall reaction conversion was also calculated. These conversions were calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. It is also worth noting that for these reactions, we initially chose reaction parameters to reflect, in so far as was possible, the previously optimised batch reaction conditions.



Scheme 2.17. Initial reactor configuration consisting of two reactor manifolds

The first reaction parameter we examined was the equivalents of LDA employed in these reactions **(Table 2.1)**. For these reactions, all reagent solutions, with the exception of the LDA solution, were prepared to a concentration of 0.5 M. We chose this concentration so as to allow for an appreciably scaled reaction to occur, whilst also reducing the chance of potential blockages resulting from reactions run at high concentrations. In the batch reaction, a slight excess of base is commonly used to ensure complete deprotonation of the ketone and enolate formation. For this reason, we chose to begin with 1.2 equivalents of LDA. Although batch reactions of this kind are typically conducted at temperatures as low as -78 °C, we wondered if higher reaction temperatures could be employed in the corresponding flow reactions due to the increased surface area to volume ratio. This would potentially allow greater control of the internal reaction temperature. For this reason, we chose -15 °C as our initial cooled reactor temperature, whilst allowing the heated reactor to remain at room temperature. In the corresponding batch reaction, the temperature would be slowly increased to rt after the addition of an electrophile to ensure complete alkylation occurs. However, it became immediately apparent that to promote conversion of **2** to **10**, use of an elevated temperature for the second reactor coil was required. Only trace amount of **10** was detected by ^{1}H NMR spectroscopy when the heated reactor coil remained at room temperature **(Table 2.1, entry 1)**. Pleasingly, an increase in conversion was observed when the heated reactor coil was heated to 75 °C **(Table 2.1, entry 2).** A yield at steady state of 19% was observed for this reaction. Increasing the equivalents of LDA from 1.2 to 1.5 equivalents resulted in a significant increase in the yield obtained, both overall and at steady state **(Table 2.1, entry 3)**. However, any further increase in the equivalents of LDA employed resulted in no further increase in the yield of and instead resulted in a decrease in yield being observed **(Table 2.1, entries 4 & 5)**. This is consistent with what is observed in batch reaction, where employing a large excess of base can be detrimental to the yield observed.[51]

Table 2.1. Optimisation of reaction parameters - LDA equivalents screen

Entry	Reagent Equiv. 2	LDA	BnBr	Cooled-reactor Temp (°C)	Heated-reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
1	1	**1.2**	1.1	-15	rt	5	trace	trace
2	1	**1.2**	1.1	-15	75	5	16%	19%
3	1	**1.5**	1.1	-15	75	5	44%	62%
4	1	**1.8**	1.1	-15	75	5	43%	53%
5	1	**2.0**	1.1	-15	75	5	31%	37%

Next, we moved to examining the equivalents of benzyl bromide used in these reactions **(Table 2.2)**. A decreased yield was observed when 1.1 equivalents of BnBr was used **(Table 2.2, entry 1)**. The greatest yield at steady state recorded was when 1.2 equivalents of BnBr was used **(Table 2.2, entry 2)**. A decreased yield was obtained once again when 1.5 equivalents of BnBr were used **(Table 2.2, entry 3)**. However, when 1.8 equivalents of BnBr was used, an increase in the overall yield calculated for this reaction was observed **(Table 2.2, entry 4)**. However, the use of 1.8 equivalents of BnBr for only a minor increase in yield seemed wasteful. Finally, a decreased yield was observed when 2.0 equivalents of BnBr was used **(Table 2.2, entry 5)**. We proceeded with optimising our next reaction parameter using 1.2 equivalents of BnBr.

Table 2.2. Optimisation of reaction parameters - alkylating agent equivalents screen

Entry	Reagent Equivalents			Cooled-reactor Temp (°C)	Heated-reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
	2	**LDA**	**BnBr**					
1	1	1.5	**1.1**	-15	75	5	44%	62%
2	1	1.5	**1.2**	-15	75	5	59%	64%
3	1	1.5	**1.5**	-15	75	5	49%	54%
4	1	1.5	**1.8**	-15	75	5	66%	62%
5	1	1.5	**2.0**	-15	75	5	56%	57%

We next looked at the temperatures employed for both the deprotonation and alkylation step. As discussed, we chose -15 °C for our initial reactions. However, batch reactions of this kind are typically performed at much lower reaction temperatures. At higher temperatures in batch, the reactive enolate intermediate species is highly unstable, and often leads to the formation of several degradation or unwanted side-products.[51] Pleasingly however, at this elevated temperature in flow, we did not observe any evidence of the formation of side products. However, in the interests of completeness, we examined a range of temperatures lower than -15 °C to see if any led to an improved yield of **10**. Lowering the reaction temperature from -15 °C to -70 °C resulted in significant decreases in the yields of **10** obtained **(Table 2.3, entries 2, 3 & 4)**. We suggest this is due to the greater temperature control offered in flow, meaning the internal temperature of the reaction mixture is more accurately maintained. This contrasts with the corresponding batch reaction, where control of the internal temperature of the reaction mixture is more challenging and less accurately controlled. These temperatures may simply have been too cold to facilitate enolate formation in flow. For this reason we decided to next increase the temperature of the cooled reactor. Pleasingly, we obtained the greatest yield for this reaction at 0 °C **(Table 2.3, entry 5)**. Further increasing the temperature to rt however was detrimental to product formation and resulted in the lowest yield obtained **(Table 2.3, entry 6)**. We suggest the reactive enolate species too unstable at such a high temperature.

Table 2.3. Optimisation of reaction parameters - cooled reactor manifold temperature screen

Entry	Reagent Equivalents			Cooled-reactor Temp (°C)	Heated-reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
	2	LDA	BnBr					
1	1	1.5	1.2	**-15**	75	5	59%	64%
2	1	1.5	1.2	**-30**	75	5	50%	53%
3	1	1.5	1.2	**-45**	75	5	49%	39%
4	1	1.5	1.2	**-70**	75	5	11%	15%
5	1	1.5	1.2	**0**	75	5	50%	70%
6	1	1.5	1.2	**rt**	75	5	21%	16%

Next, we examined the temperature of the heated reactor manifold. In batch, examples of heating reactions of this type above room temperature are rare. Our initial flow reaction gave little conversion to **10** when the heated reactor coil remained at room temperature. This may be due to two reasons: **i)** The temperature of solution being pumped through the heated reactor coil is -15 °C and may not reach adequate temperature without any external heating of the manifold and **ii)** the reaction duration in flow is significantly shorter than the corresponding batch reaction (circa 1 hr in flow versus > 24 h in batch). Again, we examined various different reaction temperatures from 30 °C to 90 °C. At temperatures lower than 75 °C we noted a decreased yield in the product obtained **(Table 2.4, entries 1, 2 & 3)**. The greatest yield of **10** was obtained when a temperature of 75 °C was used. However, increasing the reactor coil to 90 °C resulted in no product formation **(Table 2.4, entry 5)**.

Table 2.4. Optimisation of reaction parameters - heated reactor manifold temperature screen

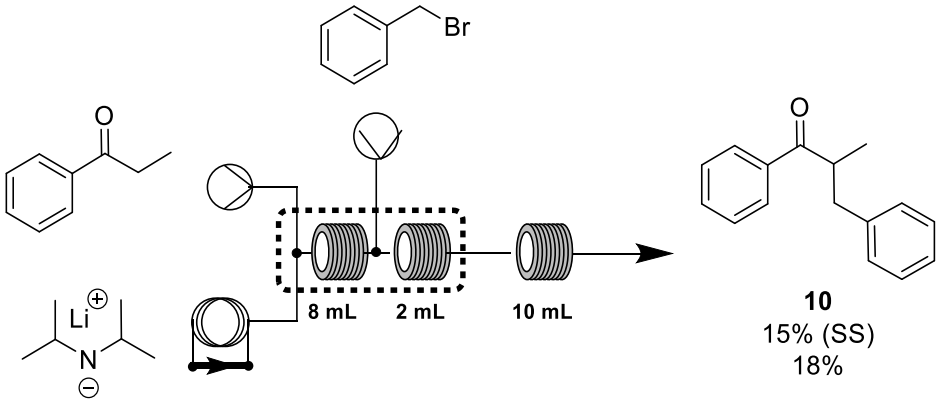
Entry	Reagent Equivalents			Cooled-reactor Temp (°C)	Heated-reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
	2	**LDA**	**BnBr**					
1	1	1.5	1.2	0	**30**	5	25%	35%
2	1	1.5	1.2	0	**45**	5	45%	45%
3	1	1.5	1.2	0	**60**	5	46%	42%
4	1	1.5	1.2	0	**75**	5	50%	70%
5	1	1.5	1.2	0	**90**	5	0%	0%

The final reaction parameter we examined using this reactor configuration was the residence time **(Table 2.5)**. In batch, if starting material remains, a prolonged reaction duration is often the first step taken to increase the yield obtained in a given reaction. We envisaged increasing the residence time of the reagents in the reactor manifold would allow for increased yield due to prolonging the time allowed for both the enolate formation and alkylation steps. Extending the residence time for this reaction, whilst keeping the reactor configuration the same, resulted in a decrease in the flow rate of each reagent. These reduced flow rates seemed to facilitate precipitation of the reagents in the reactor coils, which led to blockages of the instrument and numerous failed experiment attempts. In some instances, it was possible to isolate **10** from these reaction attempts. The greatest yield of **10** obtained was when a residence time of 5 mins was used **(Table 2.5, entry 1)**. However, variability and inconsistencies were evident in the results obtained when longer residence times were investigated **(Table 2.5, entries 2 - 5)**.

Table 2.5. Optimisation of reaction parameters - residence time screen

Entry	Reagent Equivalents			Cooled-reactor Temp (°C)	Heated-reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
	2	LDA	BnBr					
1	1	1.5	1.2	0	75	**5**	50%	70%
2	1	1.5	1.2	0	75	**7.5**	35%	42%
3	1	1.5	1.2	0	75	**10**	62%	65%
4	1	1.5	1.2	0	75	**12.5**	54%	58%
5	1	1.5	1.2	0	75	**15**	50%	39%

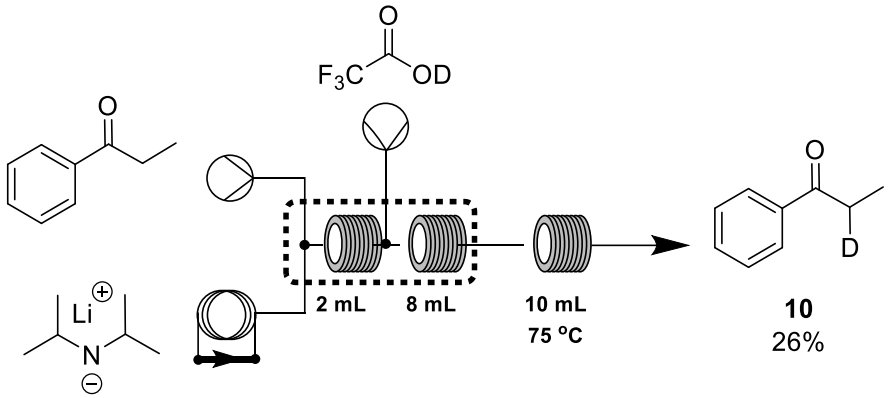
The highest yield of α-alklyated ketone **10** achieved during these optimisation reactions was 70%. Although this represented a significant increase in yield when compared to that previously obtained in batch (26% yield), we were hopeful further optimisation was possible. In all the reactions discussed, propiophenone starting material **2** remained in the crude reaction mixture. We wondered whether incomplete enolisation or incomplete alkylation was contributing to a reduced yield being obtained. For this reason we decided to alter the reactor configuration. We were suspicious that the 2 mL volume of the initial reactor coil was too short, causing insufficient enolisation of our ketone, and hence reducing the yield of alkylated product obtained. We hoped swapping the configuration of the initial dual-core reactor to allow for an 8 mL deprotonation step would allow for an increase in enolate formation, and subsequent yield of **10 (Scheme 2.18)**.



Scheme 2.18. Altered configuration of two reactor manifold system

Disappointingly however, this altered configuration resulted in decreased yield of **10**. This was an unexpected result and forced us to return to our original reactor configuration. It is

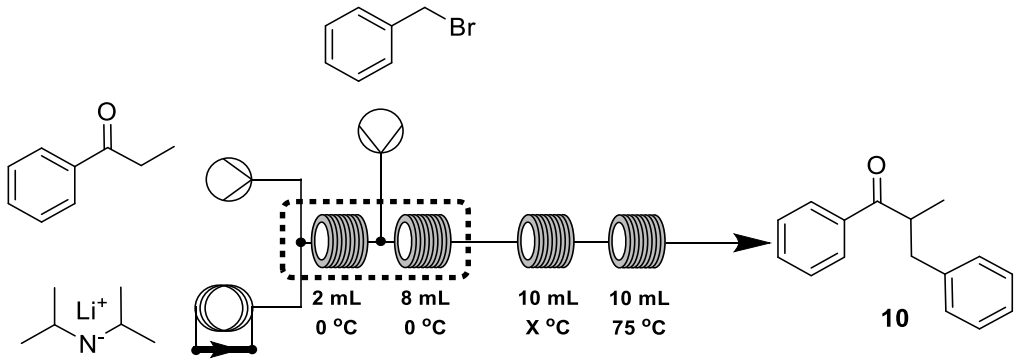
possible the enolate species was too unstable to survive these reaction conditions. To further investigate whether complete enolisation was occurring in this reaction, we decided to use an alternative quench in the reaction. We chose deuterated trifluoroacetic acid as an alternative quench. We hoped this would allow us to gain a quantitative measurement of the extent of enolisation occurring in this reaction. However, we were surprised to record a low deuterium incorporation of only 26% at steady state **(Scheme 2.19)**.



Scheme 2.19. Deuterated trifluoroacetic acid reaction

2.7.1.2 Three reactor coil configuration

As previously discussed, attempts to increase the yield of **10** obtained in this reaction by extending the reaction residence time were marred with issues. To overcome these issues, and to extend the reaction time, we next decided to introduce a third reactor coil to our system **(Scheme 2.20)**.



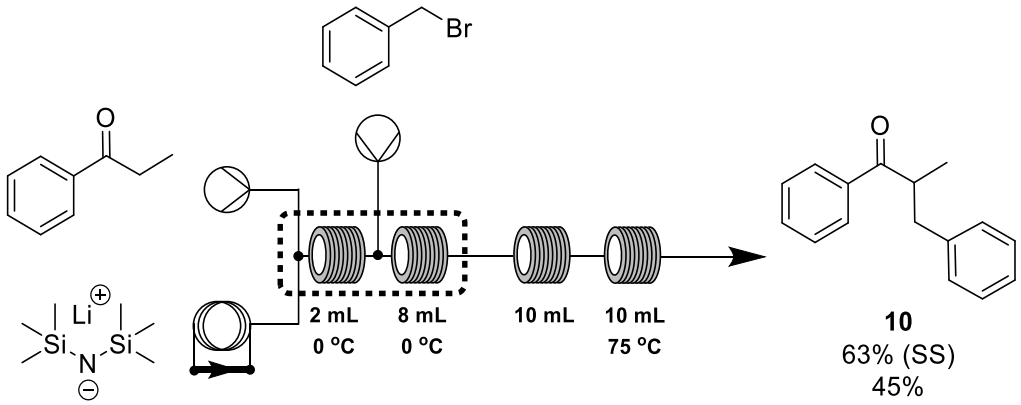
Scheme 2.20. Three reactor manifold system

Pleasingly, addition of an additional reactor coil immediately after the first dual-core cooled reactor manifold and maintaining the temperature of the reaction in this reactor at 0 °C resulted in an increased yield, both at steady state and overall **(Table 2.6, entry 1)**. We next examined whether heating this additional reactor coil would further increase the yield obtained, however, a decrease in yield was recorded **(Table 2.6, entry 2)**.

Table 2.6. Three reactor manifold temperature investigation

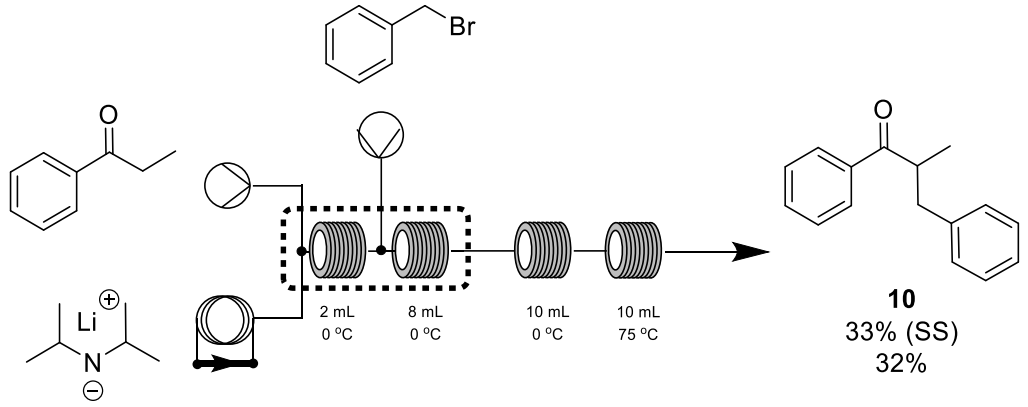
Entry	Reagent Equivalents			1st reactor Temp (°C)	2nd reactor Temp (°C)	3rd reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
	2	LDA	BnBr						
1	1	1.5	1.2	0	**0**	75	5	65%	79%
2	1	1.5	1.2	0	**75**	75	5	43%	37%

We also examined the use of an alternative lithium amide base, LiHMDS. LiHMDS is often preferred to LDA as it demonstrates increased stability in solution and a decreased tendency towards aggregation.[52] Additionally, as discussed, there is precedence for the use of LiHMDS in continuous flow. We were hopeful this would help alleviate issues associated with precipitation resulting in blockages of the system during this reaction. However, use of LiHMDS under the previously optimised reaction conditions resulted in a decreased yield of **10** being obtained **(Scheme 2.21)**.



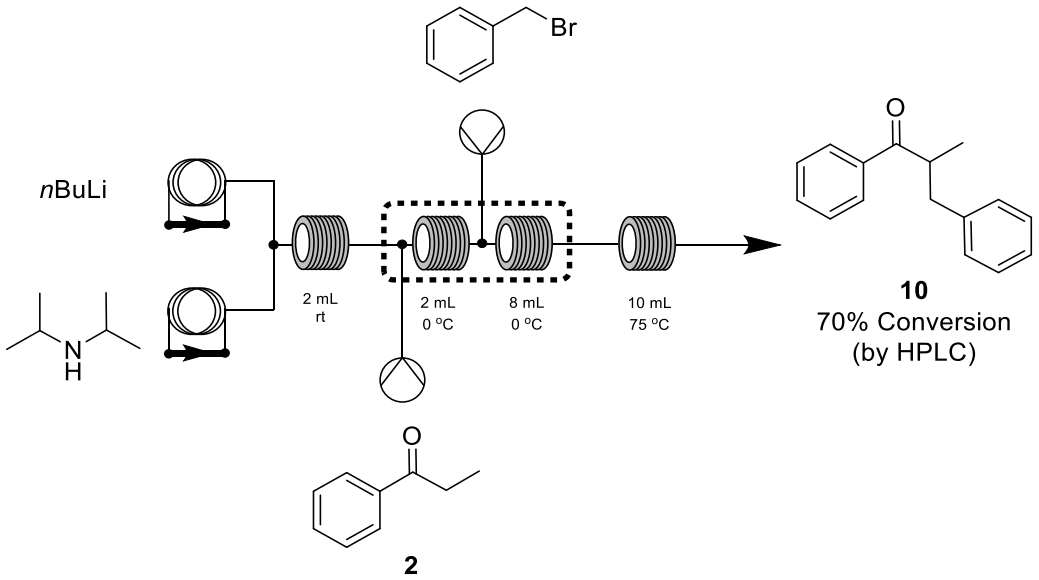
Scheme 2.21. Use of LiHMDS

With LDA proving superior, we next investigated the use of freshly prepared LDA instead of the commercially available solution. Unfortunately, this led to a reduced yield of **10** being obtained **(Scheme 2.22)**. We suggest the observed decrease may be due to the increased number of manipulations required for the *in-situ* generation of LDA. We were concerned this was possibly causing degradation of the base before the deprotonation could take place. Work to overcome these issues and optimise this process is currently underway by another member of the group.



Scheme 2.22. Reaction with freshly prepared LDA

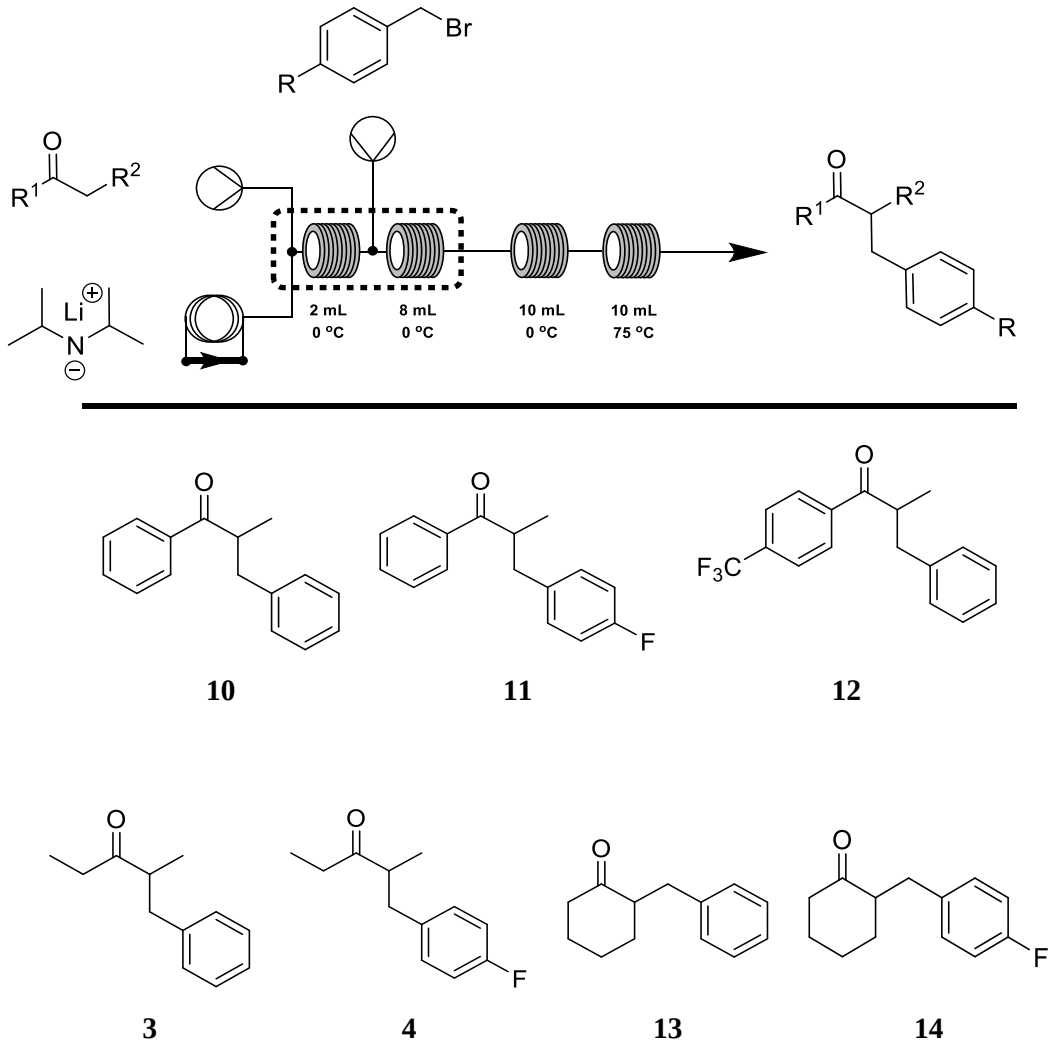
It is worth noting that whilst at Vapourtec in May 2019, it was possible to generate LDA *in-situ* within the continuous flow reactor for these alkylation reactions **(Scheme 2.23)**. The LDA was prepared by adding DIPA and *n*-BuLi to a 2 mL reactor coil *via* individual sample loops. This required the installation of a 2 mL reactor coil prior to the dual core reactor, as well as use of an additional peristaltic pump. The temperature of this reactor coil was maintained at rt and a residence time of 2 mins was used for LDA generation. Successful generation of LDA was indicated by a colour change, resulting from the use of 1,10-phenanthroline as an indicator. Disappearance of this dark colour in solution also indicated consumption of the LDA, once the ketone was introduced to the reaction. This set-up resulted in a 70% conversion of **2** to **10** being obtained, recorded by HPLC. These reactions were conducted at the onset of our optimisation studies and were not repeated in UCC due to the necessity for additional infrastructure. It is hoped this step can be introduced into our method for the synthesis of α-alkylated ketones in due course.



Scheme 2.23. *In-situ* LDA generation

2.7.2 Expanding the substrate scope of this methodology

With our optimisation reactions in hand, we wondered whether our methodology represented a general method for the α-alkylation of ketones. We chose to examine three additional ketones, 4-trifluoromethylpropiophenone, 3-pentanone and cyclohexanone. We felt these substrates were examples of representative ketones and if successful it would mean the scope of this reaction included acyclic, cyclic, symmetric and unsymmetric ketone examples. For these reactions, we chose to also include 4-fluorobenzyl bromide as an alkylating agent. Concurrent work by another member of the group demonstrated how this compound acted as a superior electrophile for reactions of this type in batch. Pleasingly, six additional α-alkylated ketones were synthesised using the conditions previously optimised **(Scheme 2.24)**.



Scheme 2.24. α-Alkylated ketones synthesised in continuous flow

For comparison, the corresponding batch reactions were also completed for each substrate **(Table 2.7)**. Encouragingly, in the majority cases, a significant increase in yield was obtained when the reaction was conducted in continuous flow **(Table 2.7, entries 1, 2, 4 & 5)**. We noted no difference between the yield of obtained in batch compared to flow for one substrate

(Table 2.7, entry 3). In both cases, a yield of 52% α-alkylated product was obtained. Disappointingly however, cyclic ketones proved less successful in flow than in the corresponding batch reaction **(Table 2.7, entries 6 & 7)**. These substrates are known to be challenging and additional optimisation efforts are required to extend this methodology to include substrates of this kind in flow.

Table 2.7. Comparison between α-alkylation reaction yields obtained in flow and in batch

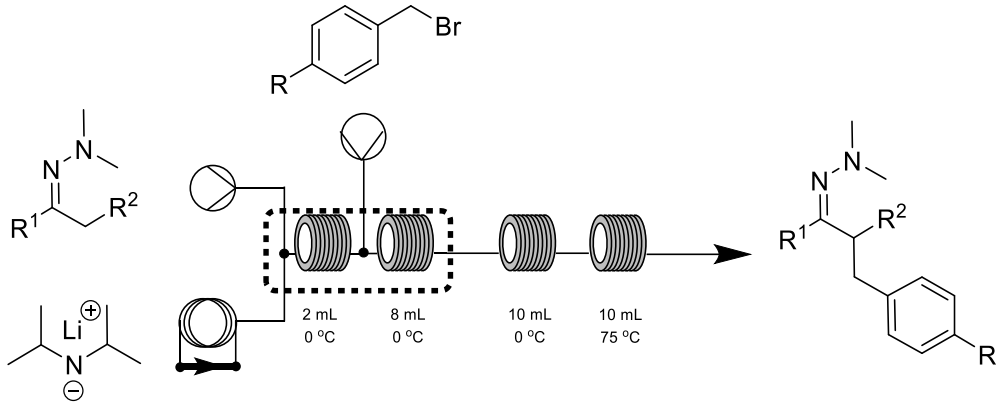
Entry	Ketone	Yield (Batch)	Yield (SS, Continuous flow)
1	**10**	26%	79%
2	**11**	48%	69%
3	**12**	52%	52%
4	**3**	17%	44%
5	**4**	26%	73%
6	**13**	57%	19%
7	**14**	49%	34%

2.8 Conclusions and future work

In conclusion, we have outlined the suitability of continuous flow for conducting α-alkylation reactions of ketones. We have made substantial progress in the development of a general method for this transformation. Numerous advantages over the corresponding batch reaction have been detailed. The work described herein represents a more efficient and industrially applicable method to access these compounds. Advantages include: **i)** significantly increased yields using continuous flow; **ii)** reduced reaction times using continuous flow; **iii)** elimination of cryogenic conditions and **iv)** increased safety profile.

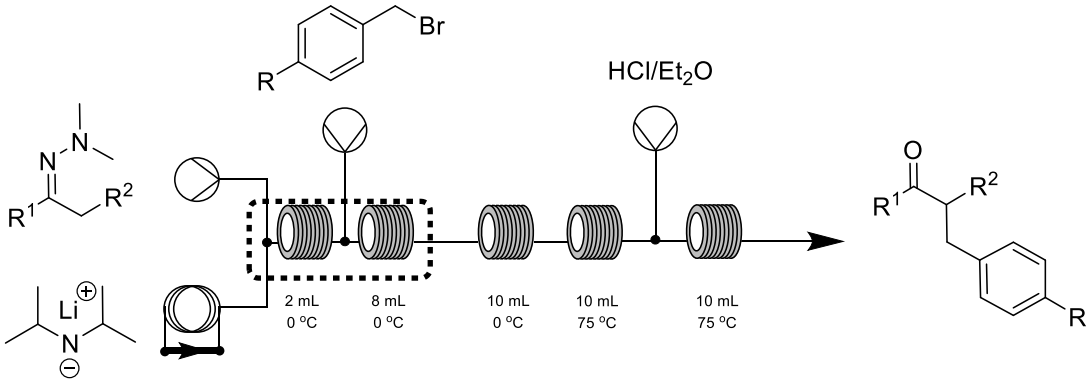
The overriding aim of this project is to develop a method for the asymmetric α-alkylation of ketones. Future work will focus on expanding this methodology to hydrazone substrates. Initially, prochiral hydrazones such as *N*,*N*-dimethylhydrazones (*N*,*N*-DMHs) will be used. As described earlier, previous work within the McGlacken group described the asymmetric α-alkylation of ketones using *N*,*N*-DMHs as ketone surrogates. The chiral ligand sparteine was

used as a chiral ligand and resulted in a moderate level of enantioselectivity.[45] To begin, a method for the α-alkylation of these hydrazones will be developed **(Scheme 2.25)**.



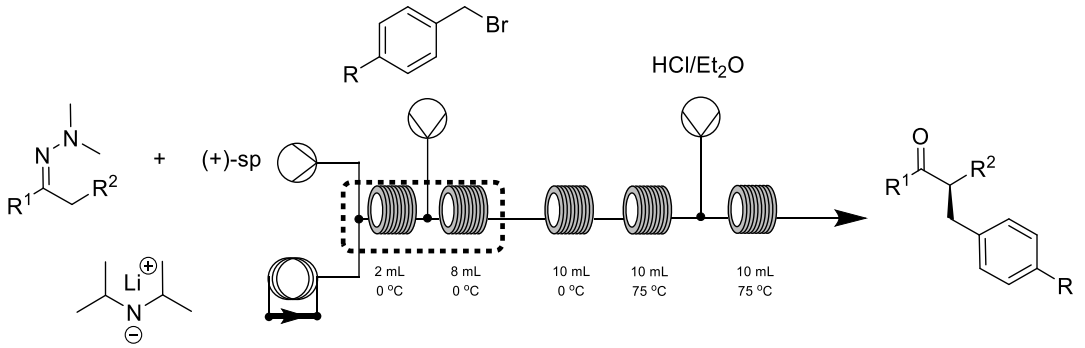
Scheme 2.25. Continuous flow α-alkylation of *N*,*N*-dimethylhydrazones

Following this, work to design an in-line hydrolysis, and unmask the parent α-alkylated ketone in continuous flow will also be undertaken **(Scheme 2.26)**.



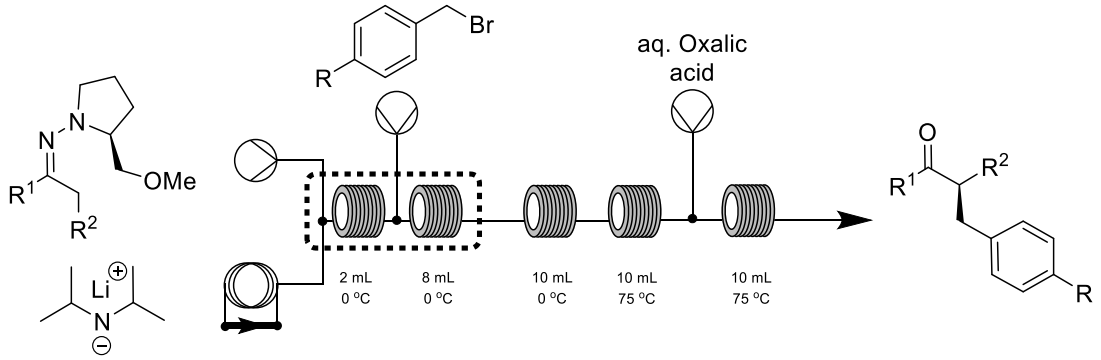
Scheme 2.26. Continuous flow α-alkylation of *N*,*N*-DMHs with in-line hydrolysis

Within the scope of this project, there will be potential for the inclusion of sparteine as a chiral ligand in these reactions, although this would require additional optimisation, including altering the reaction solvent **(Scheme 2.27)**.



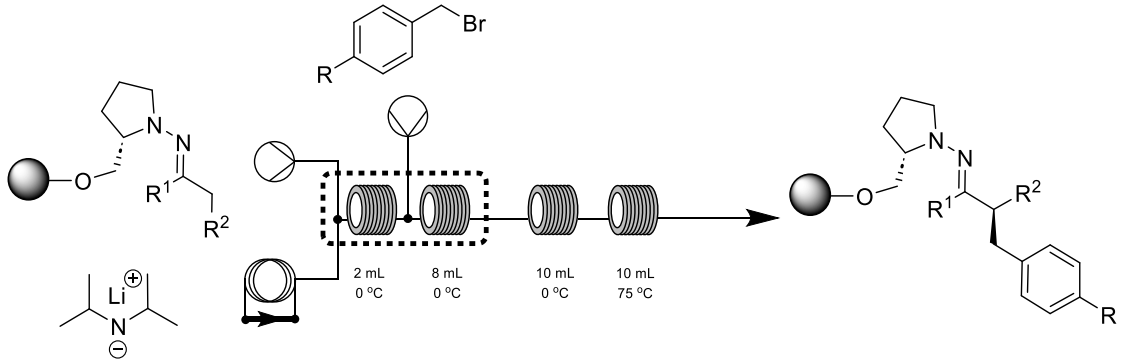
Scheme 2.27. Asymmetric α-alkylation of *N*,*N*-DMHs using (+)-sp as a chiral ligand

As discussed, the most prominent use of hydrazones is as chiral auxiliaries in asymmetric synthesis. Concurrently to the above work, *N,N*-DMHs will be substituted for SAMP hydrazones, with the intent of conducting an asymmetric α-alkylation reaction in continuous flow **(Scheme 2.28)**.



Scheme 2.28. Continuous flow α-alkylation of SAMP hydrazones

One of the significant disadvantages associated with the use of chiral auxiliaries in asymmetric synthesis is the fact the auxiliary is required in stoichiometric quantities. However, there is precedence in the literature for the use of immobilised SAMP analogues for the asymmetric α-alkylation of ketone substrates.[53-54] If the use of SAMP hydrazones proves amenable to continuous flow, it may then be possible to investigate the use of immobilised auxiliaries. This would allow for recycling of the chiral auxiliary, making for a highly efficient route to chiral α-alkylated ketones **(Scheme 2.29)**.



Scheme 2.29. Continuous flow α-alkylation of immobilised SAMP hydrazones

A protocol to regenerate the immobilised SAMP hydrazine would also be required **(Figure 2.5)**.

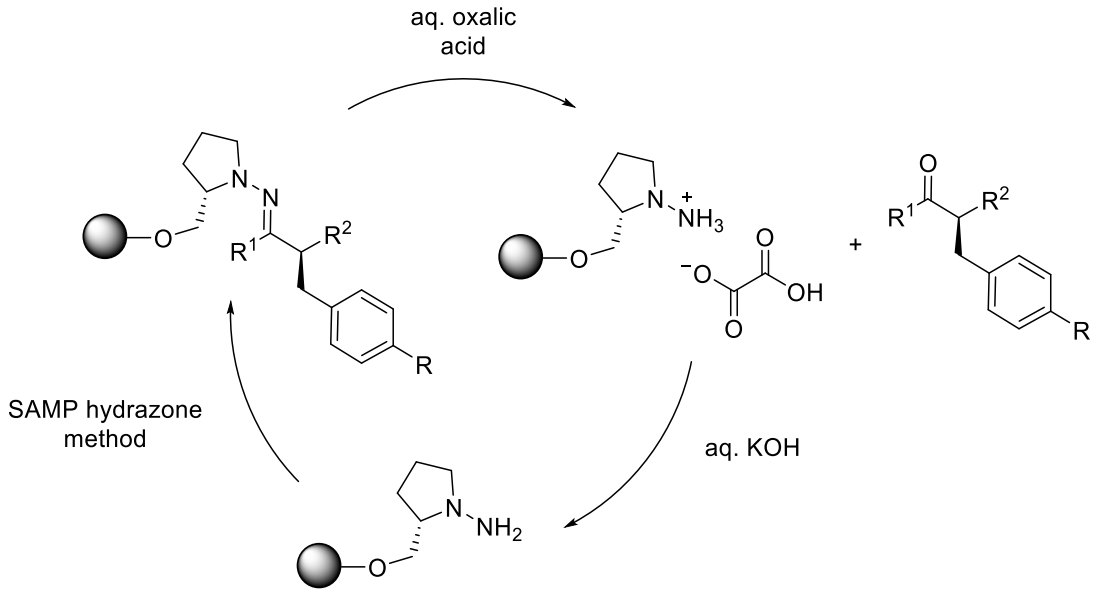


Figure 2.5. Possible recycling of immobilised SAMP

Experimental

2.9 General procedures

Solvents and reagents employed were dried prior to use as follows: THF was distilled from sodium/benzophenone ketyl[55] and stored over 3Å molecular sieves (20% w/v) in a Young's flask. All other reagents were purchased from Sigma Aldrich, Fluorochem, Alfa Aesar and Fisher Scientific and used without further purification, unless otherwise noted. All non-aqueous batch experiments were carried out under an oxygen-free nitrogen atmosphere, using flame-dried glassware and Schlenk set-up. A Julabo FT902 cryocooler was used for low temperature reactions performed in batch.

NMR spectra were run in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard at 300 K, unless otherwise stated. ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively. ^{13}C NMR (100 MHz) spectra and ^{13}C NMR (75.5 MHz) spectra were recorded on Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively in proton decoupled mode. All spectra were recorded at University College Cork. Chemical shifts δ_H and δ_C are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz) as observed and are uncorrected. Splitting patterns in ^{1}H NMR spectra are designated as a doublet (d), doublet of doublets (dd), doublet of quartets (dq), triplet (t), quartet (q) and multiplet (m). For ^{13}C NMR spectra the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. An arbitrary numbering system was employed to aid the assignment of ^{1}H NMR and ^{13}C NMR spectra.

All continuous flow experiments were performed using a Vapourtec R-Series Flow Reactor. This consists of 3 modules: a R_2C^+ module, comprised of two HPLC pumps, a R_4 module, consisting of up to four temperature-controlled reactors (a glass reactor manifold containing a specific volume reactor coil) and a R_2S module consisting of two peristaltic pumps. To prepare the reactor for operation, the complete manifold was purged with anhydrous methanol (2 mL/min, 10 mins) followed by anhydrous THF (2 mL/min, 20 mins). This included all reaction tubing, coils, inlets, pump backwash reservoirs and connections. Flow system pumps were regularly calibrated to ensure accurate flow rates were being maintained. Pumps were run at reaction flow rates to check for stability, in both reagent and solvent lines, before committing reagents. Reactors that were to be used were then cooled/heated to the desired temperatures to check system pressurisation. A stream of $N_{2(g)}$ was used to maintain an anhydrous, oxygen-free atmosphere throughout flow chemistry experiments. A stream of compressed air was

passed over $CO_{2(s)}$ and into the cooled reactor manifold to achieve temperatures below room temperature. Reagent solutions were prepared as anhydrous standard solutions, i.e., 10 mL of anhydrous solvent was not added to a compound but rather the solution was made up to a graduation mark in a 10 mL volumetric flask. These solutions were prepared under an oxygen-free nitrogen atmosphere using flame-dried glassware and Schlenk set-up. Reagents were pre-cooled to the desired temperature using the reactor manifold before introduction to the reactor coils.

Steady state approximations for the reactions completed were calculated using Vapourtec Flow Commander™ software, using a dispersion prediction algorithm.

For cleaning, all parts were flushed thoroughly with the reaction solvent and the complete manifold was then flushed with isopropyl alcohol (2 mL/min, 10 mins) followed by methanol (2 mL/min, 10 mins) and, if necessary, deionised water.

2.9.1 General specifications of the continuous flow system used

Material of tubing: PFA
Internal diameter of tubing: 1 mm
Working flow rates: 0.05 mL/min – 9.99 mL/min
Sample loop volume: 2 mL
Tubular reactor working volume: 10 mL (or 2 mL + 8 mL)
Temperature range: -70 ºC to 250 ºC

2.9.2 Analysis of known and novel compounds

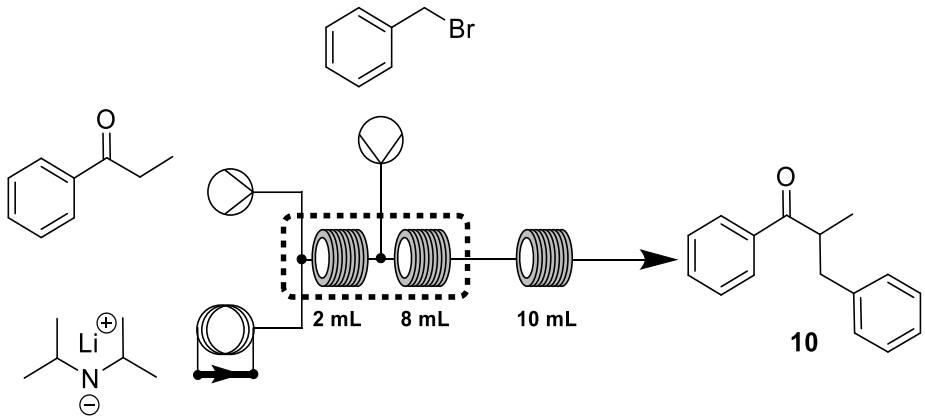
^{1}H NMR spectra, ^{13}C NMR spectra, IR and LRMS analyses were recorded for all previously reported compounds.

2.10 Synthesis of racemic α-alkylated ketones by continuous flow - Optimisation reactions

General procedure

Reactions were conducted in accordance with the schematic given. Unless otherwise noted, the reaction used for optimisation investigations was the alkylation of propiophenone using benzyl bromide. The total volume of reagents used for all reactions was dictated by the capacity of the sample loop, used to deliver LDA, which in all cases was 2 mL. After completion of each reaction, the reaction effluent was collected separately in two vials containing sat. aq. NH_4Cl (2 mL) as a quench. One vial was used to collect the product formed at steady state, whilst all other reaction material was collected in a second vial. These vials were then separately extracted with EtOAc (3 × 10 mL). The combined organic extracts for each were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude α-alkylated ketone. Conversions are quoted at steady state (% SS), indicating the conversion to desired product obtained from the portion of the reaction deemed steady state and the overall conversion, accounting for the total conversion relative to the total amount of limiting reagent consumed. Conversions quoted for optimisation reactions are not isolated yields, but rather conversions obtained from ^{1}H NMR experiments using 1,3,5-trimethoxybenzene as an internal standard.

2.10.1 Configuration one - two reactor coil system



A solution of propiophenone (0.5 M in anhydrous THF) was pumped *via* a HPLC pump into a cooled reactor manifold, set at the desired reaction temperature. Here it was mixed with a solution of commercial LDA (2 mL, 2.0 M in THF/ethylbenzene) which was added *via* sample loop. This solution was then pumped through a 2 mL reactor coil, housed within the cooled reactor manifold. After 2 mL, this solution was met with a solution of benzyl bromide (0.5 M in anhydrous THF). This solution was pumped through a further 8 mL reactor coil, housed within the same cooled reactor manifold. The resulting solution was then pumped directly

through a 10 mL reactor coil housed within a heated reactor manifold, at a second temperature before being passed through a back-pressure regulator, set at 5 bar.

2.10.1.1 LDA (commercial) equivalents

All reactions were conducted using propiophenone (1 equiv.), LDA (various equiv.) and benzyl bromide (1.1 equiv.). The cooled reactor manifold was set at a temperature of -15 ℃ and the heated reactor manifold was set to 75 ℃. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold.

1.2 equivalents of LDA

The reaction was conducted following the general procedure outlined above using propiophenone solution (6.21 mL total volume, 1.231 mL/min), LDA solution (2.0 mL total volume, 0.369 mL/min) and benzyl bromide solution (6.54 mL total volume, 1.354 mL/min). The reaction was at steady state for 2.6 mins (19% SS, 16% overall).

1.5 equivalents of LDA

The reaction was conducted following the general procedure outlined above using propiophenone solution (5.04 mL total volume, 1.164 mL/min), LDA solution (2.0 mL total volume, 0.436 mL/min) and benzyl bromide solution (5.28 mL total volume, 1.280 mL/min). The reaction was at steady state for 1.8 mins (62% SS, 44% overall).

1.8 equivalents of LDA

The reaction was conducted following the general procedure outlined above using propiophenone solution (4.26 mL total volume, 1.103 mL/min), LDA solution (2.0 mL total volume, 0.497 mL/min) and benzyl bromide solution (4.45 mL total volume, 1.214 mL/min). The reaction was at steady state for 1.4 mins (53% SS, 43% overall).

2.0 equivalents of LDA

The reaction was conducted following the general procedure outlined above using propiophenone solution (3.84 mL total volume, 1.067 mL/min), LDA solution (2.0 mL total volume, 0.533 mL/min) and benzyl bromide solution (4.00 mL total volume, 1.173 mL/min). The reaction was at steady state for 1.2 mins (37% SS, 31% overall).

2.10.1.2 Benzyl bromide equivalents

All reactions were conducted using propiophenone solution (1 equiv.), LDA solution (2.0 mL total volume, 0.436 mL/min, 1.5 equiv.) and benzyl bromide solution (various equiv.). The cooled reactor manifold was set at a temperature of -15 ℃ and the heated reactor manifold

was set to 75 °C. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold.

1.2 equivalents of benzyl bromide

The reaction was conducted following the general procedure outlined above using propiophenone solution (5.04 mL total volume, 1.164 mL/min) and benzyl bromide solution (5.70 mL total volume, 1.396 mL/min). The reaction was at steady state for 1.9 mins (64% SS, 59% overall).

1.5 equivalents of benzyl bromide

The reaction was conducted following the general procedure outlined above using propiophenone solution (5.04 mL total volume, 1.164 mL/min) and benzyl bromide solution (6.97 mL total volume, 1.745 mL/min). The reaction was at steady state for 1.8 mins (54% SS, 49% overall).

1.8 equivalents of benzyl bromide

The reaction was conducted following the general procedure outlined above using propiophenone solution (5.04 mL total volume, 1.164 mL/min) and benzyl bromide solution (8.26 mL total volume, 2.095 mL/min). The reaction was at steady state for 1.7 mins (62% SS, 66% overall).

2.0 equivalents of benzyl bromide

The reaction was conducted following the general procedure outlined above using propiophenone solution (5.04 mL total volume, 1.164 mL/min) and benzyl bromide solution (9.15 mL total volume, 2.327 mL/min). The reaction was at steady state for 1.7 mins (57% SS, 56% overall).

2.10.1.3 Deprotonation temperature

All reactions were conducted using propiophenone solution (5.04 mL total volume, 1.164 mL/min, 1 equiv.), LDA solution (2.0 mL total volume, 0.436 mL/min, 1.5 equiv.) and benzyl bromide solution (5.70 mL total volume, 1.396 mL/min, 1.2 equiv.). The temperature of the cooled reactor manifold was varied, and the temperature of the heated reactor manifold was set to 75 °C. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold.

Table 2.8. Deprotonation temperature screen

Entry	Temperature (°C)	Yield (SS)	Yield
1	0	70%	50%
2	-15	64%	59%
3	-30	53%	50%
4	-45	39%	49%
5	rt	16%	21%

2.10.1.4 Alkylation temperature

All reactions were conducted using propiophenone solution (5.04 mL total volume, 1.164 mL/min, 1 equiv.), LDA solution (2.0 mL total volume, 0.436 mL/min, 1.5 equiv.) and benzyl bromide solution (5.70 mL total volume, 1.396 mL/min, 1.2 equiv.). The temperature of the cooled reactor manifold was set to 0 °C and the temperature of the heated reactor manifold was varied. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold.

Table 2.9. Alkylation temperature screen

Entry	Temperature (°C)	Yield (SS)	Yield
1	30	35%	25%
2	45	45%	45%
3	60	42%	46%
4	75	70%	50%
5	90	0%	0%

2.10.1.5 Residence time

All reactions were conducted using propiophenone (1 equiv.), LDA (1.5 equiv.) and benzyl bromide solution (1.2 equiv.). The temperature of the cooled reactor manifold was set to 0 °C and the temperature of the heated reactor manifold was set to 75 °C. The residence time was

varied, but in all incidences, it indicates the total time reagents spent in the first, cooled reactor manifold.

7.5 mins

The reaction was conducted following the general procedure outlined above using propiophenone solution (3.83 mL total volume, 0.711 mL/min), LDA solution (2.0 mL total volume, 0.356 mL/min) and benzyl bromide solution (5.20 mL total volume, 1.067 mL/min). The reaction was at steady state for 2.6 mins (42% SS, 35% overall).

10 mins

The reaction was conducted following the general procedure outlined above using propiophenone solution (3.80 mL total volume, 0.533 mL/min), LDA solution (2.0 mL total volume, 0.267 mL/min) and benzyl bromide (5.25 mL total volume, 0.800 mL/min). The reaction was at steady state for 3.2 mins (65% SS, 62% overall).

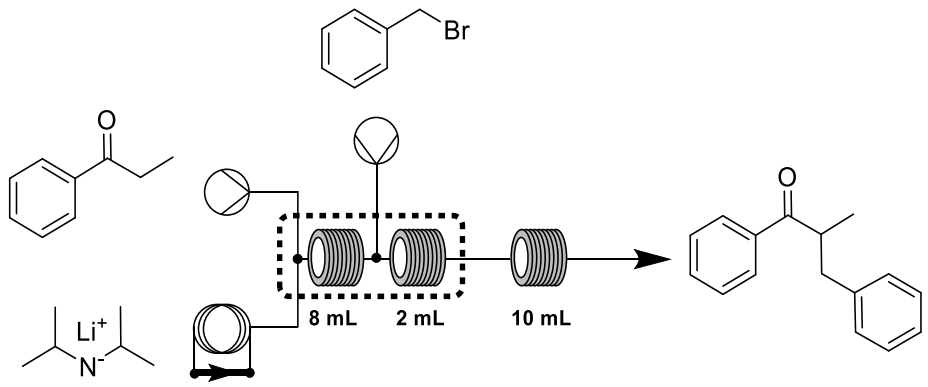
12.5 mins

The reaction was conducted following the general procedure outlined above using propiophenone solution (3.79 mL total volume, 0.427 mL/min), LDA solution (2.0 mL total volume, 0.213 mL/min) and benzyl bromide solution (5.31 mL total volume, 0.640 mL/min). The reaction was at steady state for 3.6 mins (58% SS, 54% overall).

15 mins

The reaction was conducted following the general procedure outlined above using propiophenone solution (3.79 mL total volume, 0.356 mL/min), LDA solution (2.0 mL total volume, 0.178 mL/min) and benzyl bromide solution (5.34 mL total volume, 0.533 mL/min). The reaction was at steady state for 3.8 mins (39% SS, 50% overall).

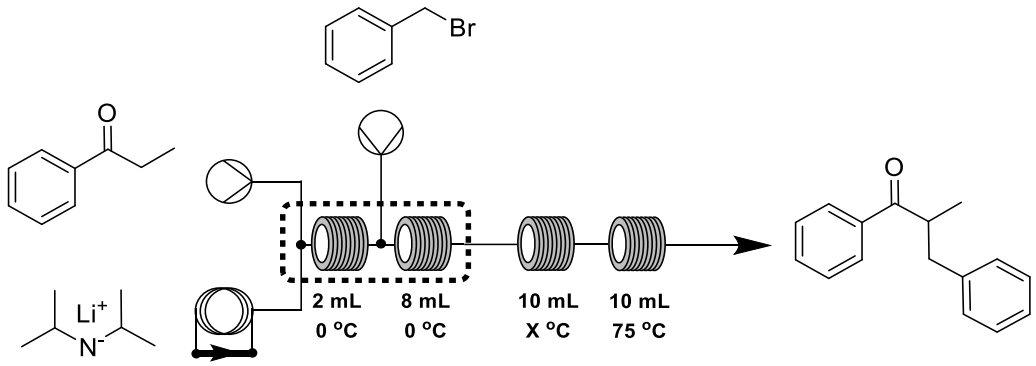
2.10.2 Configuration two - two reactor coil system



A solution of propiophenone (4.96 mL total volume, 0.5 M in anhydrous THF, 0.291 mL/min) was pumped *via* a HPLC pump into a cooled reactor manifold, set at 0 °C. Here it was mixed

with a solution of commercial LDA (2 mL total volume, 2.0 M in THF/ethylbenzene, 0.109 mL/min) which was added *via* sample loop. This solution was then pumped through an 8 mL reactor coil, housed within the cooled reactor manifold. After 8 mL, this solution was met with a solution of benzyl bromide (4.93 mL, 0.5 M in anhydrous THF, 0.349 mL/min). This solution was pumped through a further 2 mL reactor coil, housed within the same cooled reactor manifold. The resulting solution was then pumped directly through a 10 mL heated reactor coil housed within a second heated reactor manifold, set at 75 °C before being passed through a back-pressure regulator, set at 5 bar. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold. The reaction was at steady state for 8 mins (15% SS, 18% overall).

