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Studies in Asymmetric Synthesis

I. The Asymmetric α-Alkylation of *N*,*N*-dimethylhydrazones

II. The Asymmetric Aldol-Tishchenko Reaction of (*S*)-*tert*-butanesulfinyl Imines for the Introduction of 2, 3, 4 and 5 New Chiral Centres in One Pot

University College Cork

Coláiste na hOllscoile Corcaigh

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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 P. McGlacken*

Head of School: *Dr. Humphrey Moynihan*

August 2020

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Appendix I "Preparation of *anti*-1,3-Amino Alcohol Derivatives Through an Asymmetric Aldol-Tishchenko Reaction of Chiral Sulfinimines" Mackey, P.; Cano, R.; Foley, V. M.; McGlacken, G. P., *Org. Synth.* **2017**, *94*, 259-279.

Manuscript in preparation: "Tandem Double-aldol Tishchenko Reaction Forming Five Contiguous Chiral Centres: Scope and Computational Explorations of Mechanisms and Selectivities" **2020**, Mackey, P.; Turlik, A.; Ando, K.; Light, M. E.; Houk, K. N.; McGlacken, G. P.

Appendix II X-ray Crystallographic Analysis

Declaration

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

Pamela Mackey

Date

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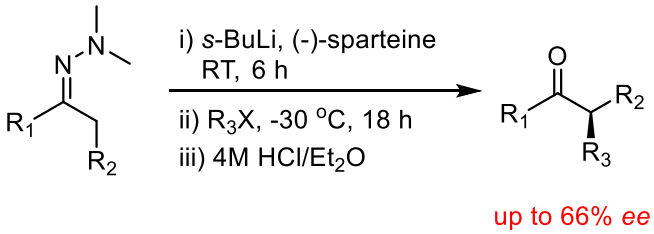
To my twin sister Katrina, thanks for always being there for me, because of you I am motivated, disciplined and hard-working. I am so glad that we will finish our PhDs together. To my sisters Caroline and Jess, thanks for being so understanding throughout my college years. To my mum, thank you for supporting me in everyway throughout my undergraduate and postgraduate studies. You have always believed in me and have always encouraged me to be an individual.

Abstract

This thesis is split into two sections based on two different areas of research.

Part 1

The asymmetric α-alkylation of ketones is one of the most fundamental yet challenging transformations in organic chemistry. Recently a new methodology to furnish enantiomerically enriched α-alkylated ketones was developed within the McGlacken group using *N*,*N*-dimethylhydrazones as ketone synthetic equivalents and the chiral diamine sparteine **(Scheme I)**.



Scheme I: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using (-)-sparteine as a chiral ligand

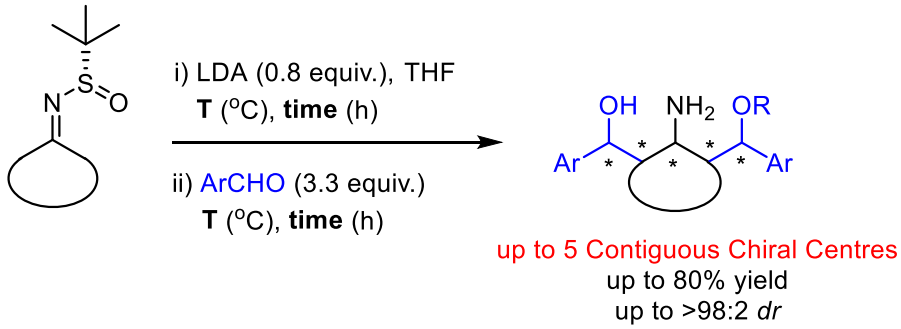
The first section of this thesis outlines efforts to further expand the scope of this methodology to include more diverse and challenging electrophiles. As a result, a number of synthetically useful ketones were prepared. Investigations were also performed in an attempt to improve the enantioselectivity of this system. This included examining a number of reaction parameters such as changing the chiral diamine, investigating different organolithium/(+)-sparteine and (+)-sparteine surrogate complexes and exploring different solvent combinations. The final section of this chapter examines the use of sub-stoichiometric amounts of chiral ligand in the asymmetric α-alkylation of hydrazones. While a number of important insights were gathered into this methodology, attempts to improve the enantioselectivity proved unsuccessful.

Part 2

Part 2 of this thesis outlines the enantio- and diastereoselective synthesis of *anti*-1,3-amino alcohol derivatives using an aldol-Tishchenko reaction. A range of acetophenone and propiophenone derived *anti*-1,3 amino alcohols was synthesised using *N*-*tert*-butanesulfinyl

imines. A number of potential aldol acceptors including aldimines and a formaldehyde equivalent were examined. A challenging yet successful, scale-up of an aldol-Tishchenko reaction is also reported.

The final section of this thesis describes the development of a remarkable novel methodology to synthesize 3-amino-1,5-diol derivatives with the simultaneous introduction of four and five chiral centres in one pot. Cyclopentanone, cycloheptanone and 2-butanone derived 3-amino-1,5-diol products were isolated in excellent diastereoselectivity (up to >98:2 *dr*) *via* a tandem double aldol-Tishchenko reaction **(Scheme II)**.



Scheme II. Double aldol-Tishchenko reaction for the introduction of four and five chiral centres in one pot

A broad range of *meta*- and *para*-substituted benzaldehydes including a number of challenging aldol acceptors was examined under the reaction conditions. Mechanistic studies were also performed using DFT calculations through a collaboration and a summary of the results of these investigations are presented. Finally, derivatisation of the double aldol-Tishchenko products was investigated.

Abbreviations

α	stereochemical descriptor
$[\alpha]_D^T$	specific rotation
Å	ångström
@	at
AA	aldol-aldol
AAA	asymmetric allylic alkylation
AAT	aldol-aldol-Tishchenko reaction
Ac	acetyl
ACC	amino cyclic carbamate
ACN	acetonitrile
AcOH	acetic acid
aq	aqueous
AT	aldol-Tishchenko reaction
β	stereochemical descriptor
BINAP	2,2'-bis-1,1'-binaphthalene
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bisoxazoline
br s	broad singlet
Bu	butyl
BuLi	butyl lithium

BQ	benzoquinone
c	centi (10^{-2})
	concentration, for rotation
ºC	Celsius degrees
^{13}C NMR	carbon nuclear magnetic resonance
ca.	circa, approximately
Calcd	calculated
cat.	catalyst, catalytic
Cbz	carboxybenzyl group
CDI	carbodiimidazole
CIPE	complex induced proximity effect
CIS-D	complex induced *syn*-deprotonation
cod	cyclooctadiene
conc.	concentrated
COSY	correlation spectroscopy
Cy	cyclohexyl
δ	NMR chemical shift
d	doublet
D	deuterium
DAAA	decarboxylative asymmetric allylic alkylation
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DCM	dichloromethane

dd	doublet of doublets
ddd	doublet of doublets of doublets
dddd	doublet of doublets of doublets of doublets
deg	degree
deprot.	deprotonation
DEPT	distortionless enhancement by polarization transfer
DFT	density functional theory
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPA	diisopropylamine
DKR	dynamic kinetic resolution
DMH	*N*,*N*-dimethylhydrazone
DMBQ	2,6-dimethylbenzoquinone
dq	doublet of quartets
dr	diastereomeric ratio
dt	doublet of triplets
dtd	doublet of triplets of doublets
DTR	dynamic thermodynamic resolution
duanphos	di-*tert*-butyl-2,3,2′,3′-tetrahydro-1*H*,1′*H*-(1,1′)biisophosphindolyl
E	electrophile
E	entegen configuration
e.g.	for example

EDG	electron donating group
EDS	enantiodetermining step
ee	enantiomeric excess
equiv.	equivalent (s)
ESI	electrospray ionization
ET	Evans-Tishchenko reaction
Et	ethyl
EWG	electron withdrawing group
g	gram (s)
GC	gas chromatography
h	hour (s)
HIV	human immunodeficiency virus
^{1}H NMR	proton nuclear magnetic resonance
HCLA	homochiral lithium amide
HMBC	heteronuclear multiple-bond correlation spectroscopy
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single-quantum correlation spectroscopy
Hx	hexyl
Hz	Hertz
i	iso
i.e.	that is

IR	infared
Im	Imidazole
Inda	Indane
J	coupling constant
k	rate constant
K	Kelvin
KDA	potassium diisopropylamide
KHMDS	potassium bis(trimethylsilyl)amide
L	litre
LDA	lithium diisopropylamide
$LiBHEt_3$	lithiumtriethylborohydride
LHMDS, LiHMDS	lithium bis(trimethylsilyl)amide
lit.	literature
LRMS	low resolution mass spectra
m	meter
	mili (10^{-3})
	multiplet
	medium
M	metal
	molar
m/*z*	mass-to-charge ratio
max	maximum
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz

min	minute (s)
mL	millilitre
mmol	millimole
mol	molecular
	mole
mol%	mole percent
m.p.	melting point
MS	mass spectrometry
ν	frequency of maximum absorption
NDA	sodium diisopropylamide
n.d.	not determined
NMR	nuclear magnetic resonance
Ns	4-nitrobenzenesulfonyl, nosyl
o	ortho
o/n	overnight
OAc	acetate
OTf	trifluoromethanesulfonate, triflate
π	type of orbital, electron
p	para
Ph	phenyl
PhD	Doctorate of Philosophy
PMP	*p*-methoxyphenyl
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate

Pr	propyl
p-TsOH	*p*-toluenesulfonic acid
Py	pyridyl
q	quartet
quin	quintet
R	rectus configuration
RAMBO	(2*R*,3a*R*,6a*R*)-2-(methoxymethyl)hexahydrocyclopenta[*b*]pyrrol-1(2*H*)-amine
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
R_f	retention factor
RT	room temperature
s	second
	singlet
S	sinister configuration
SADP	(*S*)-2-(2-methoxypropan-2-yl)pyrrolidin-1-amine
SAEP	(*S*)-2-(3-methoxypentan-3-yl)pyrrolidin-1-amine
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
SAPP	(*S*)-2-(methoxydiphenylmethyl)pyrrolidin-1-amine
sat.	saturated
sept	septet
sext	sextet
SM	starting material
SOX	sulfoxide-oxazoline
sp	sparteine

T	temperature
t	triplet
*t*BS	*N*-*tert*-butanesulfinyl imines
td	triplet of doublets
t	tert, tertiary
TADDOL	α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetra-*n*-butylammonium fluoride
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
t_R	retention time
Ts	4-toluenesulfonyl, tosyl
UV	ultraviolet
Val	valine
Z	zusammen configuration

*Note: Descriptors of stereoisomer composition and stereoselectivity used throughout, are in accordance with the original papers.

“Mystery creates wonder and wonder is the basis of man’s desire to understand”

Neil Armstrong

I

The Asymmetric α-Alkylation of *N*,*N*-dimethylhydrazones

Chapter 1

The Asymmetric α-Alkylation of *N*,*N*-dimethylhydrazones

Introduction

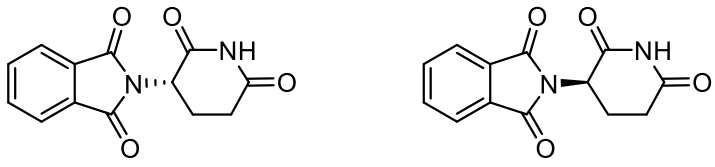
1. Introduction

1.1 Chirality

Chirality is one of life's greatest curiosities. Seldom has such a phenomenon, so critical in nature, sparked such intense scientific intrigue. Chirality, or handedness, means that an object or molecule cannot be superimposed on its mirror image.[1] The two forms of a chiral molecule are termed enantiomers. Enantiomers possess a unique architecture in the sense that they share the same molecular formula, atom-atom connectivity and bonding distance but differ in their three-dimensional arrangement of atoms.[2]

Chirality has enabled nature to be incredibly selective. Hence, chiral molecules exist almost exclusively as single enantiomers within living organisms, for example, amino acids and proteins.[3] In the environment of biological systems where structure-activity relationships may be required for affect, the pharmacological and physiological effects of a racemic drug and individual enantiomers can differ significantly.[2] As a result of these precise structure-activity relationships, in most cases living organisms respond differently to each enantiomer. One enantiomer may produce the desired therapeutic effect while the other may be inactive or produce an undesired or toxic effect.[4]

The importance of stereochemistry in drug design and development is exemplified no more so than that of the thalidomide tragedy. Thalidomide was a drug marketed as a racemate to pregnant women in the late 1950s. Tragically, however, it was found that only the (*R*)-enantiomer **(*R*)-1** produced the desired sedative and antiemetic effects while the (*S*)-enantiomer **(*S*)-1** was found to be teratogenic **(Figure 1)**.[5]



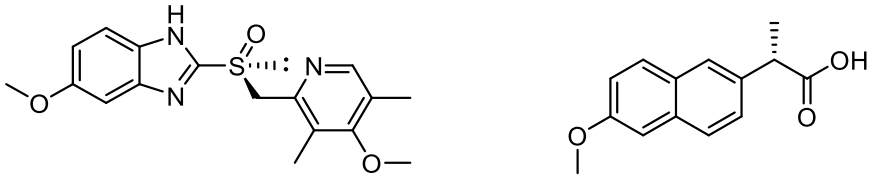
(*S*)-1 (*S*)-Thalidomide

(*R*)-1 (*R*)-Thalidomide

Figure 1. Two enantiomers of Thalidomide

Since 1992, strict regulations and policies pertaining to drug stereochemistry are now in place within the pharmaceutical industry.[6] Consequently, many drugs are now marketed as single

enantiomers resulting in improved safety and/or efficacy profiles. Over the past few decades, the demand for enantiomerically pure compounds has grown at a remarkable pace. In this respect, stereoselective synthesis now holds a privileged position within the pharmaceutical industry. Currently, more than half of the approved drugs in use are chiral.[7] Furthermore, many of the best selling drugs are now sold as single-enantiomers, for example, Nexium® **(*S*)-2**, a medication for gastroesophageal reflux disease and the nonsteroidal anti-inflammatory drug Naproxen® **(*S*)-3 (Figure 2)**.



(*S*)-2
Nexium®

(*S*)-3
Naproxen®

Figure 2. Single-enantiomer drug molecules

1.2 Methods for the synthesis of enantiomerically pure compounds

There exists three main methods to obtain enantiomerically pure or enriched compounds depending on the type of starting material used **(Figure 3)**.[8]

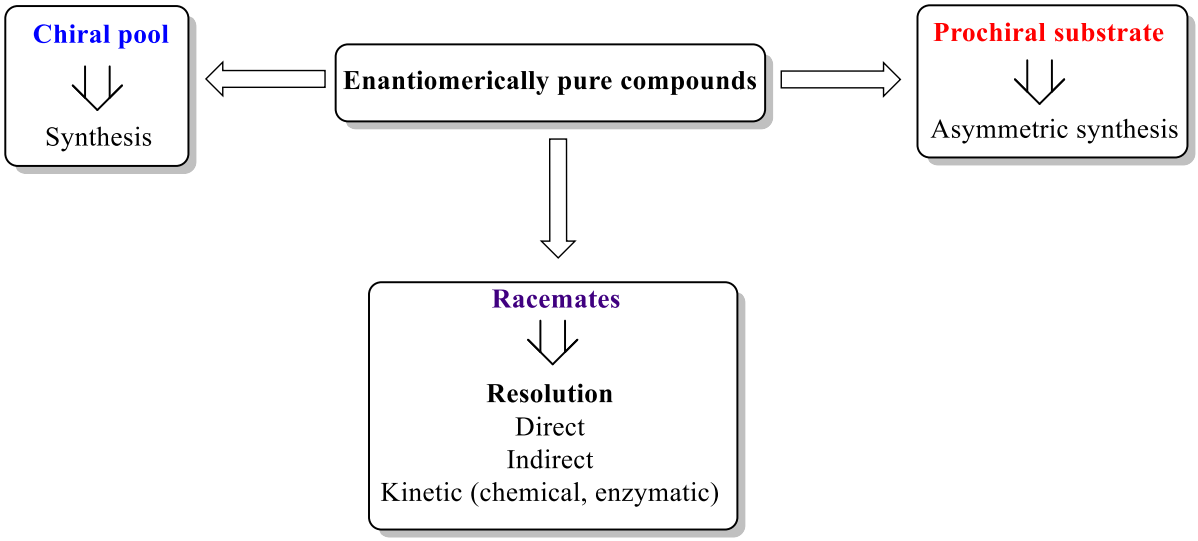
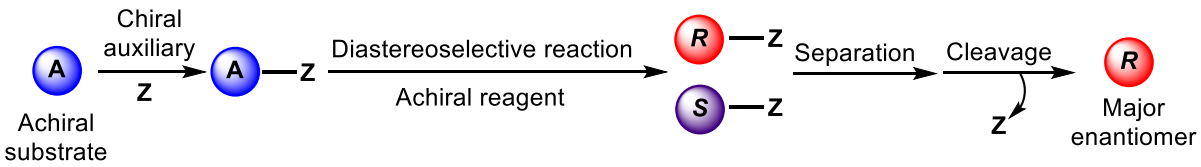


Figure 3. Methods to obtain enantiomerically pure compounds

The chiral pool approach utilises readily available sources of enantiomerically pure starting materials in the synthesis of the chiral target molecule. Nature provides a rich source of enantiomerically pure compounds, for example, amino acids, carbohydrates, terpenes and alkaloids.[9] Although this traditional approach has proved enormously powerful, it has largely been replaced by more efficient methods for the synthesis of enantiomerically pure drug compounds.[10]

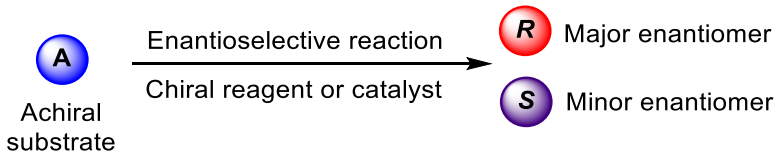
Chiral resolution remains one of the most applied techniques in industry due to it's simplicity and scalability.[11] Kinetic resolution relies on the unequal reaction rates of enantiomers with a chiral reagent or catalyst such as an enzyme.[12] Chemical resolution involves reaction between a racemate and an enantiomerically pure chiral resolving agent, resulting in diastereomeric salt formation.[7] The two diastereomers have different physical properties and thus can be separated *via* direct or indirect methods, for example, chromatography and crystallisation. Another technique involves treatment of the racemate with an enzyme which recognizes one enantiomer. It then selectively converts this enantiomer to the desired product while the other enantiomer remains unchanged.[13]

One of the most powerful strategies to obtain enantioenriched compounds is through asymmetric synthesis. Asymmetric synthesis involves the selective creation of one chiral configuration in the presence of a chiral auxiliary, reagent or catalyst.[14] Asymmetric synthesis can be divided into two classes: Diastereoselective reactions and enantioselective reactions. Diastereoselective reactions are carried out in the presence of a chiral auxiliary and involve the following steps: **i)** Addition of a chiral auxiliary to a prochiral substrate **ii)** Reaction of the chiral material with an achiral electrophile resulting in the formation of diastereomers **iii)** Separation of the formed diastereomers **iv)** Removal and recycling of the auxiliary, although recycling of the chiral auxiliary is often a challenging task in organic synthesis **(Scheme 1)**.