2.10.3 Configuration three - three reactor coil system



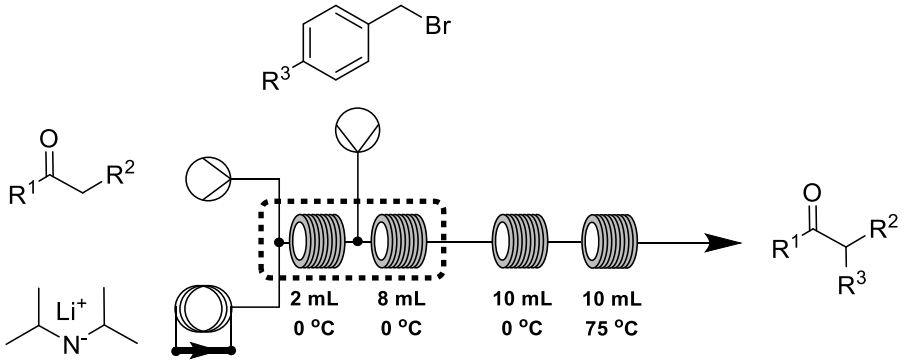
A solution of propiophenone (4.96 mL total volume, 0.5 M in anhydrous THF, 0.291 mL/min) was pumped *via* a HPLC pump into a cooled reactor manifold, set at 0 °C. Here it was mixed with a solution of commercial LDA (2 mL total volume, 2.0 M in THF/ethylbenzene, 0.109 mL/min) which was added *via* sample loop. This solution was then pumped through a 2 mL reactor coil, housed within the cooled reactor manifold. After 2 mL, this solution was met with a solution of benzyl bromide (4.93 mL, 0.5 M in anhydrous THF, 0.349 mL/min). This solution was pumped through a further 8 mL reactor coil, housed within the same cooled reactor manifold. The resulting solution was then pumped directly through a second 10 mL reactor coil, housed within a cooled reactor manifold. This solution was then subsequently pumped through a second 10 mL reactor coil, housed within a heated reactor manifold, set at 75 °C before being passed through a back-pressure regulator, set at 5 bar. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold. The reaction was at steady state for 7 mins.

Table 2.10. Three reactor coil reaction

Entry	1st reactor Temp (°C)	2nd reactor Temp (°C)	3rd reactor Temp (°C)	Residence time (min)	Yield	Yield (SS)
1	0	**0**	75	5	65%	79%
2	0	**75**	75	5	43%	37%

2.11 Synthesis of racemic α-alkylated ketones by continuous flow

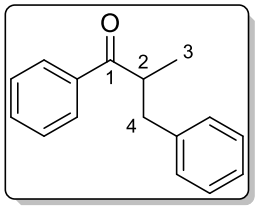
General procedure for substrate synthesis



A solution of ketone (4.96 mL total volume, 0.5 M in anhydrous THF, 0.291 mL/min) was pumped *via* a HPLC pump into a cooled reactor manifold, set at 0 °C. Here it was mixed with a solution of commercial LDA (2 mL total volume, 2.0 M in THF/ethylbenzene, 0.109 mL/min) which was added *via* sample loop. This solution was then pumped through a 2 mL reactor coil, housed within a cooled reactor manifold. After 2 mL, this solution was met with a solution of alkylating agent (4.93 mL, 0.5 M in anhydrous THF, 0.349 mL/min). This solution was pumped through a further 8 mL reactor coil, housed within the same cooled reactor manifold. The resulting solution was then pumped directly through a second 10 mL reactor coil, housed within a cooled reactor manifold, set at 0 °C. This solution was then subsequently pumped through a second 10 mL reactor coil, housed within a heated reactor manifold, set at 75 °C before being passed through a back-pressure regulator, set at 5 bar. The residence time was set to 5 mins, indicating the total time reagents spent in the first cooled reactor manifold. The reaction was at steady state for 7 mins. The SS yields quoted are isolated yields after purification by column chromatography.

Note: The procedure followed for the corresponding batch reactions are outlined in Chapter 1.

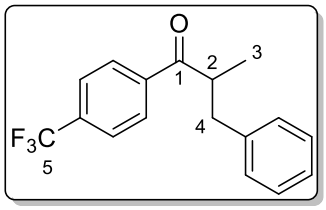
2-Methyl-1,3-diphenylpropan-1-one, 10



Prepared according to the general procedure outlined above using propiophenone and benzyl bromide (79% SS, 65% overall). Spectroscopic characteristics were consistent with previously reported data.[56]

IR (NaCl) ν_{max}: 3085, 2931 (C-H stretch), 1681 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, d, *J* = 6.8 Hz, H-3), 2.69 (1H, dd, *J* = 13.7, 7.7 Hz, one of H-4), 3.17 (1H, dd, *J* = 13.7, 6.2 Hz, one of H-4), 3.74 (1H, sext, *J* = 7.1 Hz, H-2), 7.10-7.32 (5H, m, Ar-H), 7.41-7.46 (2H, m, Ar-H), 7.51-7.56 (1H, m, Ar-H), 7.90-7.93 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.4 (C-3), 39.4 (C-4), 42.8 (C-2), 126.2 (Ar-CH), 128.3 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.1 (2 × Ar-CH), 132.9 (Ar-CH), 136.5 (Ar-C), 140.0 (Ar-C), 203.7 (C-1) ppm. MS (ESI) *m/z*: 225 $[M+H]^+$.

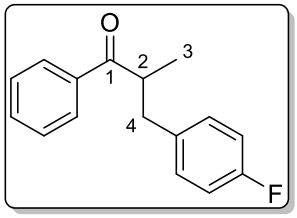
2-Methyl-3-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-one, 12



Prepared according to the general procedure outlined above using 4-trifluoromethylpropiophenone and benzyl bromide (52% SS, 28% overall). Spectroscopic characteristics were consistent with previously reported data.[57]

IR (NaCl) ν_{max}: 2973, 2935, 2863 (C-H stretch), 1688 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.21 (3H, d, *J* = 6.9 Hz, H-3), 2.71 (1H, dd, *J* = 13.5, 7.3 Hz, one of H-4), 3.16 (1H, dd, *J* = 13.7, 6.7 Hz, one of H-4), 3.73 (1H, sext, *J* = 7.1 Hz, H-2), 7.14-7.28 (5H, m, Ar-H), 7.68 (2H, d, *J* = 8.3 Hz, Ar-H), 7.97 (2H, d, *J* = 8.0 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.3 (C-3), 39.4 (C-4), 43.3 (C-2), 123.7 (q, $^1J_{C-F}$ = 272.4 Hz, C-5), 125.7 (q, $^3J_{C-F}$ = 3.8 Hz, 2 × Ar-CH), 126.4 (Ar-CH), 128.5 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.0 (2 × Ar-CH), 134.2 (q, $^2J_{C-F}$ = 32.7 Hz, Ar-C), 139.3 (Ar-C), 139.6 (Ar-C), 202.8 (C-1) ppm. HRMS (ESI) *m/z* calcd for $C_{17}H_{16}F_3O[M+H]^+$: 293.1148, found 293.1138.

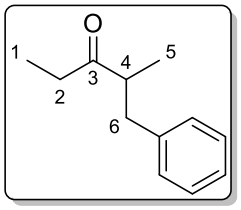
3-(4-Fluorophenyl)-2-methyl-1-phenylpropan-1-one, 11



Prepared according to the general procedure outlined above using propiophenone and 4-fluorobenzyl bromide (69% SS, 49% overall). Spectroscopic characteristics were consistent with previously reported data.[58]

IR (NaCl) ν_{max}: 2966, 2925, 2853 (C-H stretch), 1681 (C=O stretch) cm^{-1}.^{1}H NMR (600 MHz, $CDCl_3$): δ 1.20 (3H, d, *J* = 7.0 Hz, H-3), 2.68 (1H, dd, *J* = 13.9, 7.5 Hz, one of H-4), 3.13 (1H, dd, *J* = 13.7, 6.6 Hz, one of H-4), 3.71 (1H, sext, *J* = 7.1 Hz, H-2), 6.92-6.96 (2H, m, Ar-H), 7.13-7.17 (2H, m, Ar-H), 7.42-7.46 (2H, m, Ar-H), 7.52-7.56 (1H, m, Ar-H), 7.87-7.92 (2H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 17.6 (C-3), 38.5 (C-4), 42.9 (C-2), 115.1 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, 2 × Ar-CH), 128.3 (2 × Ar-CH), 128.7 (2 × Ar-CH), 130.5 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, 2 × Ar-CH), 133.0 (Ar-CH), 135.6 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 136.4 (Ar-C), 161.5 (d, $^1J_{C\text{-}F}$ = 244.8 Hz, Ar-C), 203.6 (C-1) ppm. MS (ESI) *m/z*: 243 $[M+H]^+$.

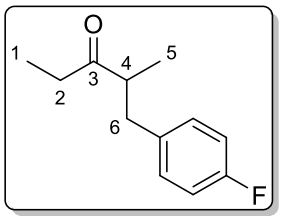
2-Methyl-1-phenylpentan-3-one, 3



Prepared according to the general procedure outlined above using 3-pentanone and benzyl bromide (44% SS, 39% overall). Spectroscopic characteristics were consistent with previously reported data.[44]

IR (ATR) ν_{max}: 3086, 2877 (C-H stretch), 1713 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.3 Hz, H-1), 1.08 (3H, d, *J* = 6.8 Hz, H-5), 2.25 (1H, dq, *J* = 16.9, 7.3 Hz, one of H-2), 2.43 (1H, dq, *J* = 16.9, 7.3 Hz, one of H-2), 2.56 (1H, dd, *J* = 13.2, 7.3 Hz, one of H-6), 2.83 (1H, sext, *J* = 6.9 Hz, H-4), 2.97 (1H, dd, *J* = 13.2, 7.3 Hz, one of H-6), 7.07-7.32 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.6 (C-1), 16.6 (C-5), 35.2 (C-2), 39.3 (C-6), 47.9 (C-4), 126.2 (Ar-CH), 128.4 (2 × Ar-CH), 128.9 (2 × Ar-CH), 139.9 (Ar-C), 214.7 (C-3) ppm. MS (ESI) *m/z*: 177 $[M+H]^+$.

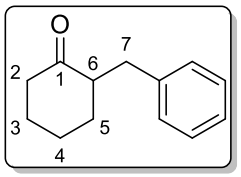
1-(4-Fluorophenyl)-2-methylpentan-3-one, 4



Prepared according to the general procedure outlined above using 3-pentanone and 4-fluorobenzyl bromide (73% SS, 65% overall). Spectroscopic characteristics were consistent with previously reported data.[59]

IR (ATR) ν_{max}: 3961, 2874 (C-H stretch), 1712 (C=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.2 Hz, H-1), 1.07 (3H, d, *J* = 7.0 Hz, H-5), 2.37 (1H, dq, *J* = 17.9, 7.2 Hz, one of H-2), 2.43 (1H, dq, *J* = 17.8, 7.3 Hz, one of H-2), 2.54 (1H, dd, *J* = 13.3, 6.9 Hz, one of H-6), 2.81 (1H, sext, *J* = 7.0 Hz, H-4), 2.94 (1H, dd, *J* = 13.4, 7.4 Hz, one of H-6), 6.90-6.98 (2H, m, Ar-H), 7.06-7.12 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.5 (C-1), 16.7 (C-5), 35.2 (C-2), 38.4 (C-6), 47.9 (C-4), 115.1 (d, $^2J_{C\text{-}F}$ = 20.8 Hz, 2 × Ar-CH), 130.3 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, 2 × Ar-CH), 135.5 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, Ar-C), 161.5 (d, $^1J_{C\text{-}F}$ = 243.9 Hz, Ar-C), 214.5 (C-3) ppm. MS (ESI) *m/z*: 195 $[M+H]^+$.

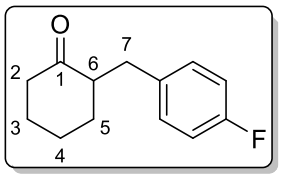
2-Benzylcyclohexan-1-one, 13



Prepared according to the general procedure outlined above using cyclohexanone and benzyl bromide (19% SS, 17% overall). Spectroscopic characteristics were consistent with previously reported data.[60]

IR (ATR) ν_{max}: 2934, 2860 (C-H stretch), 1708 (C=O stretch) cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (1H, dq, *J* = 12.2, 3.5 Hz, one of H-5), 1.50-1.88 (3H, m, one of H-3, H-4), 1.96 - 2.10 (2H, m, one of H-3, one of H-5), 2.27-2.47 (3H, m, H-2, one of H-7), 2.50-2.59 (1H, m, H-6), 3.23 (1H, dd, *J* = 13.7, 4.7 Hz, one of H-7), 7.12-7.22 (3H, m, Ar-H), 7.24-7.29 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (C-4), 28.1 (C-3), 33.4 (C-5), 35.5 (C-7), 42.2 (C-2), 52.5 (C-6), 126.0 (Ar-CH), 128.3 (2 × Ar-CH), 129.2 (2 × Ar-CH), 140.4 (Ar-C), 212.6 (C-1) ppm. MS (ESI) *m/z*: 189 $[M+H]^+$.

2-(4-Fluorobenzyl)cyclohexan-1-one, 14



Prepared according to the general procedure outlined above using cyclohexanone and 4-fluorobenzyl bromide (34% SS, 33% overall). Spectroscopic characteristics were consistent with previously reported data.[61]

IR (ATR) ν_{max}: 2934, 2861 (C-H stretch), 1710 (C=O stretch) cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (1H, dq, *J* = 12.7, 3.1 Hz, one of H-5), 1.53-1.75 (2H, m, one of H-3, one of H-4), 1.78-1.89 (1H, m, one of H-4), 1.96-2.12 (2H, m, one of H-3, one of H-5), 2.25-2.56 (4H, m, H-2, H-6, one of H-7), 3.18 (1H, dd, *J* = 14.0, 4.0 Hz, one of H-7), 6.90-7.00 (2H, m, Ar-H), 7.09-7.13 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1 (C-4), 28.0 (C-3), 33.5 (C-5), 34.7 (C-7), 42.2 (C-2), 52.5 (C-6), 115.1 (d, $^2J_{C-F}$ = 21.2 Hz, 2 × Ar-CH), 130.5 (d, $^2J_{C-F}$ = 7.6 Hz, 2 × Ar-CH), 136.0 (d, $^4J_{C-F}$ = 3.1 Hz, Ar-C), 161.4 (d, $^1J_{C-F}$ = 242.3, Hz, Ar-C), 212.4 (C-1) ppm. MS (ESI) *m/z*: 207 $[M+H]^+$.

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III

The Asymmetric Synthesis of Amino Alcohol Derivatives *via* an Aldol, Aldol-Tishchenko Reaction of (*S*)-*Tert*-butanesulfinyl Imines

“Laughter is timeless, imagination has no age, dreams are forever”

Walt Disney

3 Introduction

3.1 1,3-Amino alcohols

The 1,3-amino alcohol motif is ubiquitous in organic chemistry. Due to the remarkable synthetic utility of these compounds, the development of efficient synthetic routes to 1,3-amino alcohols is an area of significant interest.[1] 1,3-amino alcohols, and derivatives thereof, have the potential to be undergo a vast array of useful transformations to highly sought-after synthetic targets, including a diverse range of heterocycles **(Figure 3.1)**.[2]

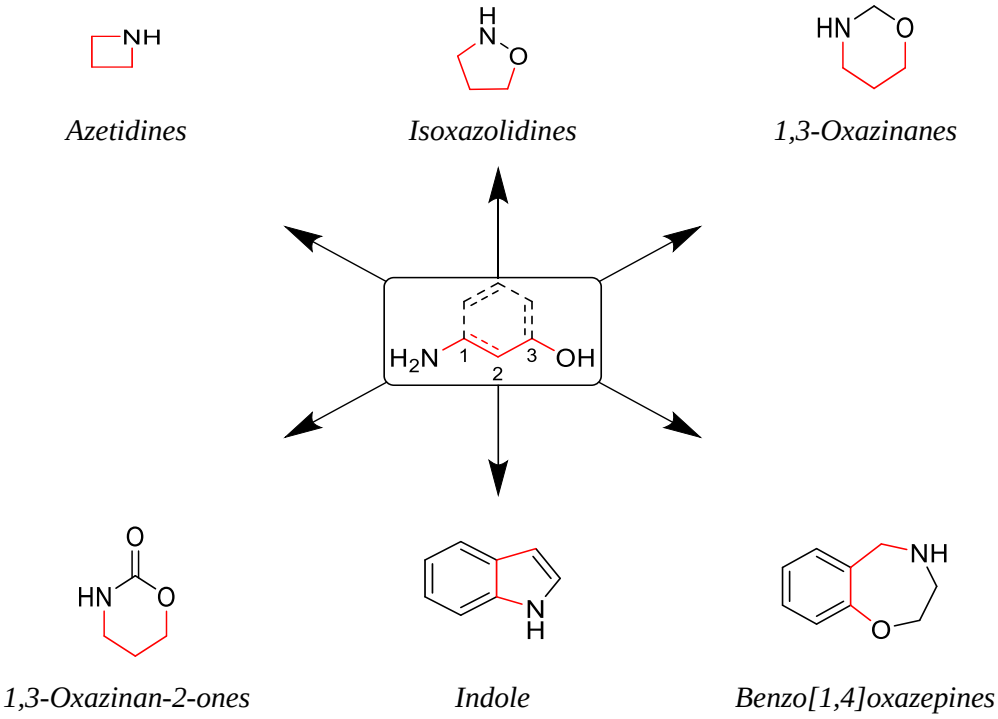
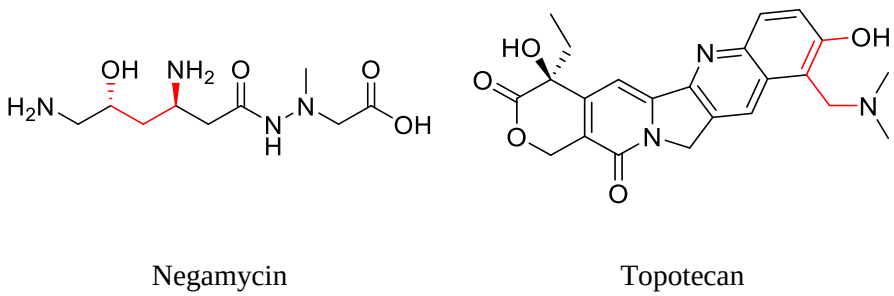


Figure 3.1. Derivatives of 1,3-amino alcohols

The 1,3-amino alcohol scaffold is also prevalent in many bioactive compounds, both those naturally occurring and synthetically derived. Examples include the natural products negamycin (antibiotic) and (+)-dienomycin (antituberculosis) and APIs haloperidol (antidepressant) and topotecan (anticancer agent) **(Figure 3.2)**.[2-4]



Negamycin Topotecan

Figure 3.2. Bioactive 1,3-amino alcohols

Due to the attractive ligation points of both heteroatoms, 1,3-amino alcohols are also widely employed as highly effective chiral ligands or auxiliaries in enantio- and diastereoselective transformations **(Figure 3.3)**.[1] Unsurprisingly, highly efficient, economic and operationally simple methods to furnishing these compounds in high stereoselectivity remains a key task for organic chemists.

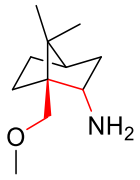


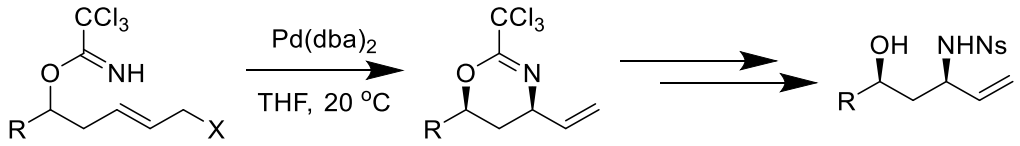
Figure 3.3. Camphor based chiral auxilary

3.2 Methods for the stereoselective synthesis of 1,3-amino alcohols

The stereoselective synthesis of 1,3-amino alcohols is oftentimes a tedious and step-intensive process.[5] Current methods to access this motif include the stereoselective construction of β-amino ketones or β-hydroxyl imines *via* Mannich[6] and aldol-type reactions,[7] and subsequent reduction steps. Effective transition metal catalysed routes also exist, including aliphatic C-H amination reactions[8] and allylic C-H amination reactions.[9] Methods for the synthesis of these compounds should satisfy the following requirements: **i)** the reactions should use inexpensive, stable and readily available starting materials; **ii)** the products should be readily cleaved to afford the free 1,3-amino alcohol motif and **iii)** both the amino and hydroxyl groups should be easily and selectively modifiable without extensive manipulations of protecting groups.[10]

3.2.1 *Syn*-1,3-amino alcohols

In 2014, Gu and co-workers reported the synthesis of 4-vinyl-5,6-dihydro-1,3-oxazines, precursors of 1,3-amino alcohols, *via* a palladium catalysed cyclisation reaction of trichloroacetimidates **(Scheme 3.1)**.[10] A range of aliphatic and aromatic substituents were tolerated within this reaction, with high yields and moderate levels of diastereoselectivity observed in all cases. A facile aqueous cleavage step allowed access to the 1,3-amino alcohol, without any loss of stereochemical integrity.



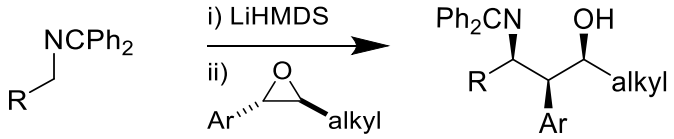
77-95%

dr > 20:1

Scheme 3.1. Gu and co-workers synthesis of *syn*-1,3-amino alcohols

Similarly, in 2017, Malcolmson and co-workers devised a route to accessing *syn*-1,3-amino alcohols, whilst simultaneously installing up to three contiguous chiral centres, in excellent levels of diastereoselectivity and yields of up to >98%, using an Umpolung approach.[11] Herein, nucleophilic 2-azaallyl anions are stereoselectively added to chiral epoxides, providing an operationally simple and efficient means to accessing challenging 1,3-amino alcohols **(Scheme 3.2a)**. The ease of accessibility to chiral epoxides adds significantly to the synthetic utility of this approach. Furthermore, in one case, derivatisation of the 1,3-amino alcohol product to the corresponding azetidine was also achieved, in an excellent yield of 81% over two steps (**Scheme 3.2b**).

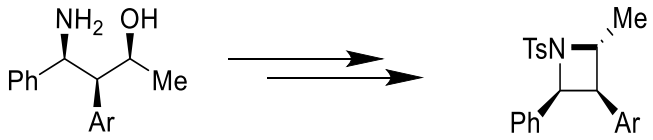
a)



up to > 98%

dr > 20:1

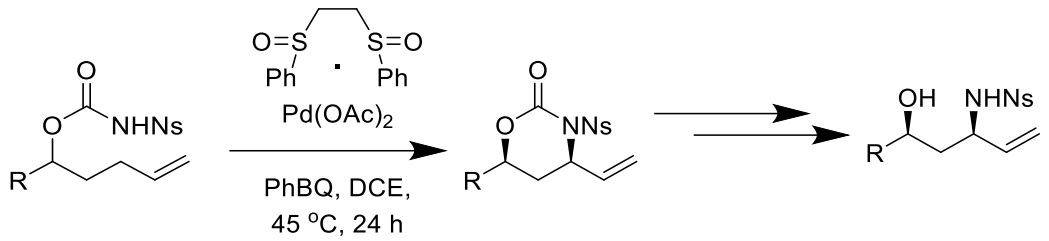
b)



81%

Scheme 3.2. Malcolmson and co-workers synthesis and derivatisation of *syn*-1,3-amino alcohols

In 2019, White and co-workers reported an efficient Pd catalysed allylic C-H amination reaction to furnish vinyl 1,3-amino alcohol precursors from terminal olefins.[9] An electron-deficient *N*-tosyl carbamate undergoes a Pd(II)-sulfoxide mediated C-H amination reaction to generate 6-membered *syn*-oxazinanones, in good yields and diastereoselectivites **(Scheme 3.3)**. Excellent chemoselectivity is observed, with preferential reactivity of terminal olefins, even in the presence of internal olefins. Subsequent cleavage of the *syn*-oxazinanones under mild reaction conditions provided the desired *syn*-1,3-amino alcohols.



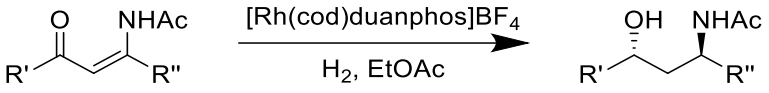
50-65%

dr up to 6.8:1

Scheme 3.3. White and co-workers synthesis of *syn*-1,3-amino alcohols

3.2.2 *Anti*-1,3-amino alcohols

In 2009, Wu and co-workers reported an operationally simple catalytic method to access *anti*-1,3-amino alcohols. Two stereogenic centres were generated in excellent levels of both enantio- and diastereoselectivity during the asymmetric hydrogenation of easily accessible β-ketoenamides. This reaction was facilitated by the use of a rhodium catalyst **(Scheme 3.4)**.

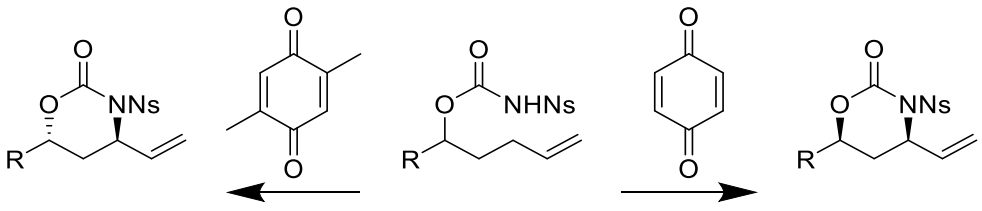


97-99%

ee & *dr* up to 99:1

Scheme 3.4. Wu and co-workers synthesis of *anti*-1,3-amino alcohols

In 2019, White and co-workers published the first C-H amination reaction to allow access to *anti*-1,3-amino alcohols, expanding upon previous work accessing the *syn*-1,3-amino alcohol framework.[12] Use of a Pd(II)/(±)-MeO-SOX catalyst coupled with the 2,5-dimethylbenzoquinone additive allowed access to the more thermodynamically favourable *anti*-isomer. Presumably this is due to the steric bulk of the oxidant when compared to the use of benzoquinone to access the analogous *syn*-isomer **(Scheme 3.5)**. 1,3-amino alcohol precursors could be synthesised using this method in moderate to good yields (average yield of 66%), up to 10:1 *anti:syn* ratio and *dr* of > 20:1.



Up to 66%

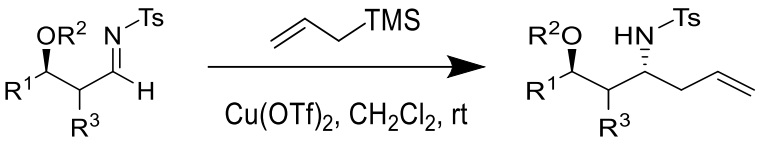
dr > 20:1

Up to 62%

dr > 20:1

Scheme 3.5. White and co-workers synthesis of both *syn* and *anti*-1,3-amino alcohols

Earlier in 2022, Shaw and co-workers reported a Cu mediated allylation reaction of chiral β-alkoxy imines, allowing access to *anti*-1,3-amino alcohols in excellent diastereoselectivities and yields up to 96% **(Scheme 3.6)**. The origin of selectivity of this reaction is deemed to result from the formation of a six-membered Cu chelate reaction intermediate, which adopts a half chair-like conformation.[13]



Up to 96%

dr up to 95:5

Scheme 3.6. Shaw and co-workers synthesis of *anti*-1,3-amino alcohols

3.3 *N-T*ert-butanesulfinyl imines

The *N-tert*-butanesulfinamide **(Figure 3.4)** first pioneered by Ellman and co-workers is a highly valuable chiral ammonia synthon, commonly used in the synthesis of a broad range of enantioenriched amines, including 1,3-amino alcohols.[14]

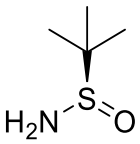
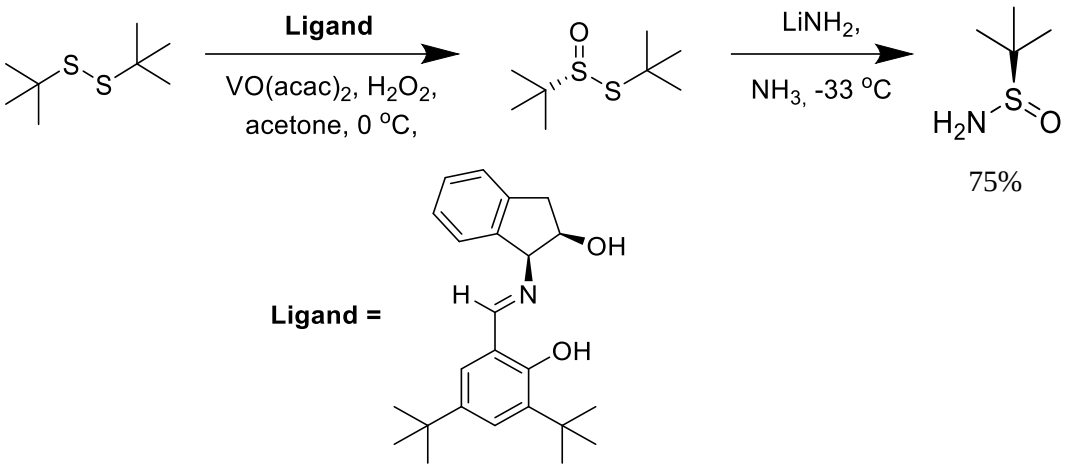


Figure 3.4. *N-tert*-butanesulfinamide

Advantageously, this compound is a bench stable, crystalline solid which is easily prepared over two steps from an inexpensive oil waste product **(Scheme 3.7)**.[15] Oxidation of *tert*-butane sulfide in the presence of a Schiff base generates the thiosulfinate intermediate, which subsequently undergoes nucleophilic addition to generate the optically pure *N-tert*-butanesulfinamide. With both enantiomers commercially available at low cost, it is unsurprising that a literature search for these compounds generates approximately 5000 hits, further highlighting the synthetic value of this compound.



Scheme 3.7. Ellman's synthesis of *N-tert*-butanesulfinamide

Use of the enantiopure *N-tert*-butanesulfinamide as a chiral auxiliary to generate *N-tert*-butanesulfinyl imines (**Figure 3.5**) has been an area of extensive research in asymmetric synthesis. The structure and reactivity of chiral *N-tert*-butanesulfinyl imines make them an attractive and versatile class of imines: **i)** the effect of the sterically bulky *tert*-butyl group is twofold, acting as an efficient chiral directing group whilst also providing sufficient shielding to prevent nucleophilic attack at the sulfur atom; **ii)** the sulfur provides a configurationally stable stereocentre and possesses a valuable metal-coordinating ability, allowing for nucleophilic addition to occur with high diastereofacial discrimination; **iii)** the *N-tert*-butanesulfinyl group mirrors the reactivity of the commonly employed *tert*-butyloxycarbonyl (Boc-) protecting group, demonstrating stability to strong bases, nucleophiles and tolerating metal-catalyse transformations; **iv)** the *N-tert*-sulfinyl group is also more hydrolytically stable than *N*-alkyl, aryl, acyl or carbamoyl imine counterparts and **v)** conveniently, the *tert*-butanesulfinyl group can be removed under acidic conditions in a protic solvent.

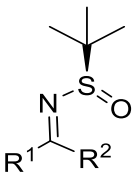
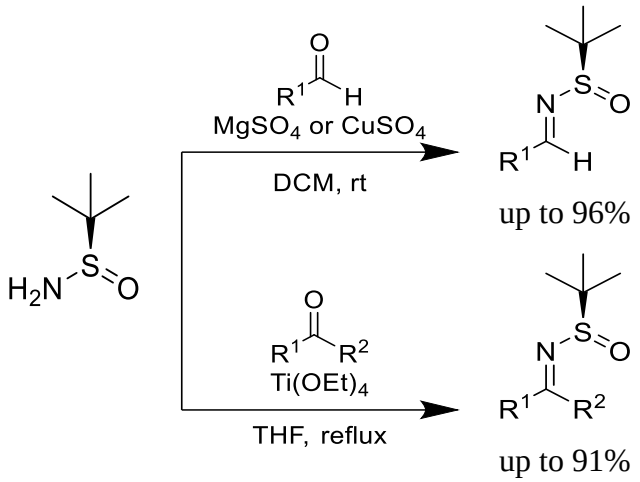


Figure 3.5. *N-tert*-butanesulfinyl imine

N-tert-butanesulfinyl imines can be synthesised directly *via* a condensation reaction between a carbonyl compound and *N-tert*-butanesulfinamide **(Scheme 3.8)**. These reactions require the use of a Lewis acid additive. The purpose of this additive is twofold, acting as a dehydrating agent whilst also activating of the carbonyl compound through co-ordination to the metal. Relatively mild reaction conditions afford aldimine derivatives in good to excellent yields. However, slightly more forceful reaction conditions are required for the synthesis of less electrophilic, more sterically demanding ketimine derivatives.[16-17]



Scheme 3.8. Synthesis of *N-tert*-butanesulfinyl imines

Since being introduced by Ellman in 1997, chiral *N-tert*-butanesulfinyl imines have garnered much attention and are now used in a variety of asymmetric syntheses **(Figure 3.6)**. A significant number of efficient routes to a variety of bioactive compounds have been reported, including access to both *syn*- and *anti*- 1,2- and 1,3-amino alcohols,[7, 18] α-branched and α,α-branched amines,[19] α- or β-amino acids/esters,[20] and vicinal chiral diamines.[21] *N-tert*-butanesulfinyl imines have also been successfully employed in the asymmetric synthesis of nitrogen containing heterocycles including optically pure aziridines[22] and chiral 2-substituted pyrrolidines,[23] to list a few.[24]

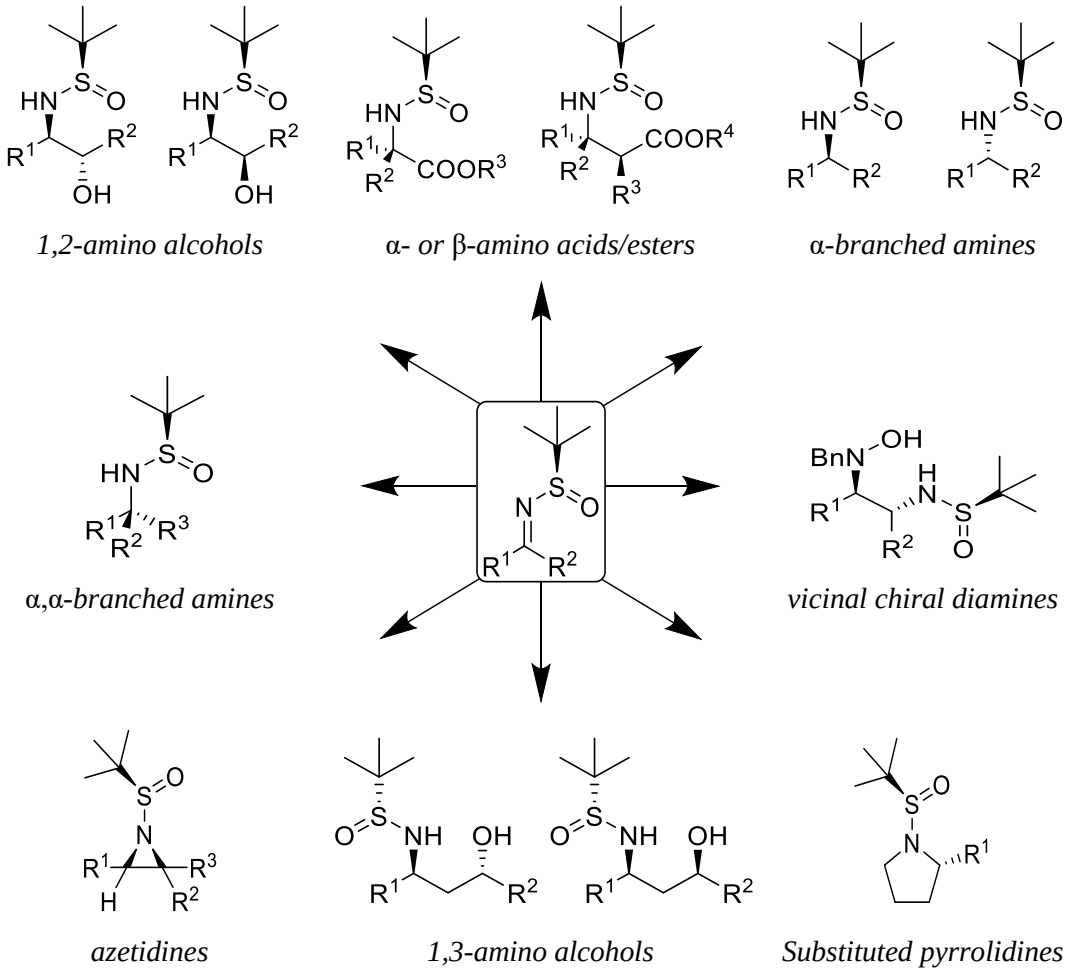
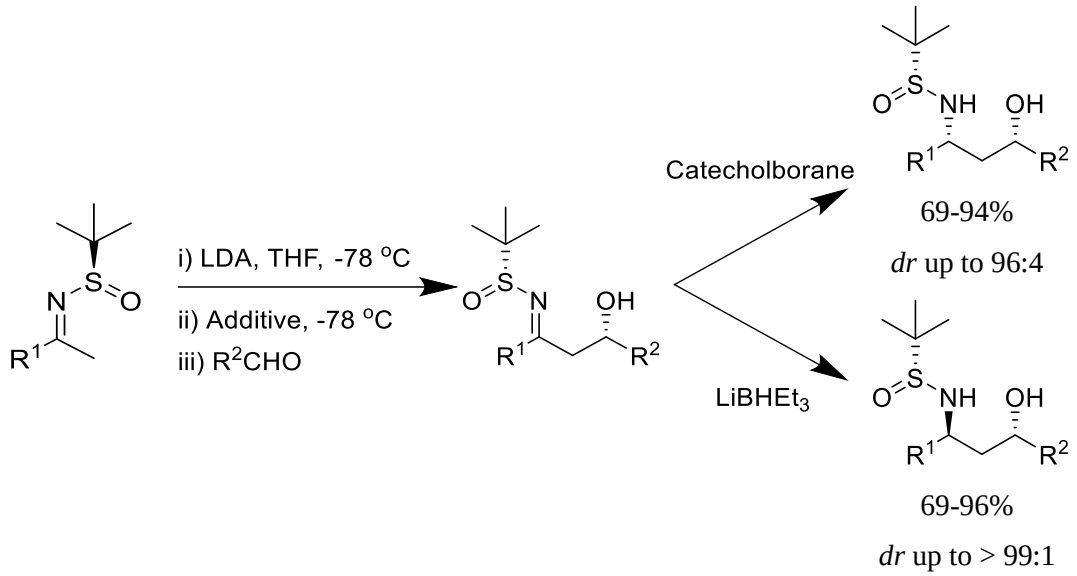


Figure 3.6. Examples of *N-tert*-butanesulfinyl imine derivatives

3.3.1 Ellman methodology for the synthesis of 1,3-amino alcohols

As previously mentioned, the most common means to accessing the 1,3-amino alcohol framework involves the diastereoselective reduction of substrates derived from aldol- or Mannich-type reactions. In 2002, work by Ellman and co-workers resulted in a general method for accessing both *syn*- and *anti*-1,3-amino alcohols, over two steps, in good to excellent yields and levels of diastereoselectivity **(Scheme 3.9)**.[7] This method involves the diastereoselective addition of metalloenamines, derived from *N-tert*-butanesulfinyl imines, to aldehydes, in the presence of metal salts, to generate β-hydroxy-*N*-sulfinyl imines. Subsequent reduction of these compounds leads to the generation of the 1,3-amino alcohol framework. Depending on the reducing agent used, the *syn*- or *anti*-diastereomer can be selectively generated.



Scheme 3.9. Ellman's synthesis of *syn*- and *anti*-1,3-amino alcohols

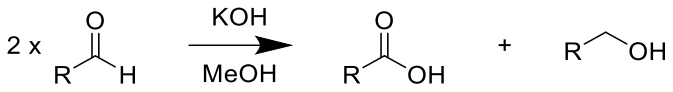
Although a highly sophisticated method for the diastereoselective synthesis of 1,3-amino alcohols, an inherent drawback of this methodology is the requirement for additives and an external reducing agent. These reducing agents, superhydride for example, are oftentimes expensive and hazardous reagents to handle.

3.4 Hydride reductions of carbonyl compounds

Methods to allow for greener synthetic routes, in terms of atom- and step-economy, are a constant challenge for organic chemists. Although valuable advances have been made in 1,3-amino alcohol synthesis, some limitations remain. The current strategies to access these compounds are multi-step and generate the amino alcohol framework indirectly. Additional reduction, cleavage or hydrolysis steps, or combinations thereof, are commonly required. An *in-situ* hydride transfer is an attractive way to obviate the need for external reducing agents, and when achieved in a diastereoselective fashion, offer an elegant pathway to stereoenriched 1,3-amino alcohols.

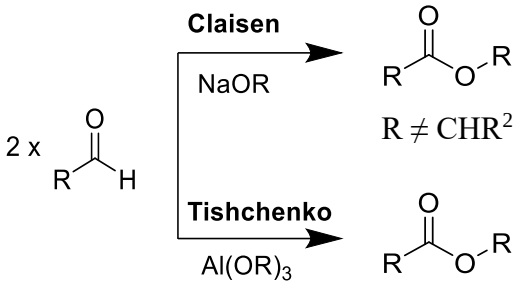
3.4.1 Pioneering hydride reductions

One of the earliest reports of an *in-situ* hydride reduction, in this context, was reported by Cannizzaro in 1853 **(Scheme 3.10)**.[25] A base induced disproportionation reaction of non-enolisable aldehydes allowed for the formation of an equimolar amount of alcohol and carboxylic acid **(Scheme 3.10)**. Mechanistic insights discounted the possibility of a radical mechanism taking place, instead suggesting a key rate-determining step for this reaction is a hydride transfer.[25] Limited only to non-enolisable aldehydes, in order to avoid competitive aldol reactions, the synthetic utility of this reaction is limited.



Scheme 3.10. Cannizzaro reaction

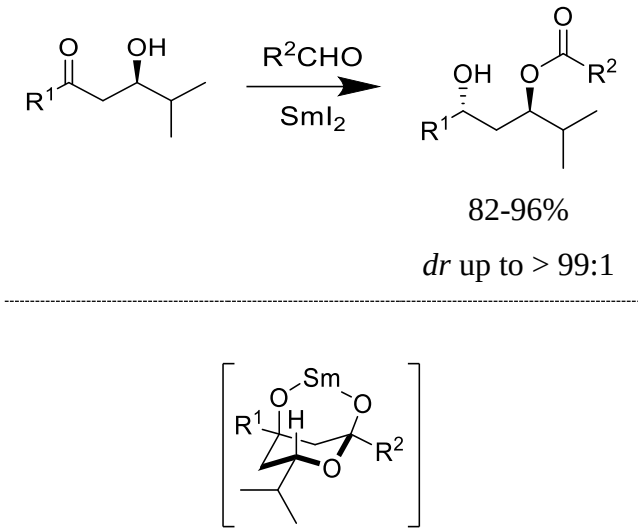
In 1906, the Tishchenko reaction was reported, often considered a variant of the Cannizzaro reaction.[25] Although initial work was conducted by Claisen, the reaction was termed the Tishchenko reaction.[26] It offers an efficient method for the synthesis of esters and is mechanistically similar to the Cannizzaro reaction. Initial work by Claisen was also limited to aldehydes lacking an enolisable proton, due to the use of sodium alkoxides as additives. However, replacing sodium alkoxides with aluminium alkoxides, a modification made by Tishchenko, significantly expanded the utility of this reaction to include aliphatic, aromatic and heterocyclic aldehydes **(Scheme 3.11)**. The reduced basicity of aluminium alkoxides when compared to sodium alkoxides was sufficient to supress competing aldol reactions.[27]



Scheme 3.11. Claisen and Tishchenko methodology

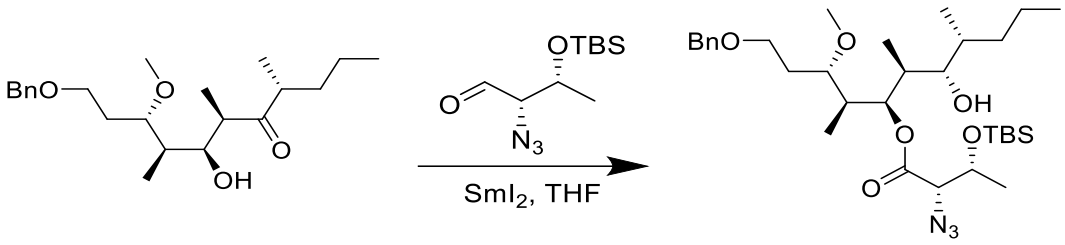
3.4.2 Evans-Tishchenko reaction

In 1990, Evans and Hoveda reported a samarium catalysed Tishchenko-type reaction, which subsequently became known as the Evans-Tishchenko reaction.[28] In this reaction, pre-formed β-hydroxy-ketones undergo an Tishchenko reduction in the presence of a samarium catalyst, generating *anti*-1,3-diol monoesters is good to excellent yields and excellent levels of diastereoselectivity **(Scheme 3.12)**. The authors suggest the active catalytic species to be a samarium(III) species, which co-ordinates to both the aldehyde and β-hydroxy-ketone, resulting in a hemiacetal-type transition state. Subsequent reduction of this structure *via* an intramolecular hydride transfer affords the 1,3-diol monoester. The high level of diastereomeric purity observed in this reaction is attributed to ligation of the catalytic species to both the oxygen atoms of the ketone and the aldehyde.



Scheme 3.12. Evans-Tishchenko synthesis of *anti*-1,3-diol monoesters

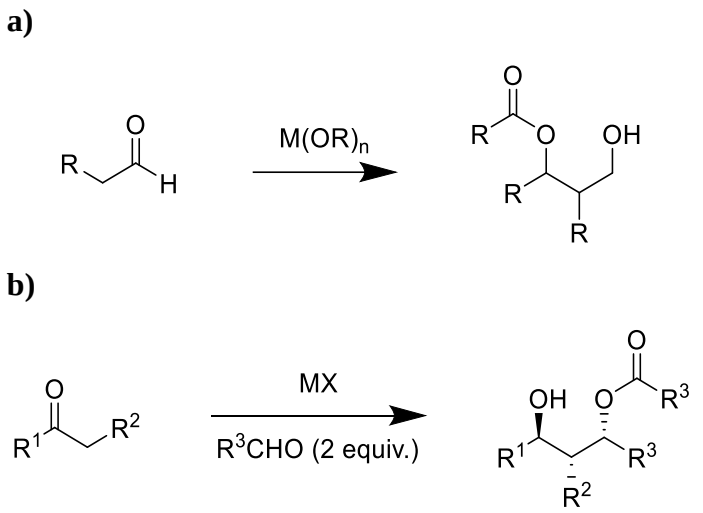
In 2017, Ye and co-workers described the first total synthesis of Hoiamide A, a natural product with anti-cancer potential.[29] This compound possesses an extremely complex molecular structure, containing no less than 15 stereocentres. The successful synthetic route to this compound hinged upon the formation of a sterically encumbered amine. An Evans-Tishchenko reaction was a critical step in the synthesis of this intermediate, affording the desired product in 86% yield **(Scheme 3.13)**.



Scheme 3.13. Evans-Tishchenko reaction in the synthesis of hoiamide A

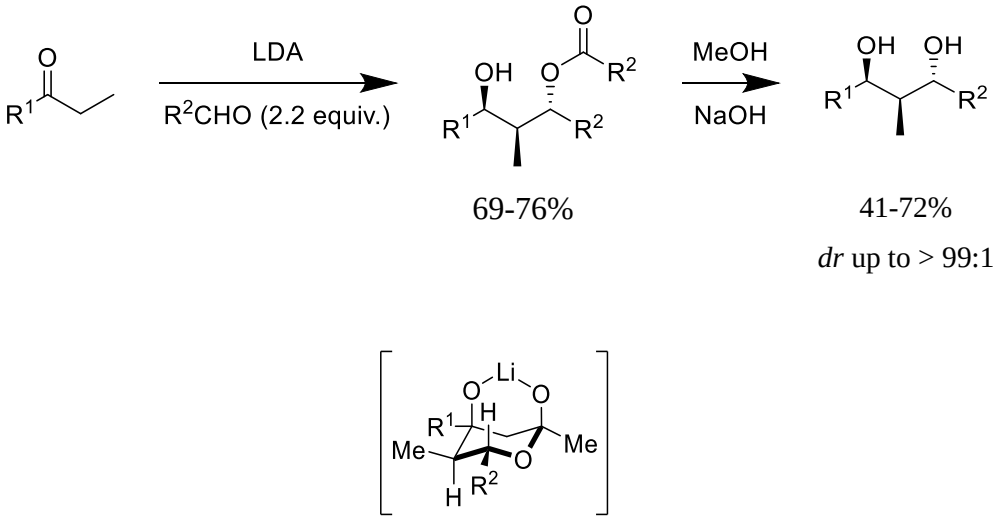
3.4.3 The aldol-Tishchenko reaction

Modification of the Tishchenko reaction led to the discovery of the aldol-Tishchenko reaction, an effective method to couple inactivated carbonyl compounds. The classic aldol-Tishchenko reaction furnishes 1,3-diol monoesters **(Scheme 3.14a)**.[30] Mechanistically, condensation of two aldehyde molecules, followed by a hydride reduction, mediated by a third aldehyde molecule, affords 1,3-diol monoesters. Cross aldol-Tishchenko reactions were later reported, wherein a ketone could undergo reaction with two equivalents of an aldehyde, *via* a metal enolate, to afford *anti*-1,3-diol monoesters, in a highly stereoselective fashion **(Scheme 3.14b)**, significantly broadening the synthetic utility of this reaction.[31]



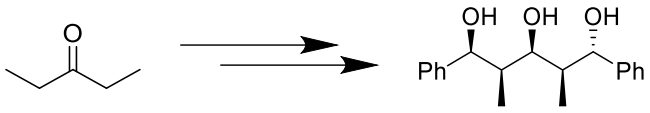
Scheme 3.14. Classic aldol-Tishchenko reaction

In 1997, Woerpel and co-workers reported a tandem aldol-Tishchenko reaction of lithium enolates for the synthesis of polyoxygenated compounds, creating up to five stereogenic centres, with a high degree of stereochemical control.[32] This operationally simple reaction protocol allowed for the synthesis of diols, and later, triols, in one-step *via* ketone enolates. Initially, reaction of a lithium enolate with 2.2 equivalents of aldehyde generated *anti*-1,3-diol monoesters in good to excellent yields and with excellent optical purity **(Scheme 3.15)**. Mechanistically, this reaction differs from conventional aldol reactions as the formation of a C-H rather than a C-C bond determines the stereochemical outcome of this enolate reaction. The authors suggest the reaction proceeds *via* a reversible aldolization step to form a hemiacetal, which subsequently undergoes the rate- and stereodefining hydride transfer step. The resulting geometry of the *anti*-1,3-diol monoester is attributed to the formation of a six-membered transition state, similar to the transition state proposed for the samarium catalysed Evans-Tishchenko reaction already discussed**.**



Scheme 3.15. Aldol-Tishchenko reaction of lithium enolates

Incredibly, further optimisation of this reaction protocol allowed for the introduction of five stereogenic centres in a single step, forming 1,3,5-triol derivatives. Initially, reaction of 3-pentanone under the previously optimised conditions failed to yield the desired 1,3-diol monoester product. Slight modification to this protocol however, increasing to 3.3 equivalents of aldehyde, allowed for the synthesis of the 1,3,5-triol framework, in moderate to good yields and excellent diastereoselectivities **(Scheme 3.16)**.

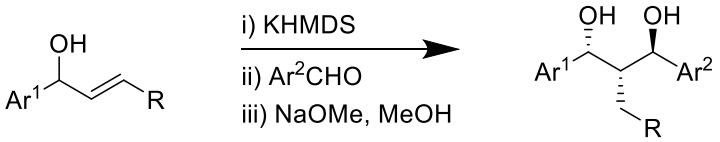


64%

dr: 86:6:5:3

Scheme 3.16. Tandem aldol-aldol-Tishchenko reaction

As recently as 2021, Sai reported the use of allylic alcohols as ketone equivalents in a tandem allylic-isomerisation/aldol-Tishchenko reaction, affording *anti*-1,3-alcohols as single diastereomers, in moderate to good yields **(Scheme 3.17)**.[33] A range of aryl and heteroaryl allylic alcohols as well as a broad range of aromatic aldehydes were tolerated in this KHMDS-promoted aldol-Tishchenko reaction.



42-79%

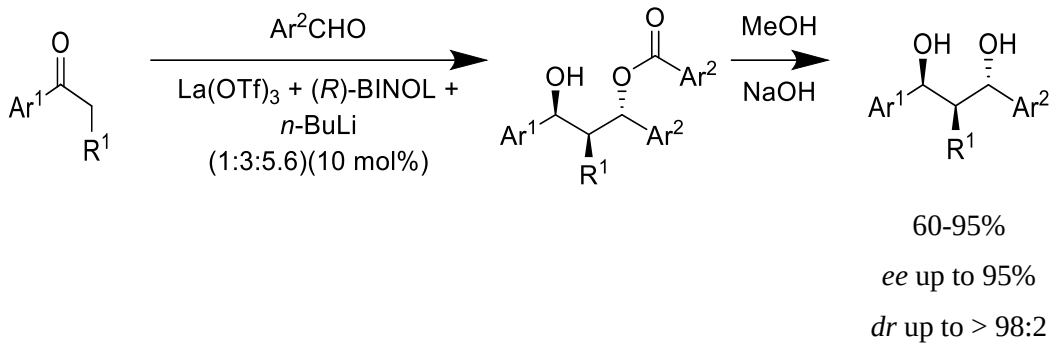
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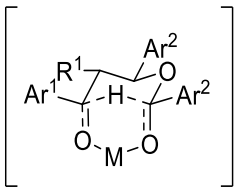
Scheme 3.17. Tandem allylic isomerisation/aldol-Tishchenko reaction of allylic alcohols

3.4.4 Catalytic aldol-Tishchenko reactions

Stereoselective, catalytic synthetic routes represent the gold-standard in organic chemistry, and continue to be the long-standing goal for organic chemists. In 2004, Shibasaki and co-workers developed a catalytic aldol-Tishchenko protocol, describing the first aldol-Tishchenko reaction of a propionate equivalent.[34] A combination of lanthanum(III) trifluoromethylsulfonate, (*R*)-BINOL and *n*-BuLi proved an effective catalyst for the formation of propiophenone derived *anti*-1,3-diol monoesters in good to excellent yields, enantio- and diastereoselectivities **(Scheme 18)**. Mechanistic investigations suggest the ketone enolate reacts reversibly with a molecule of aldehyde to generate an aldolate, showing no stereochemical preference. However, the alkyl group of a *syn*-aldolate occupies an energetically unfavourable axial position. In such cases, it is suggested the *syn*-aldolate might isomerise to the *anti*-aldolate through a retro-aldol reaction quicker than the rate of the

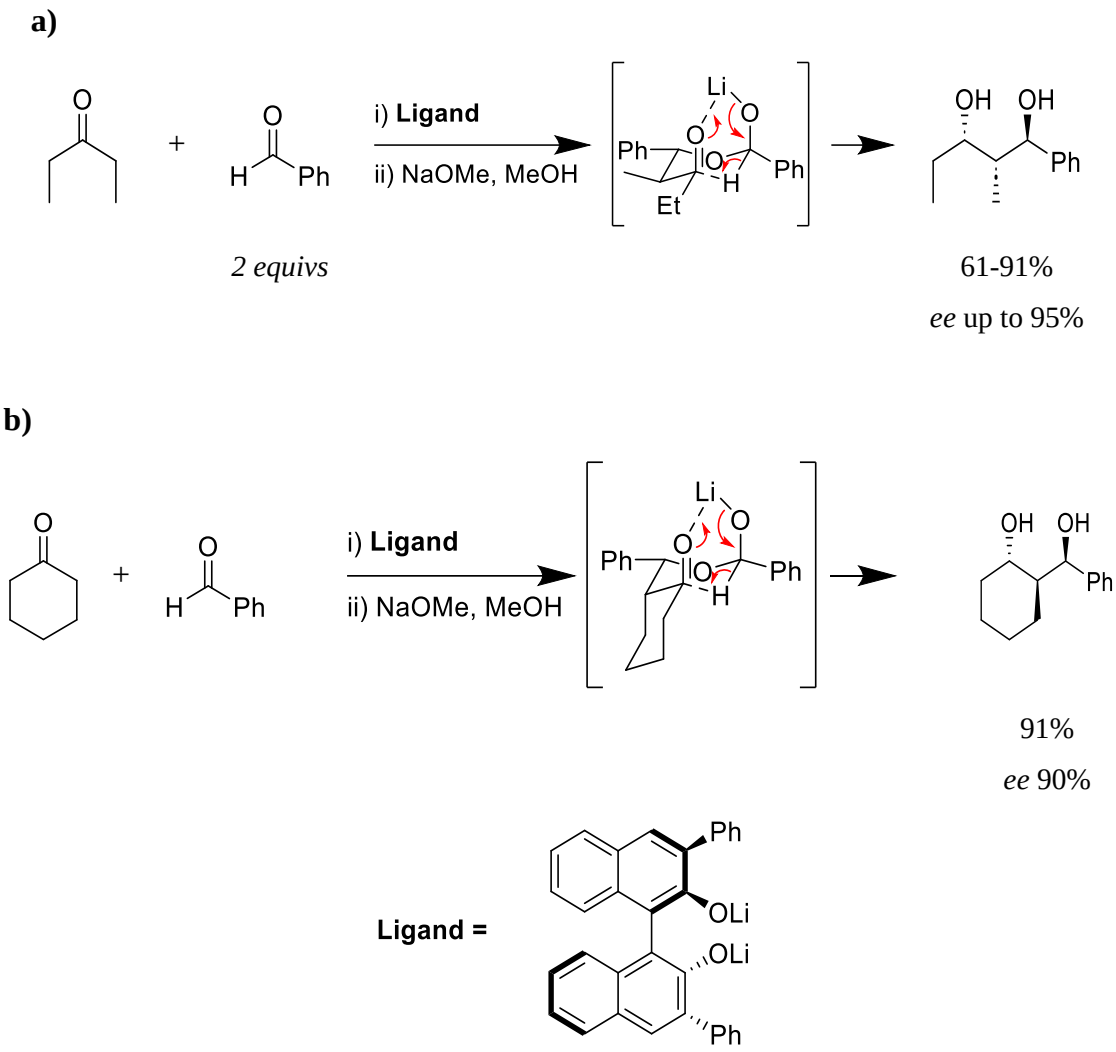
Tishchenko reaction for the *syn*-aldolate, giving rise to 1,2-*syn*-1,3-*anti* product in high diastereoselectivity.





Scheme 3.18. Catalytic aldol-Tishchenko reaction of propiophenone derivatives

More recently, in 2011 Nakajima and co-workers demonstrated that chiral lithium diphenylbinaphtholate is an effective catalyst for a highly enantioselective aldol-Tishchenko reaction.[35] The first example of a rare-metal free catalytic route for the synthesis of 1,3-diol monoesters *via* an enantioselective aldol-Tishchenko, this route offers a much improved scope, allowing both cyclic and acyclic, aromatic and aliphatic ketones to be coupled with a range of aromatic aldehydes, with a high degree of stereocontrol and in excellent yield. Interestingly, acyclic ketones afforded the usual 1,2-*syn*-1,3-*anti* products **(Scheme 3.19a)** whereas cyclic ketones gave 1,2-*anti*-1,3-*anti* products **(Scheme 3.19b)**.



Scheme 3.19. Chiral lithium diphenylbinaphtholate catalysed aldol-Tishchenko reaction

Despite significant advancements made in this area, limitations still exist: **i)** examples of the use of aliphatic aldehydes in these reactions are rare, with the more activated aromatic aldehydes more efficient hydride donors; **ii)** the reversibility of the aldol step negates the possibility of a mixed aldol-Tishchenko reaction *i.e.* reaction of ketone enolates with more than one aldehyde and **iii)** the other diastereomers in these reactions cannot be accessed, for example, 1,2-*anti*-1,3-*syn*- products. In spite of these drawbacks, both the Evans- and aldol-Tishchenko reactions offer attractive methods for the synthesis of 1,3-diols, allowing simultaneous introduction of up to five stereogenic centres, in excellent yields and optical purity.

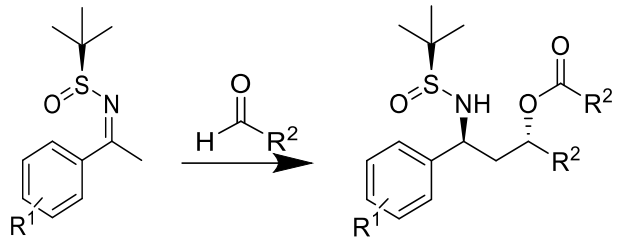
3.5 The aldol-Tishchenko reaction of *N-tert*-butanesulfinyl imines

Although reports exist for the aldol reaction of *N-tert*-butanesulfinyl imines, and derivatives thereof, prior to 2015, there had been no reports of an aldol-Tishchenko reaction of the imine derivative.[36] In 2016, our research group described a novel protocol for the synthesis of 1,3-

amino alcohol derivatives in the first example of an aldol-Tishchenko reaction of *N-tert*-butanesulfinyl imines.[37] This work describes the concomitant introduction of two and three chiral centres in one pot, and to the best of or knowledge, represents the first reported aldol-Tishchenko reduction of a C=N bond.

This methodology has shown to proceed with a high degree of stereoselectivity, affording *anti*-1,3-amino alcohols in good to excellent yields and diastereoselectivities. Acetophenone based sulfinyl imines allowed for the introduction of two chiral centres when reacted with pivaldehyde and enolisable aldehydes such as isobutyraldehyde, cylclohexane carboxaldehyde and isovaleraldehyde **(Scheme 3.20a)**. Aryl aldehydes were tolerated best when propiophenone derived sulfinyl imines were used, affording *anti*-1,3-amino alcohol monoesters in excellent diastereoselectivity and good yields **(Scheme 3.20b)**.

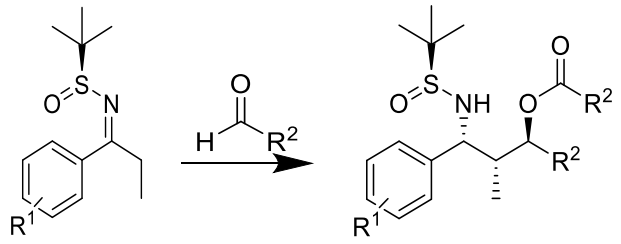
a)



40-88%

dr up to > 97:3

b)



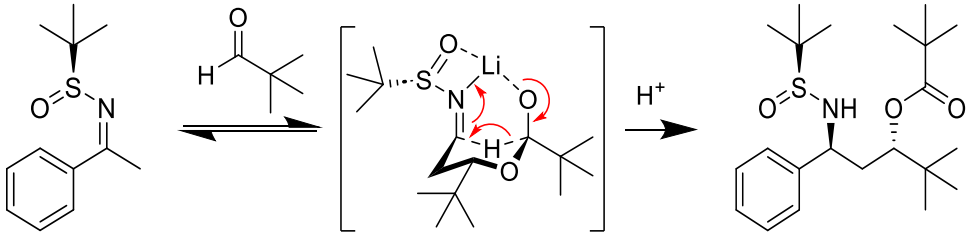
52-90%

dr up to > 98:2

Scheme 3.20. Aldol-Tishchenko reaction of chiral *N-tert*-butanesulfinyl imines

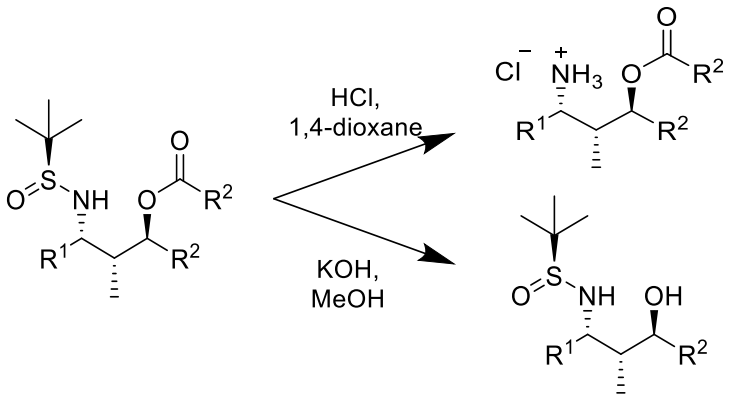
A similar mechanism to that of a classic aldol-Tishchenko reaction is proposed to be operative in this transformation. Mechanistic and computational studies of the reaction between the acetophenone-derived sulfinyl imine and pivaldehyde suggest the reaction proceeds *via* a reversible aldol step followed by an irreversible enantio- and diastereoselective hydride transfer, to afford the *anti*-1,3-amino alcohol monoester derivative **(Scheme 3.21)**. Critically, the hydride transfer step only proceeds when the sterically demanding *tert*-butyl groups are

positioned in an equatorial position in the proposed six-membered transition state. If positioned in an axial position, unfavourable 1-3-diaxial interactions are suggested to energetically favour the reverse aldol reaction and inhibit hydride transfer. Crucially, it is the formation of this six-membered transition state, analogous to that proposed by Woerpol, that leads to a diastereoselctive reaction and the use of the chiral auxiliary that is responsible for enantioselectivity.



Scheme 3.21. Proposed mechanism for the aldol-Tishchenko reaction of *N-tert*-butanesulfinyl imines

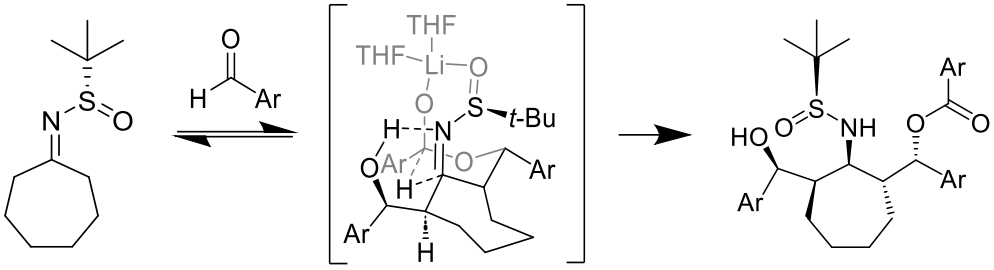
Additionally, both the ester and sulfinyl imine moieties could be selectively cleaved under mild reaction conditions whilst maintaining stereochemical integrity, providing valuable synthetic handles and allowing for further derivatisation **(Scheme 3.22)**.



Scheme 3.22. Selective cleavage of each ancillary

In 2021 our group expanded upon this work to develop a tandem double aldol-Tishchenko reaction of *N-tert*-butanesulfinyl imines. Up to five contiguous chiral centres, multiple new chemical bonds and three new functional groups could be introduced into the product, in one pot in both excellent yield and diastereoselectivity, to afford highly functionalised 3-amino-1,5-diol derivatives.[38] Both cyclic and acyclic sulfinyl imines were tolerated within this reaction, with the best results achieved using aromatic aldehydes. Consistent with previous reports, mechanistic investigations suggested a reversible aldol and aldol-type steps followed by the critical irreversible diastereoselective hydride transfer step. Density functional theory (DFT) calculations revealed a plausible six-membered transition state in a chair conformation **(Scheme 3.23)**. Both phenyl substituents, resulting from a double aldol reaction, occupy an

equatorial position, with the cycloheptyl ring orientated axially to avoid steric interaction with the bulky *tert*-butyl group of the sulfinyl imine.



36-76%

dr up to > 98:2

Scheme 3.23. Double aldol-Tishchenko reaction of *N*-*tert*-butanesulfinyl imines

The methodology offers a convenient route for the synthesis of 1,3-amino alcohol derivatives and 3-amino-1,5-diol monoesters, with numerous advantages over previously documented methods: **i)** imperatively, the use of external reductants is avoided by simply using an additional aldehyde equivalent and **ii)** this methodology represents a rare example of the introduction of up to five contiguous chiral centres in one pot.

Results & Discussion

3.6 Aims and objectives

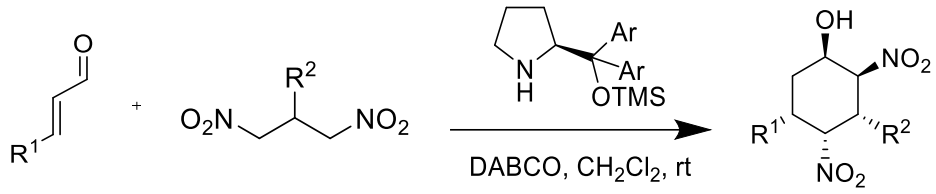
In this chapter, the asymmetric aldol-Tishchenko reaction of a range of (*S*)-*tert*-butanesulfinyl imines is discussed. One of the key aims of this project was to extend the scope of this methodology to include a range of substrates previously unexplored, or which proved unexpectedly challenging. Additionally, for many substrates previously synthesised, the absolute stereochemistry of the major diastereomer remained unknown. Efforts to determine the absolute stereochemistry underpin the work described in this chapter.

The following is a brief outline of the aims discussed:

- To determine the absolute stereochemistry of 2,2-dimethylcyclopentanone derived amino alcohol products and to gain an insight into the origins of the stereochemical outcome.
- To investigate the stereoselective synthesis of 1,3-diamines *via* the use of aldimines as aldol acceptors in an aldol-Tishchenko reaction protocol.
- To expand the scope of the aldol, aldol-Tishchenko reaction of cyclic (*S*)-*tert*-butanesulfinyl imines to include four- and six-membered cyclic (*S*)-*tert*-butanesulfinyl imines and a diverse range of aldehydes.
- To determine the absolute stereochemistry of butanone derived amino alcohol products and to gain an insight into the origins of the stereochemical outcome.
- To demonstrate the synthetic utility of the 3-amino-1,5-diol derivatives synthesised.

3.7 Project background

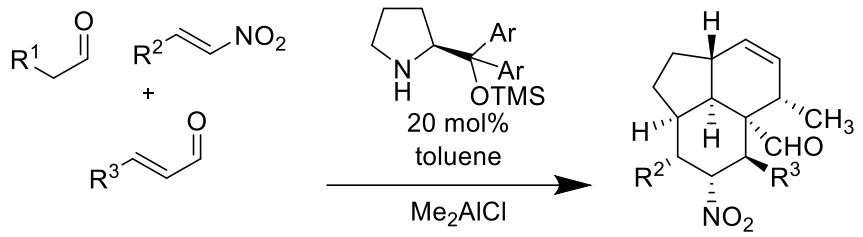
The synthesis of enantiomerically enriched compounds containing numerous chiral centres is critically important in asymmetric synthesis. Oftentimes, multiple contiguous chiral centres are introduced to molecules in a stepwise fashion, and rarely is it achieved in a one-pot procedure.[39-40] One-pot tandem asymmetric reactions provide a convenient route to introduce multiple functionalities into a molecule and consequently offer an effective method to furnish multiple chiral centres.[41] Tandem transformations also allow for increased atom economy and reaction efficiency, often requiring only one reaction solvent, work-up and purification step.[42] Organocatalysis is one area of organic synthesis which has demonstrated rapid growth and contributed to the number of emerging tandem asymmetric methodologies. For example, Jorgenson and co-workers have described the one-pot synthesis of pentasubstituted cyclohexanes **(Scheme 3.24)**.[43] Moderate yields and high enantio- and diastereoselectivites were achieved when a domino reaction cascade was developed, involving the addition of nitroalkanes to α,β-unsaturated aldehydes followed by an intramolecular Henry reaction. This reaction sequence resulted in the formation of compounds containing five contiguous chiral centres.



Up to 65%
up to 94% *ee*
up to 12:3:2 *dr*

Scheme 3.24. Synthesis of cyclohexanol derivatives with five contiguous chiral centres

In 2006, Enders and co-workers developed an efficient one-pot procedure for the synthesis of polyfunctionalised tricyclic frameworks, which possess characteristic structural features of diterpenoid natural products **(Scheme 3.25)**.[44] The organocatalytic Michael/Michael/aldol cascade/ Diels-Alder sequence resulted in the formation of five carbon-carbon bonds and a remarkable eight stereocentres.



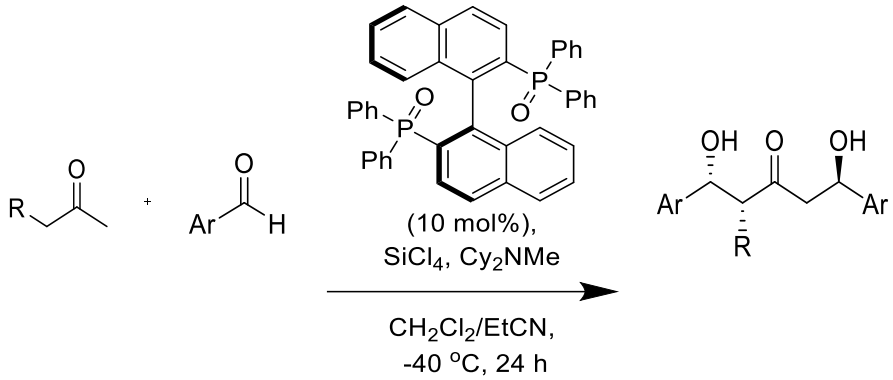
Up to 56%

ee > 99%

dr up to 15:1

Scheme 3.25. Tricyclic carbon framework resulting from triple-cascade/Diels Alder reaction

The enantioselective aldol reaction is a highly powerful reaction for the construction of carbon-carbon bonds in a stereoselective fashion.[45-48] In 2013, Nakajima and co-workers reported a novel enantioselective double aldol reaction of alkyl methyl ketones and aromatic aldehydes which resulted in the formation of 1,2-*syn*-1,5-*anti*-1,5-dihydroxy-3-pentanones in moderate to excellent yields with a high degree of stereochemical control, resulting from the use of a chiral phosphine oxide **(Scheme 3.26)**.



Up to 87%

up to 97% *ee*

up to 91:9 *dr*

Scheme 3.26. Stereoselective double aldol reaction

Enantiomerically pure amino diols **(Figure 3.7)** are prevalent in a wide array of bioactive molecules and natural products, although methods to generate these compounds are lacking.[49-51] At present, to the best of our knowledge, a publication by the McGlacken group in 2021 represents one of the only reported enantioselective methods to furnish 3-amino-1,5-diol derivatives (**Scheme 3.23**).[38]

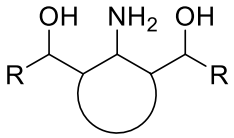
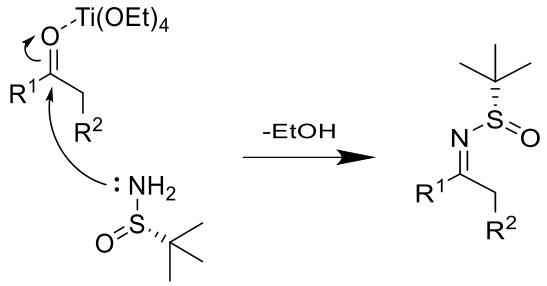


Figure 3.7. 3-Amino-1,5-diol framework

3.8 Tandem aldol, aldol-Tishchenko reaction of cyclic (*S*)-*tert*-butanesulfinyl imines for the formation of multiple contiguous chiral centres

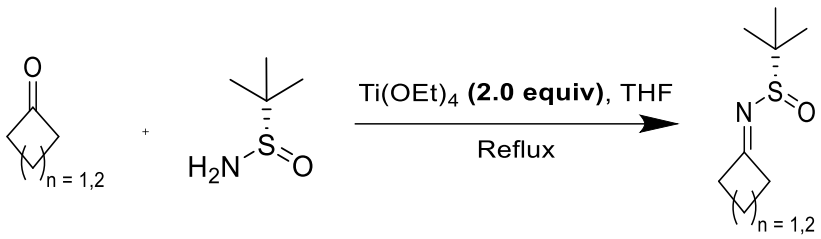
3.8.1 Synthesis of cyclic (*S*)-*tert*-butanesulfinyl imines

Work on this project began with the synthesis of a variety of cyclic (*S*)-*tert*-butanesulfinyl imines **(Scheme 3.27)**. Generally speaking, ketones can be easily converted to the corresponding (S)-*tert*-butanesulfinyl imine *via* a facile condensation reaction with (*S*)-*tert*-butanesulfinamide, in the presence of $Ti(OEt)_4$. The titanium species plays a dual role in the reaction, primarily functioning as a Lewis acid to activate the carbonyl moiety, whilst also acting as a water scavenger.

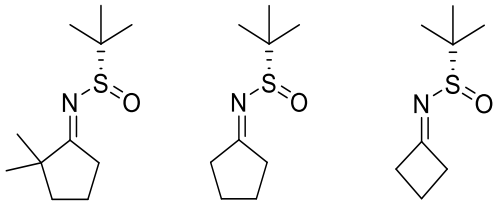


Scheme 3.27. Key mechanistic step for the formation of (*S*)-*tert*-butanesulfinyl imines

Using reaction conditions previously optimised by another member of the group, three cyclic (*S*)-*tert*-butanesulfinyl imines **(*S*)-67-(*S*)-69** were synthesised in moderate to excellent yields (53% - 82%) **(Scheme 3.28)**. These sulfinyl imines were stable to column chromatography, with no evidence of degradation, and could be stored under inert atmosphere at temperatures below 0 °C for long periods without issue.



(*S*)-66

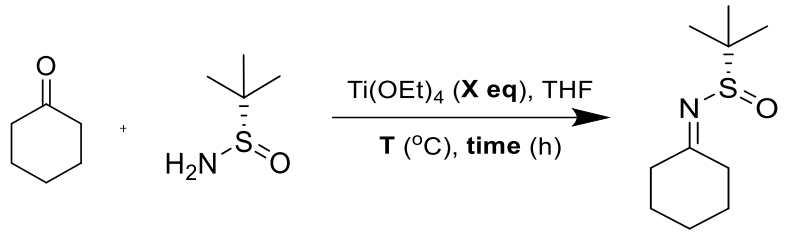


(*S*)-67, 62% **(*S*)-68,** 82% **(*S*)-69,** 53%

Scheme 3.28. (*S*)-*tert*-butanesulfinyl imines synthesised using standard reaction conditions

However, preparation of other cyclic (*S*)-*tert*-butanesulfinyl imines proved more challenging. Initial attempts to synthesise the cyclohexanone derived (*S*)-*tert*-butanesulfinyl imine **(*S*)-71** using the above conditions gave no evidence of conversion to the desired product. The synthesis of (*S*)-*tert*-butanesulfinyl ketimines is known to be accelerated at increased temperatures. However, unidentified degradation products were observed in the ^{1}H NMR spectrum of the crude reaction mixture when this reaction was attempted at 80 °C. After numerous reaction attempts (**Table 3.1**), reaction conditions previously described by Ellman gave a moderate yield of 42% of **(*S*)-*71***.[17] This sulfinyl imine proved more labile to column chromatography than all previous compounds in this series. Cleavage of this compound was observed by TLC during the purification step. Additionally, this compound was unable to be stored for short durations, even under inert conditions at low temperatures.

Table 3.1. Synthesis of (*S*)-*N*-cyclohexylidene-2-methylpropane-2-sulfinamide



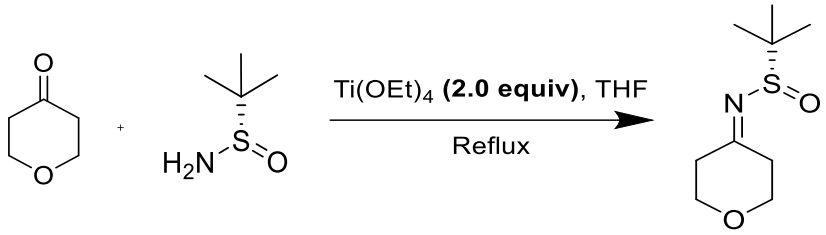
70 **(*S*)-66** **(*S*)-71**

Entry	Ketone (equiv.)	$Ti(OEt)_4$ (equiv.)	Sulfinamide (equiv.)	Time (h)	Temperature (°C)	Yield of (*S*)-*71*
1	1	2	1	20 h	80 °C	0%[a]
2	1	2	1	20 h	rt	0%[b]
3	1	1.7	1.2	4 h	60 °C	42%
4	1	1.7	1.2	18 h	60 °C	trace[c]

[a] Evidence of unidentified degradation products by ^{1}H NMR spectroscopy

[b] Only starting material evident by ^{1}H NMR spectroscopy

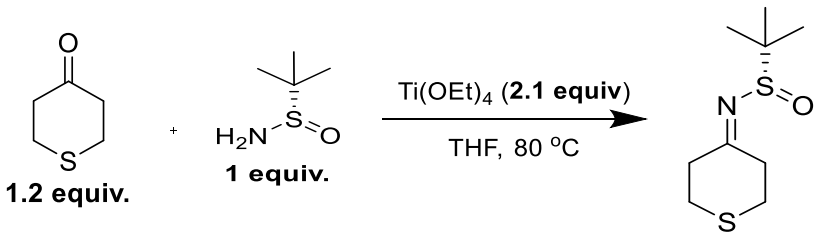
Due to the difficulties outlined above, it was decided to synthesise alternative 6-membered cyclic (*S*)-*tert*-butanesulfinyl imines **(*S*)-73** and **(*S*)-75**. Initially, the synthesis of both compounds was attempted using our standard reaction conditions. Both reactions proved problematic, however. Only a poor yield of 18% of **(*S*)-73** was obtained **(Scheme 3.29)**.



72 **(*S*)-66** **(*S*)-73**, 18%

Scheme 3.29. Synthesis of **(*S*)-73**

Alternative reaction conditions were required to access the sulfur analogue **(*S*)-75** in a moderate yield of 44% (**Scheme 3.30**).

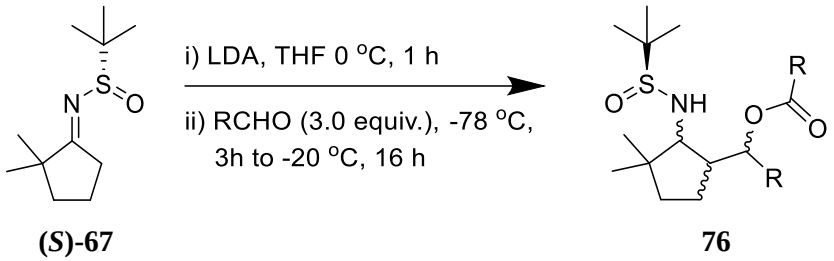


74 **(*S*)-66** **(*S*)-75**, 44%

Scheme 3.30. Synthesis of **(*S*)-75**

3.8.2 Aldol-Tishchenko reaction of 2,2-dimethylcyclopentanone

Within our group, the aldol-Tishchenko reaction has proven to be a highly diastereoselective reaction for the synthesis of *anti*-1,3-amino alcohols, resulting in the formation two and three chiral centres. Previous work, conducted by another member of the group, successfully applied aldol-Tishchenko reaction conditions to **(*S*)-67**, achieving excellent yields and diastereoselectivites **(Scheme 3.31)**.[52-53]



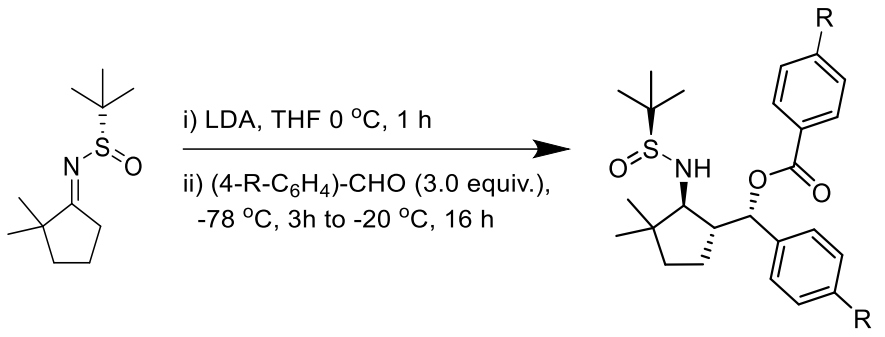
(*S*)-67 **76**

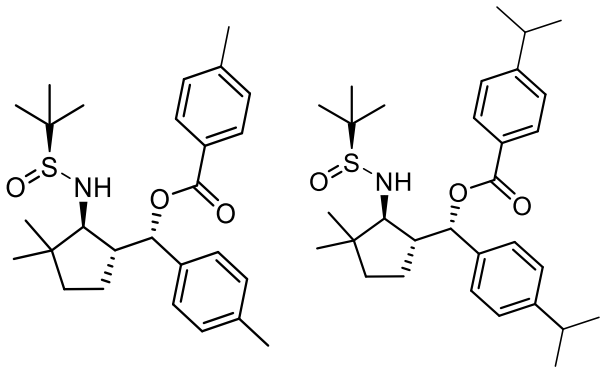
R = Ph, 82%, > 98:2 *dr*

R = *t*-Bu, 78%, 91:9 *dr*

Scheme 3.31. Aldol-Tishchenko reaction of α-cyclic sulfinyl imine

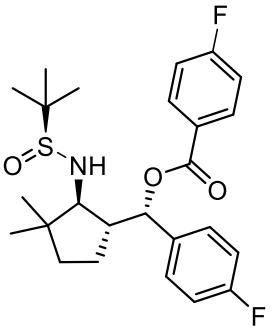
However, the absolute stereochemistry of the resulting 1,3-amino alcohol derivatives could not be determined previously. The initial goal of this work was to synthesise a range of these compounds to determine the absolute stereochemistry of the major product generated in this reaction. A range of 1,3-amino alcohol derivatives were synthesised using previously optimised reaction conditions and various substituted benzaldehydes as aldol-acceptors **(Scheme 3.32)**. Moderate to good yields (up to 61%) and excellent levels of diastereoselectivity (up to > 99:1) were achieved.



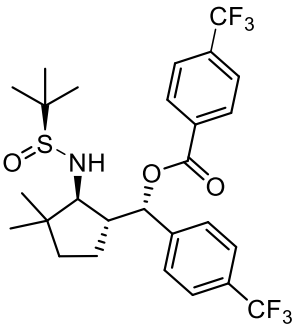


(*S,S,R,S*)-77 52%, 88:12 *dr*

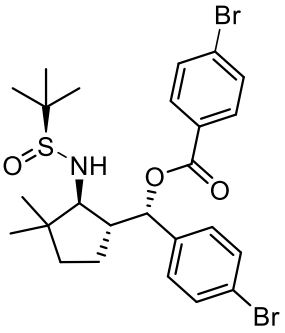
(*S,S,R,S*)-78 61%, 91:9 *dr*



(*S,S,R,S*)-79 60%, 91:9 *dr*



(*S,S,R,S*)-80 43%, > 99:1 *dr*



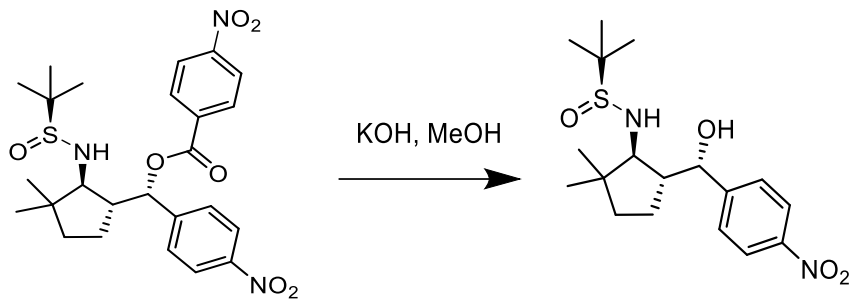
(*S,S,R,S*)-81 8% single diastereomer, *dr* nd,

Scheme 3.32. Aldol Tishchenko reaction of **(*S*)-67**

Pleasingly, a range of *p*-substituted benzaldehydes was well tolerated as aldol-acceptors. For instance, when an electron donating substituent was present at the *p*-position, in the case of *p*-methyl- and *p*-isopropyl-benzaldehyde, moderate yields (52% and 61%, respectively) and excellent diastereoselectivities (88:12 and 91:9, respectively) were observed for each aldol-Tishchenko product, **(*S,S,R,S*)-77** and **(*S,S,R,S*)-78**. When *p*-fluorobenzaldehyde was used, a similar yield and diastereoselectivity was achieved for **(*S,S,R,S*)-79**. However, although a decrease in yield was observed for the reaction of *p*-trifluoromethylbenzaldehyde with **(*S*)-67**,

excellent stereocontrol was observed in the reaction with a *dr* of > 99:1 recorded for **(*S*,*S*,*R*,*S*)-80**.

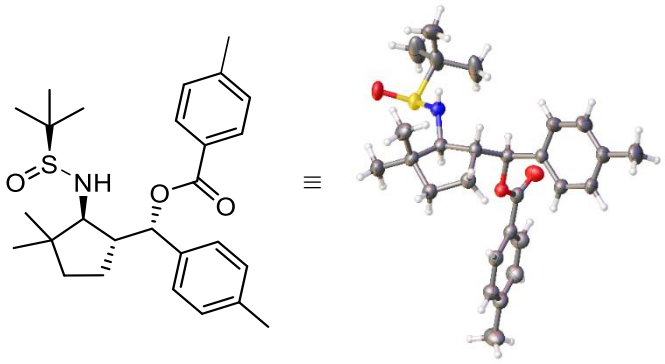
However, the reaction using 4-bromobenzaldehyde to synthesise **(*S*,*S*,*R*,*S*)-81** proved problematic, with only an 8% yield of the desired compound isolated. It was also not possible to decipher a *dr* for this reaction, due to overlapping signals in the ^{1}H NMR spectrum of the crude reaction mixture. Although complete consumption of the starting material **(*S*)-67** was evident in the ^{1}H NMR spectrum, attempts to isolate and identify any additional products from this reaction was not possible. Another reaction which resulted in only poor conversion to the desired product, measured by ^{1}H NMR spectroscopy, was the reaction using 4-nitrobenzaldehyde as an aldol-acceptor. In this instance, the aldol-Tishchenko product was not isolated and instead the crude reaction mixture was exposed to methanolic KOH (**Scheme 3.33**). This resulted in only a 7% yield of the cleaved ester product, **(*S*,*S*,*R*,*S*)-83**.



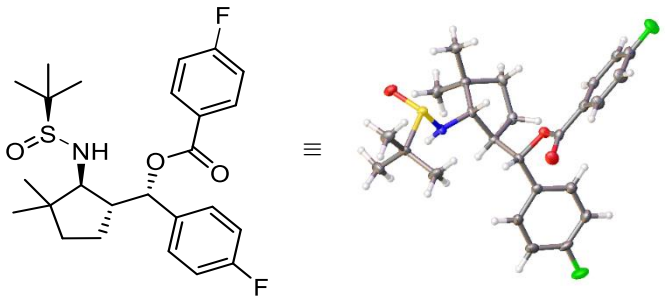
(*S*,*S*,*R*,*S*)-82 **(*S*,*S*,*R*,*S*)-83**

Scheme 3.33. Cleavage of ester moiety of **(*S*,*S*,*R*,*S*)-82**

Pleasingly, it was possible to elucidate the absolute stereochemistry of the above reaction, with crystal structures of both **(*S*,*S*,*R*,*S*)-77** and **(*S*,*S*,*R*,*S*)-79** obtained by crystallographer Dr Mark Light at the University of Southampton (**Figure 3.8**).



(*S*,*S*,*R*,*S*)-77

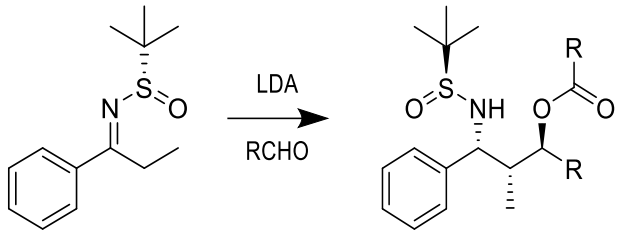


(*S*,*S*,*R*,*S*)-79

Figure 3.8. Crystallographic structure of both **(*S*,*S*,*R*,*S*)-77** and **(*S*,*S*,*R*,*S*)-79**

Additionally, with the stereochemical information for this substrate in hand, a collaborative effort between the McGlacken group and the research group of Prof Ken Houk of University of California Los Angeles sought to rationalise the mechanism and stereochemical outcome of this reaction. Previous work within the group focused on the aldol-Tishchenko reaction of propiophenone and acetophenone-derived (*S*)-*tert*-butanesulfinyl imines (**(*S*)-84** & **(*S*)-86**).[37] Whilst the same mechanistic rationale can be applied to all substrates, the stereochemical outcome varies depending on the (*S*)-*tert*-butanesulfinyl imine starting material (**Scheme 3.34**).

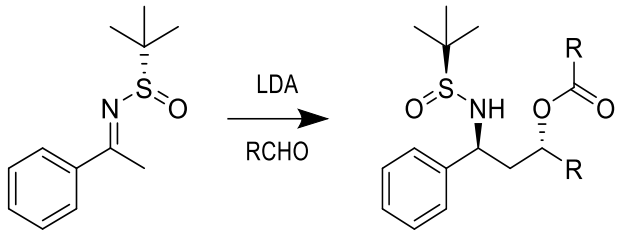
a)



(*S*)-84 **(*S,R,R,R*)-85**

R = Ph, 87%, 86:4 *dr*

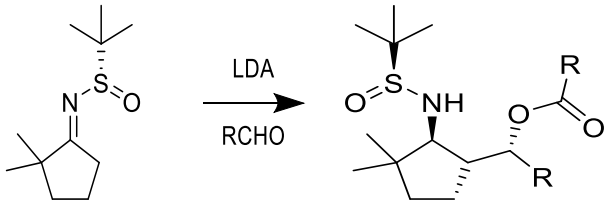
b)



(*S*)-86 **(*S,S,S*)-87**

R = ^{t}Bu, 70%, 91:9 *dr*

c)

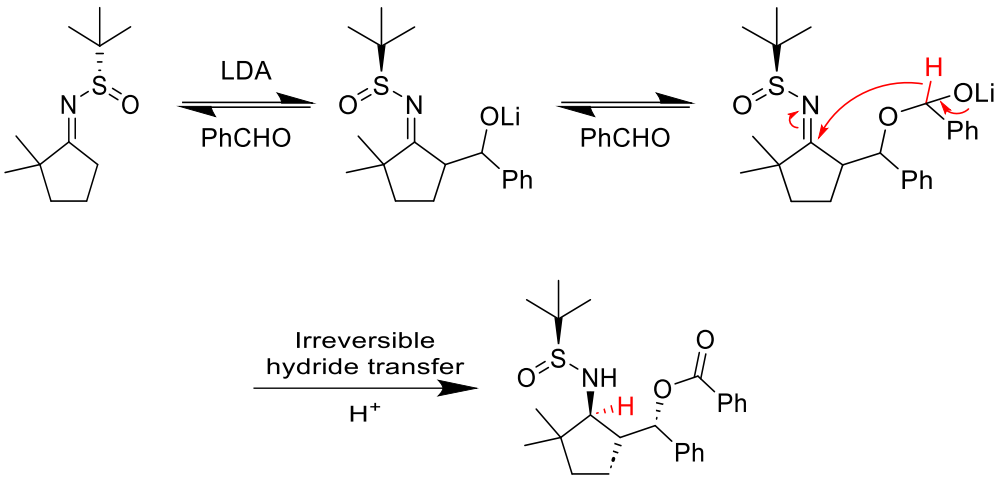


(*S*)-67 **(*S,S,R,S*)-76**

R = Ph, 82%, > 98:2 *dr*

Scheme 3.34. Divergent stereochemical outcomes with different substrate classes

Mechanistically, an initial reversible aldol reaction is followed by reaction of the resulting alkoxide with a second molecule of aldehyde to form a hemiacetal-type intermediate. This is followed by the irreversible rate- and stereo-determining hydride transfer step **(Scheme 3.35)**.



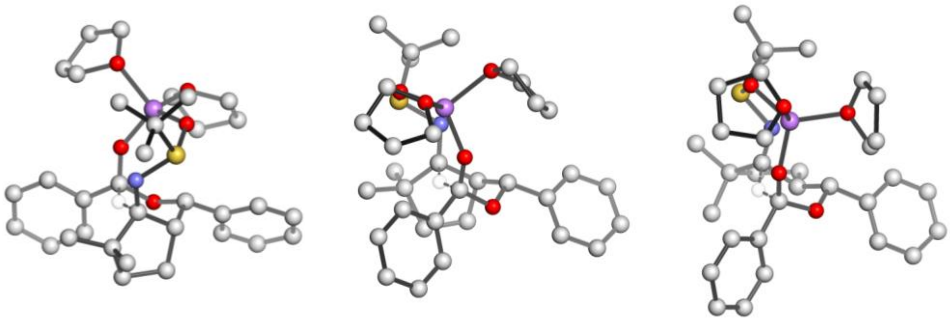
Scheme 3.35. Mechanism of aldol-Tishchenko reaction to synthesis 1,3-amino alcohol derivatives

Whilst all substrates produced the 1,3-*anti* product, the relative stereochemistry of the sulfinyl *tert*-butyl group and the amine differed between substrates. In the case of the propiophenone-derived substrate, the relative stereochemistry between both was *anti* whereas for both the acetophenone-derived compounds and the dimethylcyclopentanone analogues the relative stereochemistry of the amine and *t*-butyl group was determined to be *syn*. This proved a surprising experimental result as, despite the fact that deprotonation occurs at a methylene site for the dimethylcyclopentanone analogue as opposed to a methyl site, the stereochemical outcome matches that of acetophenone and not propiophenone. However, rationalising this experimental result proved quite challenging. No common aldehyde could be used in an aldol-Tishchenko reaction for all three sulfinyl imine substrates, meaning disentangling this result experimentally proved impossible. Instead, computational studies were conducted in order to explain these results.

Density functional theory (DFT) calculations were completed by Dr Aneta Turlik and Prof Ken Houk of University of California Los Angeles. DFT calculations were performed with Gaussian 16[54] to analyze what factors control the stereoselectivity for different substrates. For each structure, an extensive conformer search was performed with CREST[55] to locate the lowest-energy conformer of reactants and transition states. Geometry optimizations were performed with the B3LYP functional,[56-60] augmented with Grimme's D3 empirical dispersion term,[61] and the 6-31G(d) basis set. Frequency calculations confirmed the optimized structures as minima (zero imaginary frequencies) or transition state structures (one imaginary frequency) on the potential energy surface. Intrinsic reaction coordinate (IRC) calculations were performed in order to connect the transition states to the reactants and the products.

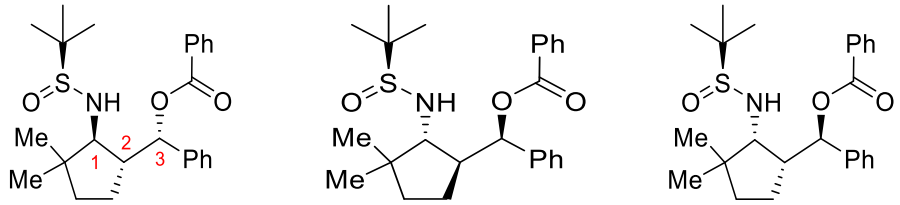
Single point energies were calculated using M06-2X-D3/6-311+G(d,p),[62] and a quasi-harmonic correction was applied using the GoodVibes program.[63]

The model reaction chosen for DFT calculations was the reaction of **(*S*)-67** and benzaldehyde (**Scheme 3.34c**). Experimentally, a yield of 82% and *dr* of 98:2 was achieved for this reaction (this reaction was conducted by another member of the McGlacken group).[52] Three of the eight possible transition states are depicted in **Figure 3.9**.



TS-13a **TS-13b** **TS-13c**

$\Delta\Delta G^{\ddagger}$ = 0.0 kcal/mol $\Delta\Delta G^{\ddagger}$ = 2.7 kcal/mol $\Delta\Delta G^{\ddagger}$ = 20.3 kcal/mol



(*S,S,R,S*)-76 **(*S,R,S,R*)-76** **(*S,R,R,R*)-76**

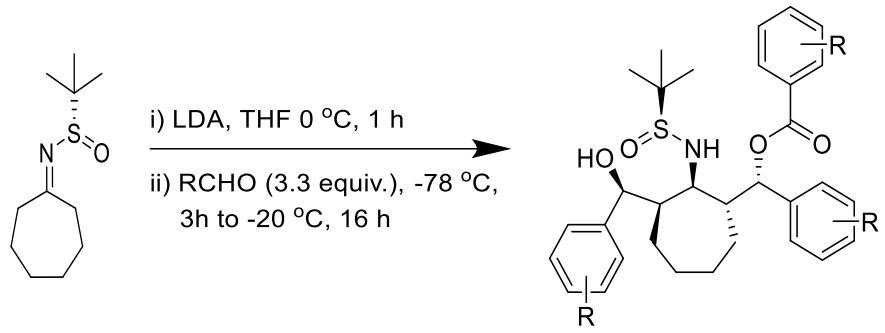
Figure 3.10. Transition state energies for possible diastereomers of **76**.

Initially, before the absolute stereochemistry of the dimethylcyclopentanone analogues was unequivocally identified using X-ray crystallography **(Figure 3.8)**, it was logically assumed the stereochemical outcome would be analogous to that of the propiophenone derivative *i.e.* **(*S,R,R,R*)-76.** However, a transition state barrier of 20.3 kcal/mol higher than that of the lowest energy transition state was recorded for that isomer, **TS-13c**. This TS suggests an equatorial arrangement of the cyclopentyl ring is highly energetically disfavoured. Presumably, this is due to an unfavourable steric interaction between the bulky *tert*-butyl group of the sulfinyl imine and the quaternary carbon of the cyclopentyl-ring. One of the lowest energy transition states, **TS-13b** is 2.7 kcal/mol higher energy than the lowest energy isomer (**TS-13a**). This energy difference, resulting from the axial orientation of the cyclopentyl-ring, correlates to a *dr* of 99.9:0.1 at -78 °C and 99.5:0.5 at -20 °C, consistent with the results observed experimentally. Furthermore, analysis of the ^{1}H NMR spectra of these compounds is suggestive of a *syn*-relationship between the protons of C2 and C3, due to the

low coupling constant (2.1 - 2.4 Hz). Contrastingly, the relatively high coupling constant (9.7 - 10.1 Hz) observed between the protons attached to C1 and C2 is suggestive of an *anti*-orientation.[64]

3.8.3 Aldol, aldol-Tishchenko reaction of an (S)-tert-butanesulfinyl imine derived from cyclopentanone

Having achieved moderate to good yields and levels of diastereoselectivity for the aldol-Tishchenko reaction of dimethylcyclopentanone-derived (*S*)-*tert*-butanesulfinyl imine **(*S*)-67**, the focus of the project turned to expanding this methodology to including more challenging symmetric, cyclic (*S*)-*tert*-butanesulfinyl imines. However, work by another member of the group, Dr Pamela Mackey, discovered that use of additional equivalents of aldehyde (3.3 equiv. instead of 2.2 equiv.) resulted in an aldol, aldol-Tishchenko reaction occurring for the cycloheptanone derived (*S*)-*tert*-butanesulfinyl imine **((*S*)-88) (Scheme 3.36)**.[38, 65]



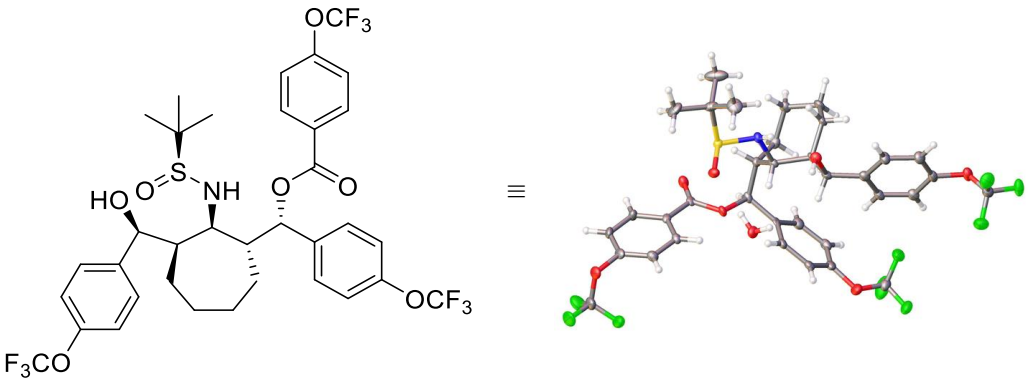
(*S*)-88 **(*S,R,R,R,S,S*)-89**

Up to 76%

Up to > 98:2 *dr*

Scheme 3.36. Aldol, aldol-Tishchenko reaction of **(*S*)-88**

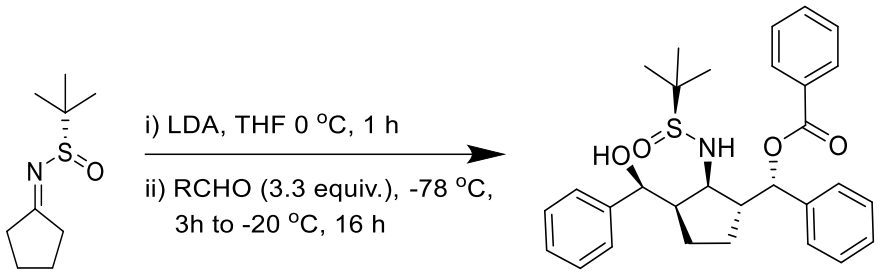
This transformation, which tolerated a wide range of substituted benzaldehydes, represented a transformation encompassing the introduction of five contiguous chiral centres, the synthesis of multiple new chemicals bonds and the addition of three new functional groups in a one-pot process. Excellent yields (up to 76%) and stereochemical control (up to > 98:2 *dr*) were also observed in this reaction. Additionally, the stereochemistry of the major diastereomer was elucidated by X-ray crystallography **(Figure 3.11)** and mechanistic insight was provided by DFT calculations.



(*S,S,R,R,R,S*)-90

Figure 3.11. X-ray crystal structure of **(*S,S,R,R,R,S*)-90**

Inspired by these results, the next objective of this project was the explore the diversity of this transformation to include four-, five- and six- membered cyclic (*S*)-*tert*-butanesulfinyl imines. As a starting point, we chose the reaction of **(*S*)-68** with benzaldehyde **(Scheme 3.37)**. Gratifyingly, it was possible to isolate a 44% yield of the aldol, aldol-Tishchenko product from this reaction, with a *dr* of 88:12 determined from the ^{1}H NMR spectrum of the crude reaction mixture.

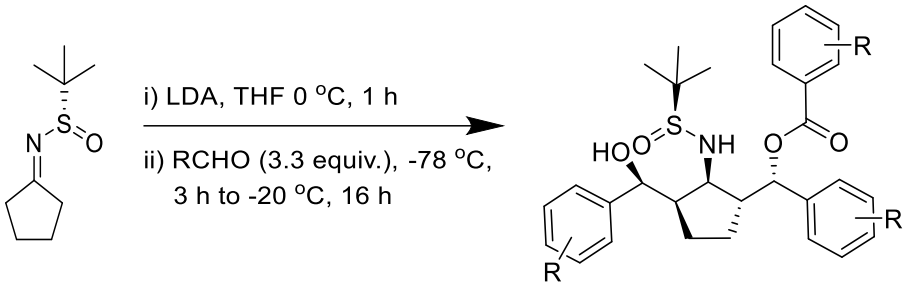


(*S*)-68 **(*S,S,R,R,R,S*)-91**

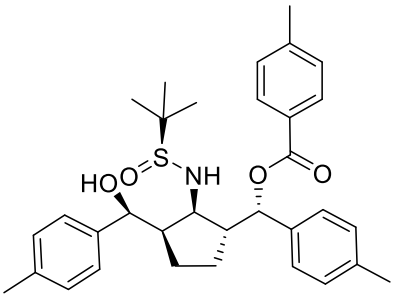
44%, 88:12 *dr*

Scheme 3.37. Aldol, aldol-Tishchenko reaction of **(*S*)-68**

This initial result prompted us to examine the scope of aldehydes which could be employed as aldol acceptors for this substrate. Firstly, we examined a range of *p*-alkyl-substituted benzaldehydes (**Scheme 3.38**). In each case, the reaction was found to be highly diasteroselective, with a *dr* of approximately 90:10 consistently observed. Moderate yields were obtained of aldol, aldol-Tishchenko product were obtained in each case with a yield of 32% of **(*S,S,R,R,R,S*)-92** obtained when *p*-methylbenzaldehyde was used, increasing to a 47% of **(*S,S,R,R,R,S*)-95** when *p-tert*-butylbenzaldehyde was employed as an aldol acceptor.