Scheme 1. Diastereoselective reaction

In an enantioselective reaction, a chiral reagent or chiral catalyst may differentiate between the enantiotopic groups or faces of an achiral molecule, resulting in the preferential formation of one enantiomer **(Scheme 2)**.



Scheme 2. Enantioselective reaction

As the demand for enantiopure compounds continues to increase, advances in the field of asymmetric synthesis are required within the foreseeable future.

1.3 Asymmetric substitution of carbonyl compounds

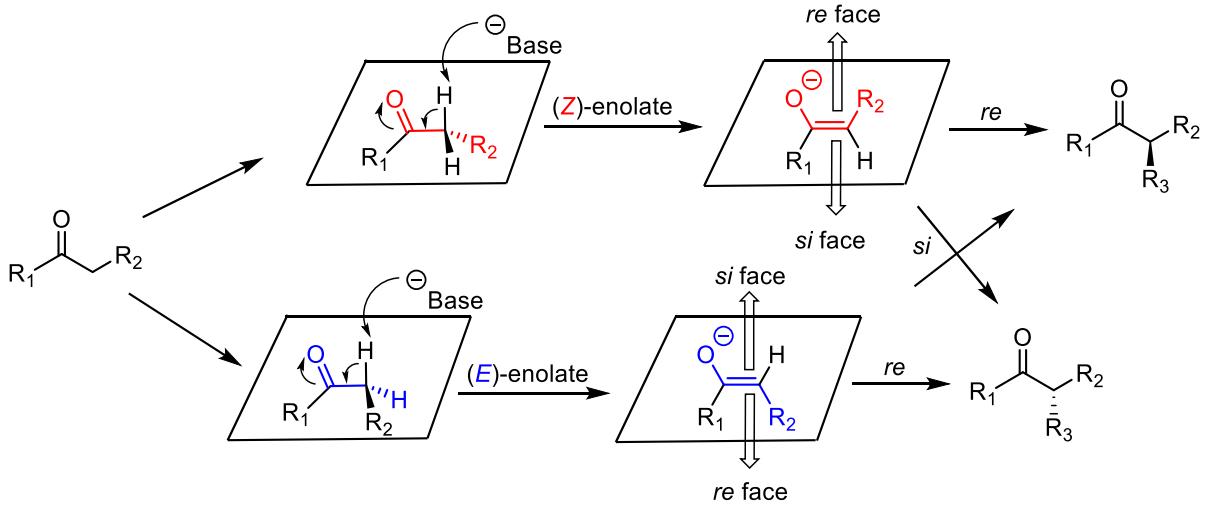
The formation of a new carbon-carbon bond alpha (α) to a carbonyl group represents one of the most fundamental transformations in organic synthesis. In many cases, this process can also lead to the formation of a new stereogenic centre. Enantiomerically enriched α-alkylated ketones constitute privileged scaffolds in numerous biologically active systems.[15] This apparently simple reaction is frequently taught at basic undergraduate level, yet has proved enormously challenging to achieve asymmetrically **(Scheme 3)**.



Scheme 3. Challenging transformation

The α-alkylation of ketones typically involves pregeneration or *in situ* formation of nucleophilic enols, enolates, or alkyl/silyl enol ethers and subsequent reaction with electrophiles.[16] However, classical carbonyl enolate chemistry is fraught with a number of problems. Oftentimes, multiple reaction pathways are possible for a given transformation, in addition to the desired one.[15] Furthermore, the stereochemical outcome of the reaction is controlled by both the geometry of the carbon-carbon bond of the enolate as well as the facial

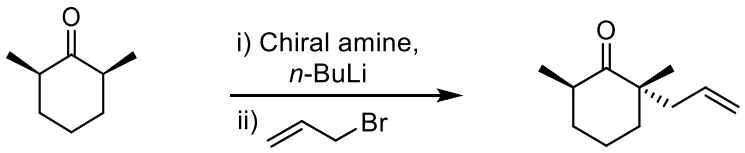
approach of the electrophile **(Scheme 4)**.[17] Unsymmetrical ketones with two sites for enolization, present the additional challenge of controlling the regioselectivity of deprotonation.



Scheme 4. Complications of carbonyl enolate chemistry

1.4 Homochiral lithium amide bases

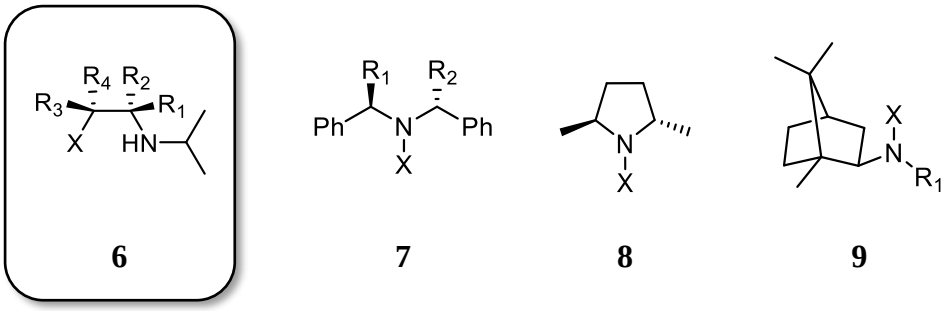
One of the early efforts to obtain enantiomerically enriched α-alkylated ketones involved the use of homochiral lithium amide bases (HCLAs). Koga[18] and Simpkins[19] independently established the use of chiral lithium amide bases for the desymmetrization of conformationally locked *meso*-ketones **(Scheme 5)**.



4 **5**

65%, 25% *ee*

Koga **Simpkins**



6 **7** **8** **9**

Scheme 5. Enantioselective deprotonation of *cis*-2,6-dimethylcyclohexanone **4** and a selection of homochiral lithium amides

The chiral base selectively discriminates between the pair of α-axial protons due to a stereoelectronic effect **(Figure 4)**.

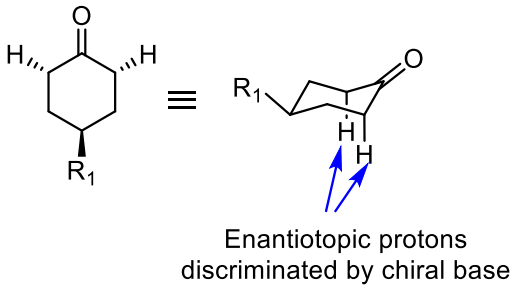


Figure 4. Stereoelectronic bias for α-axial protons

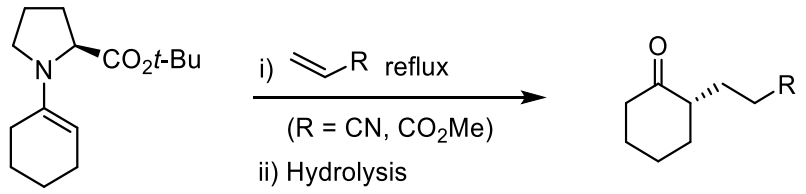
To date, a plethora of HCLA bases have been prepared. Despite extensive studies, this method has only been reported for the asymmetric α-alkylation of conformationally locked prochiral cyclic ketones, which has limited its widespread uptake. However, this approach deserves merit as it currently represents the only example of a 'direct' approach for the asymmetric α-alkylation of ketones.

1.5 Nitrogen analogues of carbonyl compounds

In recent years, metalated enamines, imines and hydrazones have been used extensively as reactive enolate equivalents.[20] In particular, 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.[10] Furthermore, azaenolates also provide a simple means of introducing a nitrogen based chiral auxiliary.[15] The chiral auxiliary methodology has been a major breakthrough in asymmetric synthesis, and prevails as the strategy of choice to access α-chiral substituted carbonyl compounds.

1.5.1 Early chiral auxiliaries for the asymmetric α-alkylation of ketones

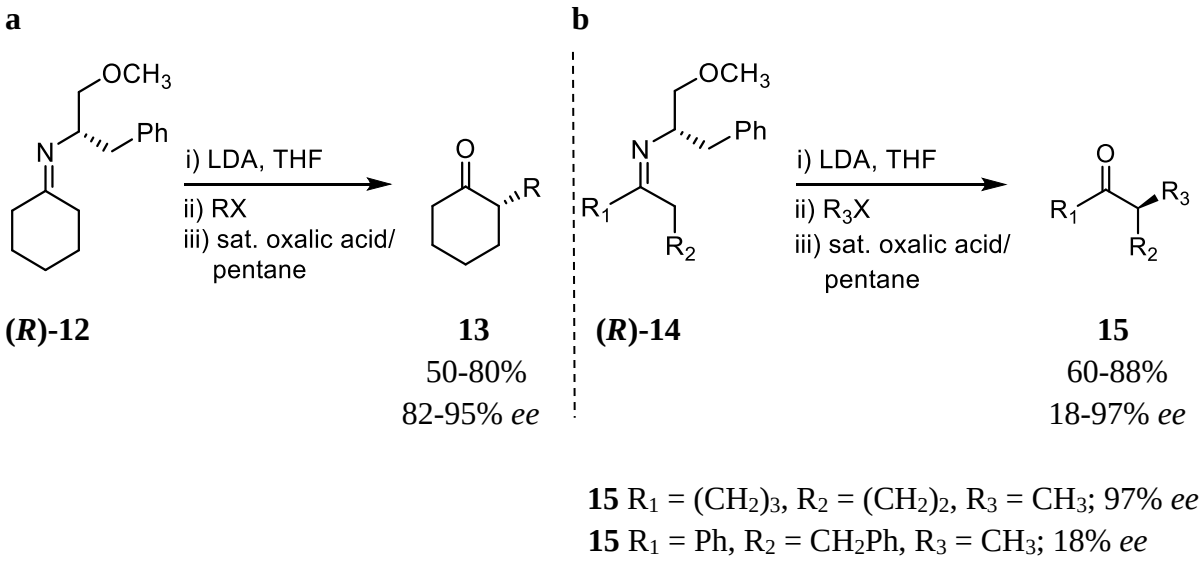
Over the past number of decades, several chiral auxiliaries have been developed for the asymmetric α-alkylation of ketones with varying degrees of success.[21] In 1969, Yamada and co-workers published the first asymmetric α-alkylation of carbonyl compounds *via* enamine chemistry based on use of an (*S*)-proline derived auxiliary. Moderate enantioselectivities were achieved for the reaction of cyclohexanone enamine **(*S*)-10** with Michael acceptors to afford **(*S*)-11 (Scheme 6)**.



(*S*)-10 **(*S*)-11**
43-59% *ee*

Scheme 6. Yamada's proline derived auxiliary

Further progress was established when Meyers reported the use of acyclic amino acid derived auxiliaries for the asymmetric α-alkylation of imines in 1976.[21c] Alkylation of cyclohexanone imine **(*R*)-12** with alkyl iodides furnished the corresponding products **13** in good yields and high enantioselectivities **(Scheme 7a)**. In a later publication by the same group,[22] this methodology was extended to include simple acyclic ketones **15 (Scheme 7b)**. Moderate to high enantioselectivities were achieved for enantioenriched products **15** with alkyl iodides. However, enantioselectivity was diminished when large substituents were present on the imine **(*R*)-14**.



Scheme 7. Meyers asymmetric α-alkylation of **a)** cyclic and **b)** acyclic ketones

While Yamada's and Meyers research laid the foundations for future developments, the scope of early efforts was very limited and normally required symmetrical, cyclic ketones. Furthermore, imines and enamines are difficult to form quantitatively and are hydrolytically unstable.[15]

1.5.2 *N*,*N*-dialkylhydrazones

N,*N*-dialkylhydrazones have proven to be very important aldehyde and ketone synthetic equivalents **(Figure 5)**. From a synthesis perspective, azaenolates derived from *N*,*N*-dialkylhydrazones offer many advantages over their corresponding enolates. The lower C-H acidity of the α-hydrogens in hydrazones (pKa ~ 30) leads to enhanced reactivity of the azaenolate towards electrophiles. Furthermore, the decreased acidity also prevents racemization of α-chiral centres by typical bases such as hydroxides and alkoxides, which is often in sharp contrast to the carbonyl analogues.[20] The presence of the dialkylamino group provides an additional coordination site for metals and thus enhances the stability of the metalated azaenolate. The regioselectivity of deprotonation is high and predictable[23] and usually takes place at the least sterically hindered site unless there is an anion stabilizing group present at the competing site.[24] Selective α-monoalkylation is also controlled *via* the dialkylamino group. Additionally, better regioselectivity is observed for *C*-alkylation reactions in contrast to aldehydes and ketones where *O*-alkylation can be a competing problem.[20]

In general, *N*,*N*-dialkylhydrazones are readily prepared *via* a facile condensation between the aldehyde or ketone and *N*,*N*-dialkylhydrazine. The reagents can be mixed neat or in benzene, dichloromethane or hexane. Ketones and less reactive or sterically hindered aldehydes may require an acid catalyst (AcOH, TFA, *p*-TsOH), heating and removal of water to achieve high conversions in reasonable reaction times.[20,25] Metalated hydrazones can be prepared *via* several methods, most commonly leading to the formation of lithium and potassium azaenolates.[20] In recent years, numerous cleavage methods have been developed to liberate the carbonyl functionality.[26] Overall, these reactive species can undergo a variety of synthetically useful transformations including α-alkylations,[25] aldol,[27] Michael[28] and Claisen-type reactions.[29]

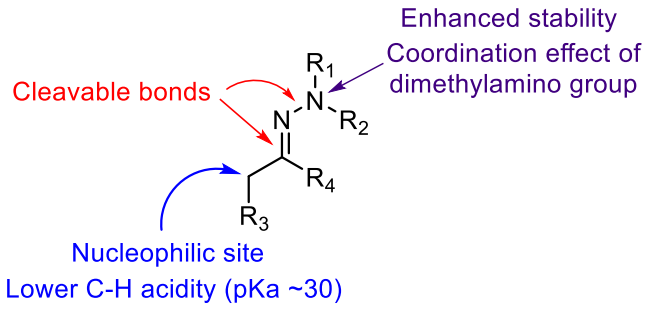


Figure 5. Reactivity sites of *N*,*N*-dialkylhydrazones

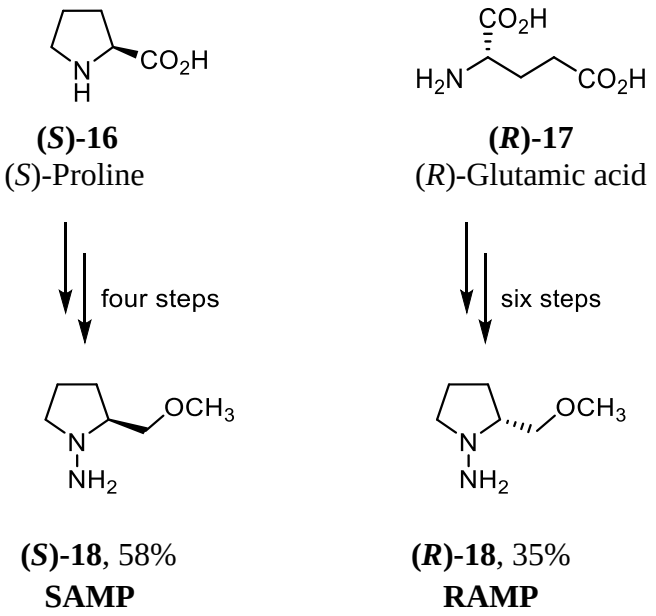
The first records for the synthetic application of *N*,*N*-dialkylhydrazones dates back to the 1960s.[30] In 1971, Stork demonstrated the first use of azaenolates derived from simple *N*,*N*-dimethylhydrazones for the asymmetric α-alkylation of *α*,*β*-unsaturated ketones.[31] However, *N*,*N*-dialkyhydrazones did not gain widespread application in synthesis until the landmark papers on the α-alkylation of metalated *N*,*N*-dialkylhydrazones were published by Enders and Corey in the years 1976-1978.[20] This pioneering work demonstrated that *N*,*N*-dialkylhydrazones could serve as important intermediates in the formation of carbon-carbon bonds. Shortly thereafter, Enders developed a powerful method for the synthesis of highly enantiomerically enriched α-substituted carbonyl compounds.[32]

1.5.3 Modern chiral auxiliaries

1.5.3.1 SAMP/RAMP methodology

(*S*)-amino-2-methoxypyrrolidine (SAMP) **(*S*)-18** and (*R*)-amino-2-methoxypyrrolidine (RAMP) **(*R*)-18** chiral auxiliaries introduced by Ender's group have so far proven to be the most effective method for the asymmetric α-alkylation of aldehydes and ketones. SAMP **(*S*)-**

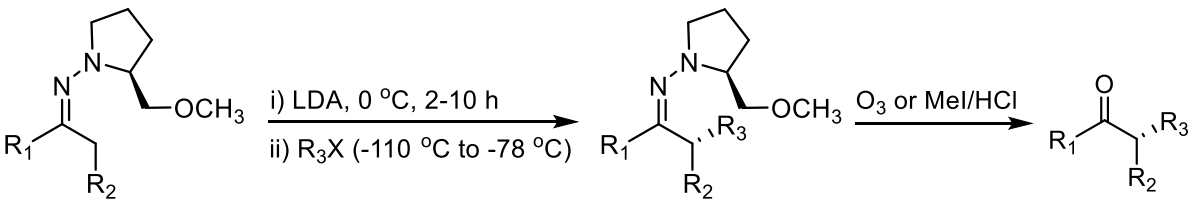
18 can be synthesised in four steps from the cheap and commercially available (*S*)-proline **(*S*)-16**.[33] However, this procedure produces an undesirable toxic nitrosamine intermediate. Thus, an alternative six-step procedure is also available which produces **(*S*)-18** in 57% yield starting from **(*S*)-16**.[34] The *R*-enantiomer (RAMP) **(*R*)-18** is obtained over six steps in 35% yield from (*R*)-glutamic acid **(*R*)-17 (Scheme 8)**.[35]



Scheme 8. Synthesis of SAMP **(*S*)-18** and RAMP **(*R*)-18** chiral auxiliaries

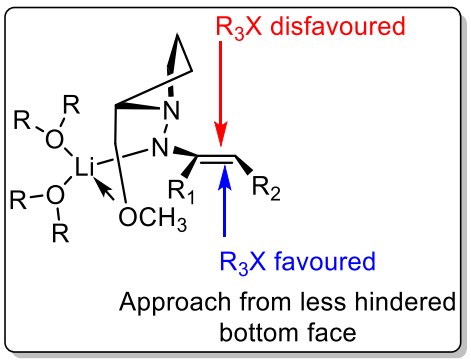
Chiral hydrazones **(*S*)-19** are easily prepared by reaction of the ketone or aldehyde with enantiomerically pure hydrazine SAMP **(*S*)-18** or its enantiomer.[25] Aldehydes react neat with SAMP **(*S*)-18** at 0 ºC. Hindered or less reactive aldehydes and ketones require acidic catalysis (AcOH, TFA, *p*-TsOH) and heating in benzene or cyclohexane with the concomitant removal of water using a Dean-Stark apparatus. The resulting hydrazones can be purified by chromatography or distillation, although purification is often unnecessary. Deprotonation of hydrazone **(*S*)-19** with lithium diisopropylamide or other lithium bases in ethereal solvents such as Et_2O and THF leads to the formation of a chiral azaenolate **(Scheme 9)**. Investigations (trapping experiments,[32a] spectroscopic investigations[36] and X-ray analysis[37]) have shown that the resulting azaenolate species exists exclusively as the $E_{CC}Z_{CN}$ isomer in both cyclic and more flexible acyclic hydrazones.