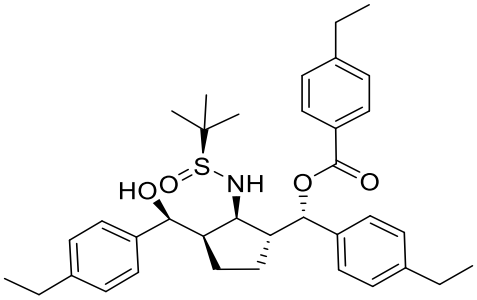


(*S*)-68



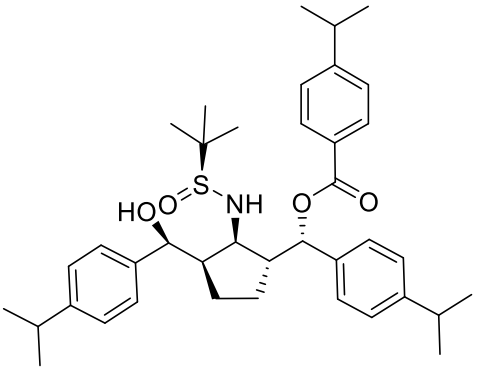
(*S,S,R,R,R,S*)-92

32%, 91:9 *dr*



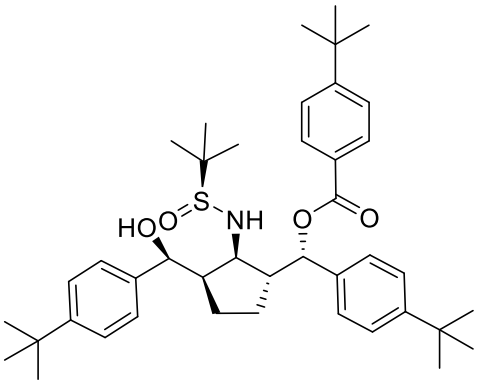
(*S,S,R,R,R,S*)-93

39%, 91:9 *dr*



(*S,S,R,R,R,S*)-94

41%, 91:9 *dr*

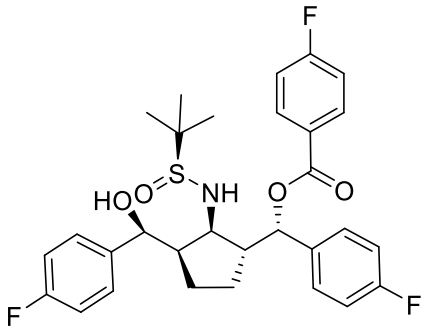


(*S,S,R,R,R,S*)-95

47%, 92:8 *dr*

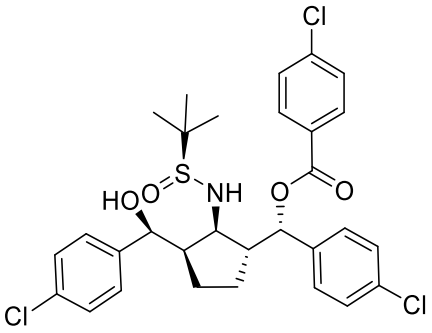
Scheme 3.38. Cyclopentanone derived 3-amino-1,5-diol derivatives

Next, we examined the effect of including electron withdrawing substituents on the benzaldehyde framework **(Scheme 3.39)**. Disappointingly, halogenated aldehydes were not as well tolerated in this reaction as their alkyl-substituted counterparts. A decrease in diastereoselectivity was observed when *p*-fluorobenzaldehyde was used in the synthesis of **(*S,S,R,R,R,S*)-96**. The diastereoselectivity of the reaction using *p*-chloro or *p*-bromo-benzaldehyde as aldol acceptor could not be determined, owing to overlapping signals in the ^{1}H NMR spectrum of the crude reaction mixture.



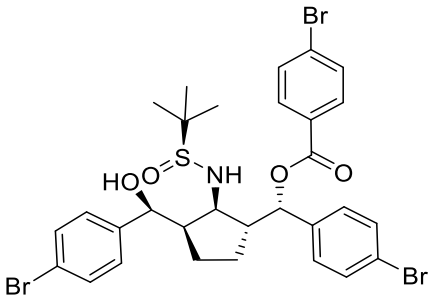
(*S,S,R,R,R,S*)-96

49%, 87:13 *dr*



(*S,S,R,R,R,S*)-97

29% single diastereomer, *dr* nd



(*S,S,R,R,R,S*)-98

29% single diastereomer, *dr* nd

Scheme 3.39. Halogenated cyclopentanone-derived 3-amino-1,5-diol derivatives

Where possible, for all cases the diastereomeric ratio was determined using the characteristic ester doublet present in the ^{1}H NMR spectrum of the crude reaction mixture **(Figure 3.12)**.

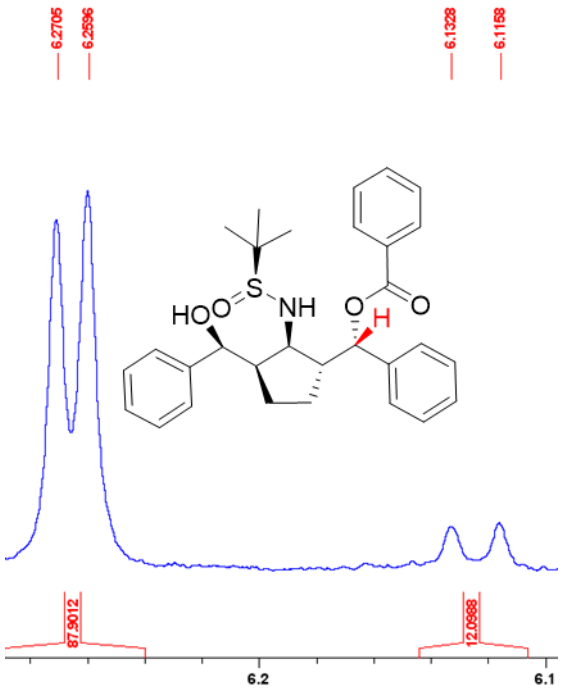
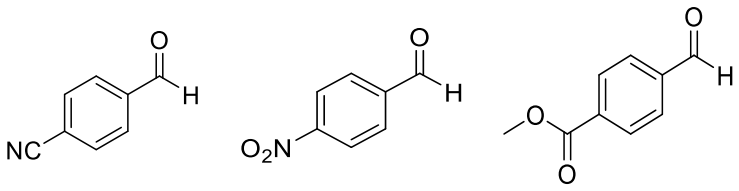


Figure 3.12. Determination of diastereomeric ratio of **(*S,S,R,R,R,S*)-91**

In an attempt to further expand the substrate scope of this reaction, a variety of challenging aldol acceptors were examined in the aldol, aldol-Tishchenko reaction of **(*S*)-68 (Figure 3.13)**. Due to success with an alternative substrate, aldehydes containing a cyano- **99**, nitro- **100** and ester **101** functionality were also investigated. It was hoped the *in-site* hydride transfer, which alleviates the need for an external reductant, would allow formation of the corresponding 3-amino-1,5-diol derivatives without any susceptibility of the aldehyde substituents to reduction. Disappointingly, none of the reactions employing these aldehydes yielded any notable conversion to the desired aldol, aldol-Tishchenko products.

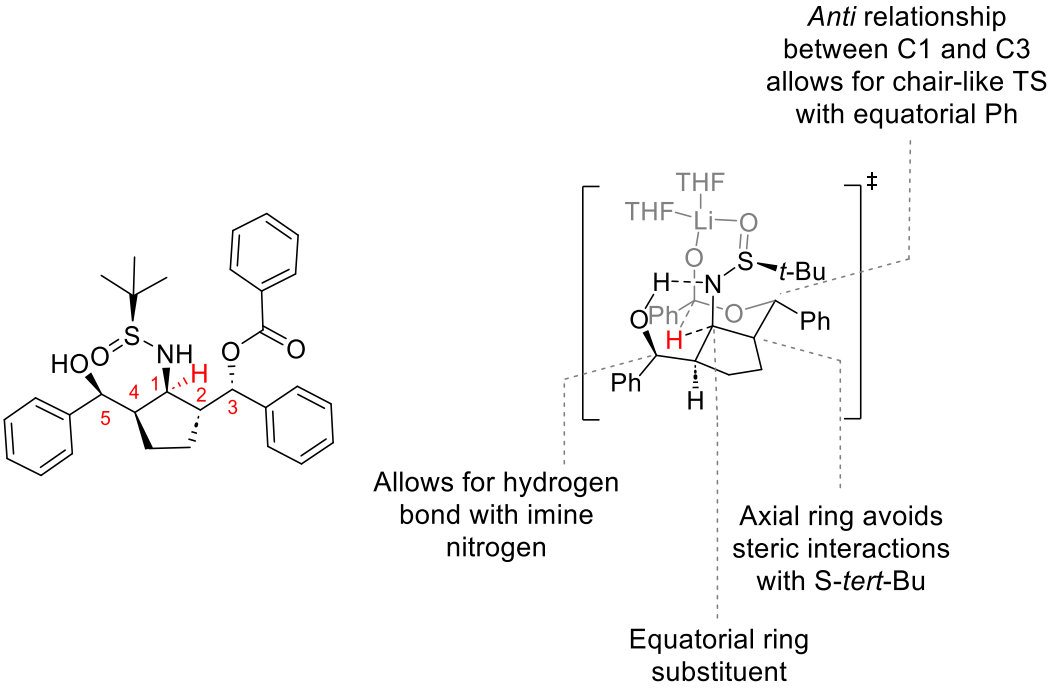


99 **100** **101**

Figure 3.13. Aldehydes unsuccessful in the aldol, aldol-Tishchenko reaction of **(*S*)-68**.

Despite numerous attempts, it proved an insurmountable challenge to elucidate the absolute stereochemistry of the cyclopentanone derived 3-amino-1,5-diol derivatives. However, another member of the group was successfully able to determine the stereochemistry of the analogous cycloheptanone 3-amino-1,5-diol derivatives **(S,S,R,R,R,S)-90** *via* X-ray crystallography. It is plausible, however, to assume the stereochemistry is consistent moving from a seven-membered ring to a five-membered ring, considering the reactivity patterns are

similar. Additional DFT calculations were performed by our collaborators, Dr Aneta Turlik and Prof Ken Houk. Whilst these calculations were in the main based on the cycloheptanone series, extension to include the cyclopentanone series was also conducted. From previously described calculations relating to the formation of two and three chiral centres *via* a single aldol-Tishchenko reaction, it was evident that an *anti*- relationship between the stereocentres at C1 and C3 is the lowest energy conformation. The formation of these stereocentres proceeds through a chair-like transition state, where the phenyl substituent of C3 is equatorial. The stereochemistry at C1 is *syn*- to the sulfinyl tert-butyl group, with the cyclopenty ring at C2 orientated axially to avoid unfavourable steric interactions with the tert-butyl group. The lowest energy transition state is also orientated to allow H-bonding to occur between the alcohol at C5 and the imine nitrogen atom. This interaction is favoured when the relative stereochemistry between C1 and C5 is *syn*-, and not possible if the opposite stereochemistry was present at C4 **(Figure 3.14)**.



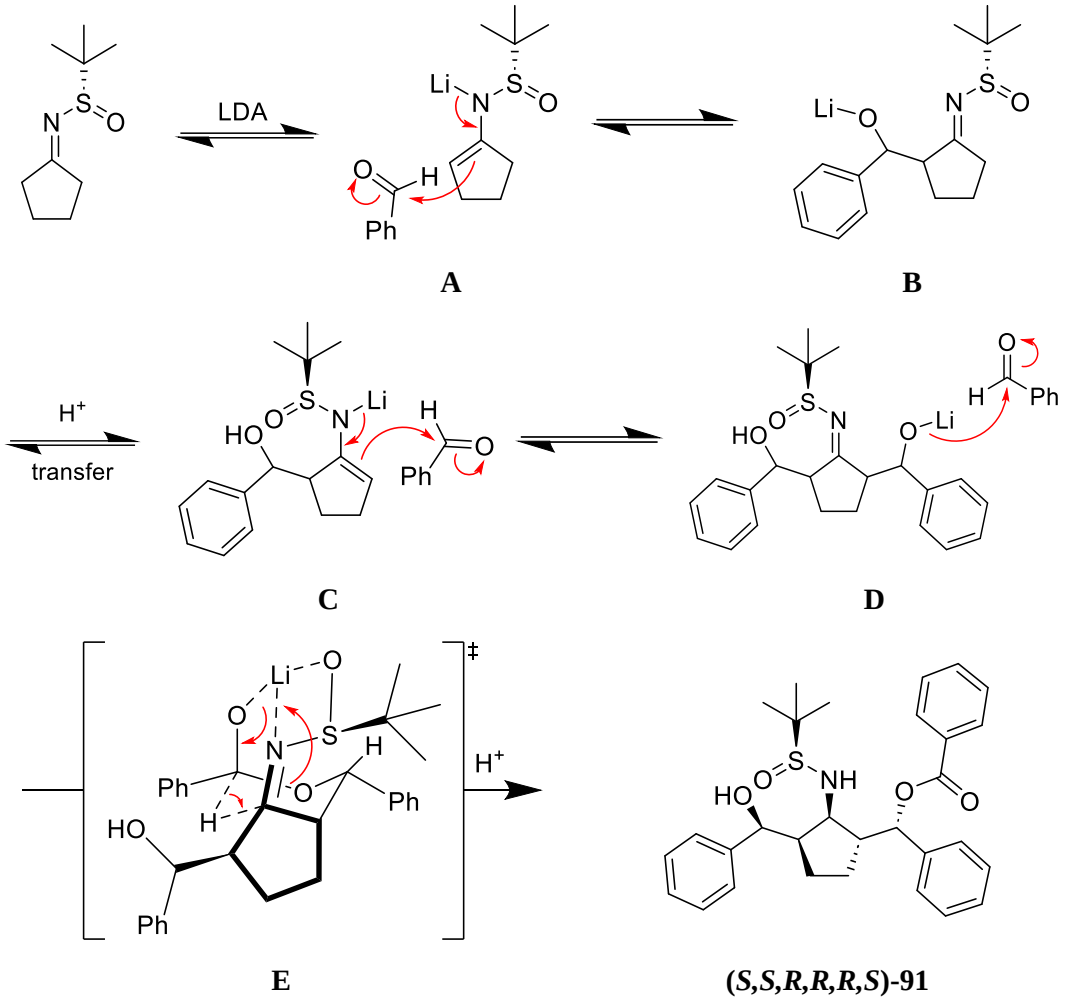
(*S*,*S*,*R*,*R*,*R*,*S*)-91 **TS-1**

ΔG = 14.0 kcal/mol

Figure 3.14. Factors affecting stereoselectivity in aldol, aldol-Tishchenko reaction of **(*S*)-68**

When the computational results are combined with the results obtained experimentally, it is possible to propose a plausible reaction mechanism accounting for the observed stereochemical outcome **(Scheme 3.40)**. Initially, deprotonation of **(*S*)-68** results in the formation of azaenolate **A**. This reaction is reversible and the reversibility is likely facilitated when sub-stoichiometric amounts of LDA are used. This is followed by the first aldol reaction, which DFT calculations have shown to be non-selective, resulting in the formation of both

syn- and *anti*-aldolate **B**. These species undergo a proton transfer to form the reactive azaenolate intermediate species **C**, which react with a second molecule of aldehyde, resulting in both the *syn*- and *anti*-double aldolate species, **D**. Next, warming of the reaction mixture to -20 °C is conducted in order to promote the Tishchenko reaction. The stereochemical outcome is suggestive that the *syn*-double aldolate **D** is the lowest energy transition state to allow for hydride transfer to occur.



Scheme 3.40. Proposed reaction mechanism of the aldol, aldol-Tishchenko reaction of **(*S*)-68** leading to major diastereomer **(*S,S,R,R,R,S*)-91**

Previous work within the group related to the single aldol-Tishchenko reaction of both propiophenone and acetophenone derived sulfinyl imines is indicative of an equilibrium effect, resulting in intermediates being funnelled towards the lowest energy transition state, ultimately leading to the high level of diastereoselectivity observed for these reactions.[37]

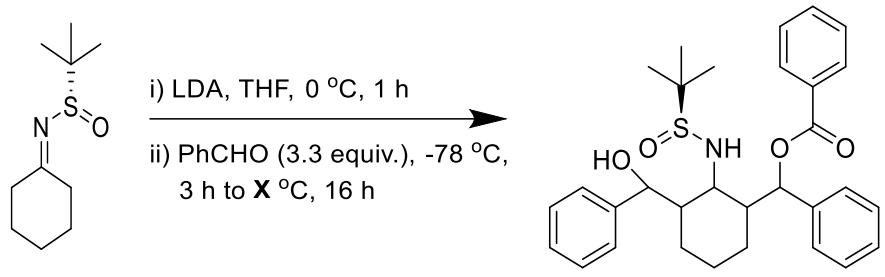
It is suggested the *anti*-double aldolate undergoes a retro-aldol reaction, regenerating the initial azaenolate **A** and a molecule of aldehyde. This essentially establishes a conversion of

the unreactive *anti*-double aldolate **D** to the *syn*-double aldolate **D**, albeit indirectly. In contrast, the relative stability of the *syn*-double aldolate **D** species means a retro-aldol reaction does not occur. Instead, this species progresses to undergo the Tishchenko step with a third molecule of aldehyde *via* an activated transition state **E**. The final, irreversible hydride transfer step results in the formation of **(*S,S,R,R,R,S*)-91**.

3.8.4 Aldol, aldol-Tishchenko reaction of (*S*)-tert-butanesulfinyl imines derived from cyclohexanone and related heterocycles

Having examined the reactivity of **(*S*)-68**, we next sought to expand this methodology to include six-membered cyclic (*S*)-*tert*-butanesulfinyl imine**(*S*)-71**. However, increasing the ring size by simply one carbon proved significantly more challenging that what we had envisaged. Firstly, as discussed, we experienced issues with the synthesis and storage of **(*S*)-71**. Having finally isolated an appreciable yield of**(*S*)-71**, the results we obtained from reactions using this substrate were disappointing **(Table 3.2)**.

Table 3.2. Aldol, aldol-Tishchenko reaction of **(S)-71**



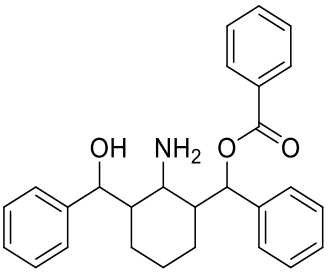
(*S*)-*71* **(*S*)-102**

Entry	LDA (equiv.)	Temperature (°C)	Product	Yield	*dr*
1	1.1	-20	Complex mixture	-[a, b]	-[a, b]
2	0.8	-20	**(*S*)-102**	26%	68:27:5
3	0.8	-45	Complex mixture	-[a, b]	-[a, b]
4	0.7	-20	**(*S*)-102**	20%	62:38
5	0.6	-20	**(*S*)-102**	-[b]	51:39:10

[a] No evidence of desired compound in ^{1}H NMR spectrum of crude reaction mixture

[b] Not isolate/determined

We began by subjecting **(*S*)-71** to the standard reaction conditions previously optimised for **(*S*)-68**, however no evidence of the desired aldol, aldol-Tishchenko product was evident in the ^{1}H NMR spectrum of the crude reaction mixture **(Table 3.2, entry 1)**. Work by another member of the group had established that the use of sub-stoichiometric amounts of LDA proved optimal for the aldol, aldol-Tishchenko reaction of **(*S*)-88**. Exposing **(*S*)-71** to these reaction conditions yielded a slightly more promising result **(Table 3.2, entry 2)**, with evidence for the formation of the aldol, aldol-Tishchenko product **(*S*)-102** present in the ^{1}H NMR spectrum of the crude reaction mixture. When we isolated this compound, we were surprised to that it was the auxiliary-free compound that was obtained. This would suggest the auxiliary was susceptible to degradation on the column, as it was the non-cleaved compound which appeared in the ^{1}H NMR spectrum of the crude reaction. This result was consistent with what was observed during attempts to purify the starting material **(*S*)-71**, further demonstrating the instability of compounds of this nature.



103

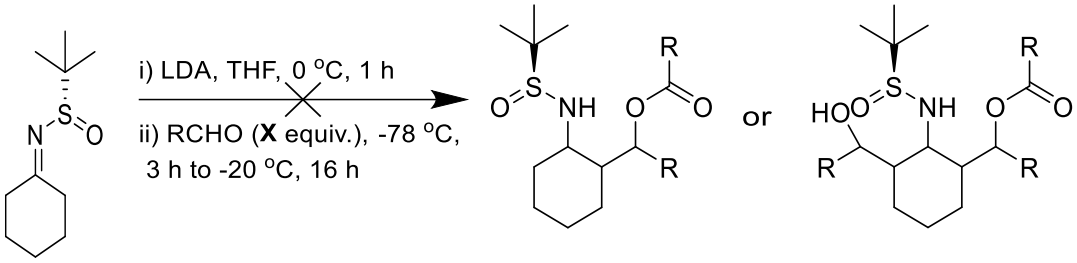
26%, 68:27:5 *dr*

Figure 3.15. Auxiliary free aldol, aldol-Tishchenko product **103**

Next, attempts were made to improve on the moderate level of diastereoselectivity achieved in these reactions. Firstly, the temperature of the Tishchenko step was reduced from -20 °C to -45°C **(Table 3.2, entry 3)**. It is known that at -78 °C, the Tishchenko step fails to occur, however, it was hoped that -45 °C would allow for the Tishchenko step to occur and also improve the diastereoselectivity of the reaction. Disappointingly, analysis of the ^{1}H NMR spectrum of the crude reaction mixture confirmed no aldol, aldol-Tishchenko product was formed at this temperature, and instead a complex mixture of unidentified compounds was evident. Attempts to isolate and identify any of these products proved difficult. We then investigated lowering the equivalents of LDA used **(Table 3.2, entries 4 & 5)**. Whilst the desired aldol, aldol-Tishchenko product **(*S*)-102** was evident in both reactions, a decrease in yield and diastereoselectivity was also observed. The absolute stereochemistry of **103** was not determined.

Finally, we also investigated the use of aliphatic aldehydes in this reaction. Pivaldehyde and the less sterically encumbered isobutyraldehyde were examined in an attempt to establish a protocol for an aldol-Tishchenko or aldol, aldol-Tishchenko reaction of **(*S*)-71**. Disappointingly however, after various reaction attempts, employing different reaction conditions each time, no evidence suggested **(*S*)-71** was not amenable to aldol-Tishchenko or aldol, aldol-Tishchenko reactions with aliphatic aldehydes **(Table 3.3)**.

Table 3.3. Attempted aldol-Tishchenko and aldol, aldol-Tishchenko reaction of **(*S*)-71** with aliphatic aldehydes



(*S*)-*71* **(*S*)-104** **(*S*)-105**



106 **107**

Pivaldehyde Isobutyraldehyde

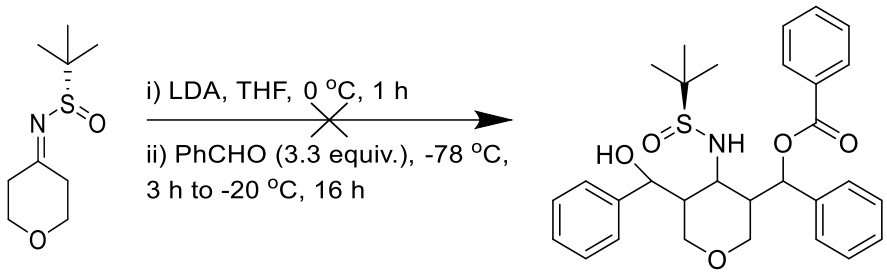
Entry	LDA (equiv.)	Aldehyde R =	Aldehyde (equiv)	Desired product[a]
1	0.8	$C(CH_3)_3$	2.2	**(*S*)-104**
2	0.8	$CH(CH_3)_2$	2.2	**(*S*)-104**
3	0.8	$C(CH_3)_3$	3.3	**(*S*)-105**
4	0.8	$CH(CH_3)_2$	3.3	**(*S*)-105**
5	1.1	$C(CH_3)_3$	2.2	**(*S*)-104**
6	1.1	$CH(CH_3)_2$	2.2	**(*S*)-104**
7	1.1	$C(CH_3)_3$	3.3	**(*S*)-105**
8	1.1	$CH(CH_3)_2$	3.3	**(*S*)-105**

[a] No evidence of desired compound in the ^1H NMR spectrum of the crude reaction mixture

Due to the fact six-membered cyclic compounds are ubiquitous in natural products and bioactive molecules,[67] coupled with the difficulties experienced using **(*S*)-71**, we decided to turn our attention towards alternative six-membered cyclic (*S*)-*tert*-butanesulfinyl imines. We began by exposing **(*S*)-73** to our standard aldol, aldol-Tishchenko reaction conditions. A

complex mixture was observed in the ^{1}H NMR spectrum of the crude reaction mixture in both cases. No evidence to suggest the formation of aldol, aldol-Tishchenko product was present.

Table 3.4. Attempted aldol, aldol-Tishchenko reaction of **(*S*)-73**

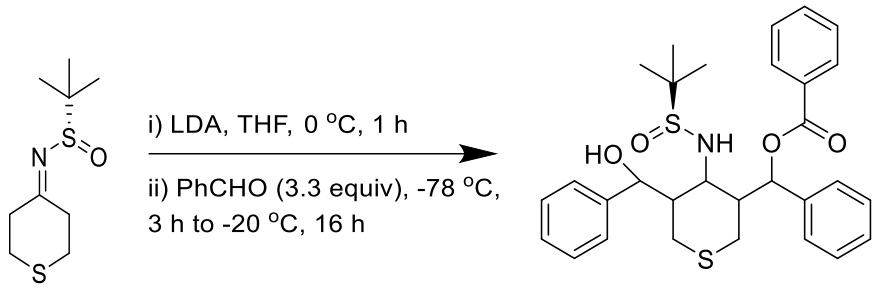


(*S*)-73 **(*S*)-108**

Entry	LDA (equiv.)
1	0.8
2	1.1

Pleasingly, we had slightly more success when we examined the sulfur analogue **(*S*)-75**. Exposing this substrate to our standard reaction conditions using benzaldehyde as an aldol acceptor yielded the target 3-amino-1,5-diol derivative, albeit in a low yield of 23% and a 50:50 diastereomeric ratio.

Table 3.5. Aldol, aldol-Tishchenko reaction of **(*S*)-75**



(*S*)-75 **(*S*)-109**

Entry	LDA (equiv.)	Yield	*dr*
1	0.8	-[a]	-[a]
2	1.1	23%	50:50

[a] No evidence of desired compound in the ^{1}H NMR spectrum of the crude reaction mixture

Again, we examined the use of aliphatic aldehydes **106** and **107** in attempted aldol-Tishchenko and aldol, aldol-Tishchenko reactions of **(*S*)-75**, mimicking the reaction conditions outlined in **Table 3.3**. However, disappointingly we had little success in these reactions. For this reason, we decided to turn our attention towards the effect of reducing the ring size of **(*S*)-68** by one carbon, and next focused our attention on cyclobutanone analogue **(*S*)-69**.

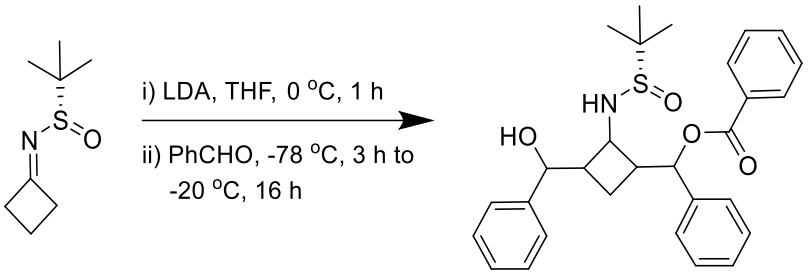
3.8.5 Aldol, aldol-Tishchenko reaction of (*S*)-*N*-cyclobutylidene-2-methylpropane-2-sulfinamide

The cyclobutane moiety was recently described as a prominent member of the medicinal chemist's toolbox.[68] Several factors contriubute to its use in medicinal chemistry including increased conformational restriction and increased metabolic stability. Drug candidates containing the cyclobutane moiety include antivirals, anti-cancer agents and autoimmune disease agents.[69-71] Efficient methods to furnish highly functionalised cyclobutane derivatives are required. Currently, methods to access enantioenriched amino alcohol derivatives of cyclobutane are rare.[72-74]

The cyclobutanone derived (*S*)-*tert*-butanesulfinyl imine **(*S*)-69** was easily prepared in a moderate yield of 53% using our standard reaction conditions. Pleasingly, exposing **(*S*)-69** to our aldol, aldol-Tishchenko reaction conditions gave the corresponding 3-amino-1,5-diol derivative **(*S*)-110** in a moderate yield of 38% and diastereomeric ratio of 75:25. Although the level of diastereoselectivity was significantly lower than that observed for the cyclopentanone

derivatives, it was possible to isolate both diastereoisomers in high purity. Attempts were made to improve on the level of diastereoselectivity observed in this reaction. Decreasing the equivalents of LDA disappointingly lead to a decrease in the *dr* observed for this reaction.

Table 3.6. Aldol, aldol-Tishchenko reaction of **(*S*)-69**



(*S*)-69 **(*S*)-110**

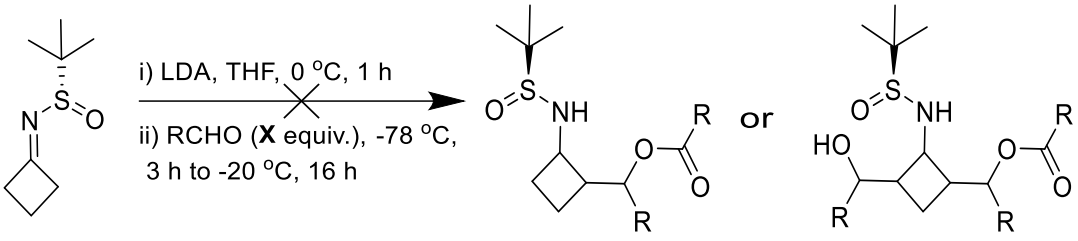
Entry	LDA (equiv.)	Yield	*dr*
1	0.8	-[a]	59:41
2	1.1	38%	75:25

[a] Not isolated

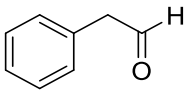
Unfortunately, as with many compounds of this type, these compounds proved impossible to crystallise and so the absolute stereochemistry of the major disastereomer of **(*S*)-110** could not be determined.

We also investigated lowering the equivalents of benzaldehyde used in an attempt to promote an aldol-Tishchenko reaction. However, only evidence of aldol, aldol-Tishchenko product **(*S*)-110** was evident in the ^{1}H NMR spectrum of the crude reaction mixture when 2.2 equivalents were used. Additionally, as with previously discussed cyclic (*S*)-*tert*-butanesulfinyl imines, we also investigated the use of aliphatic aldehydes with this substrate. For this substrate however, in addition to the reagents and reaction conditions used previously (**Table 3.3**), we also investigated the use of phenyl acetaldehyde **113 (Table 3.7)**. No reaction yielded any promising result with this substrate.

Table 3.7. Attempted aldol-Tishchenko and aldol, aldol-Tishchenko reaction of **(*S*)-71** with aliphatic aldehydes



(*S*)-69 **(*S*)-111** **(*S*)-112**



113

Phenylacetaldehyde

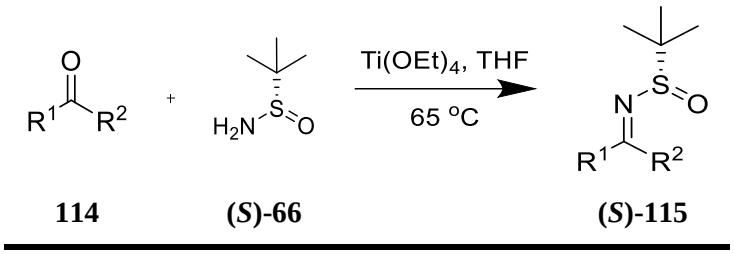
Entry	LDA (equiv.)	Aldehyde R =	Aldehyde (equiv)
1	0.8	$C(CH_3)_3$	2.2
2	0.8	$CH(CH_3)_2$	2.2
3	0.8	CH_2Ph	2.2
4	0.8	$C(CH_3)_3$	3.3
5	0.8	$CH(CH_3)_2$	3.3
6	0.8	CH_2Ph	3.3
7	1.1	$C(CH_3)_3$	2.2
8	1.1	$CH(CH_3)_2$	2.2
9	1.1	CH_2Ph	2.2
10	1.1	$C(CH_3)_3$	3.3
11	1.1	$CH(CH_3)_2$	3.3
12	1.1	CH_2Ph	3.3

[a] No evidence of desired compound in the ^1H NMR spectrum of crude reaction mixture

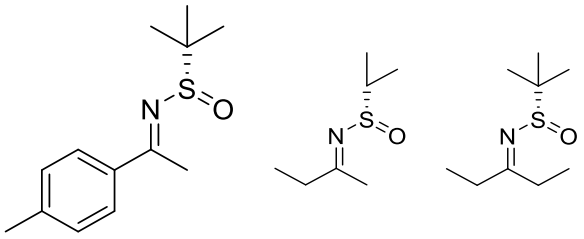
3.9 Tandem aldol, aldol-Tishchenko reaction of acyclic (*S*)-*tert*-butanesulfinyl imines for the formation of multiple contiguous chiral centres

3.9.1 Synthesis of acyclic (*S*)-*tert*-butanesulfinyl imines

Having had mixed success with the cyclic (*S*)-*tert*-butanesulfinyl imines, we next decided to focus our attention on the reaction of acyclic substrates in our aldol, aldol-Tishchenko reaction. Gratifyingly, synthesis of acyclic (*S*)-*tert*-butanesulfinyl imines proved significantly less challenging than the cyclic analogues. Five versatile acyclic (*S*)-*tert*-butanesulfinyl imines were synthesised using the standard reaction conditions outlined previously **(Scheme 3.41)**, in moderate to excellent yields (up to 80%).



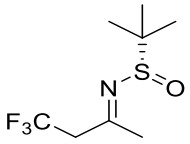
114 **(*S*)-66** **(*S*)-115**



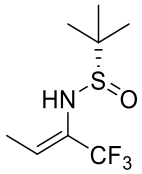
(*S*)-116 61%

(*S*)-117 57%

(*S*)-118 80%



(*S*)-119 51%



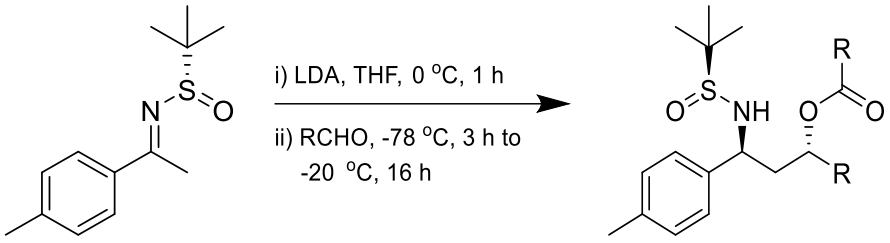
(*S*)-120 68%

Scheme 3.41. Synthesis of acyclic (*S*)-*tert*-butanesulfinyl imine

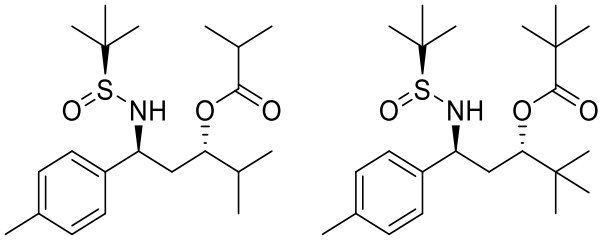
Aryl- and alkyl-substituents were well tolerated within this reaction. Pleasingly, trifluoromethyl-substituted ketones could also be converted to the corresponding (*S*)-*tert*-butanesulfinyl imines **(*S*)-119** and **(*S*)-120**. The aza-enol tautomer of **(*S*)-120** was the only observed product. Additionally, these substrates were amenable to purification by column chromatography and no issues associated with degradation were observed.

3.9.2 Aldol-Tishchenko reaction of *p*-methylacetophenone derived (*S*)-*tert*-butanesulfinyl imine

Initially, **(*S*)-116** was synthesised in order to perform a test reaction, generating a compound prepared by a previous member of the group.[52] Exposure of this substrate to the aldol-Tishchenko reaction conditions previously optimised allowed access to two 1,3-amino alcohol derivatives in moderate yields and excellent levels of diastereoselectivity **(Scheme 3.42)**.



(*S*)-116

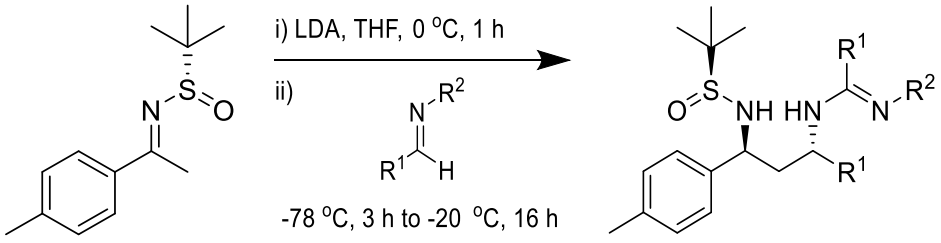


(*S,S*)-121 48%, 91:9 *dr*

(*S,S*)-122 63%, 98:2 *dr*

Scheme 3.42. Aldol-Tishchenko reaction of **(*S*)-116**

We next investigated manipulating our aldol-Tishchenko methodology to access a range of *anti*-1,3-diamines. We envisaged the use of aldimines as 'aldol acceptors' in our aldol-Tishchenko reaction would result in a novel method to access a range of enantio- and diastereoenriched *anti*-1,3-diamnes **(Scheme 3.43)**.[75-77]

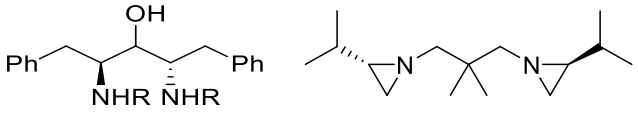


(*S*)-116

Scheme 3.43. Envisaged synthesis of 1,3-diamines *via* a modified aldol-Tishchenko reaction

The 1,3-diamine scaffold represents a highly valuable building block in organic synthesis and is widely used in the synthesis of complex bioactive molecules and APIs, for example, anti-HIV drugs.[38] Additionally, numerous asymmetric transformations, including transition metal

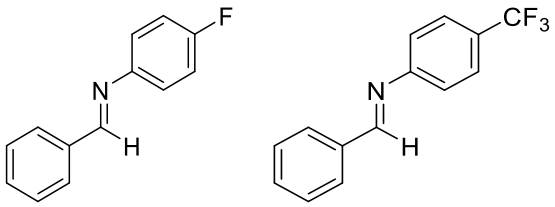
catalysed transformations, use 1,3-diamines as chiral ligands due to their potential to act as bidentate ligands **(Figure 3.16)**.[65]



(*S,S*)-123 **(S,S)-124**

Figure 3.16. Bioactive molecules and chiral ligands containing the 1,3-diamine motif

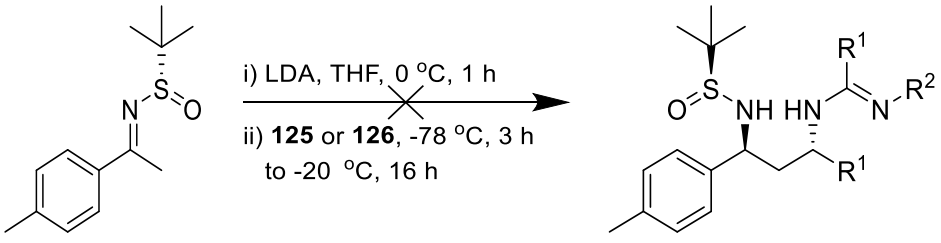
Two aldimine substrates were chosen for our initial test reactions and these compounds were synthesised by a post-doctoral researcher within our group, Dr David Jones **(Figure 3.17)**. Due to the relatively low electrophilicity of aldimines when compared to aldehydes, electron withdrawing substituents were incorporated in order to increase the reactivity of the aldimines employed, at least at the aldol stage.



125 **126**

Figure 3.17. Aldimines containing electron withdrawing substituents

Disappointingly, when these reagents were exposed to the reaction conditions outlined in **Scheme 3.44** there was no evidence to suggest formation of 1,3-diamine derivatives. Due to the fact only starting material was recovered from these reactions, we decided to focus our attention on other avenues of interest.

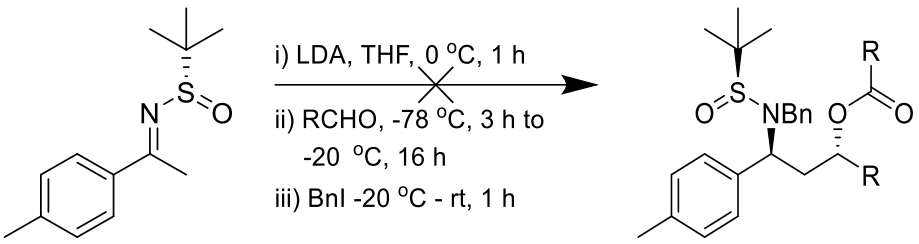


(*S*)-116

Scheme 3.44. Aldol, aldol-Tishchenko reaction using aldimines as aldol acceptors

Finally, with this substrate we also investigated an alternative reaction quench. We questioned if adding an electrophilic reagent to the reaction mixture immediately before work-up would allow us to trap the nitrogen anion, and concurrently introduce additional functionality to our 1,3-amino alcohol derivatives. We examined the consequence of adding one equivalent of BnI

to the reaction mixture at -20 °C and allowing the reaction warm to rt over 1 h **(Scheme 3.45)**. However, upon work up only **(*S,S*)-121** and **(*S,S*)-122** were evident.



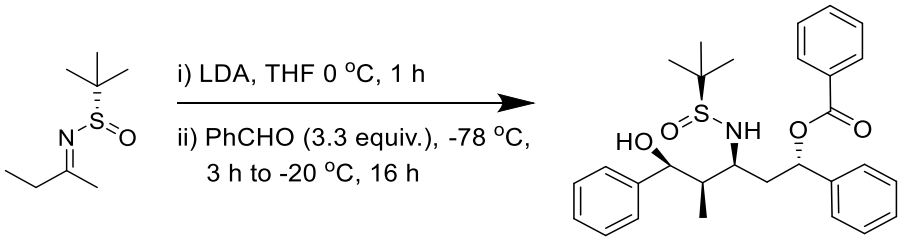
(*S*)-116

Scheme 3.45. Alternative reaction quench

Subsequently, we focused our attention on the aldol, aldol-Tishchenko reaction of acyclic (*S*)-*tert*-butanesulfinyl imines.

3.9.3 Aldol, aldol-Tishchenko reaction of butanone derived (*S*)-*tert*-butanesulfinyl imines

The initial test reactions using **(*S*)-117** were conducted by another member of the group, however the aim of the work described herein was to expand upon preliminary results obtained.[65] The use of **(*S*)-117** in an aldol, aldol-Tishchenko reaction also posed questions associated with regioselectivity. Clearly possessing two possible sites for deprotonation, we wondered whether the Tishchenko reaction would occur at the kinetically favoured methyl carbon or the thermodynamically favoured methylene carbon. We were pleased to observe the aldol, aldol-Tishchenko reaction of **(*S*)-117** with benzaldehyde was completely regioselective for the more sterically accessible methylene site, with no evidence of other regioisomers observed **(Scheme 3.46)**. A moderate yield and diastereoselectivity was obtained for this reaction.



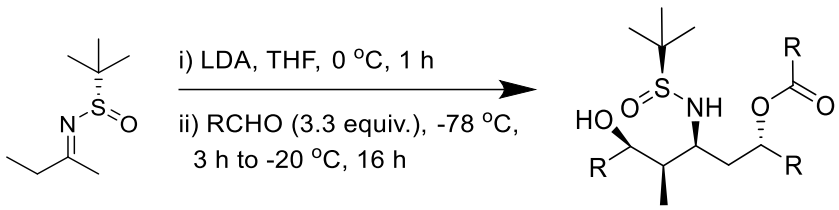
(*S*)-117 **(*S,S,R,S,S*)-127**

42%, 87:13 *dr*

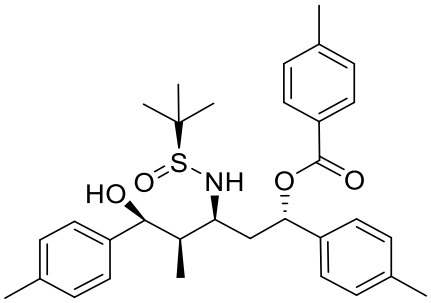
Scheme 3.46. Aldol, aldol-Tishchenko reaction of **(*S*)-116**

Encouraged by this result, we next explored the substrate scope of this transformation. A range of substituted benzaldehydes were successfully employed in this transformation, including those bearing alkly-substituents and halogens. 3-amino-1,5-diol derivatives were synthesised

in increased yield and diastereoselectivity when the steric bulk of the *p*-alkyl substituted benzaldehydes was increased **(Scheme 3.47)**.

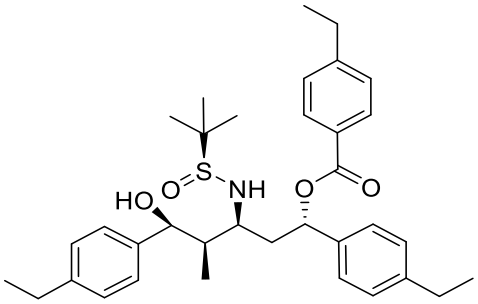


(*S*)-116



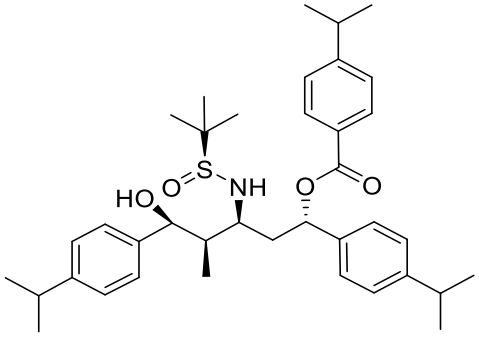
(*S*,*S*,*R*,*S*,*S*)-128

35%, 88:12 *dr*



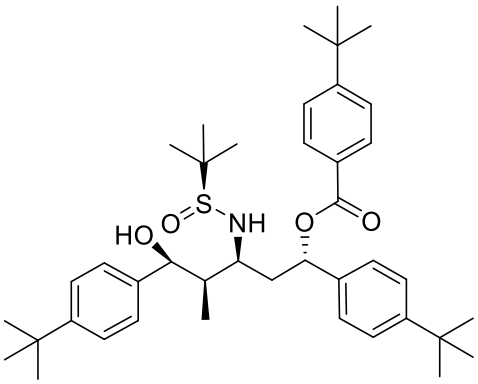
(*S*,*S*,*R*,*S*,*S*)-129

38%, 89:11 *dr*



(*S*,*S*,*R*,*S*,*S*)-130

37%, 80:20 *dr*

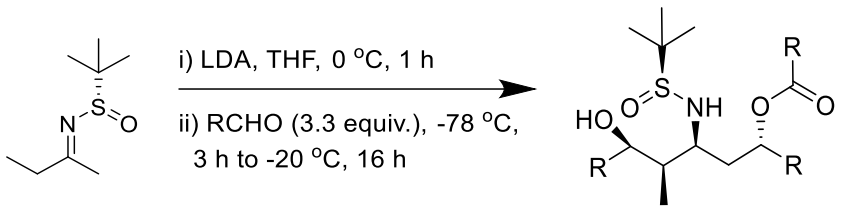


(*S*,*S*,*R*,*S*,*S*)-131

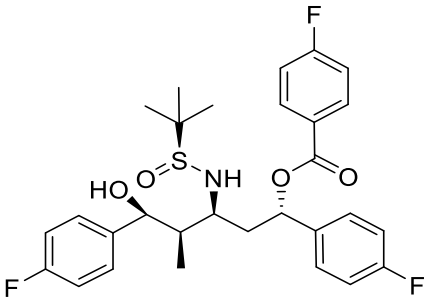
43%, 97:3 *dr*

Scheme 3.47. Aldol, aldol-Tishchenko reaction using p-alkyl-substituted benzaldehydes

However, the greatest levels of enantioselectivity (up to > 99:1) were recorded when halogen-substituted benzaldehydes were used **(Scheme 3.48)**. The brominated analogue **(*S*,*S*,*R*,*S*,*S*)-135** was the exception to this, with a slight decrease in *dr* observed. Excellent diastereoselectivity was maintained when the position of the substituent was moved from the *p*-position to the *m*-position in the cases of chlorobenzaldehyde being employed as an aldol acceptor.

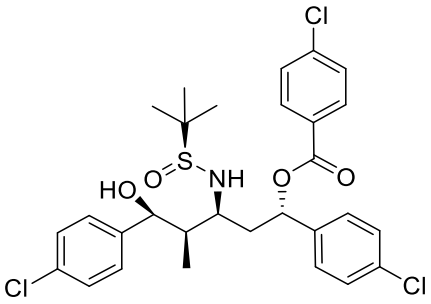


(*S*)-116



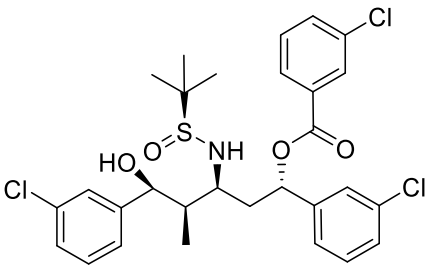
(*S*,*S*,*R*,*S*,*S*)-132

55%, 94:6 *dr*



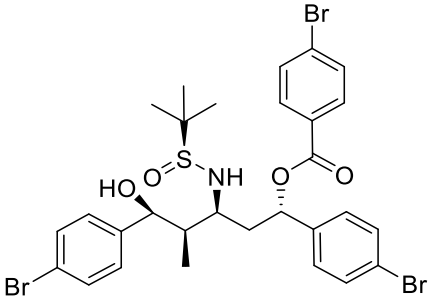
(*S*,*S*,*R*,*S*,*S*)-133

55%, >99:1 *dr*



(*S*,*S*,*R*,*S*,*S*)-134

42%, > 99:1 *dr*



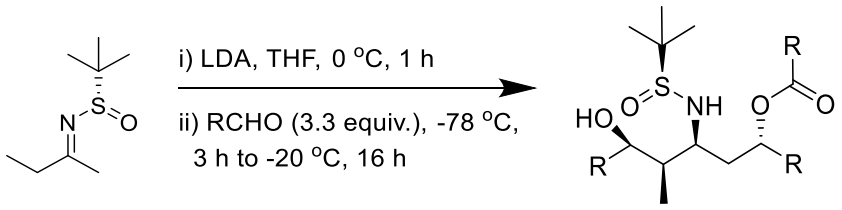
(*S*,*S*,*R*,*S*,*S*)-135

12%, 90:10 *dr*

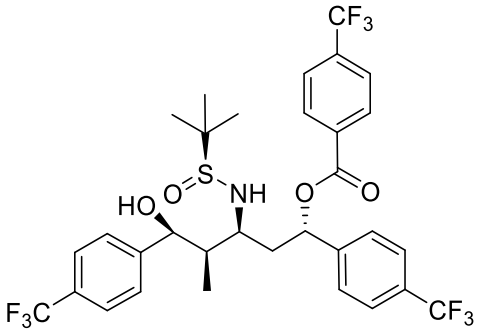
Scheme 3.48. Aldol, aldol-Tishchenko reaction using halogenated bnzaldehydes

Additional functional groups were also tolerated within this methodology **(Scheme 3.49)**. However, a significant decrease in diastereoselectivity was observed when *p*-trifluoromethylbenzaldehyde was used as an aldol acceptor **(*S*,*S*,*R*,*S*,*S*)-136**. This was an unexpected result and was not observed when this reagent was previously combined with other (*S*)-*tert*-butanesulfinyl imines. Pleasingly, excellent diastereoselectivity was seen once again when *p*-trifluoromethoxybenzaldehyde was used as an aldol acceptor **(*S*,*S*,*R*,*S*,*S*)-137**. One substrate of particular importance within the scope of this reaction was the 3-amino-1,5-diol derivative **(*S*,*S*,*R*,*S*,*S*)-138** , bearing a nitrile substituent. Whilst the yield was poor and the diastereomeric ratio achieved in this reaction was modest, the fact an aldehyde containing a substituent susceptible to reduction was tolerated is noteworthy. Access to substrates

containing these functionalities is facilitated by the *in-situ* intramolecular Tishchenko hydride transfer step, which circumvents the need for an external reductant, as would be the case in an Ellman type protocol, for example.[7, 78]

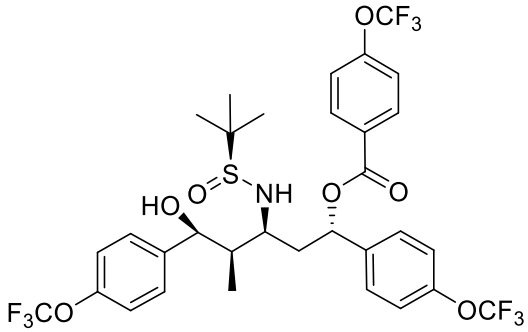


(*S*)-116



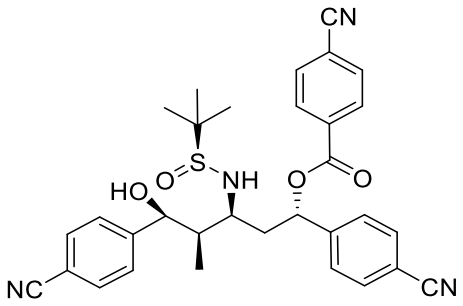
(*S,S,R,S,S*)-136

43%, 64:36 *dr*



(*S,S,R,S,S*)-137

52%, > 99:1 *dr*



(*S,S,R,S,S*)-138

14%, 84:16 *dr*

Scheme 3.49. Aldol, aldol-Tishchenko reaction of **(*S*)-116** with substituted benzaldehydes

To further probe the scope of this reaction, a range of heteroaromatic aldehydes were also examined as aldol acceptors. Firstly, due to the prevalence of the pyridine motif in natural products and bioactive molecules, 3-pyridine carboxaldehyde and 4-pyridine carboxaldehyde were examined **(Figure 3.16)**. Encouragingly, both reagents appeared to undergo the desired aldol, aldol-Tishchenko reaction, with evidence for the formation of the corresponding 3-amino-1,5-diol derivatives evident in the ^{1}H NMR spectrum of each crude reaction mixture.

However, after numerous purification and derivatisation attempts, including cleaving both Ellman's auxiliary and the ester moiety, neither compound could be isolated pure.