The resulting azaenolate can be trapped by a broad range of electrophiles to furnish diastereomerically enriched α-alkylated hydrazones **20 (Scheme 9)**. The stereochemistry of the alkylation step can be explained by the preferential approach of the electrophilic reagent (R_3X) on the conformationally rigid and chelated SAMP azaenolate from the least sterically hindered *si* face. It is thus possible to predict the resulting diastereomer based on this mechanistic pathway. Therefore, the absolute configuration can be controlled by use of either the SAMP **(*S*)-18** or RAMP **(*R*)-18** auxiliary. The original carbonyl functionality is restored utilising one of the numerous reported cleavage methods, for example, ozonolysis or HCl/MeI in pentane, to generate α-alkylated ketones or aldehydes **21**.[26] This methodology has been successfully applied across a variety of carbon-carbon bond forming reactions including α-alkylations, aldol, Michael and Claisen-type reactions.[20] In particular, the α-alkylation of SAMP/RAMP hydrazones has been employed as a key step in the asymmetric synthesis of many natural products.[38]



(*S*)-19 **20** **21**

31-99% *ee*



Scheme 9. Ender's SAMP chiral auxiliary methodology and proposed intermediate

1.5.3.2 Chiral *N*-amino cyclic carbamate (ACC) methodology

Remarkably, no alternative to the SAMP/RAMP chiral auxiliary methodology appeared until 2008 when Coltart reported the use of chiral *N*-amino cyclic carbamate (ACC) auxiliaries.[39] These auxiliaries can be easily introduced and removed with near quantitative recovery of the auxiliary. This method offers considerable improvements on the SAMP/RAMP hydrazone methodology. The enhanced acidity of these 'activated' hydrazones enables rapid deprotonation **(Figure 6)**. Alkylation also does not require extremely low reaction temperatures. The reactions proceed with excellent stereo- and regiochemical control and in high yields. A number of ACC auxiliaries have been investigated, with the camphor-based auxiliary **22** proven to give the best yields and stereoselectivities **(Figure 6)**.

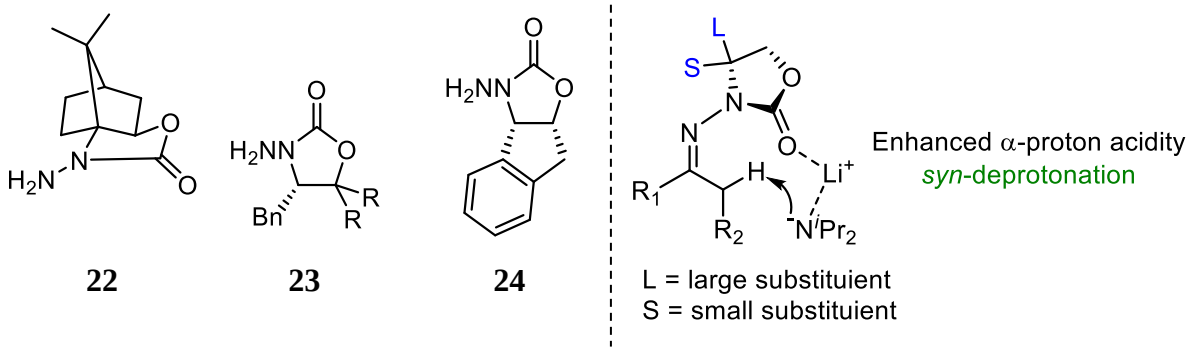
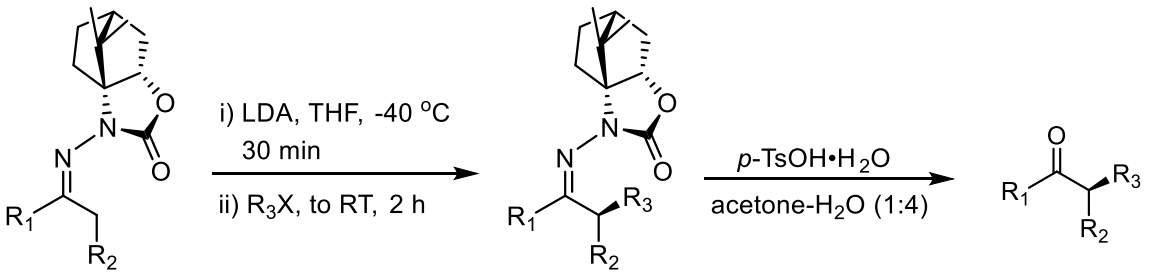
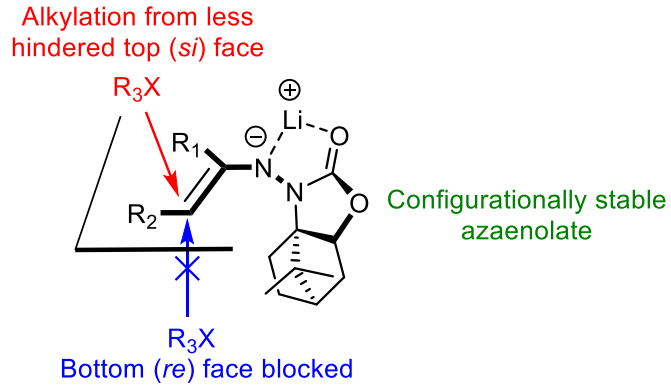


Figure 6. ACC auxiliaries and complex induced *syn*-deprotonation (CIS-D)

The proposed stereochemical model for this transformation is based on experimental[39] and computational studies by the Houk group.[40] Coordination of LDA to the carbonyl group results in the formation of a five membered chelate complex leading to *syn*-deprotonation **(Scheme 10)**. This fixes the conformation of the enolate in the $E_{CC}Z_{CN}$ configuration. Alkylation then occurs from the least sterically hindered top (*si*) face to furnish α-alkylated hydrazones **26**. The hydrazone moiety can be readily cleaved following treatment with *p*-TsOH•H_2O in a 1:4 mixture of acetone and water to afford the desired ketones **27** in near quantitative yields.

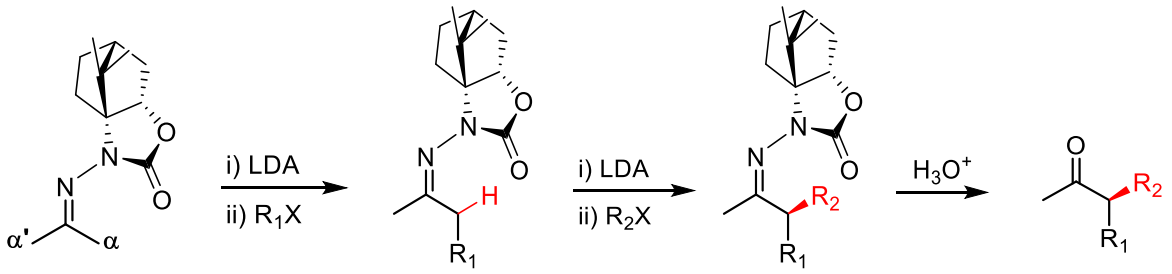


25 **26** **27**
76-99%
60-96% *ee*



Scheme 10. Coltart's *N*-amino cyclic carbamate chiral auxiliary methodology

One of the most defining features of this system is that α,α-bisalkylation of ketones is possible through complex induced *syn*-deprotonation (CIS-D) **(Scheme 11)**.[41] Kinetic LDA-mediated deprotonation of ketones, imines and *N*,*N*-dialkylhydrazones usually result in the removal of the most sterically accessible proton of two similarly acidic protons. However, the CIS-D overrides this preference enabling α,α-bisalkylation of ketones having both α and α′ protons. This has been demonstrated with acetone derived hydrazone **28**. Monoalkylation of **28** gives the α-product **29** as a single regioisomer in excellent yields with a variety of alkyl halides. A second alkylation at the α-position is then enabled through CIS-D resulting in removal of the less accessible α-proton of **29** to form the desired α,α-bisalkylated product **30** which is then cleaved to generate the desired ketone **31** in excellent yield and stereoselectivity. Additionally, both enantiomers of ketone **31** are accessible in some cases by reversing the order of addition of the alkylating agents. The ACC methodology has also been applied to a number of total syntheses.[42]



28 **29** **30** **31**

95-98%

>98% *ee*

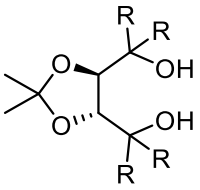
Scheme 11. Regioselective α,α-bisalkylation of ketones using ACC hydrazones

While numerous other protocols have emerged for the asymmetric α-alkylation of ketones including transition metal catalysis,[43] organocatalysis[44] and photocatalysis[45] many of these systems are limited in scope to conformationally rigid cyclic ketones. Remarkably, the majority of these routes have bypassed the use of simple and prominent acyclic ketones such as propiophenone and 3-pentanone. Reported examples in the literature are rare.[46] However, Trost[47] and Hou[48] have achieved the palladium-catalysed asymmetric allylic α-alkylation (AAA) of acyclic unsymmetrical ketones such as propiophenone. The most notable improvement in this area came in 2009 when Trost disclosed the decarboxylative asymmetric allylic alkylation (DAAA) of simple acyclic ketones with more than one enolizable proton such as 3-pentanone.[49]

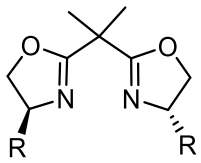
Currently, the primary route to accomplish the α-asymmetric alkylation of carbonyl compounds involves the use of chiral auxiliaries, which has proven to be a robust and reliable method. However, there are inherent limitations to this approach. Firstly, chiral auxiliaries are oftentimes very expensive. Secondly, two additional synthetic steps are required to incorporate and remove the auxiliary. In addition, catalysis is not possible due to the requirement for stoichiometric amounts of the chiral auxiliary. Thus, the development of non-chiral auxiliary based methods for the asymmetric α-alkylation of acyclic ketones would represent an important advance.

1.6 Chiral ligands in asymmetric synthesis

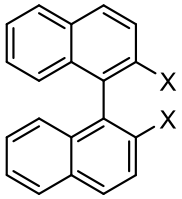
Chiral ligands have played a crucially important role in asymmetric synthesis. A chiral ligand has the ability to modify the reactivity and selectivity of the metal centre in such a way that one of two possible enantiomeric products is formed preferentially.[50] To date, a vast array of chiral ligands have been designed and tested throughout the literature. However, a few structural classes have emerged as 'privileged chiral ligands', affording high levels of enantioselectivity, across a broad spectrum of metal-catalysed reactions **(Figure 7)**.



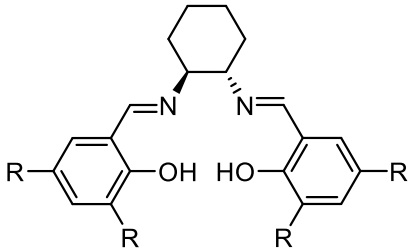
32-TADDOL



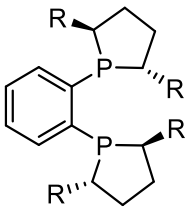
33-BOX



34
BINOL (X = OH)
BINAP (X = PPh_2)



35-Salen



36-DuPhos

Figure 7. Privileged chiral ligands

A common feature of these 'privileged ligands' is that they possess a C_2 axis of symmetry. This can have a beneficial effect on the enantioselectivity by reducing the number of competing reaction pathways.[51] Although C_2-symmetric ligands have been more prominent in the field of asymmetric synthesis, recent advances have shown that in some cases C_1-symmetric ligands can outperform their C_2 counterparts.[50] (-)-Sparteine ((-)-sp) is one such ligand possessing C_1-symmetry which has excelled in the area of enantioselective synthesis.

1.6.1 (-)-Sparteine 37 as a chiral ligand in asymmetric synthesis

(-)-Sp **37** is the most well-known C_1-symmetric ligand. It is a naturally occurring lupin alkaloid, isolated by extraction from certain papilionaceous plants such as the scotch broom *Cytisus scoparius* or the lupin *Lupinus luteus*. It is frequently combined with organolithium reagents to produce very efficient chiral bases or chiral nucleophiles. However, it has also been used successfully in tandem with other metals.[52] The cisoid conformation enables it to adopt a very attractive metal chelating conformation and function as a very efficient chiral bidentate ligand **(Figure 8)**. Its enantiomer, (+)-sp **37** is also a natural product but had not been readily available until recently, and remains expensive. It can also be obtained *via* a time-consuming, lengthy total synthesis[53] or *via* resolution and deoxygenation of the bitter lupin *Lupinus albus*.[54] Until recently, sparteine was only available in one enantiomeric form as the (-)-antipode. To overcome this problem, O'Brien introduced the (+)-sp surrogate **38** which is structurally similar to (-)-sp **37** but lacks the D-ring.[52] This *N*-Me-substituted (+)-sp surrogate **38** has been evaluated across a range of enantioselective transformations. Both (-)-sp **37** and (+)-sp surrogate **38** have been found to usually behave in an enantiocomplementary fashion. Recently, O'Brien has reported the synthesis of a (-)-sp surrogate **38** in a yield of 33% over 10 steps.[55]

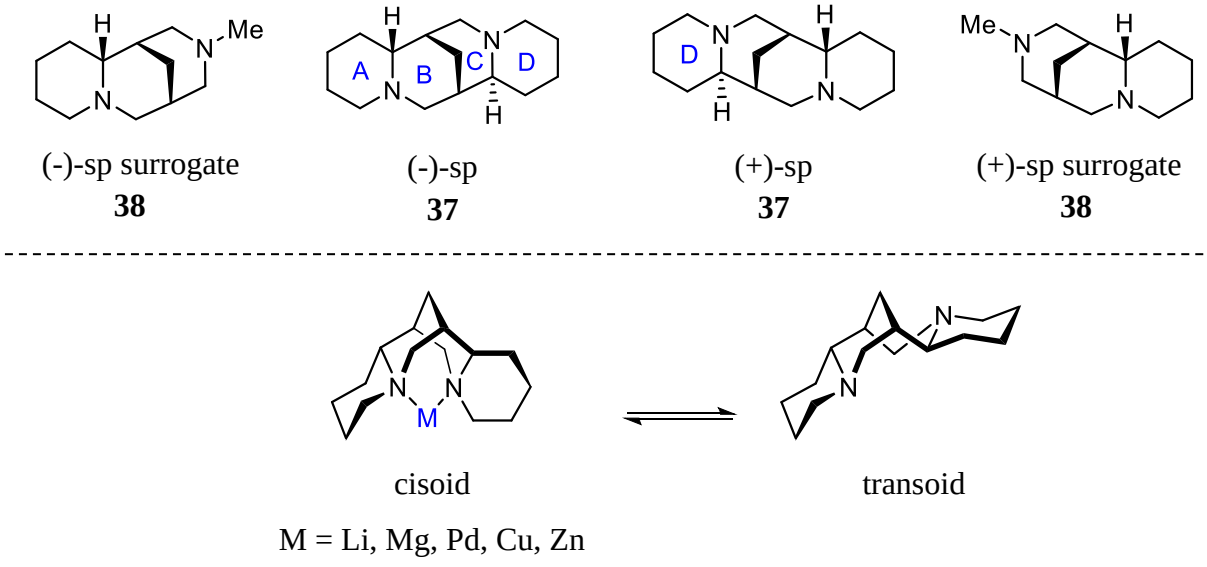


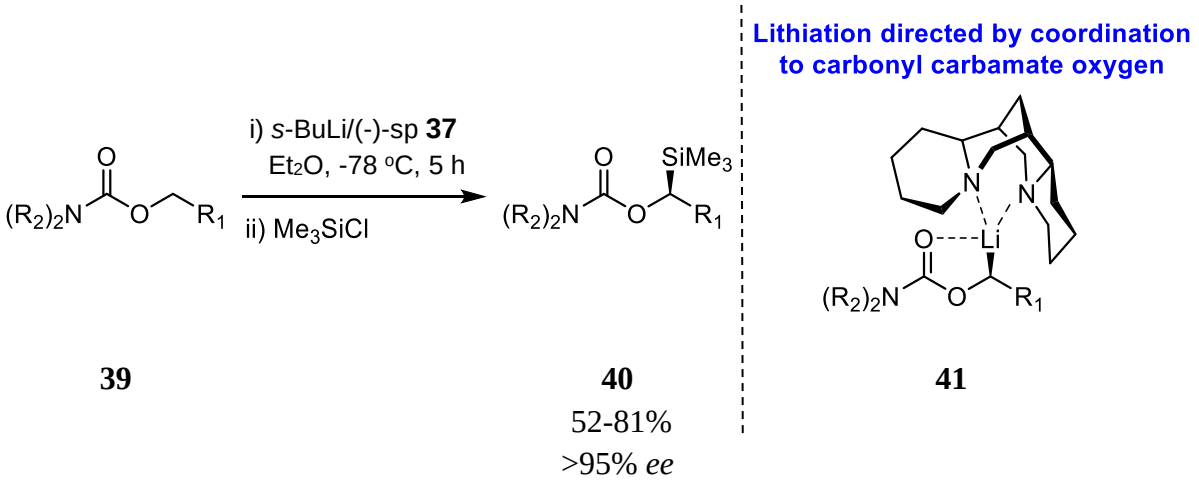
Figure 8. Sparteine and its attractive metal-chelating conformation

1.6.1.1 Application of organolithium/(-)-sparteine reagents in enantioselective synthesis

Organolithium reagents are routinely used in all facets of modern organic synthesis.[56] Since the pioneering work of Schlenk and Holtz on these highly reactive reagents,[57] organolithiums have played a pivotal role in small-scale laboratory syntheses and large-scale pharmaceutical processes. An important feature of organolithium compounds is the strong structure-reactivity relationship.[58] In the absence of co-solvents or ligands, organolithium compounds form oligomeric aggregates in solution as well as in the solid-state.[59] In general, it is known that a decrease in the degree of aggregation correlates with an increase in reactivity. Thus, deaggregation to smaller reactive compounds is often desired. Consequently, organolithium reagents are often used in conjunction with co-solvents or ligands, in particular ether compounds and nitrogen ligands, in an attempt to influence aggregation and deaggregation.[58] These compounds can have a dramatic effect on the reactivity, stereo- and regioselectivity of organolithium reagents. Coordination of these species to the lithium atoms results in stabilisation of the aggregates which enables the organolithiums to shift to an entropically favoured lower degree of aggregation.[60]

The chiral diamine (-)-sp **37** has been found to be extremely well-suited to this role. As a result, it is frequently incorporated into alkylithium/ligand systems. Indeed, these chiral adducts have proven hugely successful, enabling high levels of reactivity and selectivity in deprotonation,[61] addition,[62] rearrangement[63] and carbolithiation reactions.[64] In particular, it is through its combination with *s*-BuLi that this ligand has had its most profound influence in enantioselective synthesis.