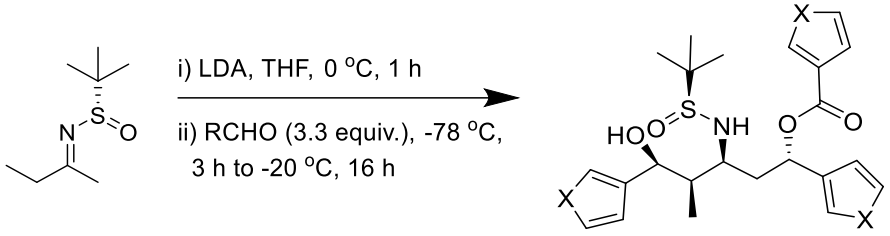


139 **140**

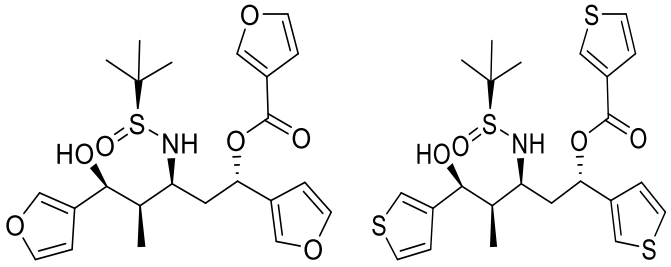
3-pyridinecarboxaldehyde 4-pyridinecarboxaldehyde

Figure 3.16. Pyridine carboxaldehydes

Not discouraged by this, we next examined the use of furan and thiophene derived aldehydes. In these reactions it was noted that the position of the heteroatom relative to the aldehyde functionality was important in the aldol, aldol-Tishchenko reaction. Neither the 2-substiuted isomer of the furan or the thiophene derived aldehyde resulted in the formation of any 3-amino-1,5-diol derivative. However, when 3-thiophene carboxaldehyde and 3-furaldehyde were employed, the corresponding aldol, aldol-Tishchenko product could be isolated in each case **(Scheme 3.50)**. Moderate yields of both **(*S,S,R,S,S*)-141** and **(*S,S,R,S,S*)-142** were obtained. However, it was not possible to determine the *dr* for the synthesis of **(*S,S,R,S,S*)-141** due to overlapping signals in the ^{1}H NMR spectrum of the crude reaction mixture.



(*S*)-116



(*S,S,R,S,S*)-141 **(*S,S,R,S,S*)-142**

43% single isomer, *dr* nd 43%, 90:10 *dr*

Scheme 3.50. Aldol, aldol-Tishchenko of **(*S*)-116** with heteroaryl aldehydes

A number of other aldehydes also proved incompatible with the aldol, aldol-Tishchenko reaction conditions employed. These included aldehydes previously examined, such as *p*-nitro- **100** and *p*-methyl ester **101** benzaldehydes.

In all cases, the diastereomeric ratio was determined using the characteristic doublet of doublets of the ester proton, present in the ^{1}H NMR spectrum of the crude reaction mixture **(Figure 3.17)**.

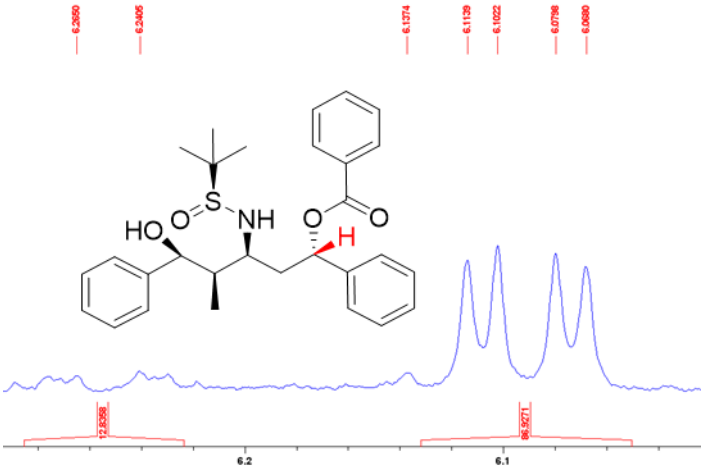
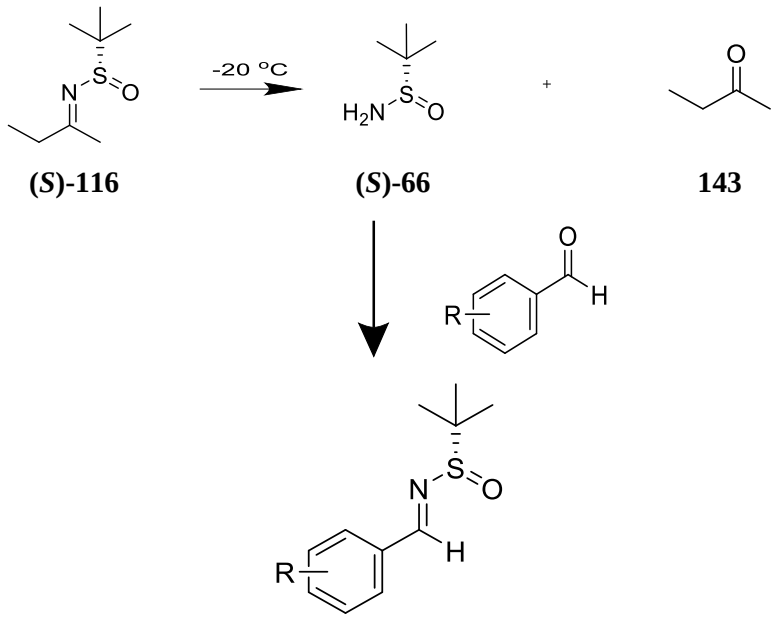


Figure 3.17. Determination of *dr* of **(*S*,*S*,*R*,*S*,*S*)-127**

It is suspected the moderate yields achieved for these substrates were as a result of the formation of two side products during the reactions of **(*S*)-116**. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture in all cases confirmed the presence of a singlet peak *circa*. 8.5 ppm **(Figure 3.18)**. This is indicative of the formation of a sulfinyl aldimine side product. It is suspected that during the Tishchenko step, when the reaction mixture was warmed to -20 °C, degradation of **(*S*)-116** occurred, generating the butanone **143** and (*S*)-*tert*-butanesulfinamide **(*S*)-66**. Subsequent reaction of the latter with the aldehyde present in the reaction mixture is thought to have generated the corresponding sulfinyl aldimine in each case **(Scheme 3.51)**.



Scheme 3.51. Formation of sulfinyl aldimine

Additionally, a singlet peak at *circa* 4.6 ppm is also present in the ^{1}H NMR spectrum of the crude reaction mixtures **(Figure 3.18)**. This chemical shift is characteristic of benzylic protons and would suggest reduction of the aldehyde to the corresponding benzylic alcohol **146** is taking place during the reaction.

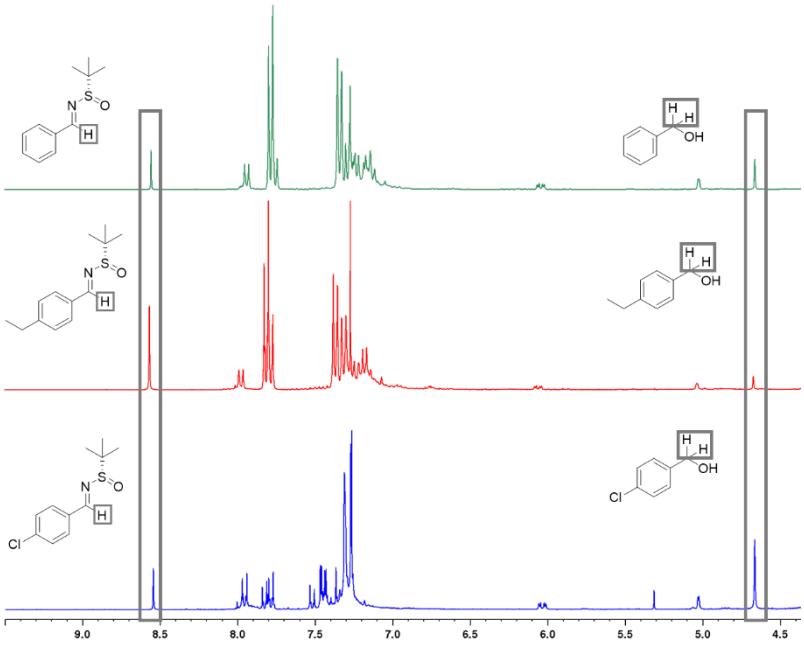
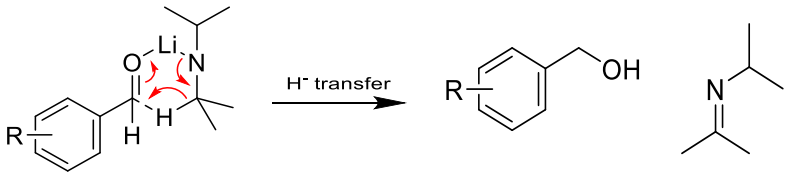


Figure 3.18. Side products formed during aldol, aldol-Tishchenko reaction of **(*S*)-116**

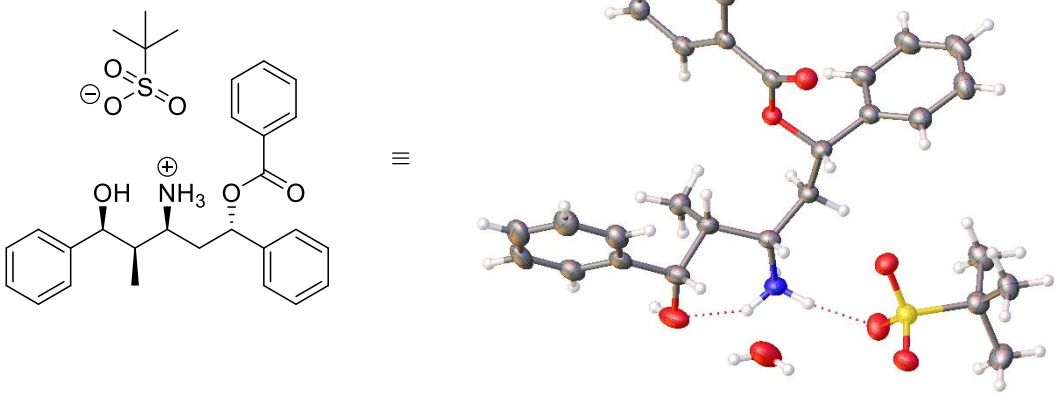
There is precedence in the literature for the LDA-mediated reduction of aldehydes and ketones, in a reaction analogous to a Meerwein-Ponndorf-Verley reaction.[79] Using this analogy, it is plausible to suggest reduction of the aldehyde occurs *via* a six-membered transition state in which a hydride is transferred from LDA to the aldehyde, and in a concerted process, the LDA is oxidised to the corresponding imine **147 (Scheme 3.52)**.



145 **146** **147**

Scheme 3.52. Reduction of benzaldehyde *via* Meerwein-Ponndorf-Verley type reaction

These substrates proved largely incompatible with crystallographic studies, with most failing to grow adequate crystals for X-ray analysis. However, attempts to grow crystals of **(*S*,*S*,*R*,*S*,*S*)-127** *via* slow evaporation of toluene resulted in the formation of degradation product **(*S*,*R*,*S*,*S*)-148**. This species proved more amenable to crystallographic studies, and gratifyingly, the absolute stereochemistry of the 2-butanone derived 3-amino-1,5-diol derivatives could be determined **(Figure 3.19)**.

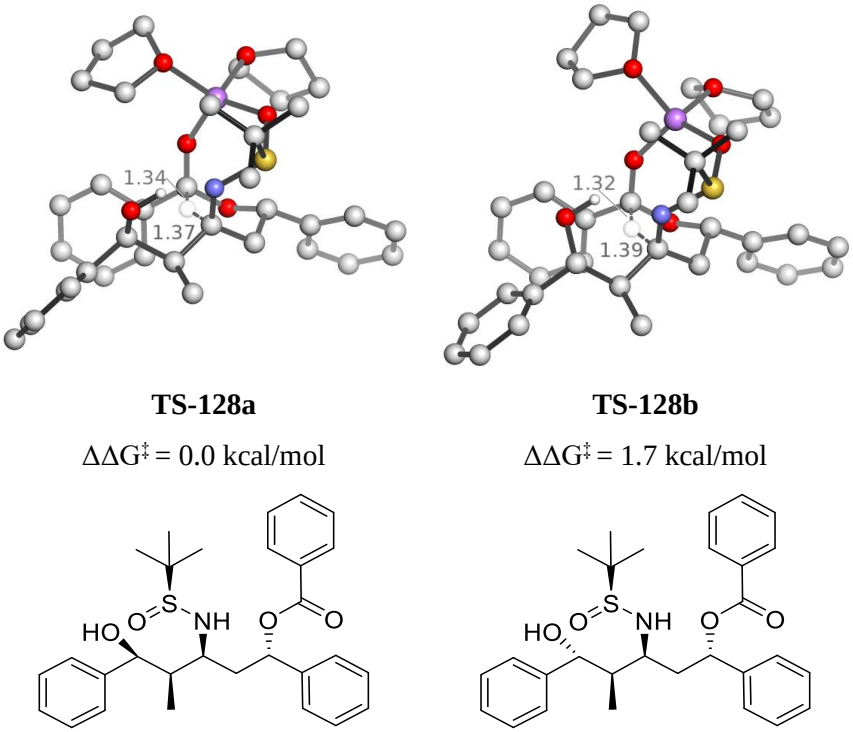


(*S*,*R*,*S*,*S*)-148

Figure 3.19. X-ray crystal structure of **(*S*,*R*,*S*,*S*)-148**

Pleasingly, the stereochemistry established for the butanone series was consistent with that determined for other substrates in this work, namely those derived from 2,2-dimethylcyclopentanone and cycloheptanone. Once again, to explain the observed stereochemical outcome of this reaction, DFT calculations were conducted by our collaborators Dr Aneta Turlik and Prof Ken Houk at UCLA. As previously discussed, the stereodetermining step in this transformation is the irreversible intramolecular hydride transfer

step. As all prior steps are reversible, it is possible to rationalise the stereochemistry of the major diastereomer by determining the relative energies of the transition states for the Tishchenko step. The energy difference calculated between the two lowest energy transition states **(Figure 3.20)** was determined to be 1.7 kcal/mol.

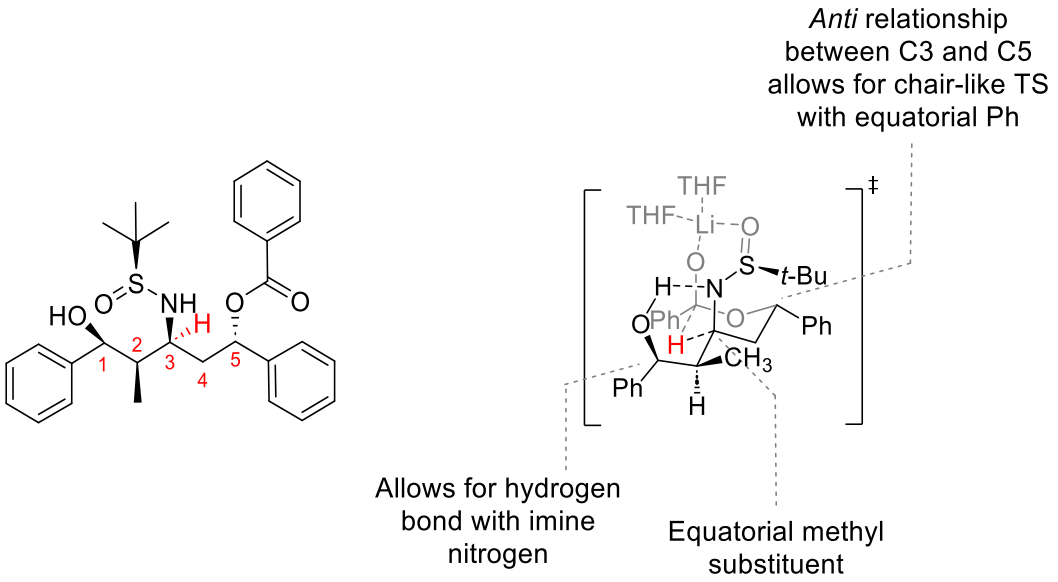


TS-128a **TS-128b**

$\Delta\Delta G^{\ddagger}$ = 0.0 kcal/mol $\Delta\Delta G^{\ddagger}$ = 1.7 kcal/mol

Figure 3.20. TS energies for experimentally observed isomers of **128**

Summarised in **Figure 3.21**, the DFT calculations were consistent with the absolute stereochemistry of ***(S,R,S,S)*-148** determined by X-ray crystallography. The lowest energy TS calculated for the butanone series suggested an *anti*- relationship between the substituents of C3 and C5, presumably to avoid any high energy steric interactions between the *tert*-butyl group of the sulfinyl imine and the bulky phenyl substituent on C5. This steric interaction also rationalises the phenyl substituent of C1 existing in an equatorial position in the chair-like TS. For the lower energy isomer, the hydroxyl group at C1 was determined to be *syn*- to the sulfinyl imine, facilitating H-bonding between the N of the imine and the hydroxyl hydrogen. The second lowest energy TS determined computationally, presumably the minor isomer observed experimentally, differed only by having the opposite stereochemistry at this position.



(*S*,*S*,*R*,*S*,*S*)-127

Figure 3.21. Factors affecting stereoselectivity in AAT reaction of **(*S*)-116**

Additionally, analysis of the vicinal coupling constants in the ^{1}H NMR spectrum of the 2-butanone derived 3-amino-1,5-diol derivatives is in agreement with the stereochemistry determined by X-ray crystallography. The Karplus equation (or Karplus curve) is used to describe the relationship between observed vicinal coupling constants and the dihedral angle between the relevant coupled protons.[80] It indicates that coupling constants will be maximal for protons in an *anti*- or eclipsed relationship i.e. at a dihedral angle of either 0° or 180°, and at a minimum where the dihedral angle is 90°. The use of vicinal coupling constants for conformational analysis of acyclic systems is more difficult than cyclic systems due to the larger number of possible conformations. However, the assignment of relative configuration of aldol products is often made using the 'Stiles House' ^{1}H NMR method.[38] A prerequisite for this rule is that an intramolecular hydrogen-bond exists between the carbonyl oxygen and the hydroxyl proton, resulting in the formation of an intramolecular hydrogen-bonded six-membered structure.

The coupling constant observed between H-1 and H-2 in the ^{1}H NMR spectrum of **(*S*,*S*,*R*,*S*,*S*)-130** is sufficiently small, at only 1.9 Hz, to suggest that these protons are, indeed, *syn* to one another i.e. at a dihedral angle of 90°. For all other substrates, the H-1 appears as a broad singlet. This observation is consistent with a coupling between the H-1 and H-2 protons that is too small to be fully resolved (vanishingly small) for the respective compounds and supports the assignment of a *syn*- conformation of these hydrogen atoms.[81]

Analysis of the Newman projections of the hydrogen bonded *syn*-diastereomer is also in agreement with the observed vicinal coupling constants, and absolute stereochemistry as confirmed by X-ray crystallography. There are three possible staggered conformations (60°, 180° and 360°). In the case of hydrogen-bonded conformers, both have a gauche interaction between H-1 and H-2, which would correlate with the small vicinal coupling constant observed (1.9 Hz). By comparison, the non-hydrogen bonded conformer has an *anti*-relationship between H-1 and H-2, and thus a larger *J* value would be expected.

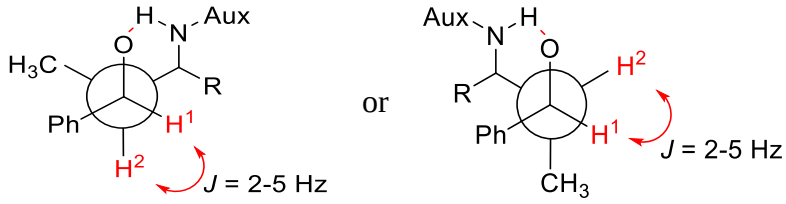
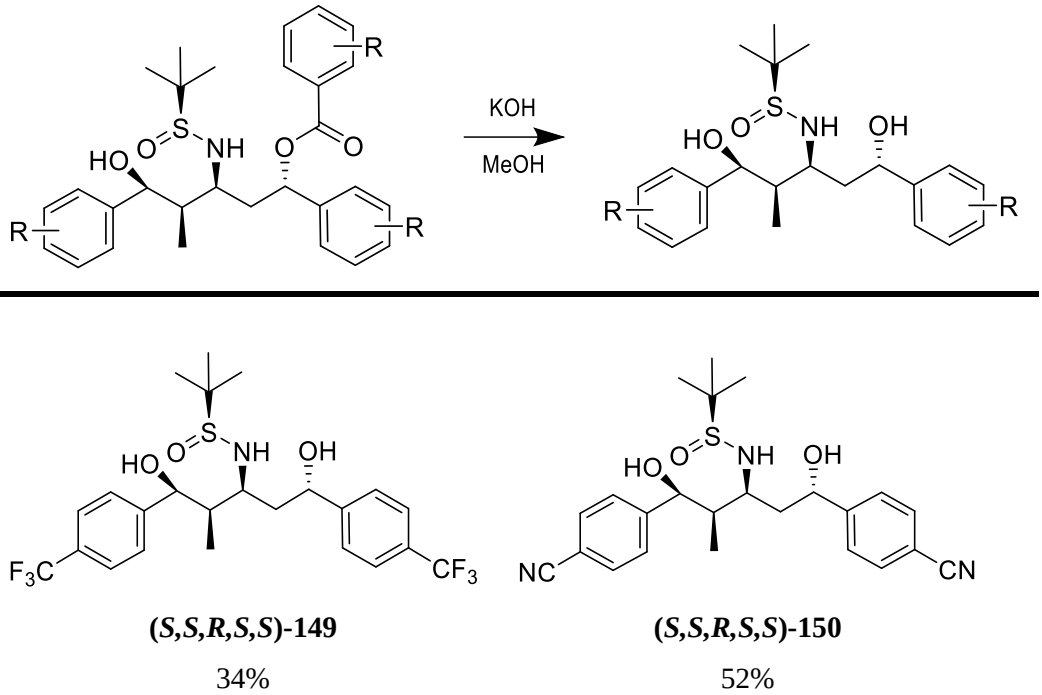


Figure 3.22. Staggered conformations for *syn*-diastereomer

Next, to probe the synthetic utility of the 3-amino-1,5-diol derivatives synthesised, we investigated cleavage of both the ester moiety and the (*S*)-*tert*-butanesulfinyl imine auxiliary. Pleasingly, exposure of two 3-amino-1,5-diol derivatives to methanolic KOH at room temperature allowed for the cleavage of the ester moiety, resulting in the formation of the 3-amino-1,5-*anti*-diols **(*S,S,R,S,S*)-149** and **(*S,S,R,S,S*)-150** in moderate yields **(Scheme 3.53)**.



(*S,S,R,S,S*)-149

34%

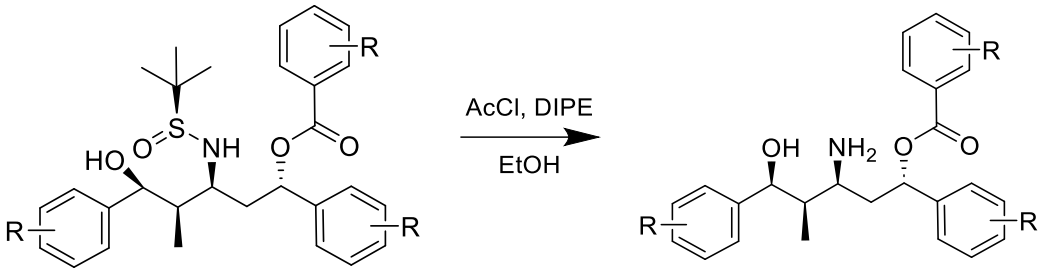
(*S,S,R,S,S*)-150

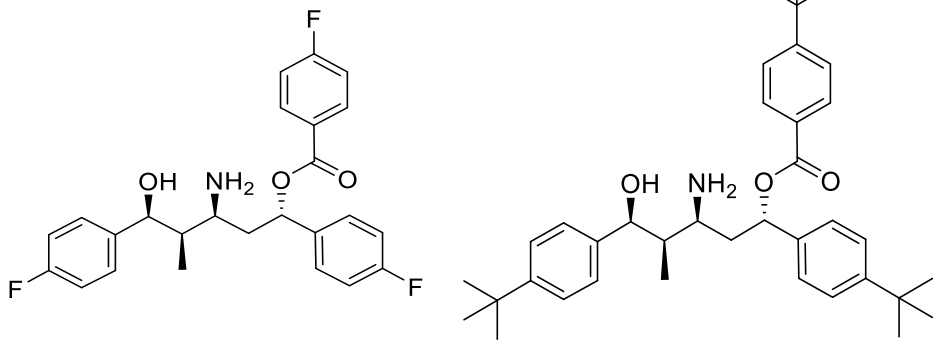
52%

Scheme 3.53. Cleavage of ester moiety

Subsequently, we investigated cleaving Ellman's auxiliary to allow access to the primary amine functionality. Following a method first reported by Qing and co-workers, removal of

the (*S*)-*tert*-butanesulfinyl imine could be achieved under mild reaction conditions without any loss of diastereomeric purity, to afford 3-amino-1,5-diol derivatives **(*S,R,S,S*)-151** and **(*S,R,S,S*)-152** in good to excellent yields **(Scheme 3.54)**.[82]



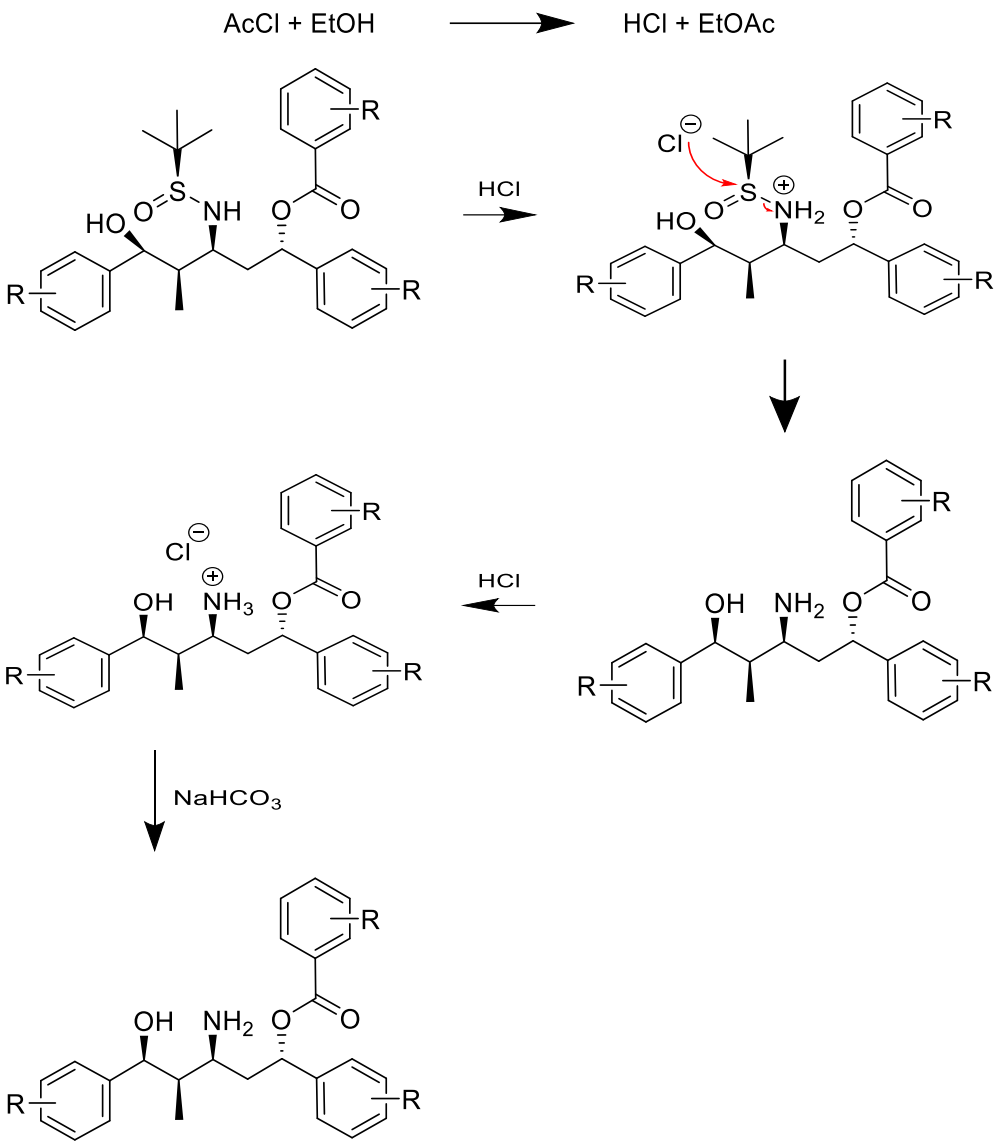


(*S,R,S,S*)-151 **(*S,R,S,S*)-152**

53% 76%

Scheme 3.54. Cleavage of Ellman's auxiliary

The cleavage reaction is likely initiated by the *in-situ* formation of anhydrous HCl *via* reaction of the EtOH with AcCl. After this, acid catalysed formation of sulfinyl iminium ion and subsequent collapse of this species results in the formation of the free amine. It is likely under these reaction conditions, this rapidly converts to an ammonium ion. Reaction of this with $NaHCO_3$ generates the free amine **(Scheme 3.55)**.



Scheme 3.55. Mechanism for the cleavage of Ellman's auxiliary under acidic conditions

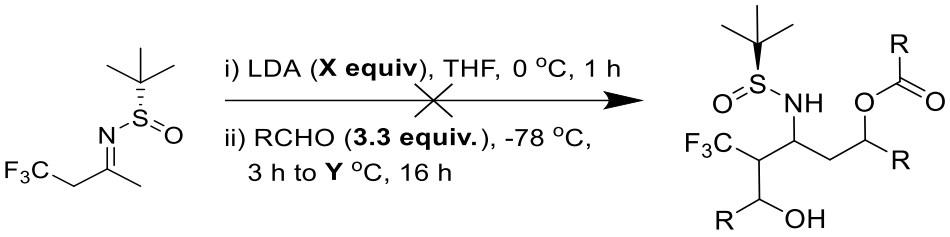
Finally, as for other substrates, attempts were made to expand the scope of this reaction to include the use aliphatic aldehydes as aldol acceptors in an aldol, aldol-Tishchenko reaction with **(*S*)-116**. To our disappointment, despite extensive efforts, no promising results emerged from these tests.

3.9.4 Aldol, aldol-Tishchenko reaction of fluorinated butanone derived (*S*)-*tert*-butanesulfinyl imines

Next, we turned our attention to alternative acyclic (*S*)-*tert*-butanesulfinyl imines. Due to the prevalence of substituting a methyl group for a trifluoromethyl substituent, especially in the realms of medicinal chemistry,[83] we first focused our attention on trifluoromethyl-substituted (*S*)-*tert*-butanesulfinyl imine **(*S*)-119**. Disappointingly, initially employing our standard aldol, aldol-Tishchenko reaction conditions, followed by a range of altered reaction conditions,

yielded no evidence of aldol. aldol-Tishchenko reaction taking place **(Table 3.8)**. In most cases, predominantly starting material was recovered from the reaction, although some unidentified side products were also present in some cases (one regioisomer of **(*S*)-153** is shown).

Table 3.8. Attempted aldol, aldol-Tishchenko reaction conditions for **(*S*)-119**

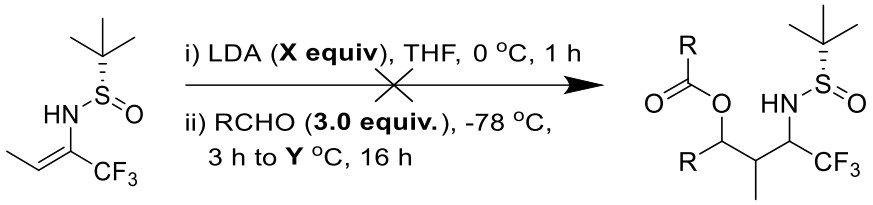


(*S*)-119 **(*S*)-153**

Entry	LDA (equiv.)	Aldehyde	Temperature (°C)
1	1.1	benzaldehyde	-20
2	1.1	*p*-fluorobenzaldehyde	-20
3	1.1	benzaldehyde	0
4	1.1	*p*-fluorobenzaldehyde	0
5	0.8	benzaldehyde	0
6	0.8	*p*-fluorobenzaldehyde	0
7	1.1	pivaldehyde	0
8	0.8	pivaldehyde	0
9	1.1	isobutyraldehyde	0
10	1.1	phenylacetaldehyde	0

Next, we investigated whether (*S*)-*tert*-butanesulfinyl imine **(*S*)-120** would be successful in an aldol-Tishchenko reaction. Various modifications were made to our standard aldol-Tishchenko reaction conditions in the hope of generating a highly functionalised 1,3-amino alcohol product **(Table 3.9)**. However, despite our best efforts, **(*S*)-120** proved to be an incompatible substrate for our aldol-Tishchenko reaction.

Table 3.9. Attempted aldol-Tishchenko reactions for **(*S*)-120**



(*S*)-120

Entry	LDA (equiv.)	Aldehyde	Temperature (°C)
1	1.1	benzaldehyde	0
2	0.8	benzaldehyde	0
3	1.1	pivaldehyde	0
4	0.8	pivaldehyde	0

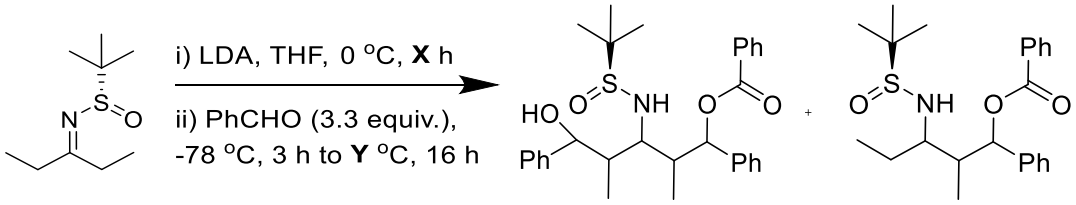
As discussed, the fluorinated (*S*)-*tert*-butanesulfinyl imines proved challenging substrates and for this reason, we next decided to examine the reactivity of a symmetric acyclic (*S*)-*tert*-butanesulfinyl imine.

3.9.5 Aldol, aldol-Tishchenko reaction of 3-pentanone derived (*S*)-*tert*-butanesulfinyl imine

3-Pentanone represents a fundamental building block in organic and natural product synthesis, and for this reason, we chose (*S*)-*tert*-butanesulfinyl imine **(*S*)-118** to initiate our investigations into developing an aldol, aldol-Tishchenko reaction protocol for symmetric acyclic (*S*)-*tert*-butanesulfinyl imines. We were aware of numerous potential challenges which might make this a difficult transformation to achieve, namely issues surrounding selectivity and competing reactions occurring at both α-positions. Additionally, it is documented in the literature that alkyl ketones other than methyl ketones are sluggish in aldol reactions. The aldol products resulting from these transformations are quick to undergo retro-aldol reactions.[84]

Nevertheless, we began our investigations by exposing **(*S*)-118** to our standard aldol, aldol-Tishchenko reaction conditions. We were pleased to see evidence for the formation of aldol, aldol-Tishchenko product **(*S*)-154,** although the major product of the reaction appeared to be aldol-Tishchenko product **(*S*)-155**. Next, we investigated if prolonging the reaction duration and increasing the reaction temperature for the Tishchenko step would promote the aldol, aldol-Tishchenko reaction. This resulted in a similar ratio of aldol, aldol-Tishchenko to aldol-Tishchenko product as what was previously observed.

Table 3.10. Aldol, aldol-Tishchenko reaction conditions attempted for **(*S*)-118**



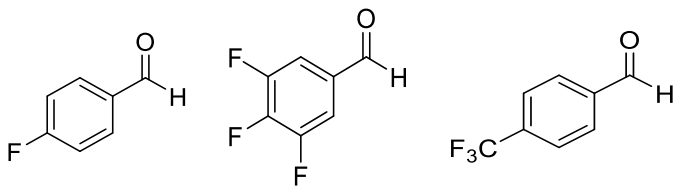
(*S*)-118 **(*S*)-154** **(*S*)-155**

Entry	Depronation time (h)	Tishchenko temperature (°C)	Product ratio[a]		Yield	
			AAT **(*S*)-154**	AT **(*S*)-155**	AAT **(*S*)-154**	AT **(*S*)-155**
1	1	-20	53 (72:28 *dr*)	47	-[b]	-[b]
2	3	0	51 (74:26 *dr*)	49	20%	26%

[a] Estimated using ^{1}H NMR spectrum of the crude reaction mixture

[b] Not isolated

To further improve the conversion to aldol, aldol-Tishchenko product observed in this reaction, we next turned our attention to the aldol acceptor. To promote the initial aldol steps occurring, it was important to choose an aldehyde which was sufficiently electrophilic to react with the less nucleophilic (*S*)-*tert*-butanesulfinyl imine **(*S*)-118**. However, it was also important to consider the subsequent Tishchenko step, where choice of a severely electron deficient aldehyde would be detrimental to the crucial hydride transfer step. We chose to initially investigate fluorine-substituted benzaldehydes, choosing three fluorinated benzaldehyde derivatives **(Figure 3.23)**.



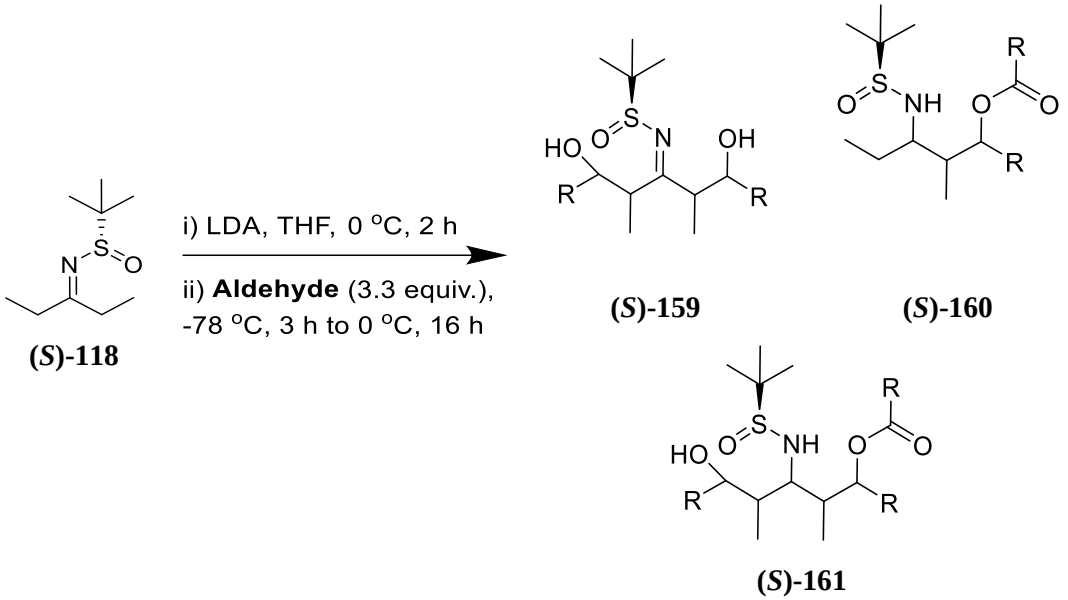
156 **157** **158**

Figure 3.23. Fluorinated benzaldehydes

We examined the propensity of these aldehydes to undergo aldol, aldol-Tishchenko reaction when exposed to our slightly altered reaction conditions. Interestingly, the results obtained were in sharp contrast to what we had observed when **(*S*)-117** was exposed to similar reaction conditions with the various aldehydes. In some cases, it was possible to isolate products of a

double aldol reaction **(*S*)-159**, aldol-Tishchenko reaction product **(*S*)-160** and aldol, aldol-Tishchenko reaction product **(*S*)-161 (Table 3.11)**.

Table 3.11. Attempted aldol, aldol-Tishchenko reaction of **(*S*)-118** with fluorinated benzaldehydes



(*S*)-118 **(*S*)-159** **(*S*)-160** **(*S*)-161**

Entry	Aldehyde	Yield		
		Diol	AT	AAT
1	**156**	**(S)-162** 30%	**(S)-163** 12%	**(*S*)-164** 8%
2	**157**	**(*S*)-165** 24%	-[a]	-[a]
3	**158**	**(*S*)-166** 28%	-[a]	**(S)-167** 4%

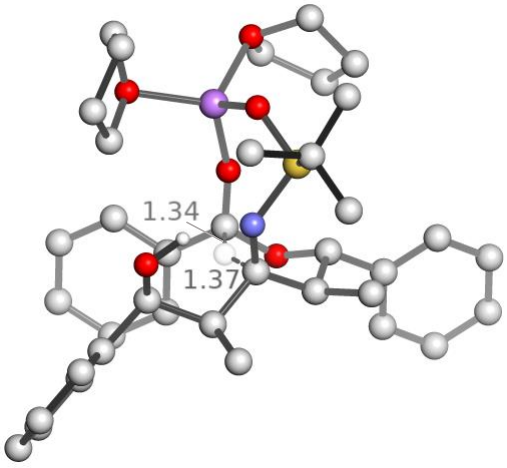
[a] No evidence of product formation in the ^{1}H NMR spectrum of the crude reaction mixture

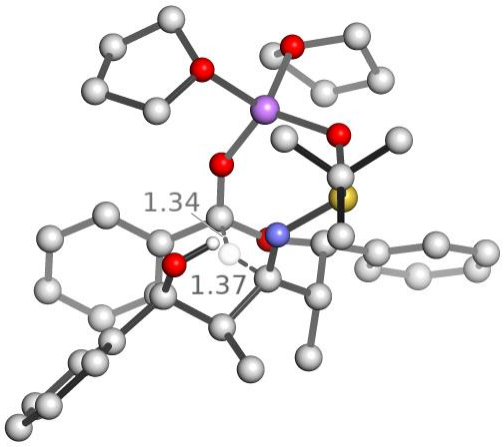
In order to explain the complex reactivity patterns we observed in these reactions, a number of factors must be considered. Firstly, the formation of aldol-Tishchenko product in the reaction of **(*S*)-118** with benzaldehyde **(Table 3.10, entry 2)** suggests an alternative reaction mechanism may be operative to that of the aldol, aldol-Tishchenko reaction of butanone-derived (*S*)-*tert*-butanesulfinyl imine **(*S*)-117**. It is possible that the Tishchenko hydride transfer step competes with a possibly sluggish second aldol reaction for this substrate, resulting in the formation of aldol-Tishchenko product. No evidence for the formation of diol

product was observed in this reaction, which may also suggest that once aldol or double aldol reaction occurs, the Tishchenko step is rapid and irreversible. However, when *p*-fluorobenzaldehyde **156** was employed as an aldol acceptor, all three reaction products could be isolated. A moderate yield of diol product was the major product **(Table 3.11, entry 1)**. This would suggest the aldol acceptor is sufficiently electron deficient to undergo the aldol reaction, however, the Tishchenko reaction is slow. This may possibly be due to the electronics of the aldehyde hindering the hydride transfer step. Only diol product was evident and isolated when 3,4,5-trifluorobenzaldehyde **157** was used as an aldol acceptor, again suggesting this aldehyde was too electron deficient to facilitate any hydride transfer step. Similarly, reaction of **(*S*)-118** with p-trifluoromethylbenzaldehyde **158** resulted mainly in the formation of diol product, with only a very poor yield of aldol, aldol-Tishchenko product being isolated, and no evidence of aldol-Tishchenko product. Again, this would suggest the rate of double aldol reaction was fast relative to the Tishchenko step.

Although the yields obtained in the reactions described above were moderate, there was little evidence to suggest degradation of the (*S*)-*tert*-butanesulfinyl imine was occurring, and no trace of aldimine observed in the ^{1}H NMR spectrum of the crude reaction mixtures. However, LDA mediated reduction of the aldehydes to the corresponding benzyl alcohols was again noticed. Disappointingly, attempts to expand this reaction to include aliphatic aldehydes proved futile.

The absolute stereochemistry of the above compounds could not be determined by X-ray crystallography. However, DFT calculations performed by our collaborators in UCLA once again provided an insight into the mechanism of this reaction and allow for tentative assignment of the relative stereochemistry of the aldol, aldol-Tishchenko products resulting from this reaction **(Table 3.10, entry 2)**. Experimentally, the *dr* observed for this reaction was modest (74:26 *dr*), which proved consistent with the relative energies calculated for the hydride transfer transition states. The two lowest energy TSs calculated differed by only 0.3 kcal/mol **(Figure 3.24)**.



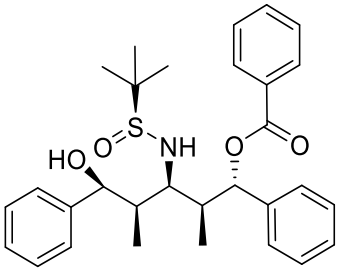


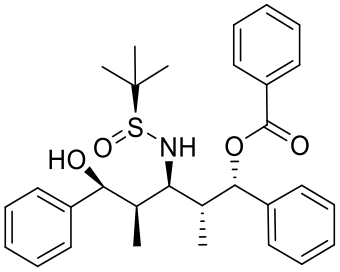
TS-91a

$\Delta\Delta G^{\ddagger}$ = 0.0 kcal/mol

TS-91b

$\Delta\Delta G^{\ddagger}$ = 0.3 kcal/mol



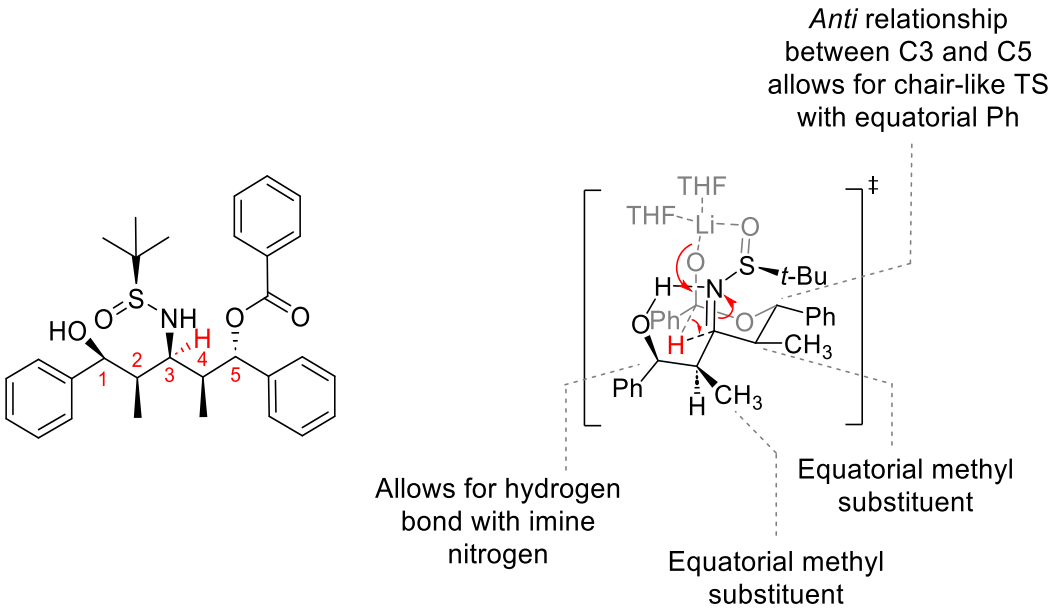


(S)-154 (*S,S,R,R,S,S*)-91

(*S,S,R,R,R,S*)-91

Figure 3.24. TSs for intramolecular hydride transfer forming **(*S*)-154**

These calculations were consistent with the computational results described previously for the butanone system. The two lowest energy TSs differ only by the orientation of the methyl group at C4. Axial orientation of this methyl group in the chair-like TS is 0.3 kcal higher in energy than if the orientated equatorially. The energy difference calculated for these substrates is significantly lower than the corresponding energy calculations for the cyclic systems, namely those derived from both cyclopentanone and cycloheptanone. For the cyclic systems, a large energy difference was observed when the orientation at this position was examined (*ca.* 1.4 kcal/mol), with the lower energy being the axial orientation. Steric interactions and ring strain contributed significantly to this difference. However, in the case of the 3-pentanone system this difference is significantly reduced as issues associated with ring strain no longer contribute and steric interactions are minimal due to the comparatively small size of a methyl group. These results are summarised in **Figure 3.25**.



(*S,S,R,R,S,S*)-91

Figure 3.25. Factors affecting stereoselectivity in aldol, aldol-Tishchenko reaction of **(*S*)-118**

The vicinal coupling constants in the ^{1}H NMR spectra of both the major and minor diastereomers of **91** are also supportive of this relative stereochemistry. The coupling constant observed between H-4 and H-5 for the major isomer is 8.4 Hz whereas for the minor isomer it is much smaller at 1.2 Hz. The larger coupling constant is suggestive of an *anti*-relationship between these protons in the major isomer. Contrastingly, the smaller coupling constant would be indicative of a a *syn*-relationship and dihedral angle of 90^{o} between the protons in the minor isomer.

3.10 Conclusions & future work

Overall, the work described herein proved moderately successful. Initially, we successfully elucidated and rationalised the mechanism and stereochemical outcome of the aldol-Tishchenko reaction of the 2,2-dimethylcyclopentanone derived (*S*)-*tert*-butanesulfinyl imine. However, attempts to expand the scope of the aldol-Tishchenko reaction of (*S*)-*tert*-butanesulfinyl imines to include the synthesis of enantio- and diastereoenriched 1,3-diamines *via* the use of aldimines as aldol acceptors proved unsuccessful. Also, attempts to introduce additional functionality into the 1,3-amino alcohol framework synthesised *via* an alternative reaction quench proved futile.

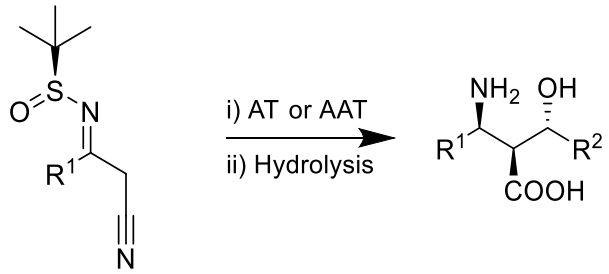
We successfully expanded upon a novel approach to synthesise 3-amino-1,5-diol derivatives *via* an aldol, aldol-Tishchenko reaction. This transformation proved a highly stereoselective

method for the introduction of up to five chiral centres, three additional functional groups and multiple new chemical bonds. Our methodology is a rare example of the concomitant introduction of multiple contiguous chiral centres in high diastereoselectivity.

Potential uses of these scaffolds are numerous and include applications in medicinal and ligand chemistry. Pleasingly, the more challenging substrates described, including butanone for example, could be used in an efficient one-pot process for the synthesis of acyclic 3-amino-1,5-diol derivatives. However, although the use of a number of challenging aldol acceptors proved successful in these reactions, efforts to broaden the scope to include aliphatic aldehydes were unsuccessful.

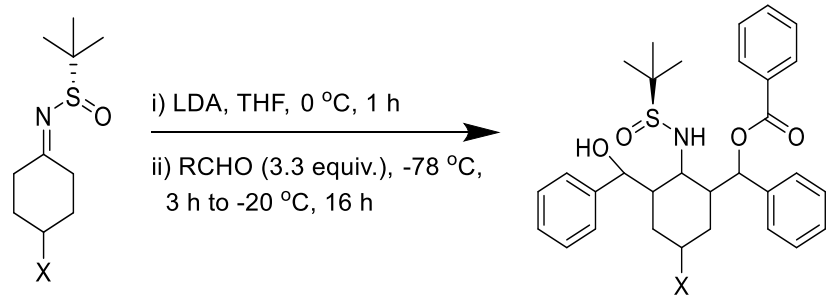
We provided detailed insights into the reaction mechanism, and in some cases, define the absolute stereochemistry of the resulting 3-amino-1,5-diol derivatives synthesised. Additionally, we demonstrated the potential synthetic value of the products through the selective cleavage of both the ester and sulfinyl imine moiety.

Our methodology could potentially offer a promising route to accessing *β*-amino acids, mainly due to the success of acyclic (*S*)-*tert*-butanesulfinyl imines, coupled with the precedence for the tolerance of aldehydes bearing reducible functional groups **(Scheme 3.56)**.



Scheme 3.56. Novel route to β-amino acids

We will also attempt to expand the scope of the aldol, aldol-Tishchenko reaction described herein to include substituted cyclic (*S*)-*tert*-butanesulfinyl imines. This has the potential to allow for desymmetrisation of these compounds **(Scheme 3.57)**.



Scheme 3.57. Desymmetrisation of cyclic (*S*)-*tert*-butanesulfinyl imines

Future work will focus on further examining the synthetic utility of these compounds. Attempts will be made to cyclise the 3-amino-1,5-diol derivatives synthesised. If successful, this would allow access to a range of important medicinal scaffolds including highly functionalised azetidines **(Scheme 3.58)**. Azetidines are highly valuable organic molecules, with some demonstrating similar bioactivity to analogous β-lactams.[85-86]

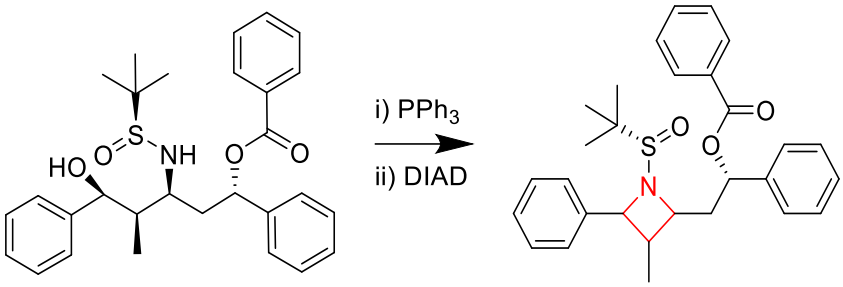
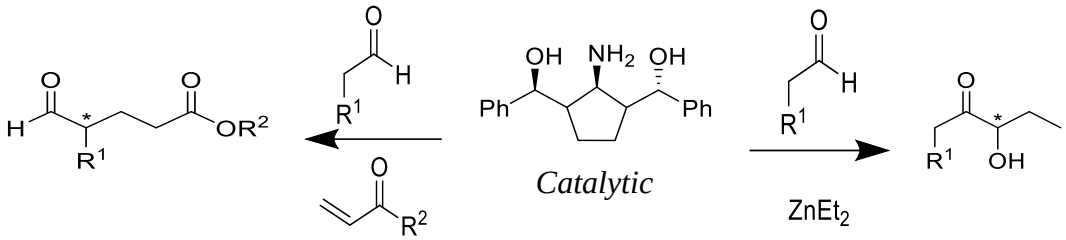


Figure 3.26. Highly functionalised azetidines

Chiral amino diols have also been shown to be highly effective chiral ligands, for example in asymmetric Michael addition reactions,[87-88] asymmetric Diels-Alder reactions[89] and enantioselective organometallic transformations.[90] Future work will include examining our 3-amino-1,5-diol products in a range of enantioselective transformations, including asymmetric conjugate addition reactions[91] and in the synthesis of chiral alcohols **(Scheme 3.59)**.[92]



Scheme 3.59. Asymmetric transformations using amino diol ligands

Experimental

3.11 General procedures

Solvents and reagents employed were dried prior to use as follows: THF was distilled from sodium/benzophenone ketyl[93] and stored over 3Å molecular sieves (20% w/v) in a Young's flask. Diisopropylamine was distilled from calcium hydride. The concentration of *n*-BuLi in hexanes was determined by titration with diphenylacetic acid.[94] All aldehydes were freshly distilled prior to use and stored under an inert atmosphere of nitrogen. All other reagents were purchased from Sigma Aldrich, Fluorochem, Alfa Aesar and Fisher Scientific and used without further purification, unless otherwise noted. All non-aqueous experiments were carried out under an oxygen free nitrogen atmosphere, using flame dried glassware and Schlenk set-up.

Wet column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin Layer Chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV light and potassium permanganate staining.

Melting points (m.p.) were recorded on a Thomas Hoover Capillary Melting Point apparatus or an Electrothermal IA9300 Digital Melting Point apparatus.
Infrared spectra were recorded on a Perkin-Elmer FTIR UATR2 spectrophotometer as neat samples or on a Perkin-Elmer FTIR Paragon 1000 spectrophotometer. For the latter, liquid samples were examined neat as a thin film on an NaCl plate. Solid samples were dissolved in DCM and dispersed on an NaCl plate as a thin film. The DCM was allowed to evaporate before any measurement was recorded.

NMR spectra were run in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard at 20 °C, unless otherwise stated. ^{1}H NMR (600 MHz) spectra, ^{1}H NMR (500 MHz) spectra, ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively. ^{13}C NMR (150 MHz) spectra, ^{13}C NMR (125 MHz) spectra, ^{13}C NMR (100 MHz) spectra and ^{13}C NMR (75.5 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively in proton decoupled mode. All spectra were recorded at University College Cork. Chemical shifts δ_H and δ_C are expressed as parts per million (ppm), positive shift being downfield from

TMS; coupling constants (*J*) are expressed in hertz (Hz) as observed and are uncorrected. Splitting patterns in ^{1}H NMR spectra are designated as a singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), doublet of quartets (dq), triplet (t), broad triplet (bt), doublet of triplets (dt), quartet (q), quarter of doublets (qd), quartet of quartets (qq), quintet (quin), septet (sept), and multiplet (m). For ^{13}C NMR spectra the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. COSY, HSQC and HMBC experiments were performed to aid the NMR assignment of novel chemical structures.

LRMS were recorded on a Waters Quattro Micro Triple Quadrupole instrument in ESI mode using 50% acetonitrile-water containing 0.1% formic acid as eluent. Samples were made up in acetonitrile. HRMS were recorded on a Waters LCT Premier ToF LC-MS instrument in ESI mode using 50% acetonitrile-water with 0.1% formic acid as eluent. HRMS were also recorded on a Waters Vion IMS instrument (SAA055K) with Waters Acquity I-class UPLC in electrospray ionization (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent and Leucine Enkephalin as reference solution. Samples were prepared in acetonitrile to a concentration of *ca.* 1 mg/mL.

Optical rotations were measured on an Autopol V Plus Automatic 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 expressed in units of 10^{-1} deg cm^2 g^{-1}. Specific rotations were employed to indicate the direction of enantioselection. Optically active samples are given the prefix of (+) or (-).

Single crystal X-ray data was obtained at the University of Southampton using a Rigaku AFC12 FREHF diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100 K. The structure was solved with the ShelXT (Sheldrick, 2015) structure solution program using the Intrinsic Phasing solution method and by using Olex2 as the graphical interface. The model was refined with version 2016/6 of ShelXL (Sheldrick, 2015) using Least Squares minimisation. Most hydrogen atom positions were calculated geometrically and refined using the riding model, but some hydrogen atoms were refined freely.

In most cases, it was possible to separate the diastereomers, however, the yield reflects the mixture of diastereomers. The major diastereomer was fully characterised in all cases. Diastereoselectivity was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Where the diastereomeric ratio was reported as not determined (nd) it was due to

overlapping signals in the ^{1}H NMR of the crude reaction mixture. In such cases, the yield quoted reflects the isolated yield of the single, major diastereomer.
An arbitrary numbering system was employed to aid the assignment of ^{1}H NMR and ^{13}C NMR spectra.

A Julabo FT902 cryocooler was used for low temperature reactions.

3.11.1 Analysis of known and novel Compounds

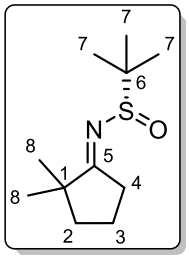
^{1}H NMR spectra, ^{13}C NMR spectra, IR and LRMS analyses were recorded for all previously reported compounds. For novel compounds, in addition to the previously mentioned analysis, HRMS was also obtained. Optical rotations were used to assign absolute stereochemistry for known chiral compounds.

3.12 Synthesis of (*S*)-*tert*-butanesulfinyl imines

3.12.1 General procedure for the synthesis of (*S*)-*tert*-butanesulfinyl imines

To a solution of $Ti(OEt)_4$ (2 equiv.) in THF (4 mL/mmol of ketone) was added ketone (1 equiv.) and (*S*)-*tert*-butanesulfinamide (1 equiv.). The resulting solution was heated at reflux and the reaction progress was monitored by TLC analysis. Upon completion, the reaction mixture was cooled to rt and brine (4 mL/mmol of ketone) was added. The resulting slurry was vigorously stirred for 30 mins. This was then filtered through Celite®. The filter cake was washed with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure, affording the crude (*S*)-*tert*-butanesulfinyl imine. Purification by column chromatography on silica gel gave pure (*S*)-*tert*-butanesulfinyl imine.

(*S*)-2-Methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide, (*S*)-67

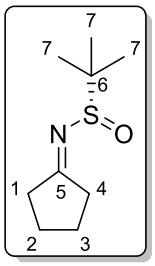


Prepared according to the general procedure outlined above using 2,2-dimethylcyclopentanone (1.12 mL, 8.9 mmol) and (*S*)-*tert*-butanesulfinamide (1.08 g, 8.9 mmol). Purification by column chromatography on silica gel (3:1, hexane:EtOAc) afforded the title compound as a pale yellow oil (1.19 g, 62%).

Spectroscopic characteristics were consistent with previously reported data.[37]

$[\alpha]_D^{25}$ + 217.2 (c 0.50, $CHCl_3$) (lit.[37] $[\alpha]_D^{23}$ +239.0 (c 1.0, $CHCl_3$)). IR ν_{max} (NaCl): 1636 (C=N stretch), 1089 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.11, 1.12 (2 × 3H, s, H-8), 1.24 (9H, s, H-7), 1.60-1.69 (2H, m, H-2), 1.76-1.91 (2H, m, H-3), 2.63 (1H, ddd, *J* = 19.7, 8.2, 6.2 Hz, one of H-4), 3.00 (1H, ddd, *J* = 19.4, 7.4, 6.3 Hz, one of H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4 (C-3), 22.3 (C-7), 26.0, 26.3 (C-8), 32.9 (C-2), 38.7 (C-4), 46.8 (C-1), 56.7 (C-6), 198.2 (C-5) ppm. MS (ESI) *m*/*z*: 216 $(M + H)^+$.

(*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide, (*S*)-68



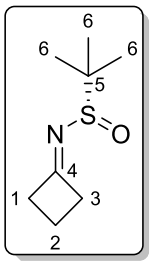
Prepared according to the general procedure above using cyclopentanone (1.80 mL, 20 mmol) and (*S*)-*tert*-butanesulfinamide (2.42 g, 20 mmol). Purification by column chromatography (3:1 hexane:EtOAc) yielded the title compound as a colourless oil (2.99 g, 82%).

Spectroscopic characteristics were consistent with previously reported data.[37]

$[\alpha]_D^{25}$ +244.5 (c 0.93, CH_2Cl_2) (lit.[37] $[\alpha]_D^{23}$ +239.0 (c 1.0, $CHCl_3$)). IR (ATR) ν_{max}: 3480 (C-H stretch), 1632 (C=N stretch), 1076 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (9H, s, H-7), 1.74-2.01 (4H, m, H-2 and H-3), 2.49-2.60 (2H, t, *J* = 7.1 Hz,

two of either H-1 or H-4, 1H, m, 1 of either H-1 or H-4), 2.90 (1H, dt, *J* = 19.0, 7.7 Hz, one of either H-1 or H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 22.1 (C-7), 23.5, 25.6 (C-2 and C-3), 33.7, 38.8 (C-1 and C-4), 56.2 (C-6), 194.7 (C-5) ppm. MS (ESI) *m/z*: 188 $[M+H]^+$.

(*S*)-*N*-cyclobutylidene-2-methylpropane-2-sulfinamide, (*S*)-69

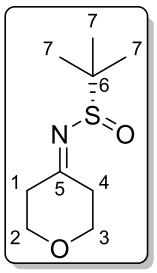


Prepared according to the general procedure outlined above using cyclobutanone (0.90 mL, 10 mmol) and *(S)-tert*-butanesulfinamide (1.21 g, 10 mmol). Purification by column chromatography (1:1 hex:EtOAc) yielded the title compound as a pale yellow oil (0.92 g, 53%).

Spectroscopic characteristics were consistent with previously reported data (for racemic compound).[95]

$[\alpha]_D^{20}$ +208.7 (c 0.20 CH_2Cl_2). IR (ATR) ν_{max}: 2964 (C-H stretch), 1663 (C=N stretch), 1054 (S=O stretch) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (9H, s, H-6), 2.11 (2H, quin, *J* = 8.3 Hz, H-2), 3.06-3.33 (3H, m, three of H-1 and H-3), 3.45-3.57 (1H, m, one of either H-1 or H-3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.1 (C-2), 22.2 (C-2), 39.9, 40.6 (C-1 and C-3), 56.7 (C-5), 186.9 (C-4) ppm. MS (ESI) *m/z*: 174 $[M+H]^+$.

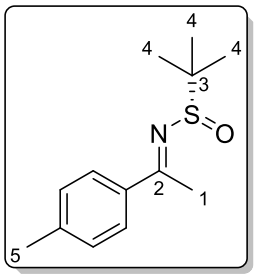
(S)-2-methyl-N-(tetrahydro-4H-pyran-4-ylidene)propane-2-sulfinamide, (*S*)-73



Prepared according to the general procedure outlined above using 4-oxatetrahydropyran (0.92 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). Purification by column chromatography (100% EtOAc) yielded the title compound as a pale yellow oil (0.36 g, 18 %).

$[\alpha]_D^{20}$ -83.3 (c 0.60 CH_2Cl_2). IR (ATR) ν_{max}: 2960 (C-H stretch), 1621 (C=N stretch), 1093 (S=O stretch), 1046 (C-O stretch) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, tentatively assigned): δ 1.25 (9H, s, H-7), 2.55 (2H, t, *J* = 5.5 Hz, H-1), 2.90 (1H, dt, *J* = 14.8 , 5.5 Hz, one of H-4), 3.17 (1H, dt, *J* = 14.5, 5.7 Hz, one of H-4), 3.83-3.97 (4H, m, H-2 and H-3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2 (C-7), 35.2 (C-4), 40.9 (C-1), 56.6 (C-5), 67.6, 68.7 (C-2 and C-3), 182.3 (C-5) ppm. HRMS (ESI) *m/z* calcd for $C_9H_{18}NO_2S$ $[M + H]^+$: 204.1053, found 204.1052.

(*S*)-2-Methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide, (*S*)-116

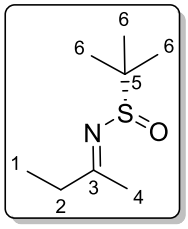


Prepared according to the general procedure outlined above using 4-methylacetophenone (1.97 mL, 15 mmol) and (*S*)-*tert*-butanesulfinamide (1.81 g, 15 mmol). Purification by column chromatography (5:1 hexane:EtOAc) yielded the title compound as a white solid (2.17 g, 61%).

Spectroscopic characteristics were consistent with previously reported data.[37]

M.p. 59-61 °C (lit.[37] M.p. 51-54 °C). $[\alpha]_D^{20}$ -43.1(c 1.49, CH_2Cl_2) (lit.[37] $[\alpha]_D^{20}$ -11.1 (c 1.0, $CHCl_3$). IR (ATR) ν_{max}: 2923 (C-H stretch), 1593 (C=N stretch), 1067 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.31 (9H, s, H-4), 2.40 (3H, s, H-5), 2.74 (3H, s, H-1), 7.20-7.23 (2H, m, Ar-H), 7.78-7.81 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 19.7 (C-1), 21.5 (C-5), 22.5 (C-4), 57.3 (C-3), 127.3 (2 × Ar-CH), 129.2 (2 × Ar-CH), 136.1 (Ar-C), 142.3 (Ar-C), 176.4 (C-2) ppm. MS (ESI) *m/z*: 238 $[M+H]^+$.

(*S*)-*N*-(butan-2-ylidene)-2-methylpropane-2-sulfinamide, (*S*)-117

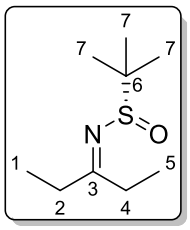


Prepared according to the general procedure outlined above using 2-butanone (0.90 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). Purification by column chromatography (4:1 hexane:EtOAc) yielded the title compound as a yellow oil (1.00 g, 57%).

Spectroscopic characteristics were consistent with previously reported data.[38]

$[\alpha]_D^{25}$ +123.4 (c 1.12, CH_2Cl_2) (lit.[38] $[\alpha]_D^{20}$ +101.4 (c 1.2, CH_2Cl_2)). IR (ATR) ν_{max}: 3475 (C-H stretch), 1625 (C=N stretch), 1072 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (3H, t, *J* = 7.4 Hz, H-1), 1.24 (9H, s, H-6), 2.32 (3H, s, H-4), 2.43, 2.44 (2 x 1H, dq, overlapping, *J* = 7.1, 2.4 Hz, H-2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 9.8 (C-1), 22.1 (C-6), 22.7 (C-4), 36.6 (C-2), 56.3 (C-5), 186.1 (C-3) ppm. MS (ESI) *m/z*: 176 $[M+H]^+$.

(*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide, (*S*)-118

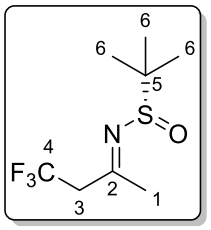


Prepared according to the general procedure outlined above using 3-pentanone (1.06 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). Purification by column chromatography (3:1 hexane:EtOAc) yielded the title compound as a yellow oil (1.52 g, 80%).

Spectroscopic characteristics were consistent with previously reported data.[96]

$[\alpha]_D^{25}$ +164.6 (c 0.25, CH_2Cl_2). IR (NaCl) ν_{max}: 2975 (C-H stretch), 1628 (C=N stretch), 1075 (S=O stretch) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.10, 1.20 (2 x 3H, t, *J* = 7.1 Hz, H-1 and H-5), 1.24 (9H, s, H-7), 2.40-2.51 (2H, m, H-2 or H-4), 2.70-2.74 (2H, m, H-2 or H-4) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.8, 11.8 (C-1 and C-5), 22.2 (C-7), 29.5, 33.5 (C-2 and C-4), 56.1 (C-6), 190.2 (C-3) ppm. MS (ESI) *m/z*: 190 $[M+H]^+$.

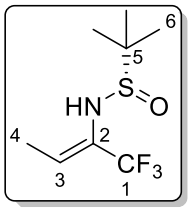
(*S*)-2-Methyl-*N*-(4,4,4-trifluorobutan-2-ylidene)propane-2-sulfinamide, (*S*)-119



Prepared according to the general procedure outlined above using 4,4,4-trifluoro-2-butanone (1.20 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). Purification by column chromatography (1:1 hexane:EtOAc) yielded the title compound as a pale yellow oil (1.17 g, 51%).

$[\alpha]_D^{20}$ +138.7 (c 1.12, CH_2Cl_2). IR (ATR) ν_{max}: 3260 (C-H stretch), 1634 (C=N stretch), 1074 (S=O stretch) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.26 (9H, s, H-6), 2.45 (3H, s, H-1), 3.19 (2H, q, *J* = 10.1 Hz, H-3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2 (C-6), 23.0 (C-1), 46.9 (q, $^2J_{C\text{-}F}$ = 28.5 Hz C-3), 57.6 (C-5), 124.3 (q, $^1J_{C\text{-}F}$ = 276.6 Hz, C-4), 172.7 (C-2) ppm. HRMS (ESI) *m/z* calcd for $C_8H_{15}F_3NOS$ $[M + H]^+$: 230.0821, found 230.0827.

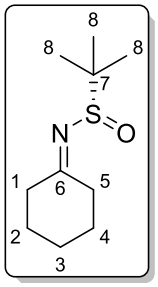
(*S*)-2-Methyl-*N*-(1,1,1-trifluorobut-2-en-2-yl)propane-2-sulfinamide, (*S*)-120



Prepared according to the general procedure outlined above using 1,1,1-trifluoro-2-butanone (1.35 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). Purification by column chromatography (1:1 hexane:EtOAc) yielded the title compound as a white solid (1.56 g, 68%). Spectroscopic characteristics were consistent with previously reported data (for racemic compound).[97]

M.p. 104-106 °C. $[\alpha]_D^{20}$ +102.5 (c 0.520, CH_2Cl_2). IR (ATR) ν_{max}: 3680 (C-H stretch), 1126 (C-N stretch), 1057 (S=O stretch) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.30 (9H, s, H-6), 1.90 (3H, dq, *J* = 7.2, 2.2 Hz, H-4), 4.64 (1H, bs, N-H), 6.20 (1H, apparent qd (qq with unresolved splitting), *J*= 7.2, 1.0 Hz, H-3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.3 (C-4), 22.5 (C-6), 57.3 (C-5), 121.6 (q, $^1J_{C\text{-}F}$ = 273.9 Hz, C-1), 125.4 (q, $^3J_{C\text{-}F}$ = 4.4 Hz, C-3), 128.3 (q, $^2J_{C\text{-}F}$ = 34.3 Hz, C-2) ppm. HRMS (ESI) *m/z* calcd for $C_8H_{15}F_3NOS$ $[M + H]^+$: 230.0821, found 230.0826.

3.12.2 Synthesis of (*S*)-*N*-cyclohexylidene-2-methylpropane-2-sulfinamide, (*S*)-71

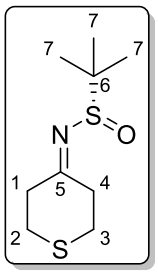


To a solution of titanium ethoxide (1.78 mL, 8.5 mmol) in anhydrous THF (9 mL) was added cyclohexanone (0.52 mL, 5 mmol). This solution was allowed to stir for 15 min before *(S)-tert*-butanesulfinamide (0.727 g, 6 mmol) was slowly added. The mixture was stirred at 60 °C for approx. 4 hrs. Brine (4 mL/mmol of ketone) was added and the resulting slurry vigorously stirred for 30 min. The slurry was then filtered through Celite®, washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield crude *(S)-tert*-butanesulfinyl imine. The crude compound was purified by column chromatography (6:1 Et_2O:EtOAc) to yield the title compound as a pale yellow oil (0.42 g, 42%).

Spectroscopic characteristics are consistent with previously reported data.[17]

$[\alpha]_D^{20}$ +146.00 (c 0.35 CH_2Cl_2). IR (ATR) ν_{max}: 2932 (C-H stretch), 1613 (C=N stretch), 1071 (S=O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (9H, s, H-8), 1.65-1.89 (6H, m, H-2, H-3 and H-4), 2.42 (2H, t, *J* = 6.5 Hz, H-1 or H-5), 2.68-2.77 (1H, m, one of either H-1 or H-5), 2.85-2.94 (1H, m, one of either H-1 or H-5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (C-8), 25.3, 27.4, 27.9 (C-2, C-3 and C-4), 34.4, 40.7 (C-1 and C-5), 55.9 (C-5), 188.7 (C-6) ppm. HRMS (ESI) *m/z* calcd for $C_{10}H_{20}NOS$ $[M + H]^+$: 202.1260, found 202.1259.

3.12.3 Synthesis of (*S*)-2-methyl-*N*-(tetrahydro-4H-thiopyran-4-ylidene)propane-2-sulfinamide, (*S*)-75



To a solution of titanium ethoxide (4.2 mL, 21 mmol) in anhydrous THF (20 mL) was added tetrahydrothiopyran-4-one (1.39 g, 12 mmol). This solution was allowed to stir for 15 min before *(S)-tert*-butanesulfinamide (1.21 g, 10 mmol) was slowly added. The mixture was stirred at 80 °C for 18 hrs. Brine (4 mL/mmol of ketone) was added and the resulting slurry vigorously stirred for 30 min. The slurry was then filtered through Celite®, washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield crude *(S)-tert*-butanesulfinyl imine. The crude compound was purified by column chromatography (1:1 Hex:EtOAc) to yield the title compound as a pale yellow oil (0.96 g, 44%).

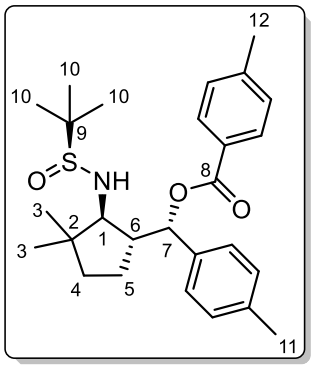
$[\alpha]_D^{20}$ +79.3 (c 0.145 CH_2Cl_2). IR (ATR) ν_{max}: 2957 (C-H stretch), 1616 (C=N stretch), 1059 (S=O stretch) cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$, tentatively assigned): δ 1.24 (9H, s, H-7), 2.73-2.95 (6H, m, H-1, H-2 and H-3), 3.00-3.09 (1H, m, one of H-4), 3.34-3.42 (1H, m, one of H-4) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2 (C-7), 30.2, 30.8 (C-2 and C-3), 36.2 (C-4), 42.4 (C-1), 56.6 (C-6), 184.6 (C-5) ppm. HRMS (ESI) *m/z* calcd for $C_9H_{18}NOS_2$ $[M + H]^+$: 220.0824, found 220.0826.

3.13 Aldol-Tishchenko reactions of (*S*)-*tert*-butanesulfinyl imines

3.13.1 Synthesis of 2,2-dimethylcyclopentanone derived *anti*-1,3-amino esters

To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinyl imine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 ℃. The resulting solution was stirred for 30 mins before being cooled to -78 ℃. Sulfinyl imine (1 equiv.) was added dropwise and stirred for 1 h at this temperature. Freshly distilled aldehyde (3.0 equiv.) was added dropwise and the temperature was maintained at -78 ℃ for a further 3 hours. The reaction mixture was warmed to -20 ℃ over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure, to afford crude product. Purification by column chromatography on silica gel yielded pure aldol-Tishchenko product.

(*S*)-((1*R*,2*S*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3,3-dimethylcyclopentyl)(*p*-tolyl)methyl 4-methylbenzoate, (*S*,*S*,*R*,*S*)-77

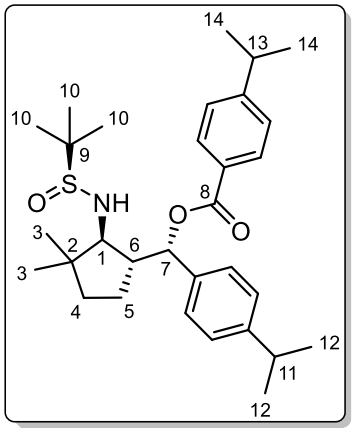


Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide (0.215 g, 1 mmol) and 4-methylbenzaldehyde (0.35 mL, 3 mmol). The crude compound (88:12 *dr*) was purified by column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound as a white solid (0.237 g, 52%).

***Major diastereomer**:*

M.p. 140-142 ℃. $[\alpha]_D^{25}$ + 17.8 (c 0.50, $CHCl_3$). IR ν_{max} (ATR): 3425 (N-H stretch), 1641 (C=O stretch), 1104 (C-N stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91, 1.17 (2 × 3H, s, H-3), 1.27 (9H, s, H-10), 1.53-1.73 (3H, m, H-4 and one of H-5), 1.90-2.04 (1H, m, one of H-5), 2.19-2.28 (1H, m, H-6), 2.30, 2.43 (2 × 3H, s, H-11 and H-12), 3.15 (1H, t, *J* = 9.7 Hz, H-1), 3.28 (1H, d, *J* = 9.7 Hz, N-H), 6.15 (1H, d, *J* = 2.2 Hz, H-7), 7.09-7.12 (2H, m, Ar-H), 7.18-7.20 (2H, m, Ar-H), 7.26-7.29 (2H, m, Ar-H), 7.96-7.99 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2 (C-5), 21.1, 21.7 (C-11 and C-12), 21.9 (C-3), 22.9 (C-10), 27.2 (C-3), 38.7 (C-4), 40.6 (C-2), 51.9 (C-6), 56.3 (C-9), 69.2 (C-1), 74.3 (C-7), 125.5 (2 × Ar-CH), 127.6 (Ar-C), 129.1 (2 × Ar-CH), 129.2 (2 × Ar-CH), 129.6 (2 × Ar-CH), 137.1 (Ar-C), 137.8 (Ar-C), 143.8 (Ar-C), 165.6 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{38}NO_3S$ $[M + H]^+$: 456.2567, found 456.2565.

(*S*)-((1*R*,2*S*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3,3-dimethylcyclopentyl)(4-isopropylphenyl)methyl 4-isopropylbenzoate, (*S,S,R,S*)-78

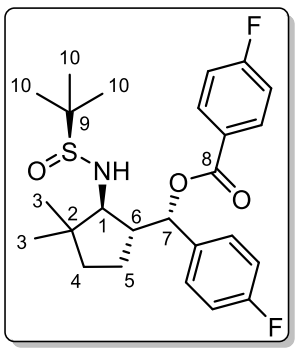


Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide (0.215 g, 1 mmol) and 4-isopropylbenzaldehyde (0.45 mL, 3 mmol). The crude compound (91:9 *dr*) was purified by column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound as a white solid (0.312 g, 61%).

***Major diastereomer**:*

M.p. 105-107 °C. $[\alpha]_D^{25}$ + 14.3 (c 0.50, $CHCl_3$). IR ν_{max} (ATR): 3426 (N-H stretch), 1640 (C=O stretch), 1107 (C-N stretch), 1054 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91, 1.18 (2 × 3H, s, H-3), 1.20 (6H, d, *J* = 6.9 Hz, H-12) 1.27 (9H, s, H-10 and 6H, d, *J* = 8.0 Hz, H-14, overlapping), 1.52-1.73 (3H, m, H-4 and one of H-5), 1.89-2.04 (1H, m, one of H-5), 2.19-2.30 (1H, m, H-6), 2.86, 2.98 (2 ×1H, sept, *J* = 7.0 Hz, H-11 and H-13), 3.15 (1H, t, *J* = 10.1 Hz, H-1), 3.36 (1H, d, *J* = 10.1 Hz, N-H), 6.17 (1H, d, *J* = 2.4 Hz, H-7), 7.13-7.27 (4H, m, Ar-H), 7.32-7.34 (2H, m, Ar-H), 7.99-8.04 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.3 (C-5), 21.8 (C-3), 22.9 (C-10), 23.7, 23.9 (C-12 and C-14), 27.2 (C-3), 33.7, 34.3 (C-11 and C-13), 38.7 (C-4), 40.6 (C-2), 51.8 (C-6), 56.4 (C-9), 69.4 (C-1), 74.3 (C-7), 125.6 (2 × Ar-CH), 126.5 (2 × Ar-CH), 126.6 (2 × Ar-CH), 128.0 (Ar-C), 129.8 (2 × Ar-CH), 138.0 (Ar-C), 148.0 (Ar-C), 154.6 (Ar-C), 165.6 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{31}H_{46}NO_3S$ $[M + H]^+$: 512.3193, found 512.3196.

(*S*)-((1*R*,2*S*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3,3-dimethylcyclopentyl)(4-fluorophenyl)methyl 4-fluorobenzoate, (*S,S,R,S*)-79



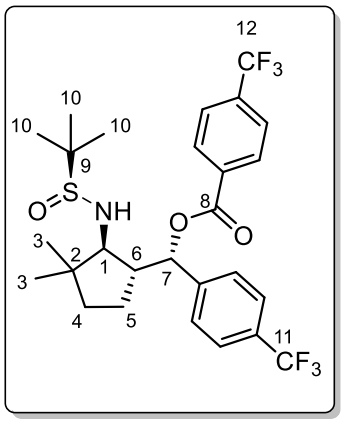
Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide (0.215 g, 1 mmol) and 4-fluorobenzaldehyde (0.32 mL, 3 mmol). The crude compound (91:9 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a white solid (0.278 g, 60%).

Major diastereomer:

M.p. 157-159 °C. $[\alpha]_D^{25}$ + 25.6 (c 0.5, $CHCl_3$). IR ν_{max} (ATR): 3433 (N-H stretch), 1638 (C=O stretch), 1110 (C-N stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.92, 1.17 (2 × 3H, s, H-3), 1.27 (9H, s, H-10), 1.52-1.67 (3H, m, H-4 and one of H-5), 1.87-1.97 (1H, m, one of H-5),

2.19-2.33 (1H, m, H-6), 3.12 (1H, t, *J* = 9.8 Hz, H-1), 3.34 (1H, d, *J* = 9.8 Hz, N-H), 6.18 (1H, d, *J* = 2.4 Hz, H-7), 6.97-7.04 (2H, m, Ar-H), 7.12-7.20 (2H, m, Ar-H), 7.25-7.33 (2H, m, Ar-H), 8.06-8.13 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.2 (C-5), 22.0 (C-3), 22.9 (C-10), 27.3 (C-3), 38.6 (C-4), 40.6 (C-2), 51.7 (C-6), 56.3 (C-9), 69.0 (C-1), 74.1 (C-7), 115.4 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, 2 × Ar-CH), 115.8 (d, $^2J_{C\text{-}F}$ = 22.0 Hz, 2 × Ar-CH), 126.3 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 127.3 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, 2 × Ar-CH), 132.1 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, 2 × Ar-CH), 136.3 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, Ar-C), 162.5 (d, $^1J_{C\text{-}F}$ = 246.5 Hz, Ar-C), 164.5 (C-8), 166.5 (d, $^1J_{C\text{-}F}$ = 254.8 Hz, Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{32}F_2NO_3S$ $[M + H]^+$: 464.2065, found 464.2065.

(*S*)-((1*R*,2*S*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3,3-dimethylcyclopentyl)(4-(trifluoromethyl)phenyl)methyl 4-(trifluoromethyl)benzoate, (*S*,*S*,*R*,*S*)-80

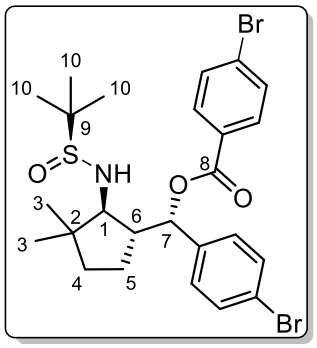


Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide (0.215 g, 1 mmol) and 4-isopropylbenzaldehyde (0.45 mL, 3 mmol). The crude compound (> 99:1 *dr*) was purified by column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.242 g, 43%).

***Major diastereomer**:*

$[\alpha]_D^{25}$ + 26.4 (c 0.5, $CHCl_3$). IR ν_{max} (ATR): 3292 (N-H stretch), 1730 (C=O stretch), 1128 (C-N stretch), 1067 (S=O stretch) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93, 1.18 (2 × 3H, s, H-3), 1.28 (9H, s, H-10), 1.53-1.66 (3H, m, H-4 and one of H-5), 1.83-1.99 (1H, m, one of H-5), 2.28-2.36 (1H, m, H-6), 3.15 (1H, t, *J* = 9.9 Hz, H-1), 3.42 (1H, d, *J* = 9.5 Hz, N-H), 6.27 (1H, d, *J* = 2.1 Hz, H-7), 7.42 (2H, d, *J* = 8.1 Hz, Ar-H), 7.58 (2H, d, *J* = 8.1 Hz, Ar-H), 7.78 (2H, d, *J* = 8.1 Hz, Ar-H), 8.20 (2H, d, *J* = 8.1 Hz, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.1 (C-5), 22.0 (C-3), 22.9 (C-10), 27.3 (C-3), 38.4 (C-4), 40.6 (C-2), 51.5 (C-6), 56.4 (C-9), 68.9 (C-1), 74.7 (C-7), 123.5, 123.9 (2 × q, $^1J_{C\text{-}F}$ = 272.4 Hz, C-11 and C-12), 125.6 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, 2 × Ar-CH), 125.8 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, 2 × Ar-CH), 125.9 (2 × Ar-CH), 130.0 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, Ar-C), 130.0 (2 × Ar-CH), 133.0 (Ar-C), 135.0 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, Ar-C), 144.1 (Ar-C), 164.3 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{27}H_{32}F_6NO_3S$ $[M + H]^+$: 564.2002, found 564.1997.

(*S*)-(4-bromophenyl)((1*R*,2*S*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3,3-dimethylcyclopentyl)methyl 4-bromobenzoate, (*S,S,R,S*)-81



Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide (0.215 g, 1 mmol) and 4-bromobenzaldehyde (0.56 g, 3 mmol). The crude compound (*dr* nd) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a colourless solid (0.047 g, 8%, single diastereomer).

M.p. 166-168 ℃. $[\alpha]_D^{25}$ + 19.8 (c 0.50, $CHCl_3$). IR ν_{max} (ATR): 3380 (N-H stretch), 1625 (C=O stretch), 1181 (C-N stretch), 1072 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.92, 1.17 (2 × 3H, s, H-3), 1.26 (9H, s, H-10), 1.55-1.62 (3H, m, H-4 and one of H-5), 1.86-1.90 (1H, m, one of H-5), 2.22-2.25 (1H, m, H-6),3.15 (1H, t, *J* = 9.9 Hz, H-1), 3.35 (1H, d, *J* = 9.8 Hz, N-H), 6.14 (1H, d, *J* = 2.4 Hz, H-7), 7.16 (2H, d, *J* = 8.5 Hz, Ar-H), 7.44 (2H, d, *J* = 8.6 Hz, Ar-H), 7.62-7.64 (2H, m, Ar-H), 7.92-7.94 (2H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.1 (C-5), 21.9 (C-3), 22.9 (C-10), 27.2 (C-3), 38.5 (C-4), 40.6 (C-2), 51.5 (C-6), 56.3 (C-9), 68.9 (C-1), 74.3 (C-7), 121.5 (Ar-C), 127.3 (2 × Ar-CH), 128.6 (Ar-C), 128.8 (ArC), 131.1 (2 × Ar-CH), 131.7 (2 × Ar-CH), 132.0 (2 × Ar-CH), 139.4 (Ar-C), 164.8 (C-8) ppm. HRMS (ESI) *m/z* calcd for $C_{35}H_{32}NO_3SBr_2$ $[M + H]^+$: 587.0391, found 587.1250.

3.13.2 Synthesis of 2,2-dimethylcyclopentanone derived *anti*-1,3-amino alcohols

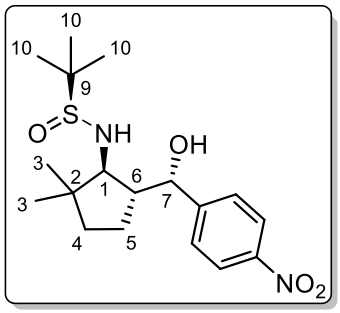
To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinyl imine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 ℃. The resulting solution was stirred for 30 mins before being cooled to -78 ℃. Sulfinyl imine (1 equiv.) was added dropwise and stirred for 1 h at this temperature. Freshly distilled aldehyde (3.0 equiv.) was added dropwise and the temperature was maintained at -78 ℃ for a further 3 hours. The reaction mixture was warmed to -20 ℃ over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude product.

Cleavage of ester moiety

To a vigorously stirred solution of the crude reaction mixture in MeOH (10 mL/mmol) was added KOH (1 pellet). The mixture was stirred at rt for 3 h. The solution was concentrated under reduced pressure. The residue was dissolved in water and the aqueous solution was

neutralised and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to give crude product, which was subsequently purified by column chromatography to yield pure 1,3-amino alcohol derivative.

(*S*)-*N*-((1*S*,5*R*)-5-((*S*)-hydroxy(4-nitrophenyl)methyl)-2,2-dimethylcyclopentyl)-2-methylpropane-2-sulfinamide, (*S*,*S*,*R*,*S*)-83



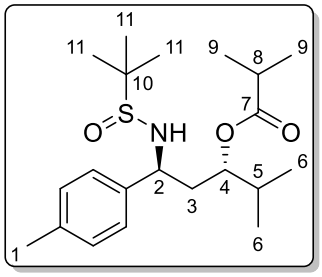
Prepared over two steps according to the general procedure outlined above using (*S*)-2-methyl-*N*-(2,2-dimethylcyclopentylidene)propane-2-sulfinamide (0.215 g, 1 mmol) and 4-nitrobenzaldehyde (0.45 g, 3 mmol). The crude compound (*dr* nd) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a pale yellow solid (0.026 g, 7%).

M.p. > 250 °C. $[\alpha]_D^{25}$ + 17.8 (c 0.53, $CHCl_3$). IR ν_{max} (ATR): 3426 (N-H stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89, 1.14 (2 × 3H, s, H-3), 1.29 (10H, m, 1 of H-5 and H-10), 1.41-1.50 (2H, m, H-4), 1.53-1.67 (1H, m, one of H-5), 2.14-2.24 (1H, m, H-6), 3.39-3.51 (2H, m, H-1 and N-H), 5.15 (1H, d, *J* = 2.0 Hz, H-7), 7.50-7.51 (2H, m, Ar-H), 8.14-8.17 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.8 (C-5), 22.0 (C-3), 22.9 (C-10), 27.2 (C-3), 38.3 (C-4), 41.2 (C-2), 52.0 (C-6), 56.4 (C-9), 66.6 (C-1), 70.7 (C-7), 123.4 (2 × Ar-CH), 126.3 (2 × Ar-CH), 149.1 (Ar-C), 152.2 (Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{28}N_2O_4SNa$ $[M + Na]^+$: 391.1662, found 391.1674.

3.13.3 Synthesis of 4-methylacetophenone derived *anti*-1,3-amino esters

To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinyl imine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 °C. The resulting solution was stirred for 30 mins before being cooled to -78 °C. Sulfinyl imine (1 equiv.) was added dropwise and stirred for 1 h at this temperature. Freshly distilled aldehyde (3.0 equiv.) was added dropwise and the temperature was maintained at -78 °C for a further 3 hours. The reaction mixture was warmed to -20 °C over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure, to afford crude product. Purification by column chromatography on silica gel yielded pure aldol-Tishchenko product.

(1*S*,3*S*)-1-((tert-butylsulfinyl)amino)-4-methyl-1-(*p*-tolyl)pentan-3-yl isobutyrate, (*S*,*S*)-121



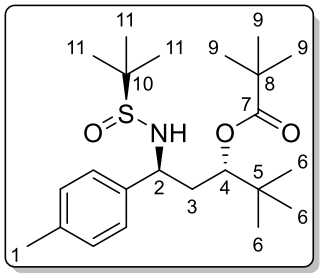
Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide (0.1 g, 0.42 mmol) and isobutyraldehyde (0.12 mL, 1.26 mmol). Purification of the crude compound (91:9 *dr*) by column chromatography (5:1 hexane:EtOAc) yielded the title compound as a colourless oil (0.077 g, 48%).

Spectroscopic characteristics were consistent with previously reported data.[37]

Major diastereomer:

$[\alpha]_D^{25}$ + 47.1 (c 1.0, $CHCl_3$) (lit.[37] $[\alpha]_D^{23}$ +49.8 (c 1.0, $CHCl_3$)). IR (NaCl) ν_{max}: 3235 (N-H stretch), 2965 (C-H stretch), 1732 (C=O stretch), 1387 (S=O stretch), 1054 (C-O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89, 0.93 (2 × 3H, d, *J* = 6.8 Hz, H-6), 1.18,1.36 (2 × 3H, d, *J* = 3.5 Hz, H-9), 1.19 (9H, s, H-11), 1.83-1.94 (1H, m, H-5), 1.99 (1H, ddd, *J* = 14.2, 9.6, 5.2, 1 of H-3), 2.20 (1H, ddd, *J* = 14.1, 9.1, 3.1 Hz, one of H-3), 2.35 (3H, s, H-1), 2.44 (1H, sept, *J* = 7.0 Hz, H-8), 3.82 (1H, d, *J* = 5.4 Hz, N-H), 4.20-4.26 (1H, m, H-2), 4.94-4.99 (1H, m, H-4), 7.13-7.16 (2H, m, Ar-H), 7.23-7.26 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 17.3, 18.3 (C-6), 19.0, 19.2 (C-9), 21.1 (C-1), 22.6 (C-11), 31.6 (C-5), 34.2 (C-8), 38.0 (C-3), 56.0 (C-10), 56.6 (C-2), 74.8 (C-4), 127.3 (2 × Ar-CH), 129.3 (2 × Ar-CH), 137.5 (Ar-C), 139.1 (Ar-C), 178.5 (C-7) ppm. MS (ESI) *m/z*: 382 $[M+H]^+$.

(1*S*,3*S*)-1-(((*S*)-*tert*-butylsulfinyl)amino)-4,4-dimethyl-1-(4-methylcyclohexa-1,3-dien-1-yl)pentan-3-yl pivalate, (*S*,*S*)-122



Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide (0.1 g, 0.42 mmol) and pivaldehyde (0.14 mL, 1.26 mmol). Purification of the crude compound (92:8 *dr*) by column chromatography (5:1 hexane:EtOAc) yielded the title compound as a white solid (0.1085 g, 63%).

Spectroscopic characteristics were consistent with previously reported data.[37]

Major diastereomer:

M.p. 146-148 °C (lit.[37] m.p. 147-150 °C). $[\alpha]_D^{25}$ + 41.8 (c 1.0, $CHCl_3$) (lit.[37] $[\alpha]_D^{23}$ +42.6 (c 1.0, $CHCl_3$)). IR (NaCl) ν_{max}: 3253 (N-H stretch), 2958 (C-H stretch), 1727 (C=O stretch), 1368 ×(S=O stretch), 1042 (C-O stretch) cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (9H, s, H-6), 1.19 (9H, s, H-11), 1.22 (9H, s, H-9), 1.90 (1H, ddd, *J* = 10.8, 6.5, 1.8 Hz, one of H-3), 2.27-2.38 (1H, m, one of H-3), 2.33 (3H, s, H-1), 4.02-4.09 (1H, m, H-2), 4.13-4.15 (1H, m,

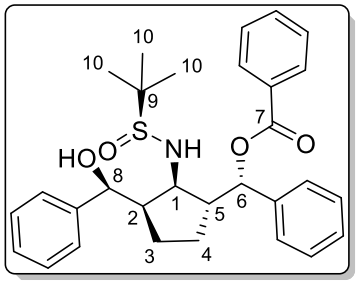
NH), 5.06 (1H, dd, *J* = 10.8, 1.4 Hz, H-4), 7.13-7.15 (2H, m, Ar-H), 7.22-7.24 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 21.1 (C-1), 22.7 (C-11), 26.1 (C-6), 27.4 (C-9), 34.8 (C-5), 37.3 (C-3), 39.1 (C-8), 56.1 (C-10), 57.0 (C-2), 77.3 (C-4), 127.3 (2 × Ar-CH), 129.2 (2 × Ar-CH), 137.3 (Ar-C), 139.1 (Ar-C), 178.5 (C-7) ppm. MS (ESI) *m/z*: 411 $[M+H]^+$.

3.14 Double aldol-Tishchenko reactions of (*S*)-*tert*-butanesulfinyl imines

3.14.1 Synthesis of cyclopentanone derived 3-amino-1,5-diol precursors

To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinyl imine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 ℃. The resulting solution was stirred for 30 mins before being cooled to -78 ℃. Sulfinyl imine (1 equiv.) was added dropwise and stirred for 1 h at this temperature. Freshly distilled aldehyde (3.3 equiv.) was added dropwise and the temperature was maintained at -78 ℃ for a further 3 hours. The reaction mixture was warmed to -20 ℃ over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography on silica gel yielded pure double aldol-Tishchenko product.

(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(phenyl)methyl)cyclopentyl)(phenyl)methyl benzoate, (*S,S,R,R,R,S*)-91



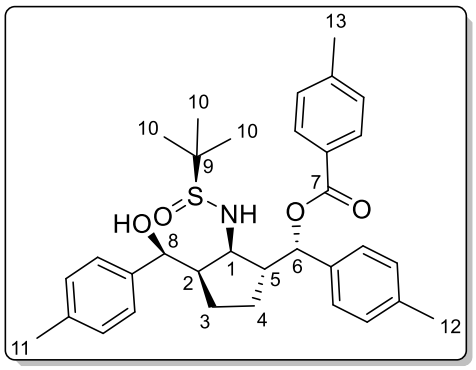
Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and benzaldehyde (0.34 mL, 3.3 mmol). The crude compound (88:12 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as pale yellow solid (0.222 g, 44%).

***Major diastereomer**:*

M.p. 79-81 ℃. $[\alpha]_D^{25}$ + 40.8 (c 0.195, CH_2Cl_2). IR ν_{max} (ATR): 3273 (N-H stretch), 2959 (C-H stretch), 1721 (C=O stretch), 1176 (C-N stretch), 1069 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.40 (2H, m, H-3), 1.28 (9H, s, H-10), 1.42-1.55 (1H, m, one of H-4), 1.72-1.84 (1H, m, one of H-4), 2.32 (1H, quin, *J* = 9.0 Hz, H-2), 2.44 (1H, dq, *J* = 9.3, 3.5 Hz, H-5), 3.45-3.56 (1H, m, H-1), 4.29 (1H, d, *J* = 6.3 Hz, N-H), 4.62 (1H, d, *J* = 9.0 Hz, H-8), 6.26 (1H, d, *J* = 3.3 Hz, H-6), 7.18-7.51 (10H, m, Ar-H), 7.44-7.51 (2H, m, Ar-H), 7.57-7.63 (1H, m, Ar-H), 8.08-8.11 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (C-4),

22.8 (C-10), 25.7 (C-3), 52.4 (C-2), 53.8 (C-5), 56.1 (C-9), 64.0 (C-1), 74.1 (C-6), 78.4 (C-8), 125.8 (2 × Ar-CH), 126.7 (2 × Ar-CH), 127.5 (Ar-CH), 127.6 (Ar-CH), 128.3 (2 × Ar-CH), 128.5 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.7 (2 × Ar-CH), 130.2 (Ar-C), 133.3 (Ar-CH), 140.1 (Ar-C), 143.1 (Ar-C), 165.7 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{36}NO_4S$ $[M + H]^+$: 506.2360, found 506.2348.

(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(*p*-tolyl)methyl)cyclopentyl)(*p*-tolyl)methyl 4-methylbenzoate, (*S*,*S*,*R*,*R*,*R*,*S*)-92

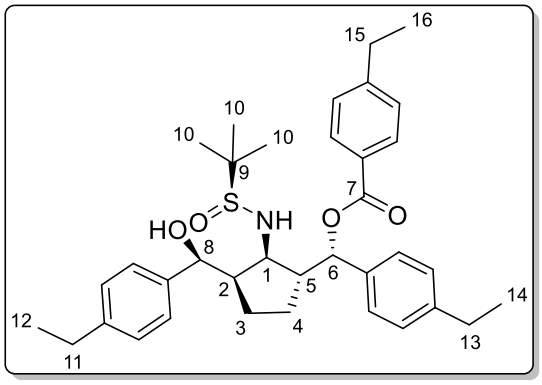


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-methylbenzaldehyde (0.39 mL, 3.3 mmol). The crude compound (91:9 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a white solid (0.175 g, 32%).

***Major diastereomer**:*

M.p. 77-78 °C. $[\alpha]_D^{25}$ + 45.7 (c 0.452, CH_2Cl_2). IR ν_{max} (ATR): 3270 (N-H stretch), 2960 (C-H stretch), 1720 (C=O stretch), 1177 (C-N stretch), 1043 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.33 (2H, m, H-3), 1.29 (9H, s, H-10), 1.46-1.56 (1H, m, one of H-4), 1.73-1.84 (1H, m, one of H-4), 2.26-2.47 (3 x 3H, s, H-11, H-13 and H-13 and 2H, m, H-2 and H-5, overlapping), 3.42-3.55 (1H, m, H-1), 4.17-4.26 (1H, m, N-H), 4.57 (1H, d, *J* = 8.9 Hz, H-8), 6.20 (1H, d, *J* = 3.2 Hz, H-6), 7.08-7.29 (10H, m, Ar-H), 7.97-7.99 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1, 21.7 (C-11, C-12 and C-13, overlapping), 21.5 (C-4), 22.8 (C-10), 25.8 (C-3), 52.3 (C-2), 53.8 (C-5), 56.1 (C-9), 64.1 (C-1), 73.9 (C-6), 78.3 (C-8), 125.8 (2 × Ar-CH), 126.6 (2 × Ar-CH), 127.5 (Ar-C), 129.0 (2 × Ar-CH), 129.1 (2 × Ar-CH), 129.2 (2 × Ar-CH), 129.7 (2 × Ar-CH), 137.1 (Ar-C), 137.2 (2 × Ar-C), 140.2 (Ar-C), 143.9 (Ar-C), 165.7 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{42}NO_4S$ $[M + H]^+$: 548.2829, found 548.2826.

(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-tert-butylsulfinyl)amino)-3-((*S*)-(4-ethylphenyl)(hydroxy)methyl)cyclopentyl)(4-ethylphenyl)methyl 4-ethylbenzoate, (*S,S,R,R,R,S*)-93

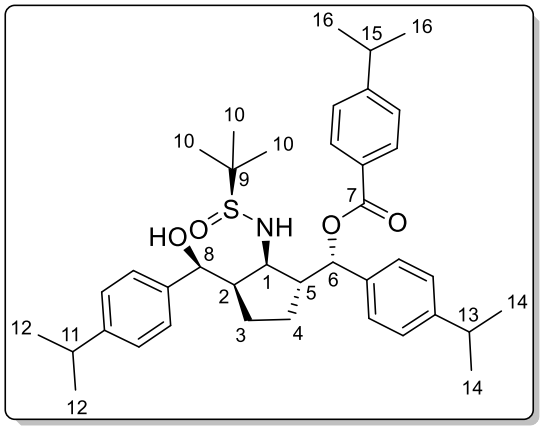


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-*t*-butyllbenzaldehyde (0.55 mL, 3.3 mmol). The crude compound (91:9 *dr*) was purified by column chromatography on silica gel (1:1 hexane:EtOAc) to give the title compound (0.230 g, 39%).

***Major diastereomer**:*

M.p. 83-86 °C. $[\alpha]_D^{25}$ + 54.2 (c 0.275, CH_2Cl_2). IR ν_{max} (ATR): 3272 (N-H stretch), 2964 (C-H stretch) 1721 (C=O stretch), 1177 (C-N stretch), 1033 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.19, 1.20, 1.28 (3 x 3H, t, *J* = 7.6 Hz, H-12, H-14 and H-16), 1.25-1.30 (2H, m, H-3 and 9H, s, H-10, overlapping), 1.47-1.56 (1H, m, one of H-4), 1.72-1.84 (1H, m, one of H-4), 2.26-2.50 (2H, m, H-2 and H-5), 2.59, 2.73 (3 x 2H, q, *J* = 7.6 Hz, H-11, H-13 and H-15), 3.46-3.54 (1H, m, H-1), 4.22 (1H, d, *J* = 6.3 Hz, N-H), 4.58 (1H, d, *J* = 8.9 Hz, H-8), 6.21 (1H, d, *J* = 3.2 Hz, H-6), 7.10-7.14 (4H, m, Ar-H), 7.20-7.32 (6H, m, Ar-H), 8.00-8.03 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.3, 15.4, 15.5 (C-12, C-14 and C-16), 21.7 (C-4), 22.8 (C-10), 25.9 (C-3), 28.5, 28.5, 29.0 (C-11, C-13 and C-15), 52.4 (C-2), 53.8 (C-5), 56.0 (C-9), 64.1 (C-1), 74.1 (C-6), 78.3 (C-8), 125.9 (2 × Ar-CH), 126.6 (2 × Ar-CH), 127.8 (2 × Ar-CH), 127.8 (Ar-C), 127.9 (2 × Ar-CH), 128.1 (2 × Ar-CH), 129.9 (2 × Ar-CH), 137.4 (Ar-C), 140.5 (Ar-C), 143.4 (Ar-C), 143.5 (Ar-C), 150.4 (Ar-C), 165.8 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{48}NO_4S$ $[M + H]^+$: 590.3299, found 590.3285.

(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-isopropylphenyl)methyl)cyclopentyl)(4-isopropylphenyl)methyl 4-isopropylbenzoate, (*S,S,R,R,R,S*)-94

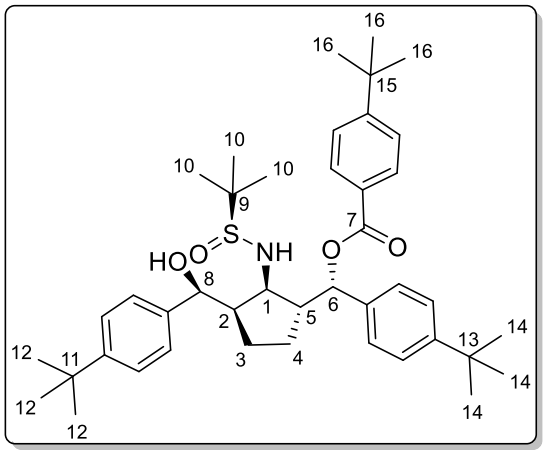


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-isopropylbenzaldehyde (0.50 mL, 3.3 mmol). The crude compound (91:9 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound (mixture of isomers) as a pale yellow solid (0.257 g, 41%).