The concept of using (-)-sp **37** and *s*-BuLi as a chiral base was first explored by Nozaki and Noyori in the late 1960s albeit with limited success.[65] Little progress was made until the first examples of highly enantioselective lithiation/substitution using *s*-BuLi/(-)-sp **37** was reported for *O*-alkyl carbamates **39** by Hoppe in 1990 **(Scheme 12)**.[61] This reaction proceeds *via* asymmetric deprotonation to provide a configurationally stable organolithium **41** capable of reacting with electrophiles to afford enantiomerically enriched products **40** in high yields and enantioselectivities.

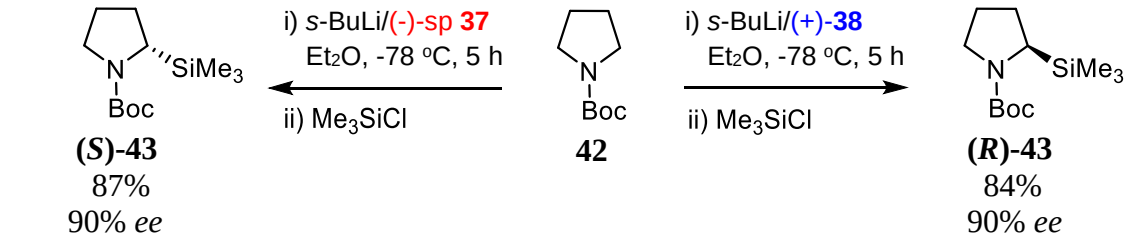


Scheme 12. First highly enantioselective lithiation using (-)-sp **37**

Shortly thereafter, Beak and Kerrick demonstrated the asymmetric α-lithiation and electrophilic trapping of *N*-Boc-pyrrolidines using the *s*-BuLi/(-)-sp **37** base.[66] This work has also been extended to other heterocycles including piperidine[67] and piperazine.[68] Furthermore, (-)-sp **37** has been successfully applied across numerous enantioselective transformations including asymmetric deprotonations α- to phosphorous,[69] asymmetric alkylations[70] *via* dynamic kinetic[71] and dynamic thermodynamic resolutions,[72] kinetic resolution of secondary alcohols,[73] asymmetric addition to imines[62] and polymerisation reactions.[74]

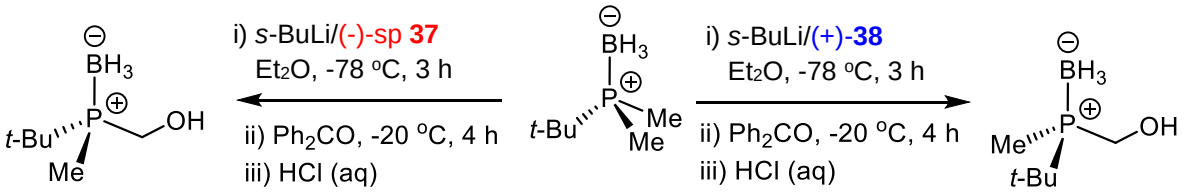
O'Brien has also evaluated use of the (+)-sp surrogate **38** across a range of these transformations.[52] A comparison between (-)-sp **37** and (+)-sp surrogate **38** in some of these reactions is presented in **Scheme 13**. Comparable levels of enantioselectivity have been achieved using diamine (+)-**38** demonstrating the versatility of this ligand. In some cases, *s*-BuLi/(+)-**38** has been shown to be much more reactive than *s*-BuLi/(-)-sp **37** which is of significant importance for less reactive substrates and catalytic asymmetric deprotonation reactions.[52]

Asymmetric deprotonation of *N*-Boc pyrrolidine



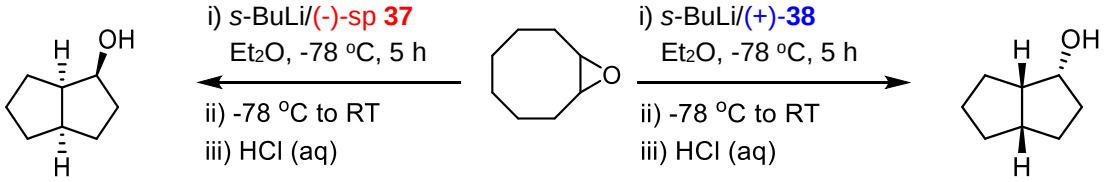
(*S*)-43 87% 90% *ee* — **42** — **(*R*)-43** 84% 90% *ee*

Asymmetric functionalisation of phosphine boranes



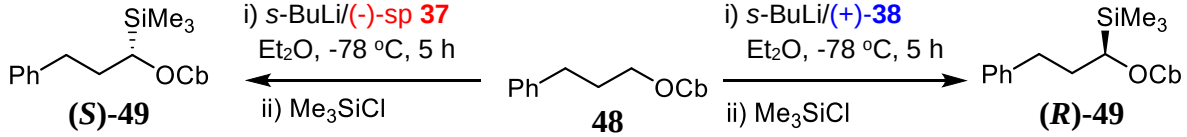
(*S*)-45 65% 96% *ee* — **44** — **(*R*)-45** 63% 82% *ee*

Asymmetric deprotonation and rearrangement of cyclooctene oxide



(-)-47 74% 66% *ee* — **46** — **(+)-47** 70% 62% *ee*

Asymmetric lithiation/substitution of *O*-alkyl carbamates



(*S*)-49 64% 96% *ee* — **48** Cb = CON*i*-Pr — **(*R*)-49** 72% 86% *ee*

Scheme 13. Asymmetric transformations using (-)-sp **37** and (+)-sp surrogate **38**

1.6.1.2 Catalytic asymmetric deprotonations

Since 2004, O'Brien and co-workers have been investigating catalytic asymmetric deprotonations and electrophilic trappings using sub-stoichiometric quantities of (-)-sp **37**. Initial investigations using sub-stoichiometric amounts of (-)-sp **37** for the asymmetric deprotonation reactions of *N*-Boc pyrrolidine[75] and *O*-alkyl carbamates[75b] generated only mixed success. In light of these results, O'Brien then proposed the use of an achiral stoichiometric diamine to displace the chiral diamine and thus allow recycling of the reactive *s*-BuLi/(-)-sp **37** complex. Several criteria must be met to achieve catalytic asymmetric deprotonation/substitution:

1. Ligand exchange must occur.
2. The organolithium must be configurationally stable before and after ligand exchange.
3. Deprotonation with *s*-BuLi/(-)-sp **37** complex must be faster than with the *s*-BuLi/achiral diamine complex.

From this work, O'Brien developed an efficient ligand exchange protocol for *s*-BuLi/diamine-mediated catalytic asymmetric deprotonations.[75b] This strategy utilises an achiral diamine, bispidine **50** which exchanges rapidly with (-)-sp **37** allowing regeneration of the reactive *s*-BuLi/(-)-sp **37** chiral base **(Figure 9)**.

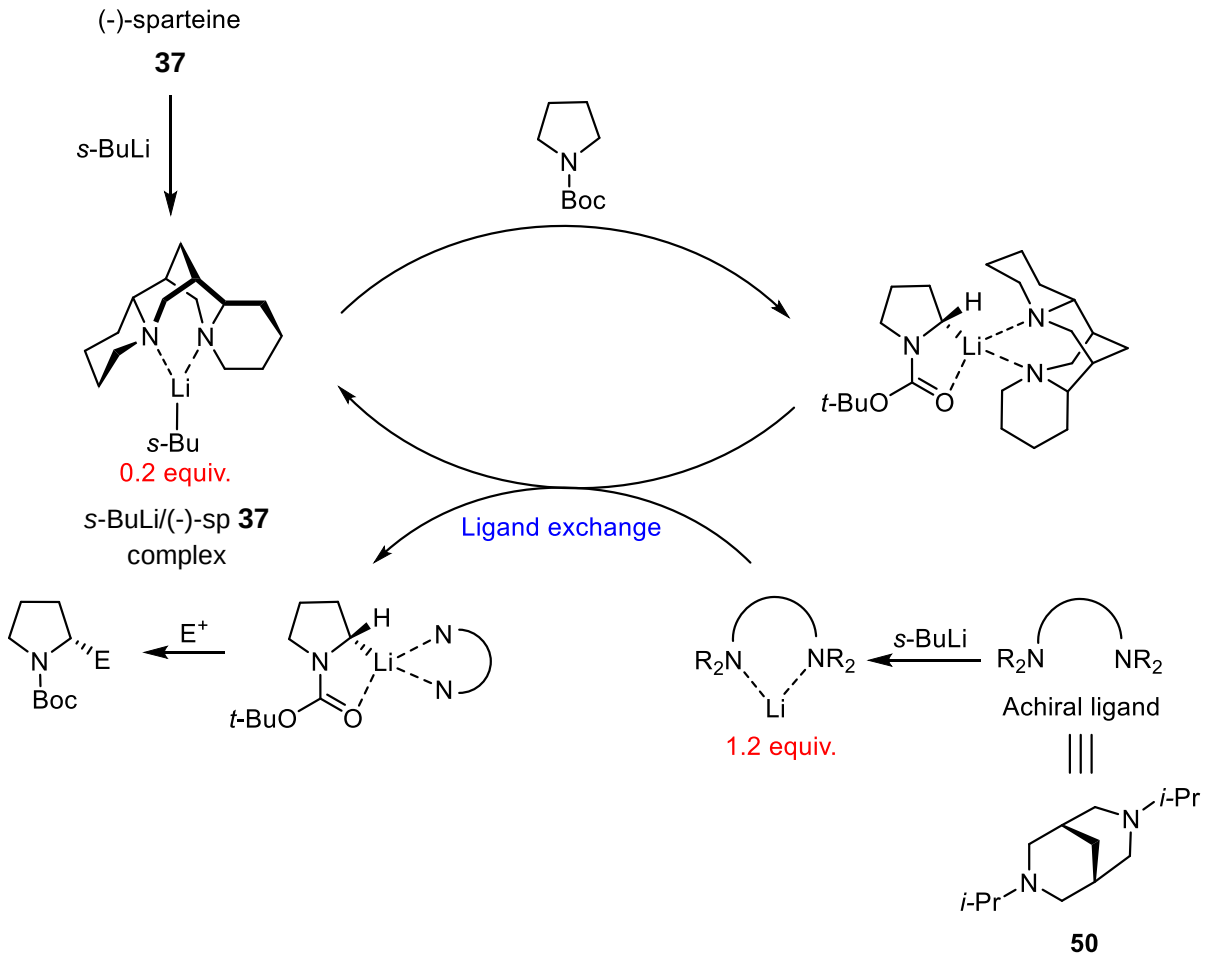
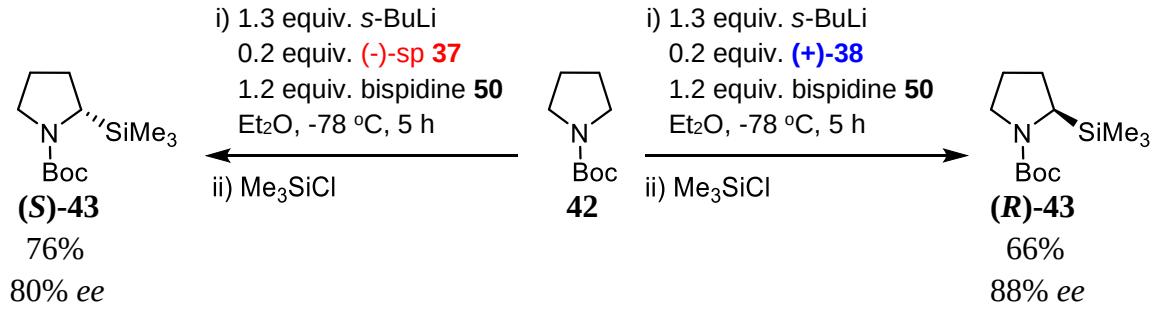


Figure 9. Catalytic asymmetric deprotonation using a ligand exchange protocol

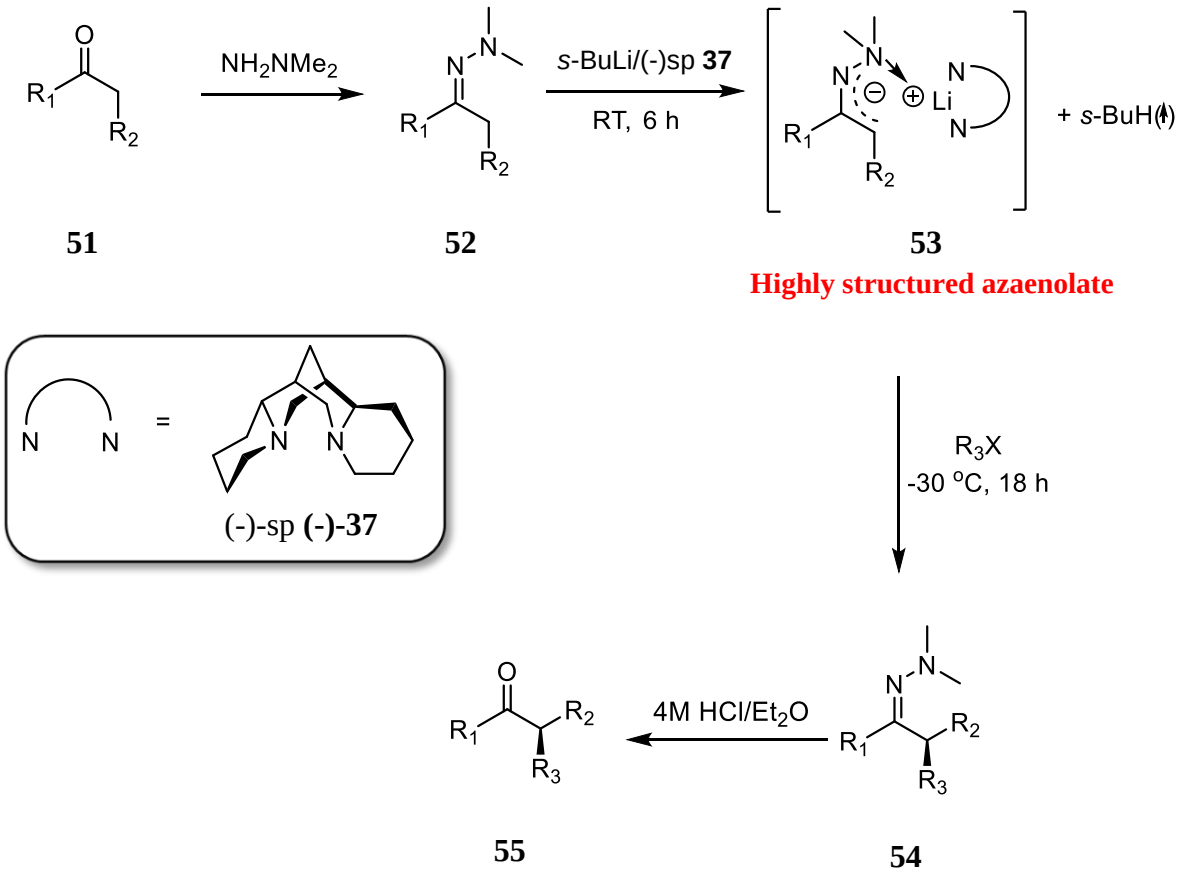
O'Brien has successfully applied this strategy to the lithiation-Me_3SiCl trapping of *N*-Boc pyrrolidine **42** using both (-)-sp **37** and (+)-sp surrogate **38 (Scheme 14)**. Similar yields and almost identical enantiomeric ratios were observed under sub-stoichiometric conditions. Using the (+)-sp surrogate **38**, even better enantioselectivity was achieved. This catalytic asymmetric deprotonation methodology has also been applied to *O*-alkyl carbamates and phosphine boranes.[75b] Catalytic asymmetric deprotonation of phosphine boranes can also be achieved *via* a one ligand catalytic cycle using both (-)-sp **37** and (+)-sp surrogate **38**.[76]



Scheme 14. Catalytic asymmetric deprotonation of *N*-Boc pyrrolidine **42** using (-)-sp **37** and (+)-sp surrogate **38**

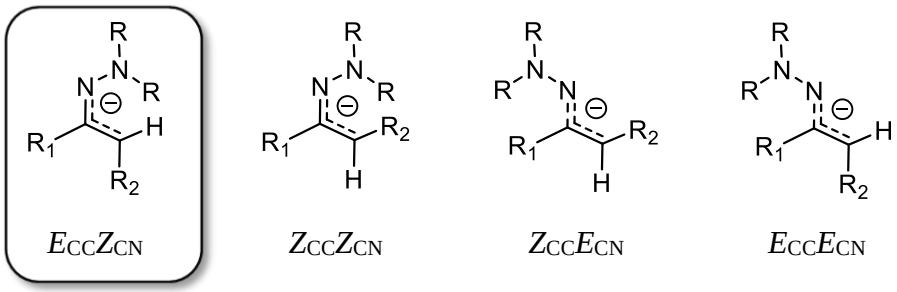
1.7 Asymmetric α-alkylation of *N,N*-dimethylhydrazones using the chiral ligand (-)-sparteine 37

In 2014, research within the McGlacken group developed a new approach to furnish enantiomerically enriched α-alkylated ketones using the chiral ligand (-)-sp **37**.[77] This methodology involves the use of simple non-chiral *N,N*-dimethylhydrazones **52** (DMHs) as ketone surrogates and affecting their asymmetric α-alkylation using the chiral diamine (-)-sp **37 (Scheme 15)**. The transfer of chiral information occurs in an intermolecular fashion. Previous enantioselective transformations of this type are exclusively based on chiral auxiliary methods of asymmetric induction. Deprotonation of *N,N*-dimethylhydrazone **52** with *s*-BuLi/(-)-sp **37** is presumed to lead to the formation of a highly structured azaenolate **53**. Central to this system is the chelation of the dimethylamino group to the lithium cation. The conformationally rigid azaenolate is then expected to undergo a facially selective reaction with the electrophile to generate α-alkylated hydrazones **54**. The resultant hydrazones **54** can be hydrolysed using a biphasic 4M HCl/diethyl ether system to regenerate the original carbonyl functionality and furnish α-alkylated ketones **55**.



Scheme 15. McGlacken's chiral ligand strategy

Deprotonation of *N*,*N*-dimethylhydrazones can theoretically lead to four geometrical isomers **(Figure 10)**. Extensive studies on *N*,*N*-dialkylhydrazones (^{1}H NMR spectroscopy and trapping experiments) have confirmed that the most stable configuration is $E_{CC}Z_{CN}$ when lithium diisopropylamide is utilised as base.[36,78]



Note: $R_1 > R_2$

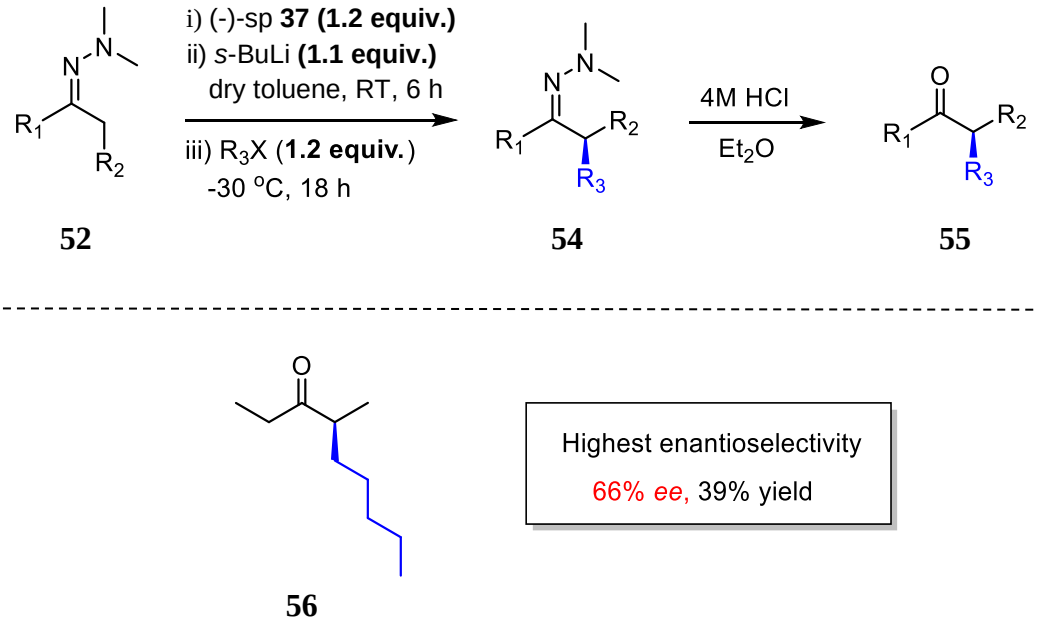
Figure 10. Configurations of lithiated *N*,*N*-dialkylhydrazones

1.7.1 Previous work on the asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using the chiral ligand (-)-sparteine 37

Previous work conducted within the McGlacken group has established an optimised set of reaction conditions for this chiral ligand methodology.[79] A number of reaction parameters were examined including suitable deprotonation and alkylation conditions, alkylithium reagents, solvents and variation of the hydrazone functionality. These optimised conditions were applied to a variety of simple symmetrical and unsymmetrical cyclic and acyclic ketones. A range of hydrolytic and oxidative procedures were also investigated.

Under the standard reaction conditions, deprotonation of *N*,*N*-dimethylhydrazone **52** with a *s*-BuLi/(-)-sp **37** complex takes place at room temperature over 6 h **(Scheme 16)**. Alkylation is then performed at -30 ^{o}C over a period of 18 h. The regeneration of the original carbonyl moiety must take place without any epimerisation and racemisation at the newly formed centre of chirality. A biphasic system of 4M HCl in the presence of diethyl ether has so far proven to be the most effective cleavage method.

The extent of asymmetric induction was found to be highly solvent dependent with toluene emerging as the prime solvent. The dimethylamino hydrazone was found to be the most effective hydrazone moiety. Slow reacting electrophiles such as alkyl iodides work best while acyclic ketones afforded higher enantioselectivities in comparison to cyclic ketones. To date, the best enantioselectivity was obtained using 3-pentanone DMH and *n*-iodopentane affording the α-alkylated ketone **56** with good enantioselectivity and moderate yield.[77]



Scheme 16. Optimised conditions for the asymmetric α-alkylation of *N*,*N*-dimethylhydrazones **52**

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Chapter 2

The Asymmetric α-Alkylation of *N*,*N*-dimethylhydrazones

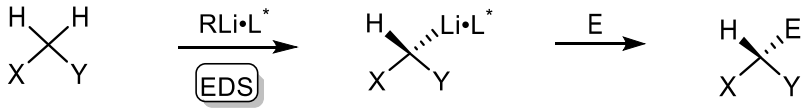
Results and Discussion

Chapter 2. The Asymmetric α-Alkylation of *N*,*N*-dimethylhydrazones using the Chiral Ligand (+)-Sparteine 37

2.1 Background to the project

At present, the McGlacken chiral ligand methodology represents a rare example of the asymmetric α-alkylation of non-chiral hydrazones involving the transfer of chiral information in an intermolecular fashion. Previous work within the group focused on establishing an optimised set of reaction conditions for this chiral ligand methodology. A substrate scope was then performed under the optimised conditions. A number of symmetrical and unsymmetrical, acyclic and cyclic ketones were examined. The electrophile scope ranged from simple alkyl halides to benzyl and allyl bromides. α-Alkylation of an aldehyde and an ester was also attempted albeit with limited success.

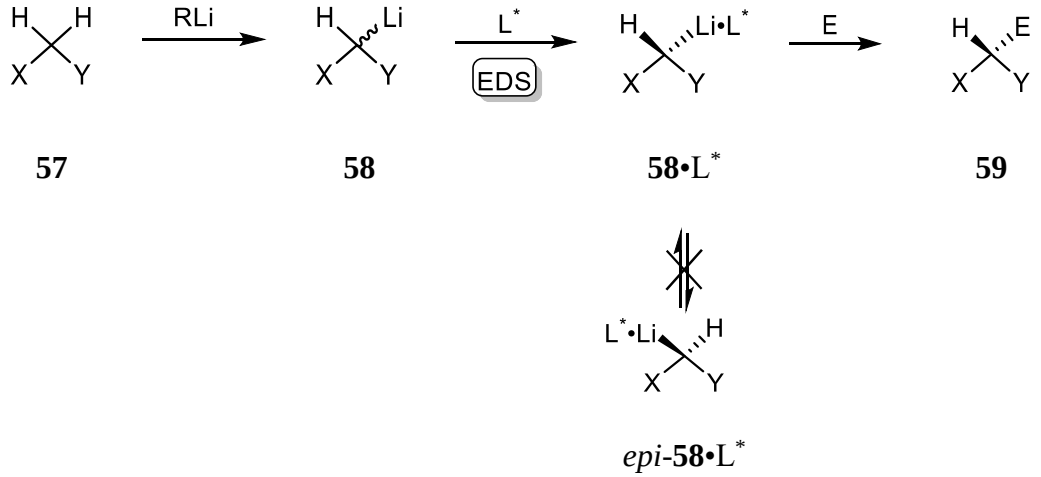
The enantiodetermining step of this asymmetric α-alkylation reaction could be either an asymmetric deprotonation or an asymmetric substitution. In an example of an asymmetric deprotonation reaction, the organolithium/chiral ligand complex (RLi•L*) selectively removes one of the enantiotopic protons from the prochiral substrate **57 (Scheme 17)**. The chiral configurationally stable organolithium **58**•L* then reacts with the electrophile to furnish the enantioenriched product **59**.



57 **58**•L* **59**

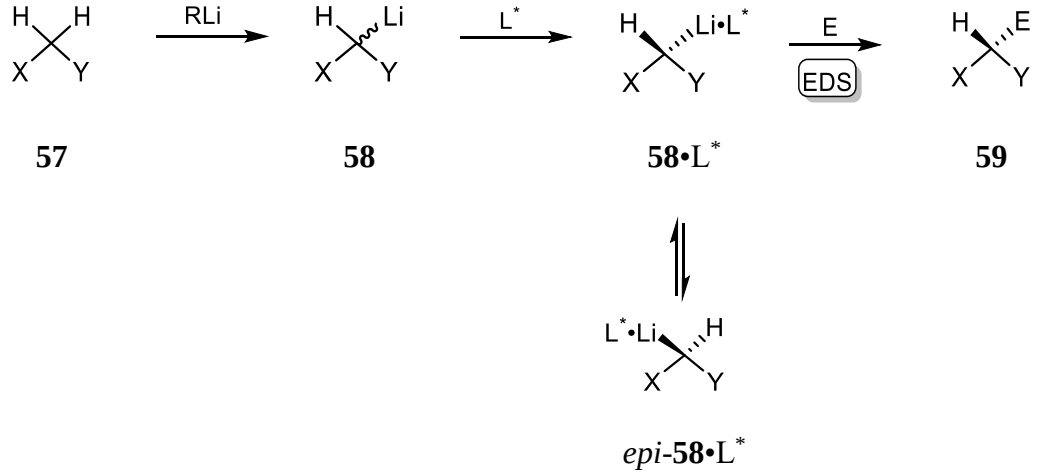
Scheme 17. Asymmetric deprotonation

For an asymmetric substitution reaction, there are two limiting pathways. Dynamic thermodynamic resolution (DTR) involves formation of configurationally stable diastereomeric complexes **58**•L* and *epi*-**58**•L* which are not interconverting with respect to the rate of reaction with the electrophile **(Scheme 18)**. In this case, the enantioselectivity is determined by the ratio of the diastereomeric complexes prior to the addition of the electrophile.



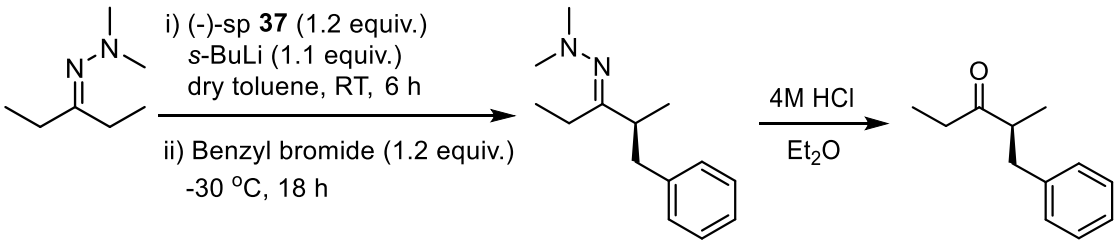
Scheme 18. Dynamic thermodynamic resolution

In a dynamic kinetic resolution (DKR), the diastereomeric complexes (**58**•L* and *epi*-**58**•L*) are configurationally labile and are rapidly interconverting **(Scheme 19)**. One of the diastereomeric complexes reacts preferentially with the electrophile to form the enantioenriched product **59**.



Scheme 19. Dynamic kinetic resolution

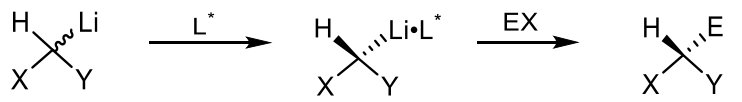
Mechanistic studies carried out prior to undertaking this project suggest that our asymmetric α-alkylation reaction most likely proceeds *via* an asymmetric substitution mechanism.[1a] For example, experiments have confirmed that comparable enantioselectivities are achieved when the *s*-BuLi/(-)-sp **37** complex is present for the deprotonation step to that obtained when (-)-sp **37** is added post deprotonation **(Scheme 20)**.



(-)-sp **37** added pre deprotonation: 54% *ee*
(-)-sp **37** added post deprotonation: 52% *ee*

Scheme 20. Mechanistic studies carried out within the group

In order to distinguish between a DTR and DKR pathway in our system, the configurational stability of the organolithium complex with respect to the rate of reaction with an electrophile was examined using the so called 'poor man's Hoffman's test'.[1] In this test, organolithium species which are diastereomeric by virtue of complexation with a chiral ligand undergo reaction with an achiral electrophile *via* diastereomeric transition states. The test can be performed by monitoring the stereoselectivity with a deficiency or excess of achiral electrophile **(Scheme 21)**. If an organolithium species is configurationally stable, the presence of excess electrophile enables both diastereomeric organolithium complexes to react to completion. The enantioselectivity will vary throughout the course of the reaction but ultimately racemic product will be formed. In the presence of deficient electrophile, the faster-reacting organolithium complex will form more product than the slower-reacting organolithium complex. Enantiomerically enriched product will be formed but the key point is that different results will be obtained in the presence of excess and deficient electrophile. If the organolithium complex is configurationally unstable, an equilibrium between the two diastereomeric organolithium complexes will be maintained. Therefore, the enantioselectivity will be independent of the extent of the reaction. In either case, the same result will be obtained in the presence of excess or deficient electrophile.



57 **58**•L* **59**

Expt 1: excess electrophile



epi-**58**•L* *epi*-**59**

Expt 2: deficient electrophile

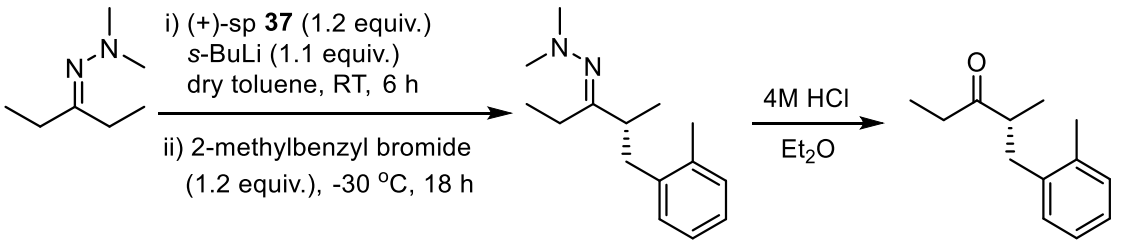
ee Expt 1 ≠ *ee* Expt 2: Configurational stable = DTR

ee Expt 1 = *ee* Expt 2: Configurational unstable = DKR

Scheme 21. Poor man's Hoffman test

Alternatively, the stereoselectivity of the product can be monitored as a function of the alkylation progress. Previous work carried out within the group applied both of Beak's tests to our asymmetric α-alkylation reaction.[1a] From this work, there is evidence to suggest a DKR mechanism as a result of examining the configurational stability of the organolithium azaenolates intermediates with respect to the rate of reaction with electrophile:

1. Identical enantiomeric ratios were achieved for the asymmetric α-alkylation of 3-pentanone DMH **60** in the presence of excess (1.2 equivalents) and deficient (0.2 equivalents) electrophile **(Scheme 22)**.[1a] This result points to a a configurationally unstable organolithium complex. However, one cannot rule out the possibility of configurationally stable complexes with indistinguishable rates of reaction of each diastereomer.

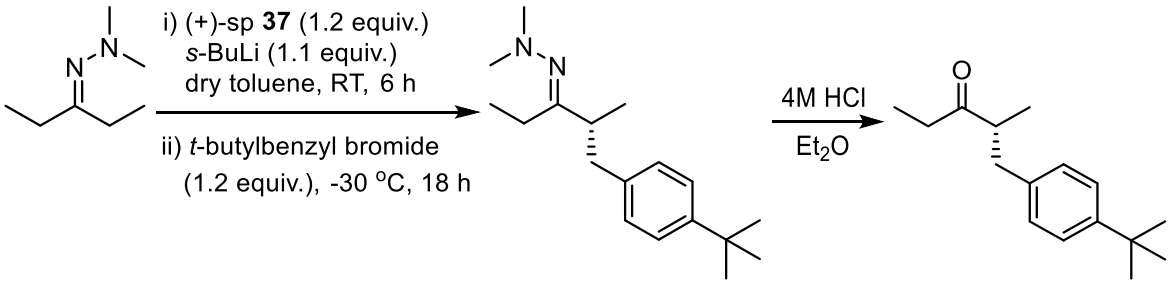


60 **(*R*)-63** **(*R*)-64**

Excess electrophile: 52% *ee*
Deficient electrophile: 52% *ee*

Scheme 22. Mechanistic investigation

2. The stereoselectivity for the asymmetric α-alkylation of 3-pentanone DMH **60** was also monitored after 2 h and 22 h and no change in the enantiomeric ratios was observed **(Scheme 23)**.[1a] This result is consistent with a mechanism of rapidly equilibrating diastereomeric complexes.

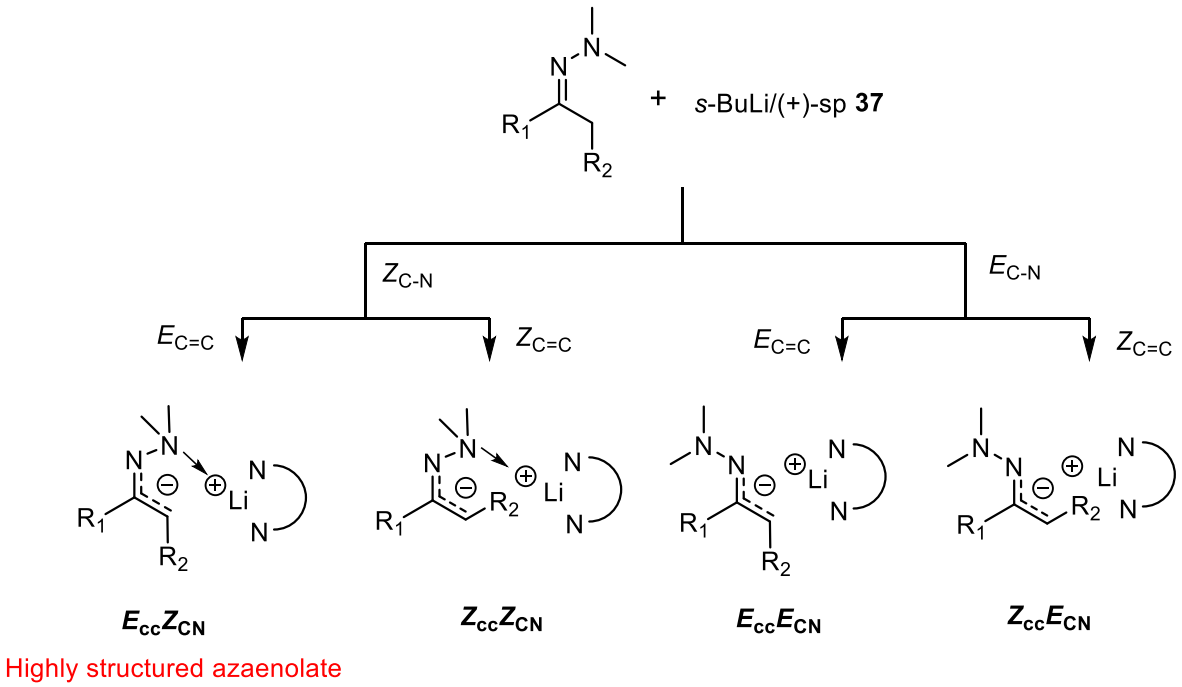


60 **(*R*)-65** **(*R*)-66**

22 h: 42% *ee*
2 h: 42% *ee*

Scheme 23. Mechanistic investigation

It is postulated that at least four azaenolate geometrical isomers could form in our system **(Scheme 24)**. DFT calculations carried out for this chiral ligand methodology have determined the $E_{CC}Z_{CN}$ geometry to be the most stable isomeric form even in the presence of chiral ligand.[1a] However, the formation of the $Z_{CC}Z_{CN}$ isomer cannot be ruled out, thus, it is possible that a mixture of isomers are forming in our system.



Note: $R_1 > R_2$

Scheme 24. Possible geometrical isomers for this asymmetric α-alkylation reaction

A number of hydrolytic and oxidative cleavage procedures were also examined to ensure that racemisation was not occurring during the cleavage step.[1a] Identical enantiomeric ratios were obtained using pH 7 buffered peroxyselenous acid cleavage, Amberlyst® 15, ozonolysis and 4M HCl in diethyl ether. Surprisingly, an oxalic acid cleavage procedure resulted in some racemisation of the newly formed chiral centre despite this method being reported as an extremely mild procedure for the cleavage of SAMP hydrazones.[2] For our methodology, the hydrazones are cleaved *via* acid hydrolysis using a biphasic mixture of 4M HCl in diethyl ether due to short reaction times. HPLC analysis of the crude α-alkylated hydrazone confirmed that racemisation was not occurring during the hydrolysis step.