***Major diastereomer**:*

M.p. 71-74 °C. $[\alpha]_D^{25}$ + 51.34 (c 0.225, CH_2Cl_2). IR ν_{max} (ATR): 3235 (N-H stretch), 2927 (C-H stretch) 1721 (C=O stretch), 1180 (C-N stretch), 1053 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13-1.32 (2H, m, H-3, 3 x 6H, d, *J* = 6.7 Hz, H-12, H14, H-16 and 9H, s H-10), 1.52-1.62 (1H, m, one of H-4), 1.72-1.86 (1H, m, one of H-4), 2.31-2.50 (2H, m, H-2, H-5), 2.78-3.05 (3 × 1H, septet, *J* = 7.3 Hz, H-11, H-13 and H-15, overlapping), 3.45-3.56 (1H, m, H-1), 4.41 (1H, d, *J* = 6.4 Hz, N-H), 4.60 (1H, d, *J* = 8.9 Hz, H-8), 6.21 (1H, d, *J* = 3.6 Hz, H-6), 7.13-7.34 (10H, m, Ar-H), 7.98-8.04 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.7 (C-4), 22.8 (C-10), 23.7, 23.9, 24.0 (C12, C-14 and C-16), 26.1 (C-3), 33.7, 33.8, 34.3 (C-11, C-13 and C-15), 52.2 (C-2), 53.6 (C-5), 56.1 (C-9), 64.3 (C-1), 74.1 (C-6), 78.4 (C-8), 125.9 (2 × Ar-CH), 126.3 (2 × Ar-CH), 126.5 (2 × Ar-CH), 126.6 (2 × Ar-CH), 126.7 (2 × Ar-CH), 127.9 (Ar-C), 129.9 (2 × Ar-CH), 137.5 (Ar-C), 140.5 (Ar-C), 148.0 (Ar-C), 148.1 (Ar-C), 154.6 (Ar-C), 165.7 (C-7) ppm. HRMS (ESI) *m/z* calcd for $C_{39}H_{54}NO_4SH$ $[M + H]^+$: 632.3768, found 632.3763.

(*S*)-(4-(*tert*-butyl)phenyl)((1*R*,2*R*,3*R*)-3-((*S*)-(4-(*tert*-butyl)phenyl)(hydroxy)methyl)-2-(((*S*)-*tert*-butylsulfinyl)amino)cyclopentyl)methyl 4-(*tert*-butyl)benzoate, (*S,S,R,R,R,S*)-95

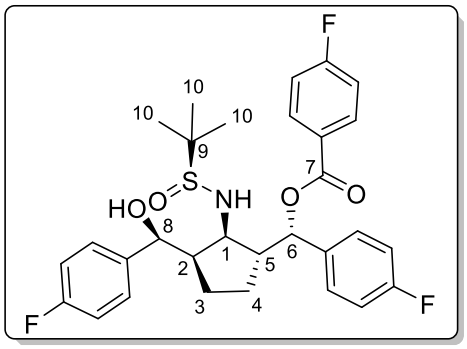


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-*tert*-butyllbenzaldehyde (0.55 mL, 3.3 mmol). The crude compound (92:8 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound (0.316 g, 47%).

***Major diastereomer**:*

M.p. 94-97 °C. $[\alpha]_D^{25}$ + 51.3 (c 0.225, CH_2Cl_2). IR ν_{max} (ATR): 3271 (N-H stretch), 2962 (C-H stretch) 1722 (C=O stretch), 1176 (C-N stretch), 1033 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-1.36 (4 x 9H, s, H-10, H-12, H-14 and H-16 and 2H, m, H-3, overlapping), 1.42-1.62 (1H, m, one of H-4), 1.72-1.86 (1H, m, one of H-4), 2.30-2.51 (2H, m, H-2 and H-5), 3.48-3.56 (1H, m, H-1), 4.33 (1H, d, *J* = 6.4 Hz, N-H), 4.60 (1H, d, *J* = 8.9 Hz, H-8), 6.21 (1H, d, *J* = 3.5 Hz, H-6), 7.21-7.32 (8H, m, Ar-H), 7.48-7.51 (2H, m, Ar-H), 8.03-8.06 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8 (C-4), 22.8 (C-10), 26.1 (C-3), 31.2, 31.3, 31.4 (C-12, C-14 and C-16), 34.5, 35.1 (C-11, C-13 and C-15, overlapping), 52.3 (C-2), 53.6 (C-5), 56.0 (C-9), 64.2 (C-1), 74.1 (C-6), 78.3 (C-8), 125.2 (2 × Ar-CH), 125.3 (2 × Ar-CH), 125.5 (2 × Ar-CH), 125.7 (2 × Ar-CH), 126.3 (2 × Ar-CH), 127.6 (Ar-C), 129.6 (2 × Ar-CH), 137.1 (Ar-C), 140.2 (Ar-C), 150.3 (Ar-C), 150.4 (Ar-C), 156.8 (Ar-C), 165.7 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{42}H_{59}NO_4SNa$ $[M + Na]^+$: 696.4057, found 696.4054.

(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3-((*S*)-(4-fluorophenyl)(hydroxy)methyl)cyclopentyl)(4-fluorophenyl)methyl 4-fluorobenzoate, (*S,S,R,R,R,S*)-96

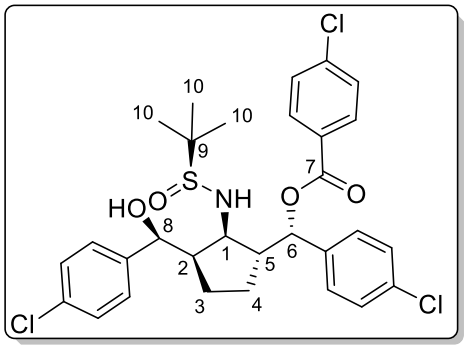


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-chlorobenzaldehyde (0.35 mL, 3.3 mmol). The crude compound (87:13 *dr*) was purified by column chromatography on silica gel ((2:1 hexane:EtOAc) to give the title compound (0.273 g, 49%).

***Major diastereomer**:*

M.p. 65-67 °C. $[\alpha]_D^{25}$ + 19.8 (c 2.82, CH_2Cl_2). IR ν_{max} (ATR): 3264 (N-H stretch), 2961 (C-H stretch), 1723 (C=O stretch), 1154 (C-N stretch), 1089 (S=O stretch) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.20-1.35 (2H, m, H-3 and 9H, s, H-10, overlapping), 1.48-1.55 (1H, m, one of H-4), 1.70-1.77 (1H, m, one of H-4), 2.27 (1H, quin, *J* = 9.0 Hz, H-2), 2.40 (1H, dq, *J* = 9.2, 3.5 Hz, H-5), 3.42-3.48 (1H, m, H-1), 4.20 (1H, d, *J* = 6.1 Hz, N-H), 4.61 (1H, d, *J* = 9.0 Hz, H-8), 6.21 (1H, d, *J* = 3.2 Hz, H-6), 6.95-7.03 (4H, m, Ar-H), 7.14-7.19 (2H, m, Ar-H), 7.25-7.32 (4H, m, Ar-H), 8.07-8.10 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (C-4), 22.8 (C-10), 25.5 (C-3), 52.4 (C-2), 53.6 (C-5), 56.1 (C-9), 63.8 (C-1), 73.6 (C-6), 77.6 (C-8), 115.2 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, 2 × Ar-CH), 115.5 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, 2 × Ar-CH), 115.8 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, 2 × Ar-CH), 126.1 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 127.5 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, 2 × Ar-CH), 128.2 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, 2 × Ar-CH), 132.2 (d, $^3J_{C\text{-}F}$ = 9.4 Hz, 2 × Ar-CH), 135.6 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 138.9 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 162.2 (d, $^1J_{C\text{-}F}$ = 245.4 Hz, Ar-C), 162.3 (d, $^1J_{C\text{-}F}$ = 246.0 Hz, Ar-C), 164.7 (C-7), 166.1 (d, $^1J_{C\text{-}F}$ = 254.9 Hz, Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{32}NO_4SF_3$ $[M + Na]^+$: 582.1896, found 582.1892.

(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*tert*-butylsulfinyl)amino)-3-((*S*)-(4-chlorophenyl)(hydroxy)methyl)cyclopentyl)(4-chlorophenyl)methyl 4-chlorobenzoate, (*S,S,R,R,R,S*)-*97*

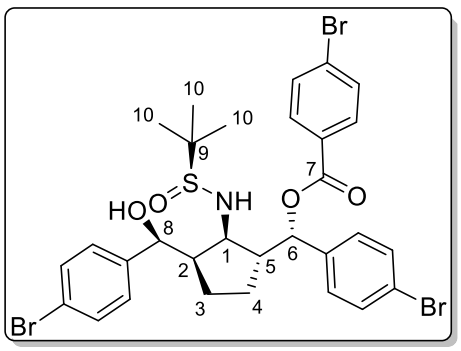


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-chlorobenzaldehyde (0.464 g, 3.3 mmol). The crude compound (*dr* nd) was purified by column chromatography on silica gel (2:1 hexane:EtOAc) to give the title compound (0.171 g, 29%, single diastereomer).

***Major diastereomer**:*

M.p. 100-103 °C. $[\alpha]_D^{25}$ + 12.3 (c 0.130, CH_2Cl_2). IR ν_{max} (ATR): 3313 (N-H stretch), 2959 (C-H stretch), 1726 (C=O stretch), 1171 (C-N stretch), 1092 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22-1.36 (2H, m, H-3 and 9H, s, H-10, overlapping), 1.44-1.56 (1H, m, one of H-4), 1.64-1.77 (1H, m, one of H-4), 2.26 (1H, quin, *J* = 8.9 Hz, H-2), 2.38 (1H, dq, *J* = 9.0, 3.4 Hz, H-5), 3.43 (1H, ddd, *J* = 9.4, 6.5, 3.0 Hz, H-1), 4.19 (1H, d, *J* = 6.4 Hz, N-H), 4.60 (1H, d, *J* = 8.8 Hz, H-8), 6.19 (1H, d, *J* = 3.3 Hz, H-6), 7.21-7.30 (8H, m, Ar-H), 7.46-7.49 (2H, m, Ar-H), 7.99 (2H, d, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2 (C-4), 22.7 (C-10), 25.4 (C-3), 52.2 (C-2), 53.5 (C-5), 56.1 (C-9), 63.9 (C-1), 73.6 (C-6), 77.7 (C-8), 127.2 (2 × Ar-CH), 128.0 (2 × Ar-CH), 128.2 (Ar-C), 128.5 (2 × Ar-CH), 128.8 (2x Ar-CH), 129.0 (2 × Ar-CH), 131.0 (2 × Ar-CH), 133.2 (Ar-C), 133.6 (Ar-C), 138.2 (Ar-C), 140.2 (Ar-C), 151.5 (Ar-C), 164.8 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{32}NO_4SCl_3$ $[M + H]^+$: 608.1190, found 608.1187.

(*S*)-(4-bromophenyl)((1*R*,2*R*,3*R*)-3-((*S*)-(4-bromophenyl)(hydroxy)methyl)-2-(((*S*)-*tert*-butylsulfinyl)amino)cyclopentyl)methyl 4-bromobenzoate, (*S,S,R,R,R,S*)-*98*

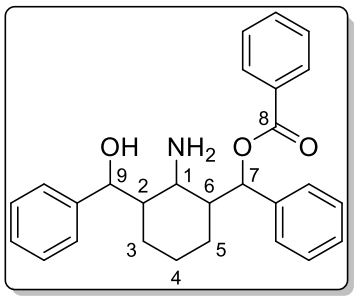


Prepared according to the general procedure outlined above using (*S*)-*N*-cyclopentylidene-2-methylpropane-2-sulfinamide (0.187 g, 1 mmol) and 4-bromobenzaldehyde (0.610 g, 3.3 mmol). The crude compound (*dr* nd) was purified by column chromatography on silica gel (2:1 hexane:EtOAc) to give the title compound as a pale yellow solid (0.215 g, 29%, single diastereomer).

***Major diastereomer**:*

M.p. 66-69 °C. $[\alpha]_D^{25}$ + 12.8 (c 0.17, CH_2Cl_2). IR ν_{max} (ATR): 3259 (N-H stretch), 2924 (C-H stretch), 1725 (C=O stretch), 1173 (C-N stretch), 1100 (S=O stretch) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.20-1.34 (2H, m, H-3 and 9H, s, H-10, overlapping), 1.44-1.53 (1H, m, one of H-4), 1.64-1.73 (1H, m, one of H-4), 2.26 (1H, quin, *J* = 9.0 Hz, H-2), 2.36 (1H, dq, *J* = 9.0, 3.2 Hz, H-5), 3.40-3.46 (1H, m, H-1), 4.30 (1H, d, *J* = 6.4 Hz, N-H), 4.60 (1H, d, *J* = 8.8 Hz, H-8), 6.16 (1H, d, *J* = 3.2 Hz, H-6), 7.16-7.19 (4H, m, Ar-H), 7.39-7.45 (4H, m, Ar-H), 7.62-7.65 (2H, m, Ar-H), 7.89-7.94 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (C-4), 22.8 (C-10), 25.4 (C-3), 52.3 (C-2), 53.4 (C-5), 56.2 (C-9), 63.6 (C-1), 73.9 (C-6), 77.4 (C-8), 121.4 (Ar-C), 121.7 (Ar-C), 127.5 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.6 (Ar-C), 128.7 (Ar-C), 131.1 (2 × Ar-CH), 131.4 (2 × Ar-CH), 131.7 (2 × Ar-CH), 132.1 (2 × Ar-CH), 138.8 (Ar-C), 141.9 (Ar-C), 164.9 (C-7) ppm. HRMS (ESI) *m/z* calcd for $C_{30}H_{33}NO_4SBr_3$ $[M + H]^+$: 739.9675, found 739.9677.

3.14.2 Synthesis of (2-amino-3-(hydroxy(phenyl)methyl)cyclohexyl)(phenyl)methyl benzoate, 103



To a Schlenk tube under N_2 atmosphere containing diisopropylamine (0.03 mLs, 0.44 mmol) and anhydrous THF (2.5 mL) was added *n*-BuLi (0.2 mLs, 2.0 M in hexanes, 0.4 mmol) dropwise at 0 °C. The resulting solution was stirred for 30 mins before being cooled to -78 °C. Sulfinyl imine (0.101 g, 0.5 mmol) was added dropwise and stirred for 1 h at this temperature. Freshly distilled benzaldehyde (0.17 mLs, 1.65 mmol) was added dropwise and the temperature was maintained at -78 °C for a further 3 hours. The reaction mixture was warmed to -20 °C over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure (68:27:5 *dr*). Purification by column chromatography on silica gel (2:1 hexane:EtOAc) yielded the title compound (0.054 g, 26 %, minor impurities remained after column chromatography).

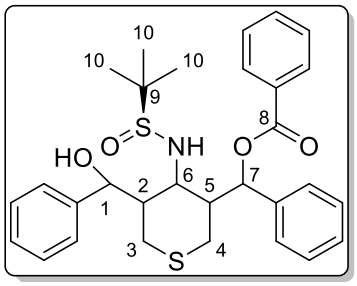
***Major diastereomer**:*

M.p. 86-89 °C. $[\alpha]_D^{25}$ + 18.3 (c 0.13, CH_2Cl_2). IR ν_{max} (ATR): 3417 (N-H stretch), 2928 (C-H stretch), 1723 (C=O stretch), 1177 (C-N stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.66-1.93 (8H, m, H-2, H-3, H-4, H-5 and H-6), 3.50 (1H, t, *J* = 9.9 Hz, H-1), 3.79-4.41 (2H, bs, NH_2), 4.54 (1H, d, *J* = 8.9 Hz, H-9), 6.66 (1H, d, *J* = 1.7 Hz, H-7), 7.20-7.67 (13H, m, Ar-H), 8.17-8.20 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.3 (C-5), 24.6 (C-4), 28.1

(C-3), 49.3 (C-2), 51.8 (C-5), 74.0 (C-7), 76.4 (C-1), 81.0 (C-9), 125.8 (2 × Ar-CH), 127.2 (2 × Ar-CH), 127.4 (Ar-CH), 127.7 (Ar-CH), 128.3 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.7 (2 × Ar-CH), 129.7 (Ar-C), 130.0 (2 × Ar-CH), 133.6 (Ar-CH), 139.2 (Ar-C), 142.9 (Ar-C), 167.1 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{23}NO$ $[M + H]^+$: 294.1852, found 294.1850.

Note: The absolute stereochemistry of this compound could not be determined.

3.14.3 Synthesis of (4-(((*S*)-*tert*-butylsulfinyl)amino)-5-(hydroxy(phenyl)methyl)tetrahydro-2H-thiopyran-3-yl)(phenyl)methyl benzoate, (*S*)-109



To a Schlenk tube under N_2 atmosphere containing diisopropylamine (0.17 mLs, 1.2 mmol) and anhydrous THF (5 mLs) was added *n*-BuLi (0.55 mLs, 2.0 M in hexanes, 1.1 mmol) dropwise at 0 ℃. The resulting solution was stirred for 30 mins before being cooled to -78 ℃. Sulfinyl imine (0.173 g, 1 mmol) was added dropwise and stirred for 1 h at this temperature. Freshly distilled benzaldehyde (0.34 mLs, 3.3 mmol) was added dropwise and the temperature was maintained at -78 ℃ for a further 3 hours. The reaction mixture was warmed to -20 ℃ over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification of the crude product (50:50 *dr*) by column chromatography on silica gel (2:1 hexane:EtOAc) yielded the title compound as a sticky yellow oil (0.123 g, 23 %, 50:50 mixture of diastereomers).

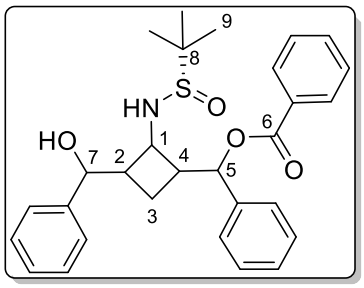
Note: Where possible, NMR signals were assigned to individual diastereomers, denoted by $_a$ or $_b$. Where no subscript label is attached, it was not possible to distinguish between diastereomers and assignment relates to either or diastereomer in the mixture.

$[\alpha]_D^{25}$ - 167.1 (c 0.32, CH_2Cl_2). IR ν_{max} (ATR): 3219 (N-H stretch), 2925 (C-H stretch) 1721 (C=O stretch), 1177 (C-N stretch), 1069 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.25, 1.27 (2 × 9H, s, H-9), 1.77 (1H, d, *J* = 14.1 Hz, one of H-4_a), 2.17-2.23 (2H, m, one of H-3_a and one of H-3_b), 2.30 (1H, d, *J* = 11.2 Hz, H-2_b), 2.54-2.63 (2H, m, H-5a and one of 4_b), 2.69 (1H, dd, *J* = 12.3, 2.1 Hz, H-2_a), 2.78 (1H, dq, *J* = 10.0, 3.2 Hz, H-5_b), 2.97 (2H, unresolved dq, *J* = 8.7, 2.3 Hz, one of H-3_a and one of H-3_b), 3.10 (1H, dd, *J* = 14.1, 3.2 Hz, one of H-4_a), 3.25 (1H, dd, *J* = 13.8, 2.4 Hz, one of H-4_b), 3.30 (1H, d, *J* = 1.7 Hz, H-6_b), 4.12 (1H, bs, H-6_a), 4.58 (1H, bs, H-1_b), 4.82 (1H, bs, H-1_a), 5.28 (1H, bs, N_b-H), 5.43 (1H, bs, N_a-H), 6.55 (1H, d, *J* = 10.2 Hz, H-7_b), 6.70 (1H, d, *J* = 10.7 Hz, H-7_a), 7.14-7.60 (28H, m, Ar-

H), 8.00 (2H, d, J = 7.6 Hz, Ar-H_b), 8.09 (2H, d. J = 7.6 Hz, Ar-H_a) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.4 (2 × C-3), 22.8, 22.8 (C-10), 23.6 (C-4_a), 23.8 (C-4_b), 42.8 (C-2_a), 43.3 (C-2_b), 44.6 (C-5_b), 45.1 (C-5_a), 54.4 (C-6_a), 55.0 (C-6_b), 55.7, 55.8 (C-9), 74.3 (C-7_b), 75.1 (C-7_a), 76.7 (C-1_b), 76.9 (C-1_a), 125.3 (2 × Ar-CH), 125.5 (2 × Ar-CH), 127.2 (Ar-CH), 127.2 (2 × Ar-CH), 127.3 (2 × Ar-CH), 127.4 (Ar-CH), 128.3 (4 x Ar-CH), 128.4 (2 × Ar-CH), 128.5 (Ar-CH), 128.6 (2 × Ar-CH), 128.7 (2 × Ar-CH), 129.0 (Ar-CH), 129.1 (2 × Ar-CH), 129.6 (2 × Ar-CH), 129.8 (2 × Ar-CH), 129.8 (Ar-C), 130.0 (Ar-C), 133.0 (Ar-C), 133.2 (2 × Ar-CH), 137.8 (Ar-C), 138.8 (Ar-C), 142.7 (Ar-C), 142.8 (Ar-C), 165.3 (C-8_b), 165.8 (C-8_a) ppm. HRMS (ESI) m/z calcd for $C_{30}H_{36}NO_4S_2$ $[M + H]^+$: 538.2080, found 538.2075.

Note: The absolute stereochemistry of this compound could not be determined.

3.14.4 Synthesis of cyclobutanone derived 3-amino-1,5-diol precursors (2-(((*S*)-*tert*-butylsulfinyl)amino)-3-(hydroxy(phenyl)methyl)cyclobutyl)(phenyl)methyl benzoate, (*S*)-*110*



To a Schlenk tube under N_2 atmosphere containing diisopropylamine (0.17 mLs, 1.2 mmol) and anhydrous THF (5 mLs) was added *n*-BuLi (0.55 mLs, 2.0 M in hexanes, 1.1 mmol) dropwise at 0 ℃. The resulting solution was stirred for 30 mins before being cooled to -78 ℃. Sulfinyl imine (0.173 g, 1 mmol) was added dropwise and stirred for 1 h at this temperature. Freshly distilled benzaldehyde (0.34 mLs, 3.3 mmol) was added dropwise and the temperature was maintained at -78 ℃ for a further 3 hours. The reaction mixture was warmed to -20 ℃ over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to RT. The reaction was diluted with NH_4Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered free of the drying agent and concentrated under reduced pressure to give crude product (75:25 *dr*). Purification by column chromatography on silica gel (2:1 hexane:EtOAc) yielded the title compound as a colourless sticky oil (0.187 g, 38 %. *Major*: 0.144g, 29%. *Minor:* 0.43 g. 9%).

***Major diastereomer**:*

$[\alpha]_D^{25}$ + 6.4 (c 1.03, CH_2Cl_2). IR ν_{max} (ATR): 3278 (N-H stretch), 2927 (C-H stretch) 1720 (C=O stretch), 1176 (C-N stretch), 1069 (S=O stretch) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, S, H-9), 1.39-1.48 (1H, m, one of H-3), 1.61-1.70 (1H, m, one of H-3), 2.40-2.43 (1H, m, H-2), 2.49-2.57 (1H, m, H-4), 3.55 (1H, q, J = 8.6 Hz, H-1), 3.81 (1H, d, J = 9.2 Hz, N-H), 4.66 (1H, d, J = 8.7 Hz, H-7), 5.95 (1H, d, J = 6.3 Hz, H-5), 7.19-7.56 (13H, m, Ar-H), 8.02-8.04 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (C-3), 21.9 (C-9), 46.4 (C-

4), 50.6 (C-2), 55.6 (C-8), 58.8 (C-1), 77.3 (C-5), 78.4 (C-7), 126.4 (2 × Ar-CH), 126.7 (2 × Ar-CH), 127.5 (Ar-CH), 128.1 (Ar-CH), 128.3 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.5 (2 × Ar-CH), 129.6 (2 × Ar-CH), 130.2 (Ar-C), 133.2 (Ar-CH), 138.8 (Ar-C), 142.2 (Ar-C), 165.6 (C-6) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{33}NO_4SNa$ $[M + Na]^+$: 514.2015, found 514.2015.

***Minor diastereomer**:*

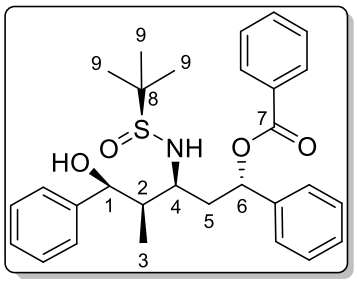
$[\alpha]_D^{25}$ - 54.0 (c 0.34, CH_2Cl_2). IR ν_{max} (ATR): 3294 (N-H stretch), 2927 (C-H stretch), 1720 (C=O stretch), 1176 (C-N stretch), 1069 (S=O stretch) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.10 (9H, s, H-9), 1.33-1.49 (1H, m, one of H-3), 1.78-1.86 (1H, m, one of H-3), 2.79-2.96 (2H, m, H-2 and H-4), 3.91-3.98 (1H, m, H-1), 4.36 (1H, d, *J* = 10.0 Hz, N-H), 4.75 (1H, d, *J* = 10.7 Hz, H-7), 6.00 (1H, d, *J* = 6.3 Hz, H-5), 7.25-7.57 (13H, m, Ar-H), 8.02-8.08 (2H, m, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (C-3), 22.5 (C-9), 45.1 (C-2), 47.5 (C-4), 54.4 (C-1), 55.7 (C-8), 73.2 (C-7), 77.2 (C-5), 126.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 128.3 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.7 (2 × Ar-CH), 130.1 (Ar-C), 133.2 (Ar-CH), 138.7 (Ar-C), 142.3 (Ar-C), 165.6 (C-6) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{33}NO_4SNa$ $[M + Na]^+$: 514.2023, found 514.2019.

Note: The absolute stereochemistry of this compound could not be determined.

3.14.5 Synthesis of 2-butanone derived 3-amino-1,5-diol precursors

To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinyl imine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 ℃. The resulting solution was stirred for 30 mins before being cooled to -78 ℃. Sulfinyl imine (1 equiv.) was added dropwise and stirred for 1 h at this temperature. Freshly distilled aldehyde (3.3 equiv.) was added dropwise and the temperature was maintained at -78 ℃ for a further 3 hours. The reaction mixture was warmed to -20 ℃ over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography on silica gel yielded pure double aldol-Tishchenko product.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-diphenylpentyl benzoate, **(*S*,*S*,*R*,*S*,*S*)-127**



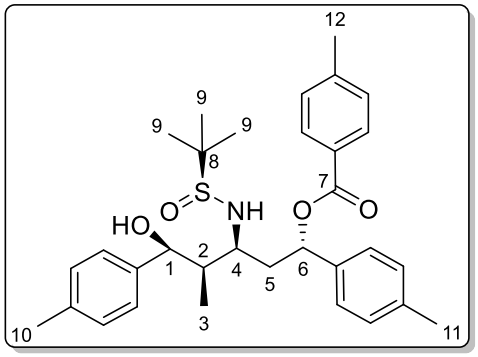
Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and benzaldehyde (0.34 mL, 3.3 mmol). The crude compound (87:13 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.207 g, 42%).

Spectroscopic characteristics were consistent with previously reported data.[38]

***Major diastereomer**:*

$[\alpha]_D^{20}$ + 42.1 (c 0.38, CH_2Cl_2) (lit.[38] $[\alpha]_D^{20}$ + 60.4 (c 0.25, $CHCl_3$)). IR ν_{max} (ATR): 3309 (N-H stretch), 2962 (O-H stretch), 1719 (C=O stretch), 1176 (C-N stretch), 1068 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 7.1 Hz, H-3), 1.30 (9H, s, H-9), 2.00-2.10 (2H, m, H-2 and one of H-5), 2.15-2.25 (1H, m, one of H-5), 3.77-3.90 (1H, m, H-4), 4.28-4.32 (2H, m, O-H, N-H), 5.04 (1H, bs, H-1), 6.08 (1H, dd, *J* = 10.4, 3.6 Hz, H-6), 7.17-7.49 (12H, m, Ar-H), 7.53-7.60 (1H, m, Ar-H), 8.02-8.06 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.0 (C-3), 22.9 (C-9), 43.2 (C-5), 44.3 (C-2), 56.5 (C-8), 58.0 (C-4), 73.5 (C-6), 75.8 (C-1), 125.8 (2 × Ar-CH), 126.2 (2 × Ar-CH), 126.8 (Ar-CH), 128.1 (2 × Ar-CH), 128.2 (Ar-CH), 128.5 (2 × Ar-CH), 128.7 (2 × Ar-CH), 129.6 (2 × Ar-CH), 130.2 (Ar-C), 133.1 (Ar-CH), 140.0 (Ar-C), 144.0 (Ar-C), 165.7 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{36}NO_4S$ $[M + H]^+$: 494.2559, found 494.2357.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-di-*p*-tolylpentyl 4-methylbenzoate, (*S*,*S*,*R*,*S*,*S*)-128



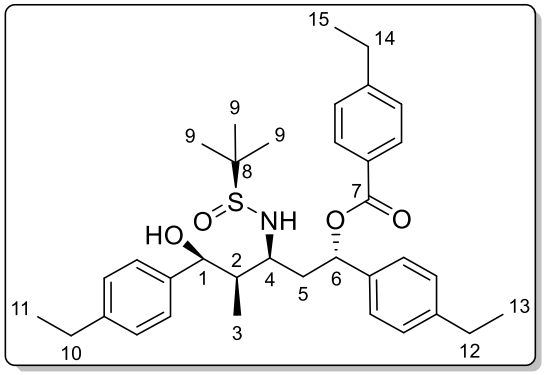
Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-methylbenzaldehyde (0.39 mL, 3.3 mmol). The crude compound (88:12 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.187 g, 35%).

Spectroscopic characteristics were consistent with previously reported data.[38]

***Major diastereomer**:*

M.p. 93-94 °C.$[\alpha]_D^{20}$ + 66.3 (c 0.20, CH_2Cl_2) (lit.[38] $[\alpha]_D^{20}$ + 78.0 (c 0.10, $CHCl_3$)). IR ν_{max} (ATR): 3228 (N-H stretch), 2957 (O-H stretch), 1717 (C=O stretch), 1177 (C-N stretch), 1042 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, d, *J* = 7.1 Hz, H-3), 1.30 (9H, s, H-9), 1.97-2.06 (2H, m, H-2 and one of H-5), 2.11-2.22 (1H, m, one of H-5), 2.32, 2.44 (3 × 3H, s, H-10, H-11 and H12, overlapping), 3.74-3.86 (1H, m, H-4), 4.11-4.24 (2H, m, O-H, N-H), 5.00 (1H, bs, H-1), 6.01 (1H, dd, *J* = 10.1, 3.8 Hz, H-6), 7.10-7.16 (3H, m, Ar-H), 7.20-7.28 (7H, m, Ar-H), 7.91-7.94 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.0 (C-3), 21.0, 21.1, 21.7 (C-10, C-11 and C-12), 22.9 (C-9), 43.2 (C-5), 44.2 (C-2), 56.4 (C-8), 58.0 (C-4), 73.1 (C-6), 75.8 (C-1), 125.7 (2 × Ar-CH), 126.2 (2 × Ar-CH), 127.6 (Ar-C), 128.8 (2 × Ar-CH), 129.1 (2 × Ar-CH), 129.3 (2 × Ar-CH), 129.7 (2 × Ar-CH), 136.3 (Ar-C), 137.8 (Ar-C), 137.9 (Ar-C), 141.0 (Ar-C), 143.7 (Ar-C), 165.8 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{41}NO_4SNa$ $[M + Na]^+$: 558.2649, found 558.2650.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-tert-butylsulfinyl)amino)-1,5-bis(4-ethylphenyl)-5-hydroxy-4-methylpentyl 4-ethylbenzoate, (*S*,*S*,*R*,*S*,*S*)-129



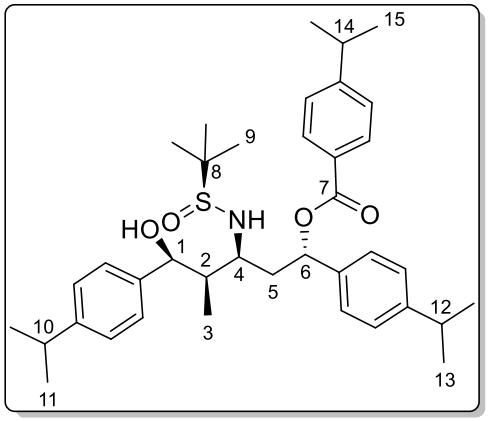
Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-chlorobenzaldehyde (0.45 mL, 3.3 mmol). The crude compound (89:11 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a colourless oil (0.220g, 38%).

***Major diastereomer**:*

M.p. 96-98 °C. $[\alpha]_D^{20}$ + 44.7 (c 0.20, CH_2Cl_2). IR ν_{max} (ATR): 3307 (N-H stretch), 2964 (C-H stretch), 1716 (C=O stretch), 1177 (C-N stretch), 1099 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 7.0 Hz, H-3), 1.21, 1.22, 1.26 (3 × 3H, t, *J* = 7.6 Hz, H-11, H-13 and H-15) 1.30 (9H, s, H-9), 1.98-2.09 (2H, m, H-2 and one of H-5), 2.14-2.24 (1H, m, one of H-5), 2.62, 2.71 (3 × 2H, q, *J* = 7.4 Hz, H-10, H-12 and H-14, overlapping) 3.75-3.85 (1H, m, H-4), 4.11 (1H, bs, N-H), 4.21 (1H, d, *J* = 6.8 Hz, O-H), 5.01 (1H, bs, H-1), 6.04 (1H, dd, *J* = 10.3, 3.6 Hz, H-6), 7.13-7.31 (10H, m, Ar-H), 7.96 (2H, d, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.1 (C-3), 15.3, 15.4, 15.5 (C11, C-13 and C-15), 22.9 (C-9), 28.4, 28.5, 29.0 (C-10, C-12 and C-14), 43.2 (C-5), 44.2 (C-2), 56.4 (C-8), 58.1 (C-4), 73.1 (C-6),

75.8 (C-1), 125.8 (2 × Ar-CH), 126.3 (2 × Ar-CH), 127.6 (2 × Ar-CH), 128.0 (2 × Ar-CH), 128.1 (2 × Ar-CH), 129.8 (2 × Ar-CH), 138.0 (Ar-C), 141.3 (Ar-C), 142.7 (Ar-C), 144.1 (Ar-C), 142.4 (Ar-C), 165.8 (Ar-C), 173.9 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{47}NO_4SNa$ $[M + Na]^+$: 600.3118, found 600.3120.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-1,5-bis(4-isopropylphenyl)-4-methylpentyl 4-isopropylbenzoate, (*S*,*S*,*R*,*S*,*S*)-130

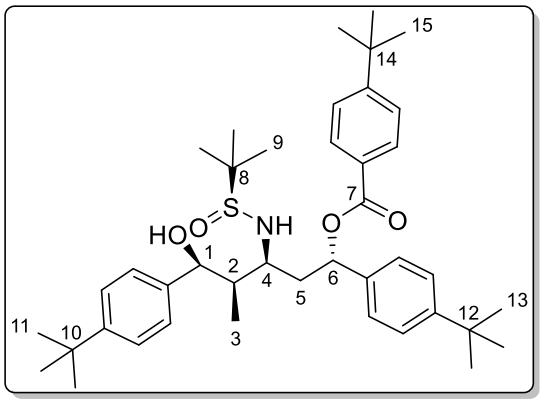


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-isopropylbenzaldehyde (0.50 mL, 3.3 mmol). The crude compound (80:20 *dr*) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a colourless oil (0.680 g, 37%).

***Major diastereomer**:*

M.p. 63-65 °C. $[\alpha]_D^{20}$ + 44.5 (c 0.20, CH_2Cl_2). IR ν_{max} (ATR): 3221 (N-H stretch), 2960 (C-H stretch) 1719 (C=O stretch), 1179 (C-N stretch), 1058 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.1 Hz, H-3), 1.19-1.32 (27H, m, H-9, H-11, H-13 and H-15), 1.97-2.13 (2H, m, H-2 and one of H-5), 2.14-2.26 (1H, m, one of H-5), 2.79-3.04 (3H, m, H-10, H-12 and H14), 3.78-3.82 (1H, m, H-4), 4.30 (1H, d, *J* = 6.5 Hz, N-H), 5.01 (1H, d, *J* = 1.9 Hz, H-1), 6.05 (1H, dd, *J* = 10.1, 3.6 Hz, H-6), 7.15-7.31 (10H, m, Ar-H), 7.97-8.00 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.2 (C-3), 22.9 (C-9), 23.7, 23.9, 24.0 (C-11, C13 and C-15), 33.7, 33.8, 34.3 (C-10, C-12 and C-14), 42.9 (C-5), 44.2 (C-2), 56.4 (C-8), 58.1 (C-4), 73.1 (C-6), 75.9 (C-1), 125.7 (2 × Ar-CH), 126.1 (2 × Ar-CH), 126.3 (2 × Ar-CH), 126.5 (2 × Ar-CH), 126.7 (2 × Ar-CH), 128.0 (Ar-C), 129.8 (2 × Ar-CH), 138.1 (Ar-C), 141.4 (Ar-C), 147.3 (Ar-C), 148.7 (Ar-C), 154.5 (Ar-C), 165.8 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{53}NO_4SNa$ $[M + Na]^+$: 642.3588, found 642.3582.

(1*S*,3*S*,4*R*,5*S*)-1,5-bis(4-(*tert*-butyl)phenyl)-3-(((*S*)-tert-butylsulfinyl)amino)-5-hydroxy-4-methylpentyl 4-(tert-butyl)benzoate, (*S*,*S*,*R*,*S*,*S*)-131

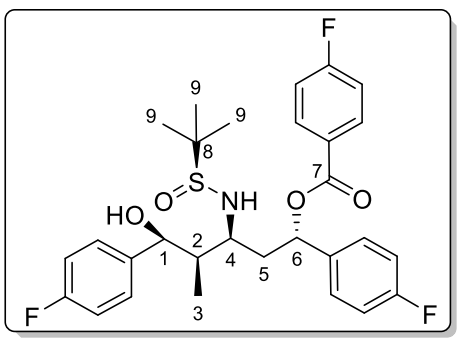


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-*tert*-butylbenzaldehyde (0.55 mL, 3.3 mmol). The crude compound (93:7 *dr*) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a colourless oil (0.870 g, 43%).

***Major diastereomer**:*

M.p. 101-103 °C. $[\alpha]_D^{25}$ + 44.1 (c 0.15, CH_2Cl_2). IR ν_{max} (ATR): 3259 (N-H stretch), 1632 (C=O stretch), 1137(C-N stretch), 1076 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0. 90 (3H, d, *J* = 7.1 Hz, H-3), 1.29, 1.30, 1.35 (4 × 9H, s, H-9, H-11, H-13 and H-15, overlapping), 1.99-2.14 (2H, m, H-2 and one of H-5), 2.15-2.27 (1H, m, one of H-5), 3.76-2.87 (1H, m, H-4), 4.09-4.32 (2H, m, N-H, O-H), 5.01 (1H, bs, H-1), 6.07 (1H, dd, *J* = 10.1, 3.4 Hz, H-6), 7.22-7.39 (10H, m, Ar-H), 7.46-7.49 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.3 (C-3), 22.9 (C-9), 31.1, 31.3, 31.4 (C-11, C-13 and C-15) 34.4, 34.6, 35.1 (C-10, C-12 and C-14), 42.9 (C-5), 44.2 (C-2), 56.4 (C-8), 58.2 (C-4), 73.0 (C-6), 75.8 (C-1), 125.0 (2 × Ar-CH), 125.4 (2 × Ar-CH), 125.5 (2 × Ar-CH), 125.6 (2 × Ar-CH), 126.0 (2 × Ar-CH), 127.6 (Ar-C), 129.5 (2 × Ar-CH), 137.7 (Ar-C), 141.0 (Ar-C), 149.6 (Ar-C), 150.9 (Ar-C), 156.7 (Ar-C), 165.7 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{41}H_{60}NO_4S$ $[M + H]^+$: 662.4238, found 662.4252.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(4-fluorophenyl)-5-hydroxy-4-methylpentyl 4-fluorobenzoate, (*S*,*S*,*R*,*S*,*S*)-132

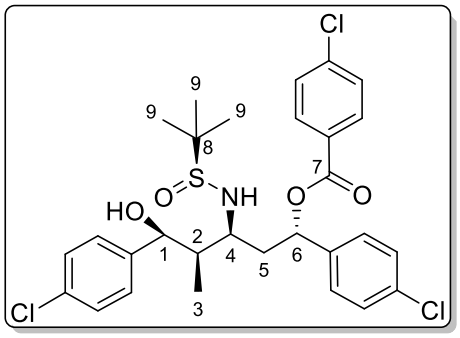


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-fluorobenzaldehyde (0.35 mL, 3.3 mmol). The crude compound (94:6 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.301 g, 55%).

***Major diastereomer**:*

M.p. 71-74 °C. $[\alpha]_D^{20}$ + 37.1 (c 0.28, CH_2Cl_2). IR ν_{max} (ATR): 3334 (N-H stretch), 2964 (O-H stretch), 1722 (C=O stretch), 1154 (C-N stretch), 1089 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 7.0 Hz, H-3), 1.31 (9H, s, H-9), 1.95-2.05 (2H, m, H-2 and one of H-5), 2.11-2.20 (1H, m, one of H-5), 3.70-3.78 (1H, m, H-4), 4.23 (1H, d, *J* = 6.7 Hz, N-H), 4.35 (1H, d, *J* = 4.9 Hz, O-H) 5.00-5.03 (1H, m, H-1), 6.04 (1H, dd, *J* = 10.3, 3.4 Hz, H-6), 6.95-7.20 (6H, m, Ar-H), 7.22-7.39 (4H, m, Ar-H), 8.00-8.05 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.0 (C-3), 22.8 (C-9), 43.1 (C-5), 44.4 (C-2), 56.6 (C-8), 57.6 (C-4), 72.9 (C-6), 75.1 (C-1), 114.9 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, 2 × Ar-CH), 115.6 (d, $^2J_{C\text{-}F}$ = 22.3 Hz, 4 × Ar-CH, overlapping), 126.2 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, Ar-C), 127.3 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 2 × Ar-CH), 128.1 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, 2 × Ar-CH), 131.1 (d, $^3J_{C\text{-}F}$ = 9.3 Hz, 2 × Ar-CH), 136.2 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 139.6 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, Ar-C), 161.8 (d, $^1J_{C\text{-}F}$ = 245.5 Hz, Ar-C), 162.4 (d, $^1J_{C\text{-}F}$ = 246.7 Hz, Ar-C), 164.7 (C-7), 165.9 (d, $^1J_{C\text{-}F}$ = 253.5 Hz, Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{32}F_3NO_4SNa$ $[M + Na]^+$: 570.1896, found 570.1897.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(4-chlorophenyl)-5-hydroxy-4-methylpentyl 4-chlorobenzoate, (*S*,*S*,*R*,*S*,*S*)-133

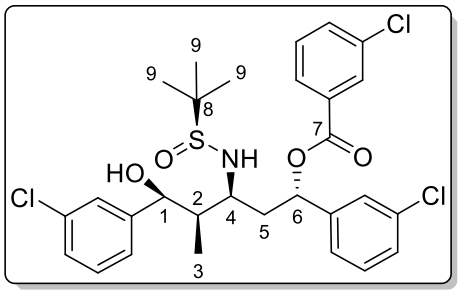


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-chlorobenzaldehyde (0.464 g, 3.3 mmol). The crude compound (> 99:1 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.287 g, 48%).

***Major diastereomer**:*

M.p. 95-97 °C. $[\alpha]_D^{20}$ + 64.6 (c 0.23, CH_2Cl_2). IR ν_{max} (ATR): 3339 (N-H stretch), 2962 (O-H stretch), 1723 (C=O stretch), 1171 (C-N stretch), 1092 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 7.1 Hz, H-3), 1.30 (9H, s, H-9), 1.92-2.07 (2H, m, H-2 and one of H-5), 2.08-2.19 (1H, m, one of H-5), 3.69-3.79 (1H, m, H-4), 4.27 (1H, d, *J* = 6.6 Hz, N-H), 4.47-4.48 (1H, m, O-H), 5.01 (1H, bs, H-1), 6.02 (1H, dd, *J* = 10.2, 3.3 Hz, H-6), 7.23-7.36 (8H, m, Ar-H), 7.42-7.46 (2H, m, Ar-H), 7.93-7.96 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.0 (C-3), 22.8 (C-9), 43.0 (C-5), 44.2 (C-2), 56.6 (C-8), 57.8 (C-4), 73.0 (C-6), 75.0 (C-1), 127.2 (2 × Ar-CH), 127.6 (2 × Ar-CH), 128.2 (2 × Ar-CH), 128.3 (Ar-C), 128.9 (2 × Ar-CH), 129.0 (2 × Ar-CH), 131.0 (2 × Ar-CH), 132.5 (Ar-C), 134.1 (Ar-C), 138.9 (Ar-C), 139.9 (Ar-C), 142.4 (Ar-C), 164.8 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{33}Cl_3NO_4S$ $[M + H]^+$: 596.1190, found 596.1191.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(3-chlorophenyl)-5-hydroxy-4-methylpentyl 3-chlorobenzoate, (*S*,*S*,*R*,*S*,*S*)-134

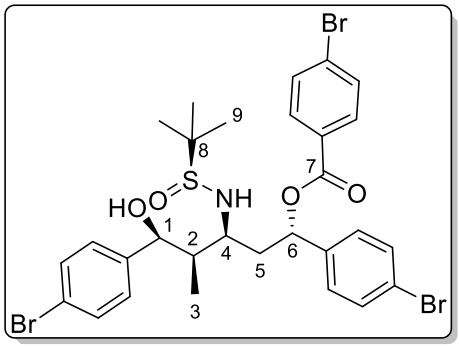


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 3-chlorobenzaldehyde (0.37 mL, 3.3 mmol). The crude compound (> 99:1 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a colourless oil (0.250 g,42 %).

***Major diastereomer**:*

M.p. 86-87 °C. $[\alpha]_D^{20}$ + 45.4 (c 0.28, CH_2Cl_2). IR ν_{max} (ATR): 3319 (N-H stretch), 2963 (O-H stretch), 1725 (C=O stretch), 1124 (C-N stretch), 1072 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 7.1 Hz, H-3), 1.32 (9H, s, H-9), 1.95-2.06 (2H, m, H-2 and one of H-5), 2.12-2.21 (1H, m, one of H-5), 3.77-3.85 (1H, m, H-4), 4.27 (1H, d, *J* = 6.5 Hz, N-H), 4.62 (1H, d, *J* = 5.3 Hz, O-H), 5.07 (1H, bs, H-1), 6.05 (1H, dd, *J* = 10.7, 3.1 Hz, H-6), 7.16-7.38 (9H, m, Ar-H), 7.42 (1H, t, *J* = 7.8 Hz, Ar-H), 7.56-7.60 (1H, m, Ar-H), 8.02-8.03 (1H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 5.7 (C-3), 22.9 (C-9), 43.2 (C-5), 44.2 (C-2), 56.7 (C-8), 57.8 (C-4), 73.1 (C-6), 75.1 (C-1), 123.9 (Ar-CH), 124.4 (Ar-CH), 125.9 (Ar-CH), 126.4 (Ar-CH), 126.9 (Ar-CH), 127.8 (Ar-CH), 128.5 (Ar-CH), 129.3 (Ar-CH), 129.7 (Ar-CH), 129.9 (Ar-CH), 130.2 (Ar-CH), 131.5 (Ar-C), 133.4 (Ar-CH), 134.1 (Ar-C), 134.7 (Ar-C), 134.8 (Ar-C), 142.4 (Ar-C), 146.1 (Ar-C), 164.4 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{33}Cl_3NO_4S$ $[M + H]^+$: 596.1190, found 596.1198.

(1*S*,3*S*,4*R*,5*S*)-1,5-bis(4-bromophenyl)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methylpentyl 4-bromobenzoate, (*S*,*S*,*R*,*S*,*S*)-135



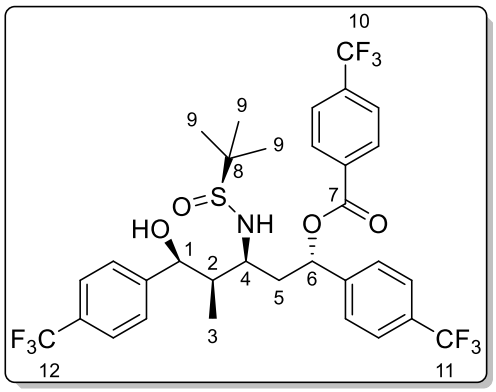
Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-bromobenzaldehyde (0.610 g, 3.3 mmol). The crude compound (86:14 *dr*) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a colourless oil (0.087 g, 12%).

***Major diastereomer**:*

M.p. 93-96 °C. $[\alpha]_D^{20}$ + 62.3 (c 0.653, CH_2Cl_2). IR ν_{max} (ATR): 3255 (N-H stretch), 1721 (C=O stretch), 1112 (C-N stretch), 1070 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0. 83

(3H, d, *J* = 7.1 Hz, H-3), 1.29 (9H, s, H-9), 1.90-2.05 (2H, m, H-2 and one of H-5), 2.09-2.19 (1H, m, one of H-5), 3.71-3.77 (1H, m, H-4), 4.32 (1H, d, *J* = 6.5 Hz, N-H), 4.54 (1H, bs, O-H), 4.96 (1H, s, H-1), 6.00 (1H, dd, *J* = 10.4, 3.2 Hz, H-6), 7.17-7.26 (4H, m, Ar-H), 7.38-7.51 (4H, m, Ar-H), 7.57-7.64 (2H, m, Ar-H), 7.85-7.90 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.0 (C-3), 22.8 (C-9), 42.7 (C-5), 44.1 (C-2), 56.6 (C-8), 57.5 (C-4), 73.1 (C-6), 75.0 (C-1), 120.6 (Ar-C), 122.2 (Ar-C), 127.6 (2 × Ar-CH), 127.9 (2 × Ar-CH), 128.5 (Ar-C), 128.7 (Ar-C), 131.1 (2 × Ar-CH), 131.2 (2 × Ar-CH), 131.9 (4 x Ar-CH), 139.4 (Ar-C), 143.0 (Ar-C), 164.9 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{32}Br_3NO_4SNa$ $[M + Na]^+$: 749.9499, found 749.9482.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-bis(4-(trifluoromethyl)phenyl)pentyl 4-(trifluoromethyl)benzoate, **(*S*,*S*,*R*,*S*,*S*)-136**

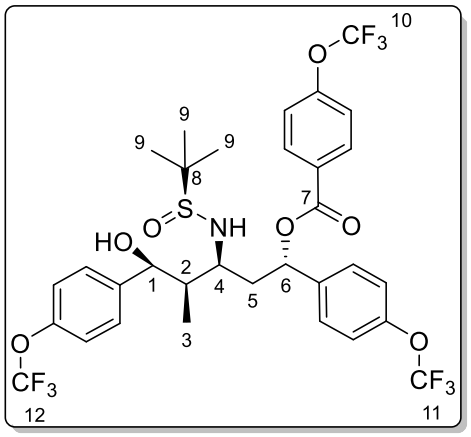


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-trifluoromethylbenzaldehyde (0.45 mL, 3.3 mmol). The crude compound (64:36 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.301 g, 43%).

***Major diastereomer**:*

$[\alpha]_D^{25}$ + 16.8 (c 0.11, CH_2Cl_2). IR ν_{max} (ATR): 3707 (N-H stretch), 3241 (O-H stretch), 1729 (C=O stretch), 1165 (C-N stretch), 1055 (C-O stretch) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 7.1 Hz, H-3), 1.34 (9H, s, H-9), 2.00-2.07 (2H, m, H-2 and one of H-5), 2.17-2.22 (1H, m, one of H-5), 3.89-3.93 (1H, m, H-4), 4.30 (1H, d, *J* = 6.7 Hz, N-H), 4.68 (1H, d, *J* = 5.2 Hz, O-H), 5.15 (1H, d, *J* = 4.5 Hz, H-1), 6.15 (1H, dd, *J* = 10.9, 2.6 Hz, H-7), 7.46 (2H, d, *J* = 8.2 Hz, Ar-H), 7.49 (2H, d, *J* = 8.2 Hz, Ar-H), 7.57 (2H, d, *J* = 8.2 Hz, Ar-H) 7.62 (2H, d, *J* = 8.2 Hz, Ar-H), 7.76 (2H, d, *J* = 8.6 Hz, Ar-H), 8.18 (2H, d, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.6 (C-3), 22.8 (C-9), 43.3 (C-5), 44.3 (C-2), 56.8 (C-8), 57.8 (C-4), 73.2 (C-6), 75.2 (C-1), 123.5, 123.8, 124.2 (q, $^1J_{C\text{-}F}$ = 272.6, 272.2, 271.8 Hz, respectively, C-10, C-11 and C-12), 125.0 (q, $^3J_{C\text{-}F}$ = 3.5 Hz, 2 × Ar-CH), 125.7 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, 2 × Ar-CH), 125.9 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-CH), 126.0 (2 × Ar-CH), 126.4 (2 × Ar-CH), 129.1 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, Ar-C), 130.0 (2 × Ar-CH), 130.6 (q, $^2J_{C\text{-}F}$ = 32.2 Hz, Ar-C), 132.8 (Ar-C), 135.0 (q, $^2J_{C\text{-}F}$ = 33.0 Hz, Ar-C), 144.2 (Ar-C), 147.8 (Ar-C), 164.5 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{33}F_9NO_4S$ $[M + H]^+$: 698.1981, found 698.1973.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-bis(4-(trifluoromethoxy)phenyl)pentyl 4-(trifluoromethoxy)benzoate, (*S*,*S*,*R*,*S*,*S*)-137

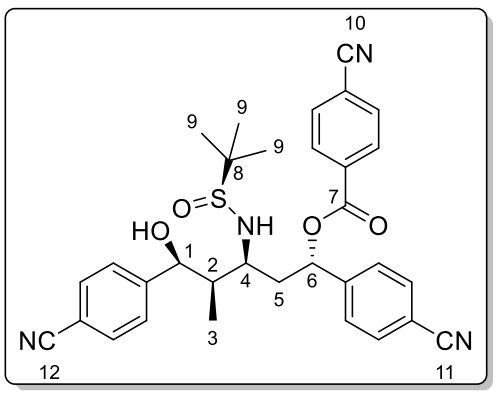


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-trifluoromethoxybenzaldehyde (0.47 mL, 3.3 mmol). The crude compound (> 99:1 *dr*) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a colourless oil (0.291 g, 52%).