* It should be noted that for this research project (+)-sp **37** was utilised for all asymmetric reactions.

2.2 Aims and objectives

The overall aim of this chapter is to further develop and extend the chiral ligand mediated strategy for the asymmetric α-alkylation of carbonyl compounds. Due to the available diversity of carbonyl compounds and electrophiles, we felt that the scope of this methodology could be further expanded. Hence, the first section of this chapter aims to broaden the scope of this methodology. As a result, a number of objectives were followed:

- Investigate the direct asymmetric α-alkylation of ketones using (+)-sp **37** as a chiral ligand.
- Examine a range of symmetrical and unsymmetrical ketones using our (+)-sp **37** DMH methodology.
- Utilise an oxime substrate in place of the dimethylamino hydrazone.
- Apply this methodology to more challenging electrophiles.

In the second part of this chapter, a number of reaction parameters will be examined:

- Investigate a range of BOX (bis)oxazoline ligands.
- The effect of different organolithium/(+)-sp **37** and (+)-sp surrogate **38** complexes on the enantioselectivity in this system will be probed.
- Evaluate the use of sub-stoichiometric amounts of chiral ligand.

2.3 Synthesis of racemic mixtures *via* the parent carbonyl compound

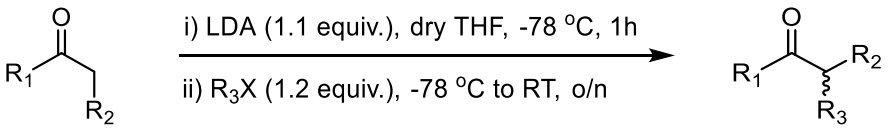
The initial aim of this project was to expand the scope of this methodology by investigating a versatile range of symmetrical and unsymmetrical ketones. Prior to synthesising their asymmetric counterparts, most compounds were prepared as racemic mixtures unless previously synthesised within the group. The racemic compounds were fully characterized *via* ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry and IR spectroscopy. GC conditions for the separation of enantiomers were fully optimised which would then serve as a reference standard for the enantioenriched mixture. The racemic mixtures would also enable us to identify suitable isolation and purification methods.

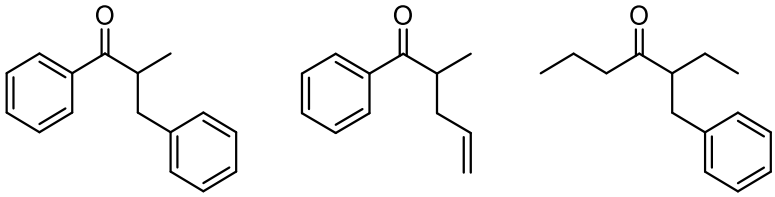
To begin, a small series of α-alkylated ketones was prepared using the parent ketones **(Scheme 25)**. The ketones were deprotonated at -78 ^{o}C in anhydrous THF for 1 h. Ketone enolates are unstable at higher temperature, thus it was necessary to perform the deprotonation step at -78 ^{o}C in order to limit potential side reactions. The electrophile was added dropwise at -78 ^{o}C and the reaction mixture was slowly warmed to room temperature overnight. The crude α-alkylated ketones were purified *via* column chromatography on silica gel.

Initially our attention was focused on examining the unsymmetrical propiophenone ketone. As previously discussed in chapter 1 **(Section 1.5.3.2)**, much of the reported methodologies for the asymmetric α-alkylation of ketones have bypassed this simple yet prominent ketone. Benzyl and allyl bromide were examined as electrophiles which in general are associated with enhanced S_N2 reactivity. The traditional viewpoint is that the accelerated reaction rates are as a result of π-conjugative effects in the transition state.[3] However, this has recently been refuted by Allen and co-workers.[4] They have proposed that substrate-nucleophile electrostatic interactions govern S_N2 reaction rate trends.

The yields obtained for these reactions were poor to modest (12-39%) **(Scheme 25)**. With regard to the propiophenone substrates, it was observed that the reactions did not go to completion in the timescale of the reaction. Additionally, significant difficulties were encountered in trying to separate propiophenone from the benzylated product **67** due to their identical R_f values. Thus, a low yield of 14% was obtained for this product. The major fraction isolated from the column contained mainly product and <15% of starting material. The best yield was achieved for the α-allylated ketone **68**. The C_2-symmetric 4-heptanone ketone was

also utilised. A poor yield of 14% was achieved for the benzylated 4-heptanone compound **69**. This is most likely due to the volatility of the final product.





67, 14% **68**, 39% **69**, 14%

Scheme 25. Racemic α-alkylated ketones prepared *via* the parent ketone

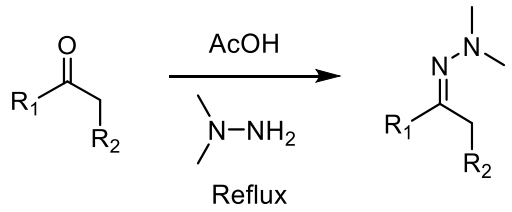
2.4 Preparation of *N,N*-dimethylhydrazones

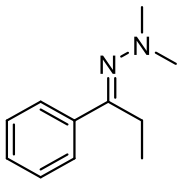
As previously discussed, *N,N*-dimethylhydrazones have been shown to be versatile intermediates in the alkylation of aldehydes and ketones, promoting better yields, reactivity and selectivity.[5] Previous studies conducted within the group have also established that the use of DMHs results in improved levels of regioselectivity in unsymmetrical substrates when two sites are available for deprotonation.[6] Following the poor results and low yields obtained when alkylation was performed using the ketone compounds, further alkylation studies were conducted using the *N,N*-dimethylhydrazone surrogates.

The first step of this methodology involved the preparation of a range of *N,N*-dimethylhydrazones (**Scheme 26)**. This was readily accomplished by heating the parent ketone or aldehyde with 1.0-2.0 equivalents of *N,N*-dimethylhydrazine under reflux conditions. A few drops of AcOH was necessary to increase the electrophilicity of the ketone substrates and promote reaction turnover. The crude *N,N*-dimethylhydrazones were purified *via* Kugelrohr distillation. Good to excellent yields (52-87%) were obtained for the majority of substrates. Particularly high yields were observed for the propiophenone and aldehyde DMHs **(70** and **73)**. Decreased yields were observed for aliphatic DMHs **60** and **71**. Due to the volatile nature of

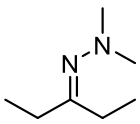
the low molecular weight cyclobutanone DMH **74**, this compound was not purified prior to the alkylation step. In addition, the reaction conditions were slightly modified to accommodate a clean reaction. Cyclobutanone was gently stirred with 1.0 equivalent of *N*,*N*-dimethylhydrazine at room temperature in the absence of acetic acid. Pleasingly, the crude compound was pure enough to be brought forward to the next step without further purification.

Unsymmetrical hydrazones **70** and **72** were individually isolated as inseparable mixtures of *E*:*Z* isomers which was evident by NMR spectroscopy (^{1}H and ^{13}C NMR spectroscopy). In both cases, it can be presumed that the least sterically hindered *E* isomer was the major isomer. For the aldehyde DMH **73**, only one 6H singlet was observed in the ^{1}H NMR spectrum.

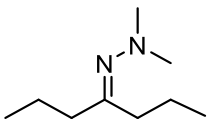




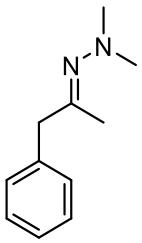
70, 86% (8:1 *E*:*Z*)



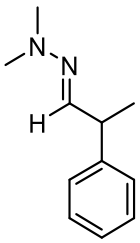
60, 52%



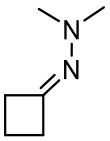
71, 62%



72, 82% (3:1 *E*:*Z*)



73, 87%

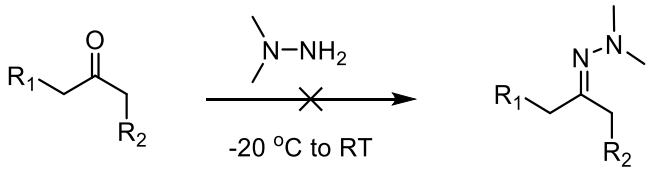


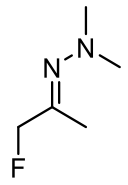
74, 77%

Scheme 26. Synthesis of *N*,*N*-dimethylhydrazones

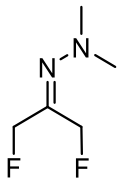
Efforts were also made to synthesize α-fluorinated DMHs **75** and **76 (Scheme 27)**. α-Fluorinated ketones are valuable building blocks for many bioactive compounds.[7] Once again,

the procedure was slightly modified to account for the reactive nature of 1,3-difluoroacetone and fluoroacetone. *N,N*-dimethylhydrazine (1.0 equiv.) was added slowly, dropwise to a solution of ketone in Et_2O at -20 °C. The reaction mixtures were then warmed to room temperature overnight under a nitrogen atmosphere. Surprisingly, the resulting hydrazones were not detectable using TLC analysis, thus, it was necessary to monitor the reaction *via* ^1H NMR spectroscopy. The ^1H NMR spectra after 24 h of both hydrazones showed that the reaction had gone to completion. Unfortunately, attempts to isolate the hydrazones following work-up proved unsuccessful. In each case, the hydrazones were extremely air sensitive and immediate decomposition of the products was observed following exposure to air. A complex mixture of products was observed upon work-up. Due to the difficulty in isolating these DMHs, we decided not to pursue this area of investigation.





75



76

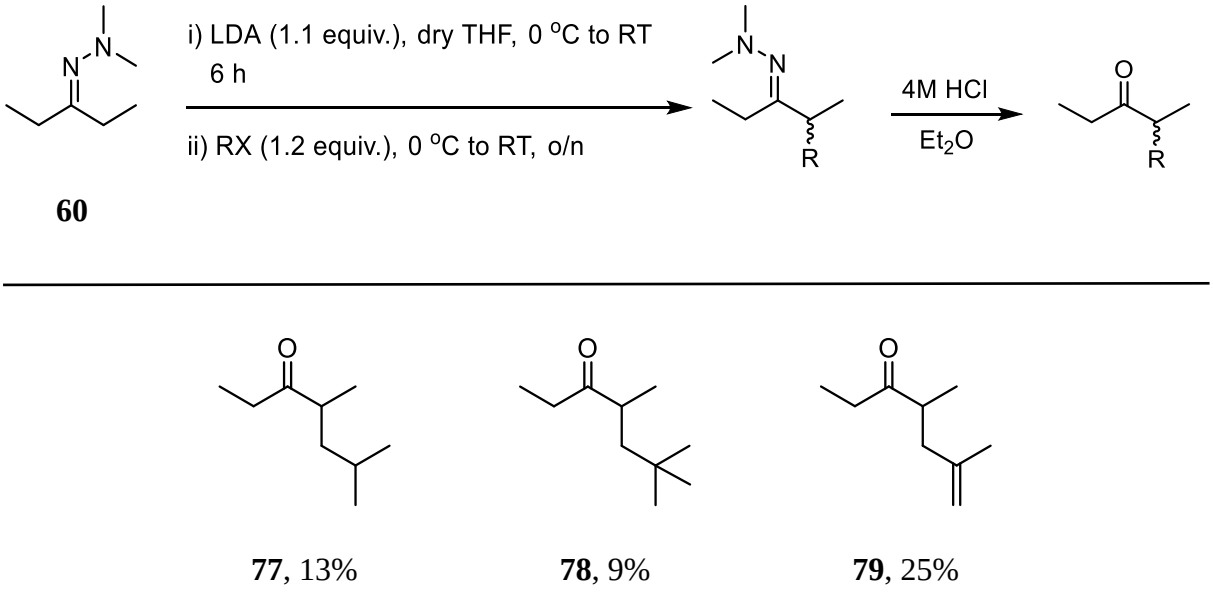
Scheme 27. Attempted synthesis of α-fluorinated DMHs

2.5 Preparation of racemic mixtures *via N,N*-dimethylhydrazones

Next, a small substrate scope was examined using 3-pentanone DMH **60 (Scheme 28)**. 3-pentanone has proven to be a very useful building block in the synthesis of polyketides and propionate-based natural products.[8] Due to the higher stability of azaenolates compared to enolates, it was possible to carry out the deprotonation step at room temperature over 6 h. Alkylation was then performed at 0 °C and the mixture was slowly warmed to room temperature overnight. The crude compounds were then hydrolysed using a biphasic mixture of 4M HCl in diethyl ether and purified *via* column chromatography to furnish the α-alkylated ketones.

Firstly, the effect of increasing the steric bulk of the electrophile was examined. 3-pentanone DMH **60** was reacted with 1-iodo-2-methylpropane and 1-iodo-2,2-dimethylpropane to afford the corresponding products **77** and **78**. Unfortunately, the sterically bulky electrophiles proved relatively unreactive and poor yields were obtained for compounds **77** and **78**. A further decrease in yield was observed when the steric bulk was increased to a *t*-butyl group **(78)**.

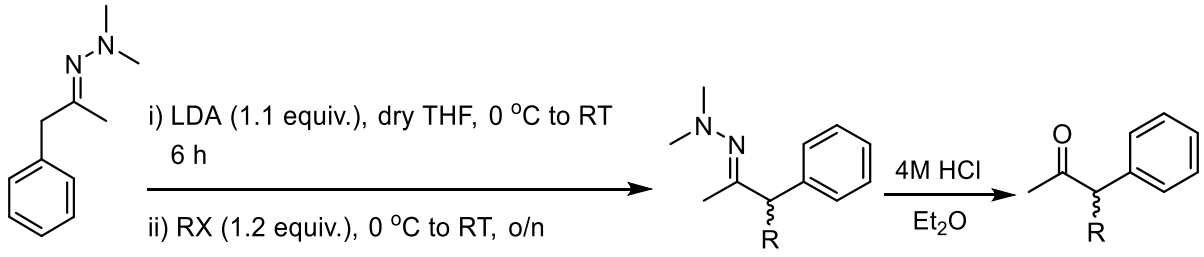
Next, 3-pentanone DMH **60** was reacted with an alkenyl based alkyl halide (allyl bromide) to generate the corresponding product **79** in an improved yield of 25%. However, overall poor yields were obtained for these small molecular weight ketones. Notably, a significant decrease in yield was observed upon lengthy rotary evaporation due to the volatile nature of these substrates.



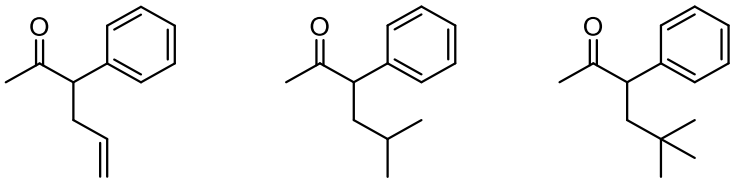
Scheme 28. Alkylation of 3-pentanone DMH **60**

The next challenge was to examine the unsymmetrical phenylacetone DMH **72 (Scheme 29)**. This substrate possesses two sites for deprotonation and has the potential to form regioisomers upon alkylation. A series of electrophiles were probed including allyl bromide and the previously utilised sterically hindered electrophiles (1-iodo-2-methylpropane and 1-iodo-2,2-dimethylpropane). Pleasingly, in all cases, alkylation occurred exclusively at the more thermodynamically favoured benzylic site. Thus, no problems were encountered separating regioisomers. The α-allylated product **80** was isolated in a good yield of 51%. Reduced yields

were observed for the less reactive and sterically demanding electrophiles affording ketones **81** and **82**. Surprisingly, an increase in yield was observed for the *t*-butyl substituted ketone **82** in comparison to the less sterically hindered *i*-propyl substituted ketone **81**.



72

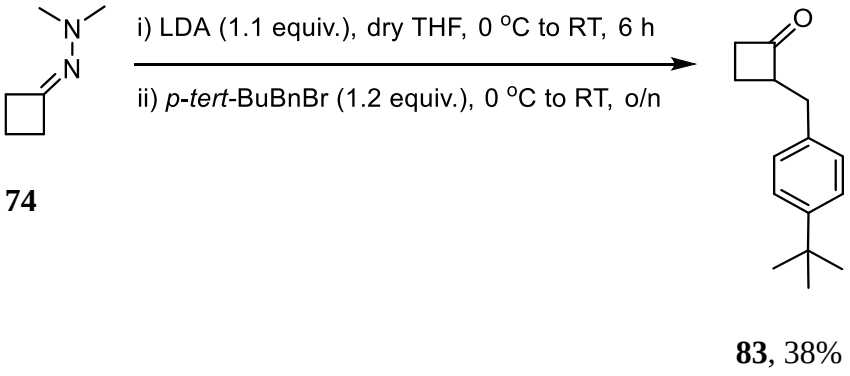


80, 51% **81**, 17% **82**, 31%

Scheme 29. α-Alkylation of unsymmetrical DMH **72**

In order to further develop our methodology we decided to investigate the asymmetric α-alkylation of cyclobutanone DMH **74**. Previous research carried out within the McGlacken group established that cyclic ketones could be successfully alkylated using our chiral ligand methodology.[6,9] Five, six and seven-membered cyclic ketones were alkylated using simple alkyl halides and allyl bromide albeit with poor to moderate levels of enantioselectivity (6-36% *ee*). The asymmetric α-alkylation of cyclobutanones represents a far greater challenge due to the enhanced carbonyl electrophilicity[10] associated with the increased ring strain (26-28.6 kcal/mol) of these compounds.[11] This in turn often limits manipulation of these compounds. Moreover, enolization of these compounds is impeded by an increase in ring strain upon enolate formation (31-34 kcal/mol).[12]

Due to the high volatility of the cyclobutanone DMH **74**, *t*-butyl benzyl bromide was chosen as a suitable electrophile to increase the molecular weight of the resulting ketone **83 (Scheme 30)**. Pleasingly, alkylation of hydrazone **74** afforded **83** in a good yield of 38%.



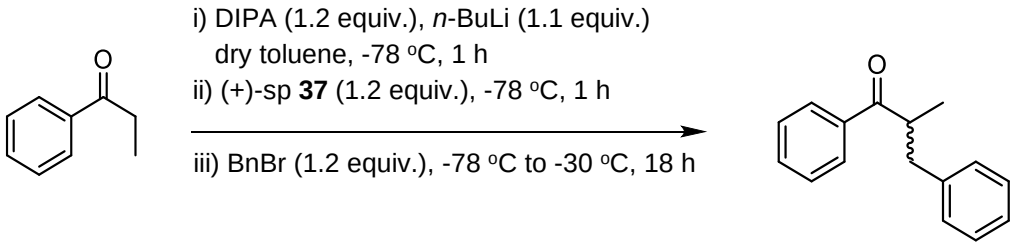
Scheme 30. α-Alkylation of cyclobutanone DMH **74**

Following isolation and purification of the above series of racemic ketones, each of the compounds were subjected to GC analysis in order to achieve optimised separation conditions for the enantioenriched products. Disappointingly, despite several attempts to optimise conditions for the cyclobutanone derived ketone **83** and the phenylacetone based ketone **82**, the enantiomers could not be resolved.