***Major diastereomer**:*

M.p. 85-87 °C. $[\alpha]_D^{20}$ + 32.9 (c 0.24, CH_2Cl_2). IR ν_{max} (ATR): 3681 (N-H stretch), 3325 (O-H stretch), 2961 (C-H stretch), 1725 (C=O stretch), 1165 (C-N stretch), 1055 (S=O stretch) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0. 86 (3H, d, *J* = 7.1 Hz, H-3), 1.31 (9H, s, H-9), 1.98-2.07 (2H, m, H-2 and one of H-5), 2.15-2.21 (1H, m, one of H-5), 3.76-3.81 (1H, m, H-4), 4.33 (1H, d, *J* = 6.5 Hz, N-H), 4.62 (1H, d, *J* = 4.9 Hz, O-H), 5.04-5.07 (1H, m, H-1), 6.10 (1H, dd, *J* = 2.9, 10.5 Hz, H-6), 7.13 (2H, d, *J* = 8.1 Hz, Ar-H), 7.29 (2H, d, *J* = 7.8 Hz, Ar-H), 7.34-7.41 (6H, m, Ar-H), 8.07-8.10 (2H, m, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 5.9 (C-3), 22.8 (C-9), 42.9 (C-5), 44.3 (C-2), 56.6 (C-8), 57.7 (C-4), 72.9 (C-6), 74.9 (C-1), 120.3, 120.4, 120.5 (4 x q, $^1J_{C\text{-}F}$ = 258.9, 257.7, 256.9 Hz, respectively, C-10, C-11 and C-12), 120.4 (2 × Ar-CH), 120.5 (2 × Ar-CH), 121.3 (2 × Ar-CH), 127.1 (2 × Ar-CH), 127.7 (2 × Ar-CH), 128.2 (Ar-C), 131.6 (2 × Ar-CH), 139.0 (Ar-C), 142.6 (Ar-C), 148.0 (q, $^3J_{C\text{-}F}$ = 1.4 Hz, Ar-C), 149.0 (q, $^3J_{C\text{-}F}$ = 1.6 Hz, Ar-C), 153.0 (q, $^3J_{C\text{-}F}$ = 1.5 Hz, Ar-C), 164.5 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{33}NO_7SF_9$ $[M + H]^+$: 746.1828, found 746.1840.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(4-cyanophenyl)-5-hydroxy-4-methylpentyl 4-cyanobenzoate, (*S*,*S*,*R*,*S*,*S*)-138

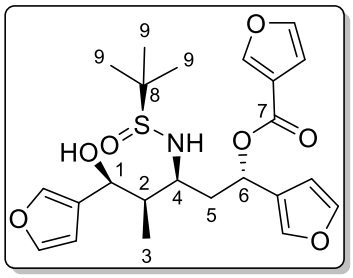


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 4-cyanobenzaldehyde (0.542 g, 3.3 mmol). The crude compound (84:16 *dr*) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound as a colourless oil (0.080 g, 14%).

***Major diastereomer**:*

$[\alpha]_D^{20}$ + 28.8 (c 0.12, CH_2Cl_2). IR ν_{max} (ATR): 3328 (N-H stretch), 2925 (O-H stretch), 2228 (C≡N stretch), 1728 (C=O stretch), 1096 (C-N stretch), 1034 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.80 (3H, d, *J* = 7.1 Hz, H-3), 1.35 (9H, s, H-9), 1.99-2.06 (2H, m, H-2 and one of H-5), 2.13-2.18 (1H, m, one of H-5), 3.89-3.93 (1H, m, H-4), 4.28 (1H, d, *J* = 6.7 Hz, N-H), 4.78 (1H, d, *J* = 5.2 Hz, O-H), 5.16 (1H, d, *J* = 4.8 Hz, H-1), 6.14 (1H, dd, *J* = 8.8, 2.3 Hz, H-6), 7.45-7.48 (4H, m, Ar-H), 7.61-7.68 (4H, m, Ar-H), 7.79-7.83 (2H, m, Ar-H), 8.15-8.19 (2H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.5 (C-3), 22.8 (C-9), 43.3 (C-5), 44.1 (C-2), 56.9 (C-8), 57.8 (C-4), 73.2 (C-6), 75.1 (C-1), 110.7 (Ar-C), 112.5 (Ar-C), 117.1 (Ar-C), 117.7, 118.2, 118.9 (C-10, C-11 and C-12), 126.4 (2 × Ar-CH), 126.8 (2 × Ar-CH), 130.1 (2 × Ar-CH), 132.0 (2 × Ar-CH), 132.5 (2 × Ar-CH), 132.8 (2 × Ar-CH), 133.2 (Ar-C), 145.2 (Ar-C), 149.1 (Ar-C), 164.0 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{33}N_4O_4S$ $[M + H]^+$: 569.2217, found 569.2203.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-di(furan-3-yl)-5-hydroxy-4-methylpentyl furan-3-carboxylate, (*S*,*S*,*R*,*S*,*S*)-141

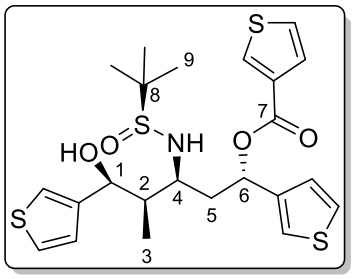


Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and 3-furaldehyde (0.28 mL, 3.3 mmol). The crude compound (*dr* not determined) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a colourless oil (0.199 g, 43%, single diastereomer).

***Major diastereomer**:*

M.p. 90-93 °C. $[\alpha]_D^{20}$ + 27.8 (c 0.15, CH_2Cl_2). IR ν_{max} (ATR): 3310 (N-H stretch), 3149 (O-H stretch), 2956 (C-H stretch), 1719 (C=O stretch), 1160 (C-N stretch), 1075 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, d, *J* = 7.3 Hz, H-3), 1.28 (9H, s, H-9), 1.95-2.07 (2H, m, H-2 and one of H-5), 2.11-2.20 (1H, m, one of H-5), 3.67-3.75 (1H, m, H-4), 4.11 (1H, d, *J* = 6.9 Hz, N-H), 4.38 (1H, d, *J* = 5.2 Hz, O-H), 5.00-5.02 (1H, m, H-1), 6.04 (1H, dd, *J* = 9.9, 3.3 Hz, H-6), 6.29-6.30 (1H, m, Ar-H), 6.42-6.43 (1H, m, Ar-H), 6.73 (1H, dd, *J* = 2.0, 0.7 Hz, Ar-H), 7.36-7.39 (3H, m, Ar-H), 7.43-7.46 (2H, m, Ar-H), 8.00-8.01 (1H, m, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.5 (C-3), 22.8 (C-9), 41.3 (C-5), 42.9 (C-2), 56.5 (C-8), 57.4 (C-4), 65.1 (C-6), 70.5 (C-1), 108.5 (Ar-CH), 108.8 (Ar-CH), 109.8 (Ar-CH), 119.3 (Ar-C), 124.7 (Ar-C), 128.6 (Ar-C), 139.5 (Ar-CH), 140.5 (Ar-CH), 143.0 (Ar-CH), 143.4 (Ar-CH), 143.8 (Ar-CH), 147.7 (Ar-CH), 162.3 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}NO_7S$ $[M + H]^+$: 464.1737, found 464.1750.

(1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-di(thiophen-3-yl)pentyl thiophene-3-carboxylate, (*S*,*S*,*R*,*S*,*S*)-142



Prepared according to the general procedure outlined above using (*S*)-*N*-(butan-2-ylidene)-2-propane-2-sulfinamide (0.175 g, 1 mmol) and thiophene-3-carboxaldehyde (0.29 mL, 3.3 mmol). The crude compound (90:10 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a colourless oil (0.173 g, 34%).

***Major diastereomer**:*

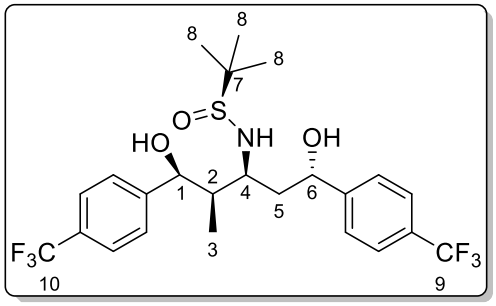
M.p. 111-114 °C. $[\alpha]_D^{20}$ + 26.4 (c 0.18, CH_2Cl_2). IR ν_{max} (ATR): 3707 (N-H stretch), 3325 (O-H stretch), 2981 (C-H stretch), 1715 (C=O stretch), 1162 (C-N stretch), 1076 (S=O stretch) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 7.0 Hz, H-3), 1.29 (9H, s, H-9), 2.05-2.11 (2H, m, H-2 and one of H-5), 2.18-2.24 (1H, m, one of H-5), 3.70-3.74 (1H, m, H-4), 4.18 (1H, d, *J* = 6.8 Hz, N-H), 4.36 (1H, d, *J* = 4.8 Hz, O-H), 5.06-5.11 (1H, m, H-1), 6.16 (1H, dd, *J* = 9.9, 3.3 Hz, H-6), 6.97 (1H, dd, *J* = 4.9, 1.2 Hz, Ar-H), 7.12 (1H, dd, *J* = 5.0, 1.3 Hz, Ar-H), 7.19-7.20 (1H, m, Ar-H), 7.23-7.33 (4H, m, Ar-H), 7.51 (1H, dd, *J* = 1.2, 5.1 Hz, Ar-H), 8.10 (1H, dd, *J* = 1.1, 3.0 Hz, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 6.6 (C-3), 22.8 (C-9), 42.1 (C-5), 43.5 (C-2), 56.5 (C-8), 57.4 (C-4), 68.8 (C-6), 73.5 (C-1), 120.6 (Ar-CH), 122.5 (Ar-CH), 125.5 (Ar-CH), 125.6 (Ar-CH), 125.9 (Ar-CH), 126.2 (Ar-CH), 126.4 (Ar-CH), 127.9 (Ar-CH), 132.9 (Ar-CH), 133.5 (Ar-C), 141.3 (Ar-C), 145.5 (Ar-C), 161.2 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}NO_4S_4$ $[M + H]^+$: 512.1052, found 512.5051.

3.14.6 Derivatisation of 2-butanone derived 3-amino-1,5-diol precursors

3.14.6.1 Cleavage of ester moiety

To a vigorously stirred solution of 3-amino-1,5-diol derivative in MeOH (10 mL/mmol) was added KOH (1 pellet). The mixture was stirred at rt for 3 h. The solution was concentrated under reduced pressure. The residue was dissolved in water and the aqueous solution was neutralised with aq. HCl (1.0 M) and extracted with CH_2Cl_2 (3 x 15 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford crude 3-amino-1,5-diol, which was subsequently purified by column chromatography on silica gel.

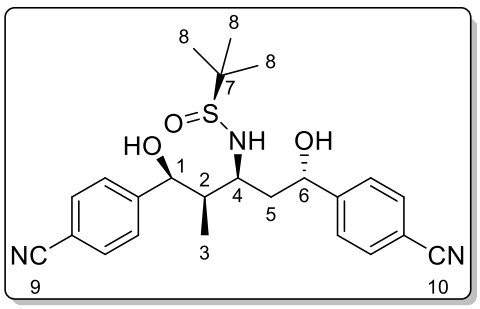
(*S*)-*N*-((1*S*,2*R*,3*S*,5*S*)-1,5-dihydroxy-2-methyl-1,5-bis(4-(trifluoromethyl)phenyl)pentan-3-yl)-2-methylpropane-2-sulfinamide, (*S*,*S*,*R*,*S*,*S*)-149



Prepared according to the procedure outlined above using (1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-bis(4-(trifluoromethyl)phenyl)pentyl 4-(trifluoromethyl)benzoate (0.140 g, 0.2 mmol). The crude compound (1 diastereomer) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to yield the title compound as a pale yellow sticky oil (0.036 g, 34%).

$[\alpha]_D^{25}$ + 27.1 (c 0.46, CH_2Cl_2). IR ν_{max} (ATR): 3342 (O-H stretch), 1163 (C-N stretch), 1124 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.75 (3H, d, *J* = 7.1 Hz, H-3), 1.31 (9H, s, H-8), 1.76-1.80 (1H, m, one of H-5), 1.84-1.88 (1H, m, one of H-5), 1.95-1.99 (1H, m, H-2), 3.07 (1H, s, O-H), 4.08-4.11 (1H, m, H-4), 4.50 (1H, d, *J* = 5.6 Hz, N-H), 4.81 (1H, d, *J* = 5.2 Hz, O-H), 4.96 (1H, d, *J* = 10.0 Hz, H-6), 5.16 (1H, d, *J* = 4.5 Hz, H-1), 7.42-7.45 (4H, m, Ar-H), 7.55 (2H, d, *J* = 8.0 Hz, Ar-H), 7.60 (2H, d, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.3 (C-3), 22.8 (C-9), 44.6 (C-5), 46.1 (C-2), 56.5 (C-7), 57.5 (C-4), 70.3 (C-6), 75.5 (C-1), 124.1, 124.2 (q, $^1J_{C\text{-}F}$ = 271.9, 278.9 Hz, respectively, C-9, C-10), 125.0 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-CH), 125.6 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, 2 × Ar-CH), 125.7 (2 × Ar-CH), 125.9 (2 × Ar-CH), 128.9 (q, $^2J_{C\text{-}F}$ = 31.8 Hz, Ar-C), 129.8 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, Ar-C), 148.0 (Ar-C), 148.9 (Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{24}H_{29}F_6NO_3S$ $[M + H]^+$: 526.1845, found 526.1858.

(*S*)-*N*-((1*S*,2*R*,3*S*,5*S*)-1,5-bis(4-cyanophenyl)-1,5-dihydroxy-2-methylpentan-3-yl)-2-methylpropane-2-sulfinamide, (*S*,*S*,*R*,*S*,*S*)-150



Prepared according to the procedure outlined above using (1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(4-cyanophenyl)-5-hydroxy-4-methylpentyl 4-cyanobenzoate (0.050 g, 0.088 mmol). The crude compound (1 diastereomer) was purified by column chromatography on silica gel (2:1, hexane:EtOAc) to yield the title compound as a pale yellow sticky oil (0.020 g, 52%).

Major diastereomer:

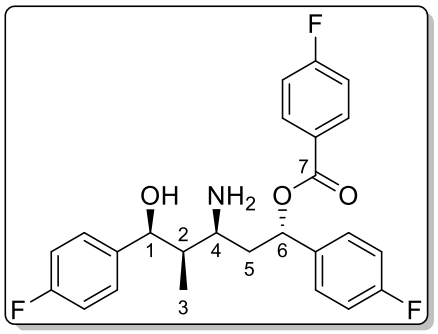
$[\alpha]_D^{25}$ + 131.7 (c 0.12, CH_2Cl_2). IR ν_{max} (ATR): 3292 (N-H stretch), 2963, 2926 (O-H stretch), 2229 (C≡N stretch), 1136 (C-N stretch), 1041 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$)

δ 0.74 (3H, d, *J* = 7.2 Hz, H-3), 1.34 (9H, s, H-8), 1.70-1.75 (1H, m, H-5), 1.79-1.84 (1H, m, H-5), 1.94-1.98 (1H, m, H-2), 2.59-2.62 (1H, m, O-H), 4.10-4.14 (1H, m, H-4), 4.33 (1H, d, *J* = 6.5 Hz, N-H), 4.88 (1H, d, *J* = 5.3 Hz, O-H), 4.94 (1H, d, *J* = 9.4 Hz, H-6), 5.19 (1H, d, J = 4.7 Hz, H-1), 7.43-7.47 (4H, m, Ar-H), 7.59-7.65 (4H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 5.3 (C-3), 22.8 (C-8), 44.6 (C-2), 46.3 (C-5), 56.6 (C-8), 57.7 (C-4), 70.1 (C-6), 75.3 (C-1), 110.5 (Ar-C), 111.4 (Ar-C), 118.8, 119.0 (C-9 and C-10), 126.1 (2 × Ar-CH), 126.4 (2 × Ar-CH), 131.9 (2 × Ar-CH), 132.5 (2 × Ar-CH), 149.4 (Ar-C), 150.1 (Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{24}H_{29}N_3O_3S$ $[M + H]^+$: 440.2002, found 440.2003.

3.14.6.2 Cleavage of tert-butanesulfinyl auxiliary[82]

To a solution of 3-amino-1,5-diol derivative (1 equiv.) in EtOH (4 mL/mmol) was added diisopropyl ether (4 mL/mmol). The resulting solution was cooled to 0 °C and acetyl chloride (3 equiv.) was added dropwise. The mixture was stirred at 0 °C for 18 h. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in H_2O and washed with CH_2Cl_2. $NaHCO_3$ was added and the aqueous layer extracted twice with CH_2Cl_2. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure to afford the crude product.

(1*S*,3*S*,4*R*,5*S*)-3-Amino-1,5-bis(4-fluorophenyl)-5-hydroxy-4-methylpentyl 4-fluorobenzoate, (*S*,*R*,*S*,*S*)-151

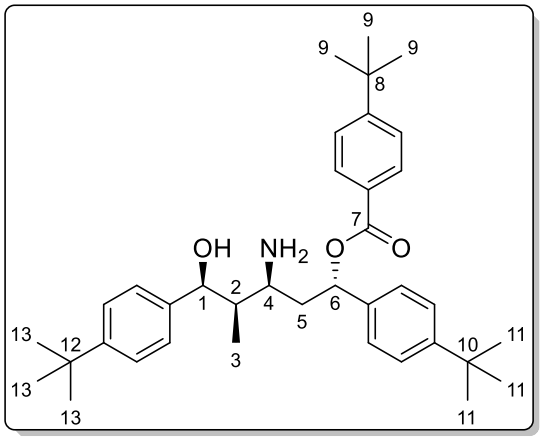


Prepared according to the general procedure outlined above using (1*S*,3*S*,4*R*,5*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(4-fluorophenyl)-5-hydroxy-4-methylpentyl 4-fluorobenzoate (0.130 g, 0.237 mmol). The crude compound was purified by column chromatography on silica gel (CH_2Cl_2, 2% - 5% MeOH) to give the title compound as a pale yellow oil (0.056 g, 53% of pure diastereomer).

$[\alpha]_D^{25}$ + 15.1 (c 0.38, CH_2Cl_2). IR ν_{max} (ATR): 3280 (N-H stretch), 2923 (C-H stretch), 1715 (C=O stretch), 1154 (C-N stretch), 1055 (C-O stretch) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.71 (3H, d, *J* = 7.3 Hz, H-3), 1.70-1.75 (1H, m, H-2), 1.85-1.94 (1H, m, one of H-5), 2.16-2.22 (1H, m, one of H-5), 2.90-3.39 (2H, bs, NH_2), 3.18 (1H, d, *J* = 9.2 Hz, H-4), 4.97 (1H, s, H-1), 6.20 (1H, dd, *J* = 10.2, 3.8 Hz, H-6), 6.96-7.00 (2H, m, Ar-H), 7.06-7.09 (2H, m, Ar-H), 7.12-7.16 (2H, m, Ar-H), 7.26-7.28 (2H, m, Ar-H), 7.40-7.43 (2H, m, Ar-H), 8.07-8.10 (2H, m, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.1 (C-3), 43.1 (C-2), 45.6 (C-5), 53.0 (C-4), 72.8 (C-6), 78.0 (C-1), 114.7 (d, $^2J_{C\text{-}F}$ = 20.9 Hz, 2 × Ar-CH), 115.8 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, 2

× Ar-CH), 115.9 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, 2 × Ar-CH), 126.0 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 127.2 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz, 2 × Ar-CH), 128.2 (d, $^{3}J_{C\text{-}F}$ = 8.1 Hz, 2 × Ar-CH), 132.3 (d, $^{3}J_{C\text{-}F}$ = 9.4 Hz, 2 x Ar-CH), 136.0 (d, $^{4}J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 139.2 (d, $^{4}J_{C\text{-}F}$ = 2.8 Hz, Ar-C), 161.6 (d, $^{1}J_{C\text{-}F}$ = 244.3 Hz, Ar-C), 162.6 (d, $^{1}J_{C\text{-}F}$ = 247.2 Hz, Ar-C), 166.0 (d, $^{1}J_{C\text{-}F}$ = 254.9 Hz, Ar-C), 165.2 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{25}NO_3F_3$ $[M + H]^+$: 444.1781, found 444.1784.

(1S,3S,4R,5S)-3-amino-1,5-bis(4-(tert-butyl)phenyl)-5-hydroxy-4-methylpentyl 4-(*tert*-butyl)benzoate, (*S*,*R*,*S*,*S*)-152



Prepared according to the general procedure outlined above using (1*S*,3*S*,4*R*,5*S*)-1,5-bis(4-(*tert*-butyl)phenyl)-3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-4-methylpentyl 4-(*tert*-butyl)benzoate (0.100 g, 0.150 mmol). The crude compound was purified by trituration from Et_2O to give the title compound as a sticky white solid (0.064 g, 76% of pure diastereomer).

M.p. 102-104 °C. $[\alpha]_D^{25}$ + 40.9 (c 0.64, CH_2Cl_2). IR ν_{max} (ATR): 3680 (N-H stretch), 2981 (C-H stretch) 1713 (C=O stretch), 1188 (C-N stretch), 1033 (C-O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (3H, d, *J* = 7.1 Hz, H-3), 1.30, 1.31, 1.35 (3 × 3H, s, H-9, H-11 and H-13), 1.73-7.80 (1H, m, H-2), 1.84-1.93 (1H, m, one of H-5), 2.14-2.24 (1H, m, one of H-5), 3.23 (1H, d, *J* = 9.3 Hz, H-4), 4.98 (1H, d, *J* = 1.4 Hz, H-1), 6.22 (1H, dd, *J* = 10.2, 3.8 Hz, H-6), 7.23-7.50 (10H, m, Ar-H), 8.01-8.05 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 4.21 (C-3), 31.1, 31.3, 31.4 (C-9, C-11 and C-13), 34.4, 34.6, 35.1 (C-8, C-10 and C-12), 43.1 (C-2), 45.7 (C-5), 72.9 (C-6), 78.5 (C-1), 124.8 (2 × Ar-C), 125.4 (2 × Ar-CH), 125.5 (2 × Ar-CH), 125.6 (2 × Ar-CH), 126.1 (2 × Ar-CH), 127.2 (Ar-C), 129.7 (2 × Ar-CH), 137.5 (Ar-C), 140.6 (Ar-C), 149.3 (Ar-C), 151.2 (Ar-C), 151.2 (Ar-C), 157.0 (Ar-C), 166.3 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{37}H_{52}NO_3$ $[M + H]^+$: 558.3942, found 558.3949.

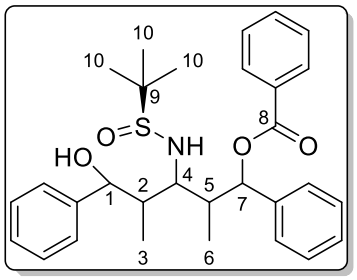
3.14.7 Synthesis of 3-pentanone derived 3-amino-1,5-diol precursors

To a Schlenk tube under N_2 atmosphere containing diisopropylamine (1.2 equiv.) and anhydrous THF (5 mL/mmol of sulfinyl imine) was added *n*-BuLi (1.26 M in hexanes, 1.1 equiv.) dropwise at 0 °C. The resulting solution was stirred for 30 mins before sulfinyl imine (1 equiv.) was added dropwise and stirred for 2 h at this temperature. The reaction was cooled to -78 °C. Freshly distilled aldehyde (3.3 equiv.) was added dropwise and the temperature was

maintained at -78 °C for a further 3 hours. The reaction mixture was warmed to 0 °C over 16 h. The reaction was quenched with NH_4Cl (2 mL) and allowed to warm to rt. The reaction was diluted with NH_4Cl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered to remove the drying agent and concentrated under reduced pressure. Purification by column chromatography on silica gel yielded pure double aldol-Tishchenko product.

Note: Absolute configuration of the following compounds could not be determined.

3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-2,4-dimethyl-1,5-diphenylpentyl benzoate, (*S*)-154



Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and benzaldehyde (0.34 mL, 3.3 mmol). The crude compound (74:26 *dr*) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.102 g, 20%).

***Major diastereomer**:*

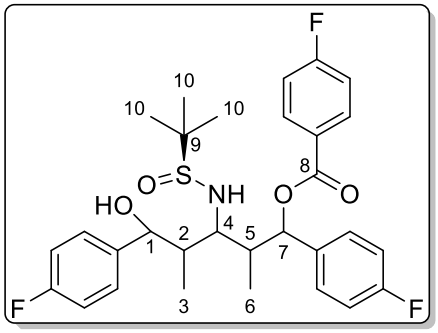
$[\alpha]_D^{25}$ + 15.9 (c 0.46, CH_2Cl_2). IR ν_{max} (ATR): 3340 (N-H stretch), 2967 (O-H stretch), 1720 (C=O stretch), 1177 (C-N stretch), 1053 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 7.0 Hz, H-3), 0.96 (3H, d, *J* = 7.1 Hz, H-3), 1.29 (9H, s, H-10), 2.00-2.16 (1H, m, H-2), 2.29-2.40 (1H, m, H-5), 3.85 (1H, d, *J* = 7.7 Hz, N-H), 3.91-3.96 (1H, m, H-4), 4.17 (1H, d, *J* = 4.6 Hz, O-H), 4.98-5.03 (1H, m, H-1), 5.77 (1H, d, *J* = 8.4 Hz, H-7), 7.21-7.59 (13H, m, Ar-H), 7.99-8.02 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8 (C-3), 12.2 (C-6), 23.0 (C-10), 43.9 (C-5), 44.8 (C-2), 56.7 (C-9), 59.9 (C-4), 76.2 (C-1), 78.2 (C-7), 125.9 (2 × Ar-CH), 126.8 (Ar-CH), 127.3 (2 × Ar-CH), 128.1 (2 × Ar-CH), 128.2 (Ar-CH), 128.4 (2 × Ar-CH), 128.5 (2 × Ar-CH), 129.6 (2 × Ar-CH), 130.2 (Ar-C), 133.1 (Ar-CH), 138.9 (Ar-C), 144.0 (Ar-C), 165.5 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{38}NO_4S$ $[M + H]^+$: 508.2516, found 508.2521.

***Minor diastereomer**:*

$[\alpha]_D^{25}$ + 64.2 (c 0.30, CH_2Cl_2). IR ν_{max} (ATR): 3707 (N-H stretch), 3334 (O-H stretch), 1723 (C=O stretch), 1176 (C-N stretch), 1055 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 7.0 Hz, H-3), 0.97 (3H, d, *J* = 7.1 Hz, H-3), 1.39 (9H, s, H-10), 1.94-1.97 (1H, m H-5), 2.02-2.24 (1H, m, H-2), 3.64-3.67 (1H, m, H-4), 4.45 (1H, d, *J* = 6.3 Hz, N-H), 4.83 (1H, d, *J* = 4.5 Hz, O-H), 5.10 (1H, s, H-1), 6.40 (1H, d, *J* = 1.2 Hz, H-7), 7.20-7.25 (4H, m, Ar-H), 7.30-7.33 (4H, m, Ar-H), 7.35-7.37 (2H, m, Ar-H), 7.51-7.53 (2H, m, Ar-H), 7.62-

7.65 (1H, m, Ar-H), 8.12-8.14 (2H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.8 (C-3), 10.3 (C-6), 23.1 (C-10), 40.5 (C-2), 45.0 (C-5), 57.0 (C-9), 62.8 (C-4), 74.5 (C-7), 76.0 (C-1), 125.3 (2 × Ar-CH), 125.7 (2 × Ar-CH), 126.6 (Ar-CH), 127.3 (Ar-CH), 128.0 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 129.7 (2 × Ar-CH), 130.3 (Ar-C), 133.2 (Ar-CH), 140.4 (Ar-C), 144.3 (Ar-C), 165.3 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{38}NO_4S$ $[M + H]^+$: 508.2516, found 508.2519.

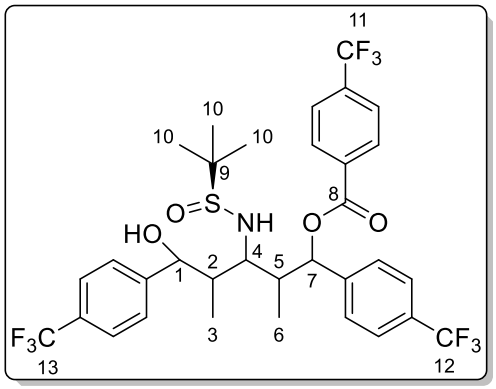
3-(((*S*)-*tert*-butylsulfinyl)amino)-1,5-bis(4-fluorophenyl)-5-hydroxy-2,4-dimethylpentyl 4-fluorobenzoate, (*S*)-164



Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and 4-fluorobenzaldehyde (0.35 mL, 3.3 mmol). The crude compound (*dr* nd) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.045 g, 8%).

$[\alpha]_D^{25}$ + 43.6 (c 0.14, CH_2Cl_2). IR ν_{max} (ATR): 3344 (O-H stretch), 2925 (C-H stretch), 1721 (C=O stretch), 1154 (C-N stretch), 1089 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, d, *J* = 6.9 Hz, H-6), 0.97 (3H, d, *J* = 6.9 Hz, H-3), 1.30 (9H, s, H-10), 1.96-2.03 (1H, m, H-2), 2.23-2.31 (1H, m, H-5), 3.80-3.89 (2H, m, H-4 and N-H), 4.05 (1H, s, O-H), 4.97 (1H, s, H-1), 5.68 (1H, d, *J* = 9.0 Hz, H-7), 6.98-7.15 (6H, m, Ar-H), 7.26-7.34 (4H, m, Ar-H), 7.93-7.98 (2H, m Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.4 (C-3), 11.9 (C-6), 23.0 (C-10), 44.1 (C-5), 44.8 (C-1), 56.8 (C-9), 59.1 (C-4), 75.7 (C-1), 77.6 (C-7), 115.0 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, 2 × Ar-CH), 115.5 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, 2 × Ar-CH), 115.7 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, 2 × Ar-CH), 126.2 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, Ar-C), 127.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, 2 × Ar-CH), 129.1 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, 2 × Ar-CH), 132.1 (d, $^3J_{C\text{-}F}$ = 9.4 Hz, 2 × Ar-CH), 134.6 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 139.6 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, Ar-C), 161.8 (d, $^1J_{C\text{-}F}$ = 245.4 Hz, Ar-C), 162.6 (d, $^1J_{C\text{-}F}$ = 247.7 Hz, Ar-C), 164.4 (C-8), 165.9 (d, $^1J_{C\text{-}F}$ = 255.0 Hz, Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{35}F_3NO_4S$ $[M + H]^+$: 562.2233, found 562.2233.

3-(((*S*)-*tert*-butylsulfinyl)amino)-5-hydroxy-2,4-dimethyl-1,5-bis(4-(trifluoromethyl)phenyl)pentyl 4-(trifluoromethyl)benzoate, (*S*)-167



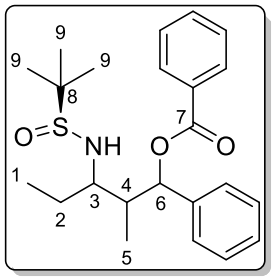
Prepared according to the general procedure outlined above using (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and 4-trifluoromethylbenzaldehyde (0.45 mL, 3.3 mmol). The crude compound (*dr* nd) was purified by column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound as a sticky colourless oil (0.028 g, 4%).

$[\alpha]_D^{25}$ + 94.8 (c 0.40, CH_2Cl_2). IR ν_{max} (ATR): 3707 (N-H stretch), 3339 (O-H stretch), 2981 (C-H stretch), 1732 (C=O stretch), 1165 (C-N stretch), 1055 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 7.2 Hz, H-6), 0.98 (3H, d, *J* = 6.8 Hz, H-3), 1.39 (9H, s, H-10), 1.94-1.99 (1H, m, H-2), 2.18-2.23 (1H, m, H-5), 3.66-3.69 (1H, m, H-4), 4.51 (1H, d, *J* = 6.2 Hz, N-H), 4.95 (1H, d, *J* = 6.0 Hz, O-H), 5.16 (1H, d, *J* = 5.7 Hz, H-1), 6.47 (1H, bs, H-7), 7.32 (2H, d, *J* = 8.3 Hz, Ar-H), 7.48 (2H, d, *J* = 8.3 Hz, Ar-H), 7.59 (4H, m, Ar-H), 7.81 (2H, d, *J* = 8.3 Hz, Ar-H), 8.25 (2H, d, *J* = 8.3 Hz, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.6 (C-6), 10.2 (C-3), 22.3 (C-10), 40.3 (C-5), 44.8 (C-1), 57.2 (C-9), 62.7 (C-4), 74.6 (C-7), 75.5 (C-1), 125.0 (q, $^3J_{C\text{-}F}$ = 3.3 Hz, 2 × Ar-CH), 125.5 (2 × Ar-CH), 125.6 (q, $^3J_{C\text{-}F}$ = 4.1 Hz, 2 × Ar-CH), 125.6, 125.7, 125.8 (3 × q, $^1J_{C\text{-}F}$ = 273.4, 270.1, 274.3 Hz, respectively, C-11, C-12 and C-13), 125.9 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, 2 × Ar-CH), 126.0 (2 x Ar-CH), 129.0 (q, $^2J_{C\text{-}F}$ = 32.5 Hz, Ar-C), 130.0 (q, $^2J_{C\text{-}F}$ = 34.3 Hz, Ar-C), 130.1 (2 × Ar-CH), 132.9 (Ar-C), 134.9 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, Ar-C), 144.0 (Ar-C), 148.1 (Ar-C), 164.1 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{35}F_9NO_4S$ $[M + H]^+$: 712.2146, found 712.218.

3.14.7.1 3-Pentanone derived 1,3-ester derivatives

In some of the above reactions it was possible to isolate single aldol-Tishchenko products as side-products. The major diastereomer is characterised in such cases.

3-(((*S*)-*tert*-butylsulfinyl)amino)-2-methyl-1-phenylpentyl benzoate, (*S*)-155

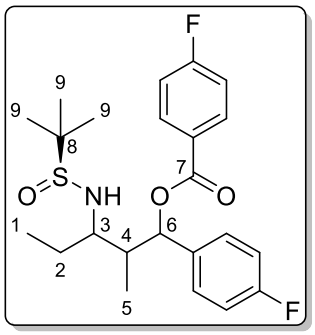


Isolated as a side product of the reaction of (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and benzaldehyde (0.34 mL, 3.3 mmol) as a pale yellow oil (0.104 g, 26%, *dr* 68:17:15).

Major diastereomer:

$[\alpha]_D^{25}$ + 25.7 (c 0.44, CH_2Cl_2). IR ν_{max} (ATR): 3707 (N-H stretch), 2967 (C-H stretch), 1723 (C=O stretch), 1177 (C-N stretch), 1056 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, d, *J* = 7.1 Hz, H-5), 0.97 (3H, t, *J* = 7.3 Hz, H-1), 1.19 (9H, s, H-9), 1.49-1.57 (1H, m, one of H-2), 1.66-1.74 (1H, m, one of H-2), 2.71-2.77 (1H, m, H-4), 3.31-3.35 (1H, m, H-3), 3.75 (1H, d, *J* = 8.6 Hz, N-H), 5.93 (1H, d, *J* = 10.0 Hz, H-6), 7.25-7.34 (3H, m, Ar-H), 7.42-7.45 (2H, m, Ar-H), 7.47-7.48 (2H, m, Ar-H), 7.54-7.57 (1H, m, Ar-H), 8.10-8.11 (2H, m, Ar-H) ppm. ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 11.7 (C-1), 13.5 (C-5), 22.9 (C-9), 24.7 (C-2), 42.6 (C-4), 56.3 (C-8), 62.1 (C-3), 79.4 (C-6), 127.5 (2 × Ar-CH), 128.2 (Ar-CH), 128.4 (2 × Ar-CH), 128.5 (2 × Ar-CH), 129.8 (2 × Ar-CH), 130.1 (Ar-C), 133.2 (Ar-CH), 139.5 (Ar-C), 165.4 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{32}NO_3S$ $[M + H]^+$: 402.2097, found 402.2097.

3-(((*S*)-*tert*-butylsulfinyl)amino)-1-(4-fluorophenyl)-2-methylpentyl 4-fluorobenzoate, (*S*)-163



Isolated as a side product of the reaction of (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and 4-fluorobenzaldehyde (0.45 mL, 3.3 mmol) as a pale yellow oil (0.053 g, 12%, *dr* nd).

Major diastereomer:

$[\alpha]_D^{25}$ + 12.2 (c 0.18, CH_2Cl_2). IR ν_{max} (ATR): 3681 (N-H stretch), 2966 (C-H stretch), 1725 (C=O stretch), 1154 (C-N stretch), 1057 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (3H, d, *J* = 7.2 Hz, H-5), 0.98 (3H, d, *J* = 7.2 Hz, H-1), 1.20 (9H, s, H-9), 1.49-1.54 (1H, m, H-2), 1.60-1.77 (1H, m, one of H-2), 2.65-2.71 (1H, m, H-4), 3.29-3.38 (1H, m, H-3), 3.60 (1H, d, *J* = 8.9 Hz, N-H), 5.90 (1H, d, *J* = 10.2 Hz, H-6), 7.02 (2H, t, *J* = 8.6 Hz, Ar-H), 7.10 (2H, t, *J* = 8.6 Hz, Ar-H), 7.42-7.47 (2H, m Ar-H), 8.09-

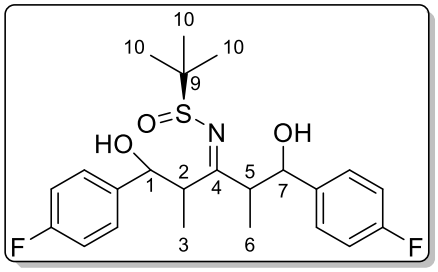
8.14 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.7 (C-1), 13.2 (C-5), 22.8 (C-9), 25.0 (C-2), 42.6 (C-4), 56.3 (C-8), 61.9 (C-3), 78.7 (C-6), 115.5 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, 2 × Ar-CH), 115.7 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, 2 × Ar-CH), 126.3 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 129.2 (d, $^3J_{C\text{-}F}$ = 8.3 Hz, 2 × Ar-CH), 132.4 (d, $^3J_{C\text{-}F}$ = 9.4 Hz, 2 × Ar-CH), 135.3 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, Ar-C), 162.5 (d, $^1J_{C\text{-}F}$ = 247.2 Hz, Ar-C), 164.4 (C-7), 166.0 (d, $^1J_{C\text{-}F}$ = 254.8 Hz, Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}F_2NO_4S$ $[M + H]^+$: 438.1909, found 438.1918.

3.14.7.2 3-Pentanone derived double aldol products

In some of the above double aldol-Tishchenko reactions it was possible to isolate double aldol-type reaction products as side-products. The major diastereomer is characterised in such cases. The absolute stereochemistry could not be determined for these substrates.

Note: ^{1}H NMR assignement is based off the assumtion that H-bonding between the C1-OH and the sulfinyl group, as is the case for other substrates of this nature, results in deshielding of the O-H, causing it to appear downfield relative to the second O-H in the molecule.

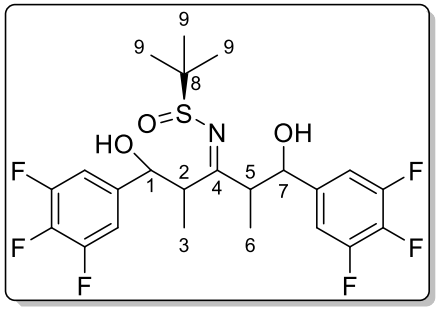
(*S*)-*N*-(1,5-bis(4-fluorophenyl)-1,5-dihydroxy-2,4-dimethylpentan-3-ylidene)-2-methylpropane-2-sulfinamide, (*S*)-162



Isolated as a side product of the reaction of (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and 4-fluorobenzaldehyde (0.45 mL, 3.3 mmol) as a pale yellow oil (0.131 g, 30%, *dr* nd).

$[\alpha]_D^{25}$ + 88.7 (c 0.85, CH_2Cl_2). IR ν_{max} (ATR): 3706 (N-H stretch), 3287 (O-H stretch), 2973 (C-H stretch), 1605 (C=N stretch), 1157 (C-N stretch), 1059 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, *J* = 6.8 Hz, H-6), 0.97 (3H, d, *J* = 6.5 Hz, H-3), 1.39 (9H, s, H-9), 3.01-3.11 (1H, m, H-5), 3.85-3.95 (1H, m, H-2), 4.58 (1H, t, *J* = 10.4 Hz, H-1), 4.77-4.90 (2H, m, H-7 and O-H), 5.68 (1H, d, *J* = 10.3 Hz, O-H), 7.07 (4H, t, *J* = 8.8 Hz, Ar-H), 7.40-7.50 (4H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.9 (C-3), 18.1 (C-6), 22.3 (C-9), 47.5 (C-5), 50.6 (C-2), 58.0 (C-8), 73.9 (C-1), 78.9 (C-7), 115.1 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, 2 × Ar-CH), 115.5 (d, $^2J_{C\text{-}F}$ = 21.7 Hz, 2 × Ar-CH), 128.8 (bs, 2 × Ar-CH), 128.9 (bs, 2 × Ar-CH), 137.3 (Ar-C), 137.5 (Ar-C), 162.2 (d, $^1J_{C\text{-}F}$ = 245.4 Hz, Ar-C), 162.6 (d, $^1J_{C\text{-}F}$ = 246.1 Hz, Ar-C), 194.2 (C-4) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{30}F_2NO_4S$ $[M + H]^+$: 438.1909, found 438.1909.

_N_-(1-hydroxy-2,4-dimethyl-5-oxo-1,5-bis(3,4,5-trifluorophenyl)pentan-3-yl)-2-methylpropane-2-sulfinamide, (_S_)-165

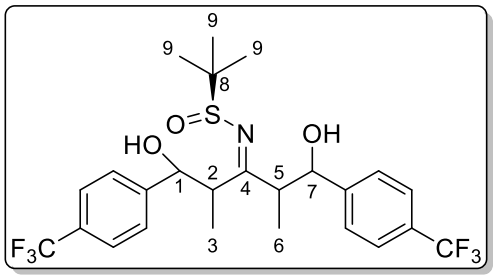


Isolated as a the only product of the reaction of (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and 3,4,5-trifluorobenzaldehyde (0.37 mL, 3.3 mmol) as a pale yellow oil (0.122 g, 24%, *dr* nd).

Major diastereomer:

$[\alpha]_D^{25}$ + 107.1 (c 0.26, CH_2Cl_2). IR ν_{max} (ATR): 3706 (N-H stretch), 3350 (O-H stretch), 2973 (C-H stretch), 1620 (C=N stretch), 1153 (C-N stretch), 1050 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 6.7 Hz, H-6), 1.01 (3H, d, *J* = 6.7 Hz, H-3), 1.38 (9H, s, H-9), 2.91-2.98 (1H, m, H-5), 3.78-3.87 (1H, m, H-2), 4.46 (1H, bt, *J* = 10.7 Hz, H-1), 4.75-4.81 (2H, m, H-7, O-H), 5.93 (1H, d, *J* = 10.2 Hz, O-H), 7.09 (2H, bt, *J* = 7.3 Hz, Ar-H), 7.17 (2H, bt, *J* = 7.3 Hz, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8 (C-3), 17.9 (C-6), 22.2 (C-9), 47.5 (C-5), 50.2 (C-2), 58.1 (C-8), 73.5 (C-1), 78.3 (C-7), 111.4 (td, $^3J_{C\text{-}F}$ = 13.0 Hz, $^4J_{C\text{-}F}$ = 4.2 Hz, 2 × Ar-C), 137.8 (ddd, $^2J_{C\text{-}F}$ = 26.2 Hz, $^3J_{C\text{-}F}$ = 11.4 Hz, $^4J_{C\text{-}F}$ = 4.8 Hz, 4 × Ar-CH), 139.3 (dt, $^1J_{C\text{-}F}$ = 251.9 Hz, $^2J_{C\text{-}F}$ = 15.2 Hz, Ar-C), 139.5 (dt, $^1J_{C\text{-}F}$ = 252.4 Hz, $^2J_{C\text{-}F}$ = 15.2 Hz, Ar-C), 151.2 (ddd, $^1J_{C\text{-}F}$ = 250.6 Hz, $^2J_{C\text{-}F}$ = 26.8 Hz, $^3J_{C\text{-}F}$ = 10.8 Hz, 4 × Ar-C), 192.8 (C-4) ppm. HRMS (ESI) *m/z* calcd for $C_{23}H_{26}F_6NO_3S$ $[M + H]^+$: 510.1532, found 510.1540.

(_S_)-_N_-(1,5-dihydroxy-2,4-dimethyl-1,5-bis(4-(trifluoromethyl)phenyl)pentan-3-ylidene)-2-methylpropane-2-sulfinamide, (_S_)-_166_



Isolated as a side product of the reaction of (*S*)-2-methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide (0.187 g, 1 mmol) and 4-trifluoromethylbenzaldehyde (0.37 mL, 3.3 mmol) as a pale yellow oil (0.151 g, 28%, *dr* nd).

Major diastereomer:

$[\alpha]_D^{25}$ + 86.4 (c 0.26, CH_2Cl_2). IR ν_{max} (ATR): 3706 (N-H stretch), 3350 (O-H stretch), 2973 (C-H stretch), 1620 (C=N stretch), 1153 (C-N stretch), 1050 (S=O stretch) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.7 Hz, H-6), 1.01 (3H, d, *J* = 6.7 Hz, H-3), 1.40 (9H, s, H-9), 3.07-3.12 (1H, m, H-5), 3.89-3.94 (1H, m, H-2), 4.67 (1H, t, *J* = 10.4 Hz, H-1), 4.88 (1H,

bs, O-H), 4.92 (1H, d, *J* = 10.3 Hz, H-7), 5.93 (1H, d, *J* = 10.3 Hz, O-H), 7.55-7.66 (8H, m, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 13.8 (C-3), 17.9 (C-6), 22.2 (C-9), 47.5 (C-5), 50.2 (C-2), 58.1 (C-8), 74.0 (C-1), 78.9 (C-7), 124.1, 124.2 (2 × q, $^1J_{C\text{-}F}$ = 272.3, 271.9 Hz, respectively, C-10 and C-11), 125.3 (q, $^3J_{C\text{-}F}$ = 3.1 Hz, 2 × Ar-CH), 125.6 (q, $^3J_{C\text{-}F}$ = 3.0 Hz, 2 × Ar-CH), 127.6 (2 × Ar-CH), 127.7 (2 × Ar-CH), 130.3 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, Ar-C), 130.4 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, Ar-C), 193.6 (C-4) ppm. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{30}F_6NO_3S$ $[M + H]^+$: 538.1845, found 538.1840.

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Appendix I

Publications

"Organolithium Bases in Flow Chemistry: A Review" Power, M., Alcock, E., McGlacken, G.P., *Org. Process. Res. Dev.* **2020**, *24*, 1814-1838

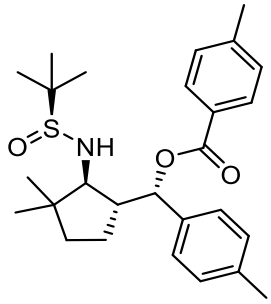
"Mechanism and Origins of Stereoselectivity of the Aldol-Tishchenko Reaction of Sulfinimines" Turlik, A., Anko K., Mackey, P., Alcock E., Light, M., McGlacken, G.P., Houk K.N., *J. Org. Chem.* **2021**, *86*, 4296-4303

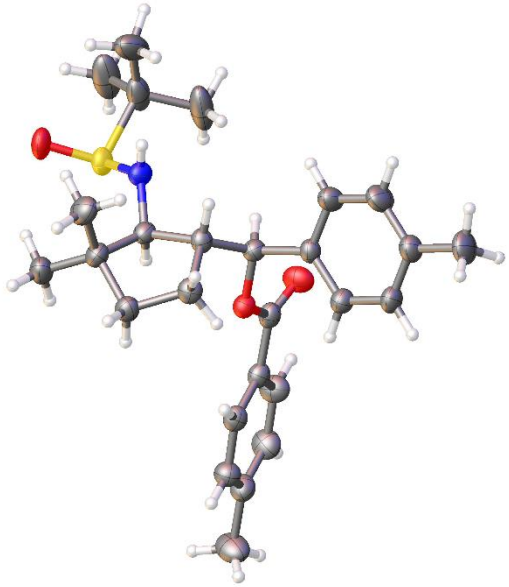
"The aldol-Tishchenko Reaction of Butanone, Cyclobutanone and 3-Pentanone Derived Sulfinylimine and DFT Calculations of the Stereo-determining Step" Alcock E., Mackey P., Turlik A., Bhatt K., Light M., Houk K.N., McGlacken G.P., *Chem. Eur. J*. **2023**, *29*, e202203029

"Continuous Flow Solves Some Issues with Ketone Alkylation" Cooper, E*., Alcock E*., Power, M., McGlacken G.*P.*, *React. Chem. Eng.* **2023**, *manuscript accepted*

Appendix II

X-ray Crystallographic Data for **(*S*,*S*,*R*,*S*)-77**

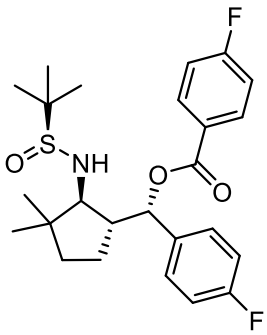


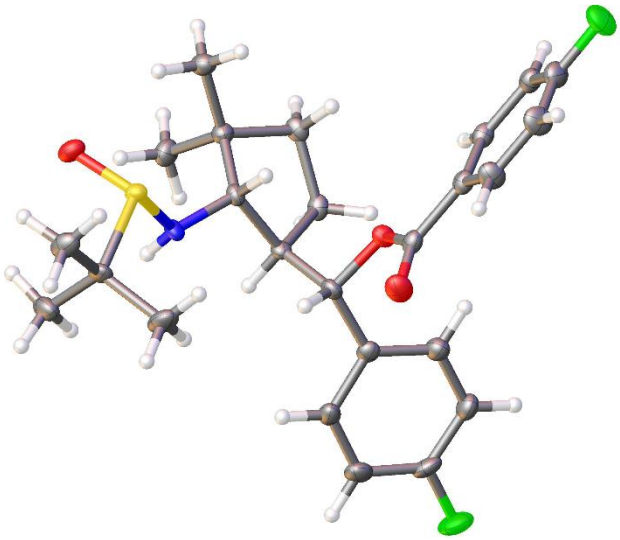


Empirical formula	$C_{27}H_{37}NO_3S$	
$D_{calc.}$/ g cm^{-3}	1.148 g cm^{-3}	
m	0.149 mm^{-1}	
Formula Weight	455.63 g mol^{-1}	
Colour	clear colourless	
Shape	prism	
Size	0.36×0.18×0.04 mm^3	
T	100 K	
Crystal System	orthorhombic	
Flack Parameter	0.00	
Hooft Parameter	0.02	
Space Group	$P2_12_12_1$	
Unit cell dimensions	a = 11.12360 Å	α = 90˚
	b = 18.9136 Å	β = 90˚
	c = 25.0705 Å	γ = 90˚
V/	5274.52 Å	
Z	8	
Z'	2	
Wavelength	0.71073 Å	

Radiation type	Mo K_a
Q_{min}	2.942°
Q_{max}	29.138°
Measured Refl's.	57089
Indep't Refl's	12429
Refl's I≥2 *s*(I)	9653
R_{int}	0.0524
Parameters	620
Restraints	24
Largest Peak	0.285
Deepest Hole	-0.384
Goodness of Fit on F^2	1.081
wR_2 **(all data)**	0.1398
wR_2	0.1258
R_1 **(all data)**	0.0727
R_1	0.0538

X-ray Crystallographic Data for **(*S*,*S*,*R*,*S*)-79**

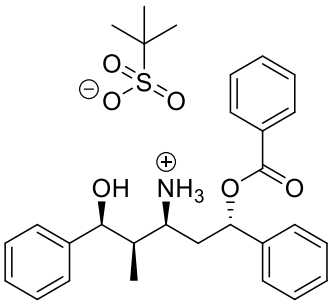


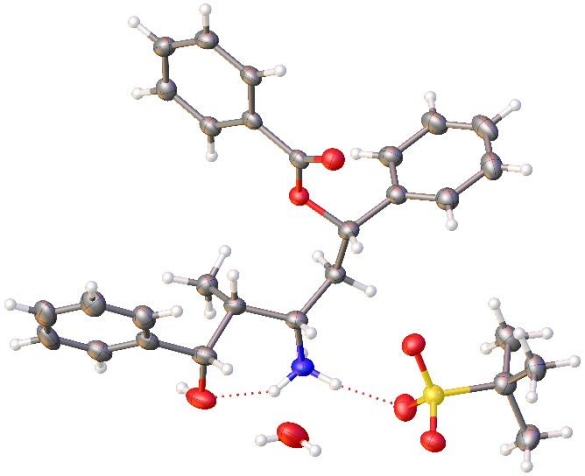


Empirical formula	$C_{25}H_{31}NO_3SF_2$	
$D_{calc.}$/ g cm^{-3}	1.243 g cm^{-3}	
m	0.171 mm^{-1}	
Formula Weight	463.57 g mol^{-1}	
Colour	clear colourless	
Shape	prism	
Size	0.24×0.15×0.04 mm^3	
T	100 K	
Crystal System	orthorhombic	
Flack Parameter	-0.01	
Hooft Parameter	-0.01	
Space Group	$P2_12_12_1$	
Unit cell dimensions	a = 10.7171 Å	$\alpha = 90^\circ$
	b = 18.7688 Å	$\beta = 90^\circ$
	c = 24.6349 Å	$\gamma = 90^\circ$
V/	4955.24 Å	
Z	8	
Z'	2	
Wavelength	0.71073 Å	

Radiation type	Mo K_a
Q_{min}	2.885°
Q_{max}	28.499°
Measured Refl's.	50204
Indep't Refl's	12533
Refl's I≥2 *s*(I)	10860
R_{int}	0.0593
Parameters	595
Restraints	0
Largest Peak	0.532
Deepest Hole	-0.347
Goodness of Fit on F^2	1.125
wR_2 **(all data)**	0.1189
wR_2	0.1137
R_1 **(all data)**	0.0810
R_1	0.0663

X-ray Crystallographic Data for **(*S*,*R*,*S*,*S*)-148**





Empirical formula	$C_{29}H_{38}NO_6S$	
***D*$_{calc.}$/ g cm^{-3}**	1.258 g cm^{-3}	
m	01.377 mm^{-1}	
Formula Weight	536.66 g mol^{-1}	
Colour	clear colourless	
Shape	Needle-shaped	
Size	0.08×0.02×0.02 mm^3	
T	100 K	
Crystal System	monoclinic	
Flack Parameter	0.013	
Hooft Parameter	-0.003	
Space Group	$P2_1$	
Unit cell dimensions	a = 13.3814 Å	α = 90˚
	b = 6.0054 Å	β = 106.236˚
	c = 18.3562 Å	γ = 90˚
V/	1416.29 Å	
Z	2	
Z'	1	
Wavelength	1.54184 Å	
Radiation type	Cu K_a	

Q_{min}	3.440˚
Q_{max}	76.790˚
Measured Refl's.	17812
Indep't Refl's	5479
Refl's I≥2 *s*(I)	4842
R_{int}	0.0473
Parameters	352
Restraints	1
Largest Peak	0.281
Deepest Hole	-0.501
Goodness of Fit on F^2	1.050
wR_2 **(all data)**	0.1069
wR_2	0.1024
R_1 **(all data)**	0.0474
R_1	0.0400

“It always seems impossible, until it’s done”

Nelson Mandela