2.6 Direct asymmetric α-alkylation of ketones using the chiral ligand (+)-sparteine 37

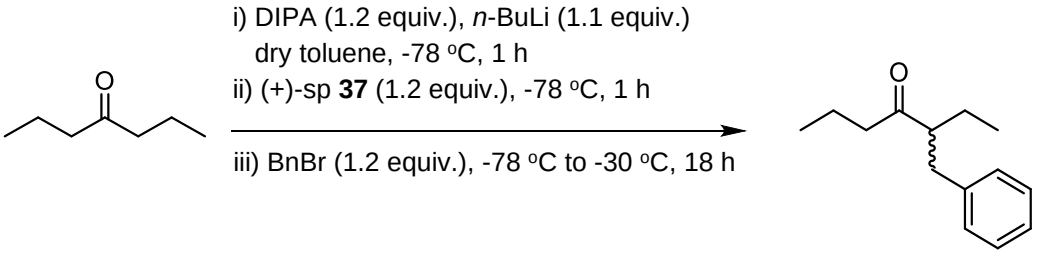
Having prepared a series of racemic α-alkylated ketones and established optimised conditions by GC analysis, we then wished to explore the substrate scope using our chiral ligand methodology. Firstly, we were interested if we could carry out an enantioselective transformation directly using the parent ketone. These asymmetric α-alkylation reactions were air sensitive and thus all reactions were performed under a nitrogen atmosphere. For these reactions, the recovery of (+)-sp **37** could be achieved by simply washing the organic layer with a sat. aq. NH_4Cl solution. For our study, we chose to investigate the α-benzylation of propiophenone and 4-heptanone **(Scheme 31)**. Due to the increased electrophilicity of ketones, it was decided to use the non-nucleophilic base, LDA rather than *s*-BuLi. Previous work carried out within the group established that (+)-sp **37** could be added post deprotonation without affecting the enantioselectivity of the product prepared *via* this protocol.[1a,6]

Propiophenone **84** and 4-heptanone **85** were deprotonated using LDA (generated *in situ*) at -78 ^oC for 1 h. (+)-sp **37** was then added post deprotonation at -78 ^oC and the reaction was held at this temperature for 1 h. Finally, benzyl bromide was added at -78 ^oC and the reaction mixture was warmed to -30 ^oC over 18 h. GC analysis of the crude reaction mixtures indicated that no enantioenrichement had occurred and only trace amounts of racemic mixtures were recovered for **67** and **69**.



84 **67**

Trace, racemic

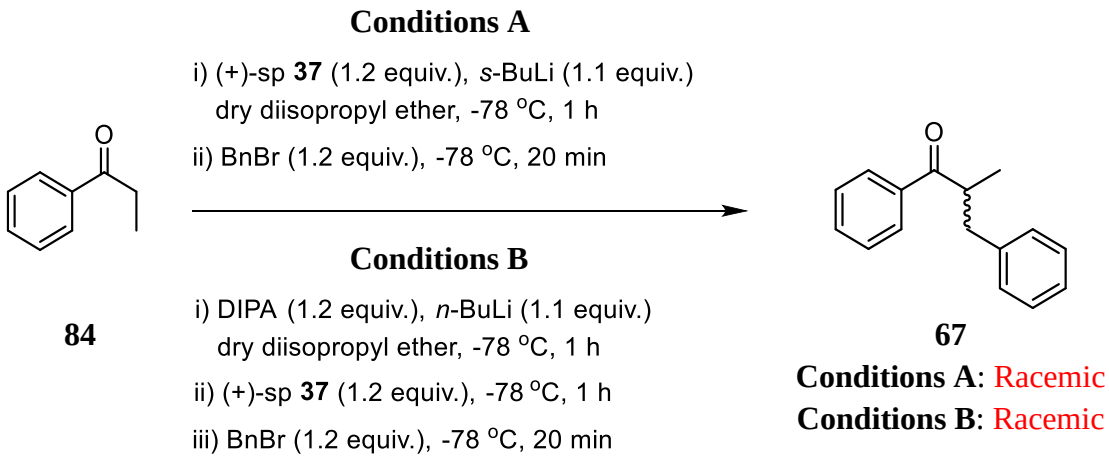


85 **69**

Trace, racemic

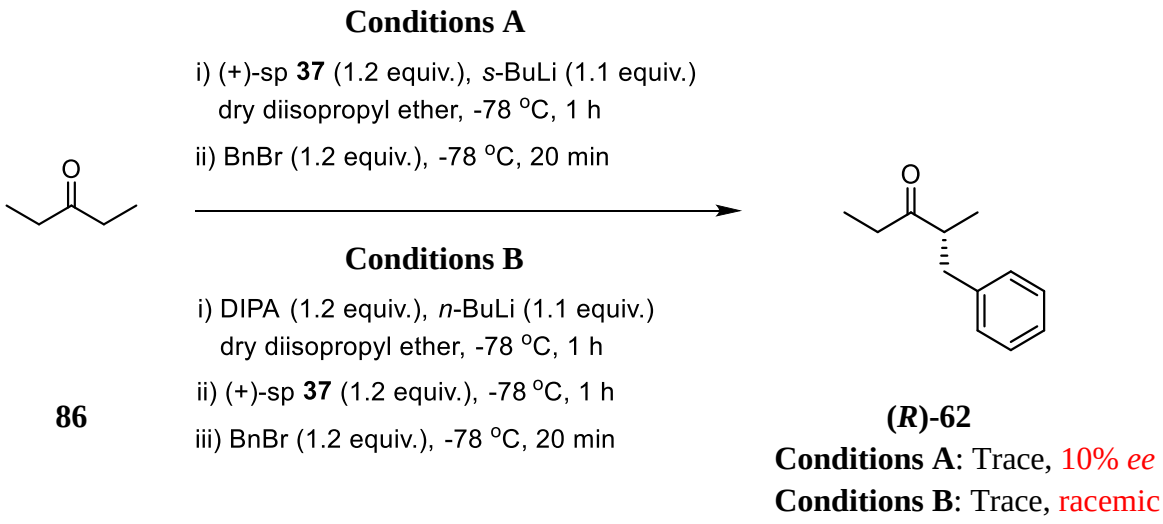
Scheme 31. Direct asymmetric α-alkylation of ketones using (+)-sp **37**

The direct asymmetric α-alkylation of ketones was also evaluated using diisopropyl ether as solvent. Despite extensive solvent screens conducted within the group, diisopropyl ether was not evaluated as an alternative solvent for our asymmetric α-alkylation reaction. Solvents can play a crucial role in the structure and reactivity of organolithium reagents.[13] Firstly, the α-benzylation of propiophenone was investigated using *s*-BuLi and LDA **(Scheme 32)**. Due to the high reactivity of ketones, we decided to quench the reaction 20 mins after the addition of the electrophile with the anticipation that higher selectivity would be achieved at these lower temperatures. The reaction was then extracted with diethyl ether. The solvent was removed and the sample was immediately analysed *via* gas chromatography. Unfortunately, racemic mixtures were obtained in both cases and only a trace amount of product was detected.



Scheme 32. Direct asymmetric α-alkylation of propiophenone **84** using (+)-sp **37** in diisopropyl ether

The aforementioned reaction conditions were also applied to 3-pentanone **86** using (+)-sp **37** **(Scheme 33)**. In this case, 10% *ee* was observed using *s*-BuLi, however, only a trace amount of product was detected. A trace amount of racemic mixture was also observed using LDA as base. Due to these disappointing results, future work was carried using the *N*,*N*-dimethylhydrazones as ketone surrogates.



Scheme 33. Direct asymmetric α-alkylation of 3-pentanone **86** using (+)-sp **37** in diisopropyl ether

2.7 Asymmetric α-alkylation of *N,N*-dimethylhydrazones using the chiral ligand (+)-sparteine 37

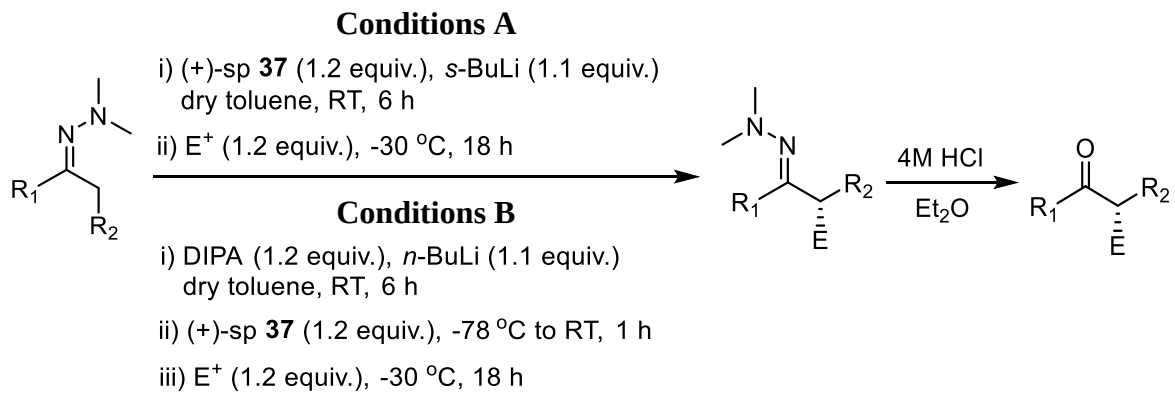
Following on from this work, the next step was to evaluate our racemic α-alkylated ketone series using our (+)-sp **37** DMH methodology. All of the enantioenriched products were subjected to GC analysis before and after purification in an effort to obtain the most accurate *ee* values. The values were then compared before and after purification. This ensured that racemisation of the newly formed chiral centre overtime could be detected. However, the differences before and after purification were found to be within the error of the GC instrument.

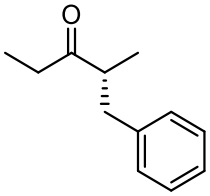
In order to become familiar with this methodology, the asymmetric α-alkylation of 3-pentanone DMH **60** with benzyl bromide was investigated as a model reaction **(Scheme 34)**. The first step of this reaction involves preparation of the *s*-BuLi/(+)-sp **37** complex. Dropwise addition of *s*-BuLi to a toluene solution of (+)-sp **37** was performed at -78 ^{o}C. The reaction mixture was then stirred at this temperature for 30 mins and a bright yellow solution indicated that the complex had formed. 3-Pentanone DMH **60** was deprotonated at -78 ^{o}C followed by warming to room temperature over a period of 6 h. Subsequent alkylation at -30 ^{o}C with benzyl bromide over 18 h afforded the α-alkylated hydrazone. Restoration of the original carbonyl moiety was achieved using a biphasic mixture of 4 M HCl in diethyl ether. This cleavage protocol proved applicable to our methodology and the resulting ketones could be isolated within 30 minutes. Purification of the crude product using column chromatography on silica gel afforded ketone **(*R*)-62** in a 46% *ee* and yield of 19%.

Next, the effect of increasing the length of the carbon chain of the ketone moiety on the enantioselectivity was examined using 4-heptanone DMH **71**. Deprotonation of the hydrazone was carried out using LDA (generated *in situ*) and (+)-sp **37** was added post deprotonation. Pleasingly, an increase in selectivity was observed for ketone **(*R*)-69** (55% *ee*) in comparison to the benzylated 3-pentanone ketone **(*R*)-62** (46% *ee*).

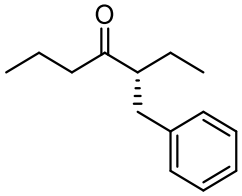
The use of more sterically hindered electrophiles led to significant erosion of enantioselectivity using 3-pentanone DMH **60**. An *ee* of 20% was obtained for the *i*-propyl derivative **(*R*)-77**. Unfortunately, the *t*-butyl based electrophile (1-iodo-2,2-dimethylpropane) failed to react under the reaction conditions and only starting material and electrophile was recovered. A

substantial increase in enantioselectivity was observed when the alkenyl based electrophile was used, furnishing ketone **(*R*)-79** with a 39% *ee*.

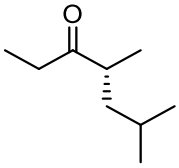




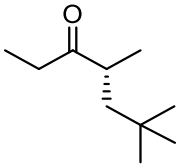
(*R*)-62
E^+ = BnBr
Conditions A
19%, 46% *ee*



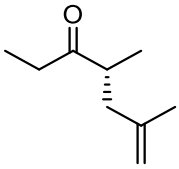
(*R*)-69
E^+ = BnBr
Conditions B
17%, 55% *ee*



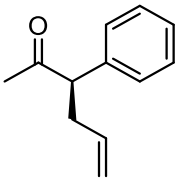
(*R*)-77
$E^+ = (CH_3)_2CHCH_2I$
Conditions A
18%, 20% *ee*



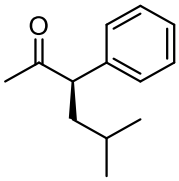
(*R*)-78
$E^+ = (CH_3)_3CCH_2I$
Conditions A
n.d.[a]



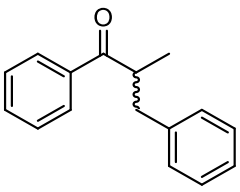
(*R*)-79
E^+ = AllylBr
Conditions A
20%, 39% *ee*



(*R*)-80
E^+ = AllylBr
Conditions A
19%, 22% *ee*



(*R*)-81
$E^+ = (CH_3)_2CHCH_2I$
Conditions A
41%, 10% *ee*



67
E^+ = BnBr
Conditions B
21%, 0% *ee*

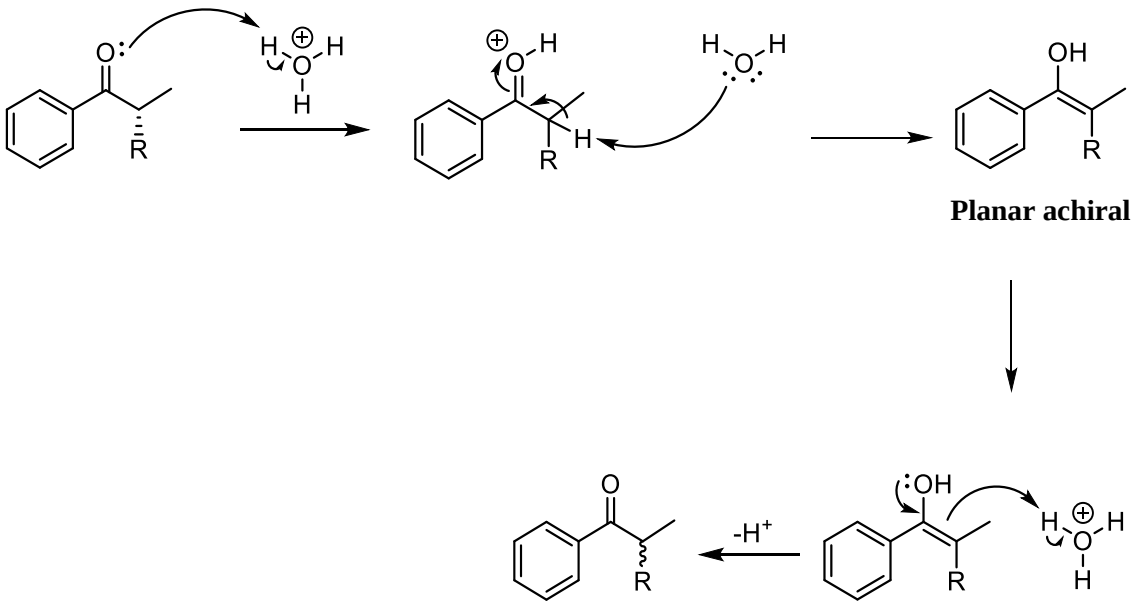
Scheme 34. Substrate scope

[a]n.d. - only unreacted starting material and electrophile was recovered from the crude reaction mixture.

The unsymmetrical phenylacetone DMH **72** was then subjected to our reaction conditions using allyl bromide and 1-iodo-2-methylpropane **((*R*)-80** and **(*R*)-81) (Scheme 34)**. Similar to the

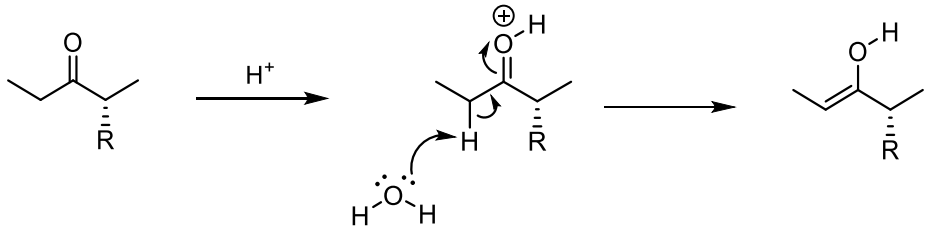
racemic ketones **80** and **81**, alkylation was favoured at the more thermodynamically favoured benzylic site. Poor enantioselectivities were observed for both of these transformations (22% *ee* for **(*R*)-80** and 10% *ee* for **(*R*)-81**). Enders and co-workers have previously alkylated phenylacetone using the SAMP chiral auxiliary and methyl iodide.[14] Using the SAMP chiral auxiliary, alkylation was also favoured at the benzylic site and only a small amount of the kinetic isomer (1:9) was observed. It is interesting to note that Enders has reported dramatically lower enantioselectivities (10-30%) when a phenyl group was directly attached to the newly formed centre of chirality. This phenomenon has also been observed in the Meyers system in which a phenylalaninol-methylether is utilised as a chiral auxiliary.[15] Enders has partially attributed these results to the formation of a mixture of $E_{CC}Z_{CN}/Z_{CC}E_{CN}$ isomers. Despite the poor *ee*'s obtained using our reaction conditions, a much improved yield of 41% was obtained for the *i*-propyl derivative **(*R*)-81** in the presence of (+)-sp **37** in comparison to the racemic ketone (**81**, 17%).

The asymmetric α-alkylation of propiophenone DMH **70** was then examined. Hydrazone **70** was deprotonated using LDA (generated *in situ*) under the standard reaction conditions (room temperature over 6 h). Disappointingly, alkylation with benzyl bromide resulted in only a racemic mixture **67**. In this case, we considered that it was possible that the unsymmetrical nature of this substrate results in the formation of a different azaenolate geometrical isomer in solution. This azaenolate species may lead to a transition state which does not result in facial discrimination in comparison to the previous substrates. The lack of asymmetric induction may also be explained by the presence of only one enolizable site alpha to the carbonyl functionality **(Scheme 35)**. Protons alpha to a carbonyl group are acidic and the adjoined carbon centre is therefore prone to racemisation. Thus, racemisation of the chiral centre could be occurring during cleavage of the hydrazone in the presence of 4M HCl.



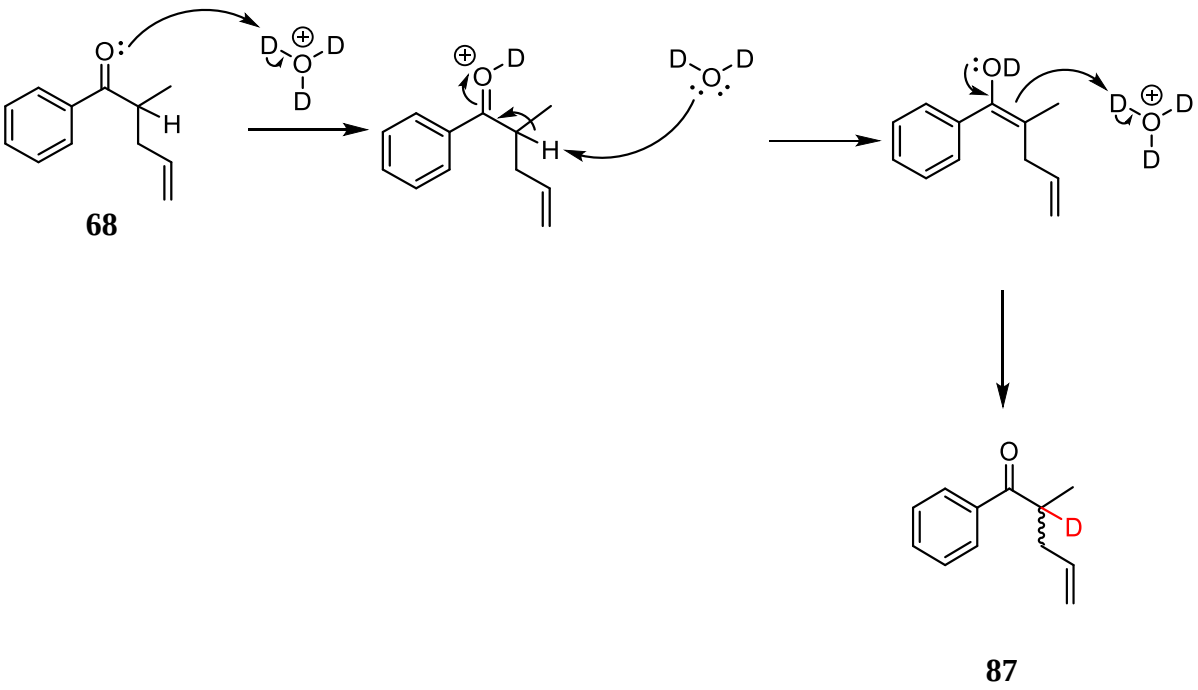
Scheme 35. Racemisation of an unsymmetric substrate following re-protonation of the planar achiral enol

In comparison, the presence of a second enolizable site on a symmetric substrate such as 3-pentanone may preserve the chirality of the newly formed stereogenic centre **(Scheme 36)**.



Scheme 36. Symmetric substrate possessing two enolizable sites

Therefore, we sought to investigate this hypothesis by performing a deuterium exchange experiment on the α-alkylated propiophenone substrate **68**. The racemic α-alkylated ketone **68** was prepared and hydrolysis was carried out in the presence of DCl and D_2O **(Scheme 37)**. Deuterium incorporation was monitored at the α-site, however, no trace of the deuterated product **87** was detected by ^1H NMR spectroscopy or mass spectrometry analysis. Thus, racemisation of the chiral centre during hydrolysis was not considered the reason for the poor *ee* in the propiophenone ketone product **67**.



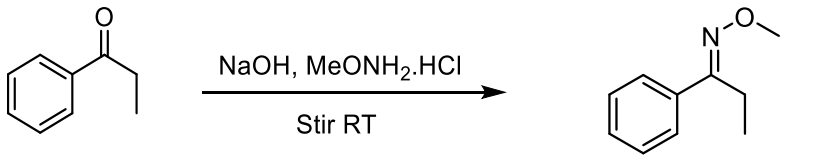
68 **87**

Scheme 37. Deuterium exchange experiment with α-allylated propiophenone **68**

2.8 Variation of the hydrazone moiety

A minor investigation was then conducted to examine the effect of alteration of the dimethylamino group of the hydrazone function. Previous research within the group investigated the effect of various *N*,*N*-dialkylhydrazones on the enantioselectivity in this system but limited success was achieved in this regard.[6] For our study, we wanted to examine the effect of the oxime moiety on the enantioselectivity. It was speculated that the presence of the less sterically hindered and more electronegative oxygen might enhance coordination of the azaenolate species to the organolithium/(+)-sp **37** complex. Propiophenone *O*-methyl oxime **88** was prepared according to a literature procedure.[16] Propiophenone and methoxyamine hydrochloride were stirred neat at room temperature overnight **(Scheme 38)**. The reaction was diluted with EtOAc (30 mL), washed with brine (10 mL) and extracted with EtOAc (3 × 20 mL). The solvent was removed and concentrated to afford the crude oxime as a 1:0.4 mixture of *E*:*Z* isomers. Purification by column chromatography furnished the *E* isomer of propiophenone *O*-methyl oxime **88** in a yield of 37%. Spectroscopic data was consistent with previously reported data for the *E* isomer.[17] Efforts to separate the *Z* isomer from the

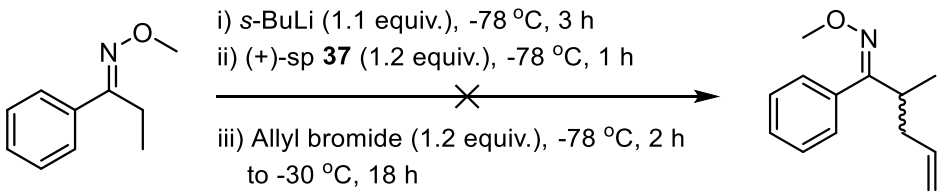
propiophenone starting material proved unsuccessful as both compounds had identical R_f values.



84 **88**, 37% (*E* isomer)

Scheme 38. Preparation of propiophenone oxime **88**

The deprotonation and alkylation conditions were slightly modified according to a procedure by Mears and co-workers.[18] Deprotonation of propiophenone oxime ether **88** was carried out at -78 ^oC over 3 h in the presence of *s*-BuLi **(Scheme 39)**. (+)-sp **37** was then added post deprotonation at -78 ^oC and held at this temperature for 1 h. Allyl bromide was added at a low temperature of -78 ^oC. The reaction mixture was kept at this temperature for 2 h followed by slowly warming to -30 ^oC over a period of 18 h. Unfortunately, no conversion to product was observed. Only unreacted starting material and electrophile were recovered from the crude reaction mixture.



88 **89**

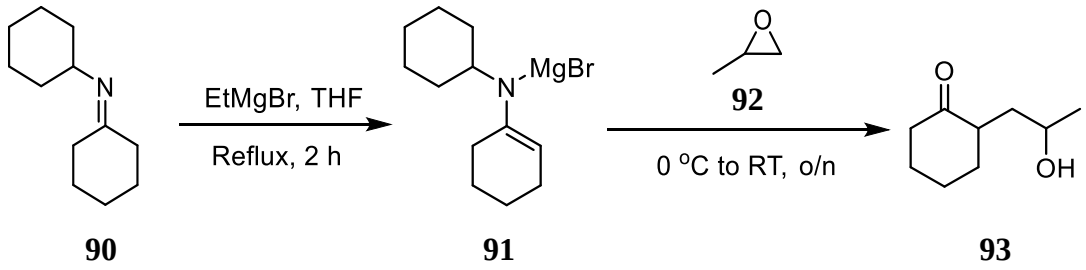
Scheme 39. Attempted asymmetric α-alkylation of propiophenone oxime **88**

2.9 Challenging electrophile substrate scope

Our next challenge was to investigate if our *N*,*N*-dimethylhydrazone/(-)-sp **37** mediated strategy could be applied to more diverse electrophiles. For this study, a range of challenging electrophiles was examined. In order to gain an insight into the reactivity of these electrophiles, the racemic mixtures were first prepared prior to their asymmetric counterparts.

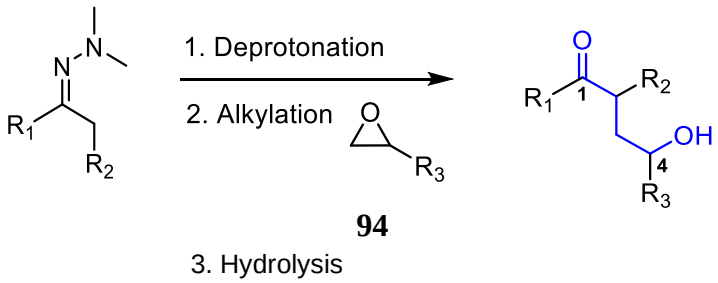
2.9.1 Epoxides as electrophiles

Epoxides are one of the most versatile building blocks in organic synthesis and can be ring opened with a range of carbon nucleophiles.[19] Tarbell and Harvey first reported the use of magnesium azaenolates **91** derived from cyclohexanone imine **90** to ring open epoxides **(Scheme 40)** without additional activating agents.[20] The magnesium azaenolate **91** was generated *in situ* by reaction of *N*-cyclohexylcyclohexanimine **90** with EtMgBr, which was subsequently treated with propylene oxide **92** to give 2-(2-hydroxypropyl)cyclohexanone **93**.



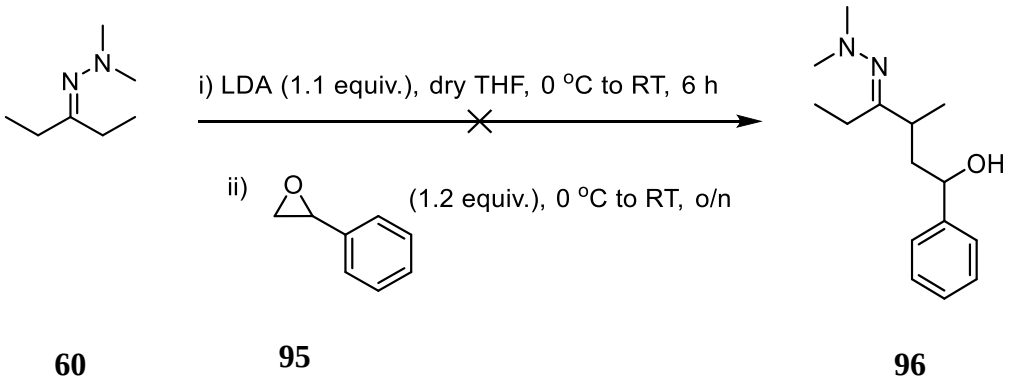
Scheme 40. Tarbell's ring opening of epoxides

In light of this report, we sought to investigate the ring opening of epoxides using *N*,*N*-dimethylhydrazones. Hydrolysis of the resulting products would lead to the formation of 1,4-hydroxy ketones which are useful synthetic precursors **(Scheme 41)**.[21]



Scheme 41. Possible route to generate 1,4-hydroxy ketones

Initial investigations involved reacting the *N*,*N*-dimethylhydrazone azaenolate directly with the epoxide **(Scheme 42)**. It was expected that the metalated azaenolate would undergo an S_N2 attack on the epoxide at the least sterically hindered position.[22] However, attempts to react 3-pentanone DMH **60** with styrene oxide **95** failed under the standard reaction conditions. No α-functionalisation was observed and ^{1}H NMR analysis indicated the presence of only starting material and electrophile. This is most likely due to the relatively low reactivity of azaenolates with epoxides.



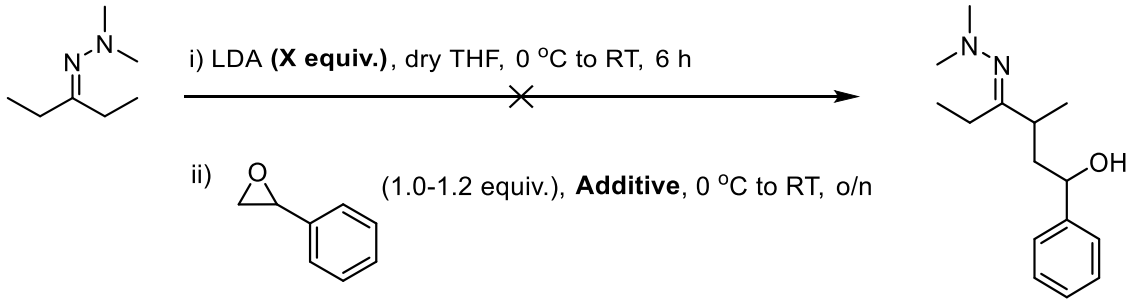
Scheme 42. Attempted ring opening of styrene oxide with 3-pentanone DMH **60**

A review of the literature found that ring opening of epoxides could be achieved with azaenolates in the presence of a large excess of the azaenolate species and anhydrous lithium chloride.[19,23] The lithium chloride increases the electrophilicity of the epoxide by activating the epoxide for nucleophilic attack through coordination to the oxygen atom. A procedure by Géant and co-workers was first examined.[24] Applying Géant's procedure to our work, 5.3 equivalents of 3-pentanone DMH **60** was reacted with 1.0 equivalent of styrene oxide **95** at room temperature overnight **(Table 1, entry 1)**. Unfortunately, this did not improve the results and only starting material and electrophile was recovered. We then attempted to apply a procedure reported by Enders, who described the ring opening of an epoxide with 9.2 equivalents of 3-pentanone SAEP-hydrazone in the presence of 6.0 equivalents of anhydrous LiCl.[23] This also proved unsuccessful using 3-pentanone DMH **60** and styrene oxide **95 (Table 1, entry 2)**.

Finally, in one last attempt to ring open epoxides using *N*,*N*-dimethylhydrazones, a procedure reported by Crotti and co-workers was examined.[25] In this report, Crotti demonstrated the metal salt catalysed inter- and intramolecular addition of lithium enolates derived from ketones to epoxides using $Sc(OTf)_3$ and $Y(OTf)_3$. Unfortunately, addition of 20 mol% of $Sc(OTf)_3$ to our

reaction failed to promote epoxide ring opening **(Table 1, entry 3)**. Analysis of the ^{1}H NMR spectrum of the crude reaction mixture indicated the formation of a complex mixture of products. The γ-hydroxy ketone **96** was tentatively identified in the crude reaction mixture by mass spectrometry analysis, however, attempted isolation of the product was unsuccessful.

Table 1. Ring opening of epoxides with azaenolates



60 **95** **96**

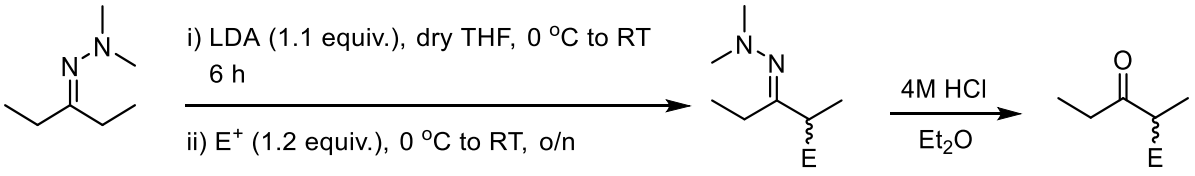
Entry	Hydrazone (Equiv.)	LDA	Additive (Equiv.)	Result
1	**60**, 5.3	5.8	None	Unreacted SM and E^+
2	**60**, 9.2	10.1	LiCl, 6.0	Unreacted SM and E^+
3	**60**, 1.0	1.1	$Sc(OTf)_3$, 20 mol%	Complex mixture

2.9.2 Reactions with other challenging electrophiles

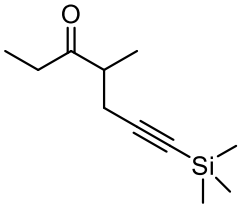
Following these results, a number of other challenging electrophiles were evaluated. 3-pentanone DMH **60** was reacted with a series of diverse electrophiles leading to a number of synthetically useful ketones **(Scheme 43)**. For example, the Si-C and carbon-carbon triple bonds of **97** are useful molecular handles for further transformations.[26] Ketone **98** also contains the important γ-ketoester moiety.[27] Good yields (43 and 48%) were obtained for both of these compounds. In addition, both of these ketones are novel compounds. Unfortunately, suitable GC conditions for the separation of enantiomers for **98** could not be achieved.

Another useful transformation involved the reaction of 3-pentanone DMH **60** with benzyloxymethyl chloride. Subsequent cleavage of the hydrazone generated the α-alkylated ketone **99** which is known as the Paterson ketone. This compound serves as a very important

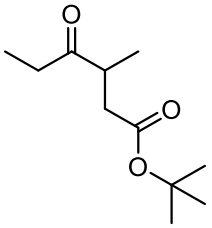
intermediate in aldol reactions for the synthesis of polyketide derived natural products, for example, the macrolide antibiotic (+)-concanamycin F.[28] Carbon-sulfur bond formation was also investigated. The synthesis of α-thio ketone **100** was achieved by reacting 3-pentanone DMH **60** with LDA followed by diphenyl disulfide which provides a convenient source of the phenyl sulphide moiety.



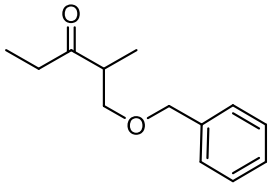
60



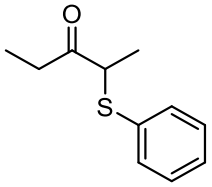
97, 43%
$E^+ = BrCH_2C{\equiv}CSi(CH_3)_3$



98, 48%
$E^+ = BrCH_2CO_2C(CH_3)_3$



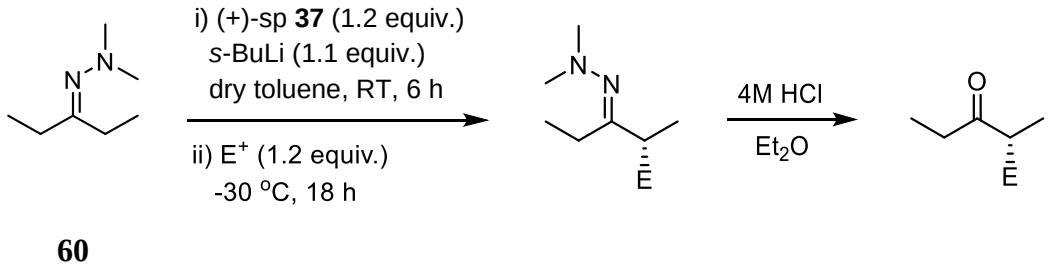
99, 47%
$E^+ = C_6H_5CH_2OCH_2Cl$



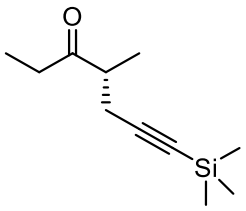
100, 26%
E^+ = PhSSPh

Scheme 43. Valuable synthetic precursors

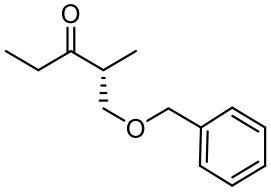
Next, the enantioselective synthesis of ketones **97**, **99** and **100** was attempted using our chiral ligand strategy **(Scheme 44)**. Applying our established set of reaction conditions, ketones **(*R*)-97** and **(*R*)-99** were isolated in moderate yields and enantioselectivity. Unfortunately, only a racemic mixture was recovered for α-thio ketone **100**.



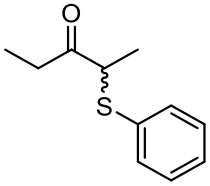
60



(*R*)-97
$E^+ = BrCH_2C{\equiv}CSi(CH_3)_3$
37%, 19% *ee*



(*R*)-99
$E^+ = C_6H_5CH_2OCH_2Cl$
35%, 34% *ee*[a]



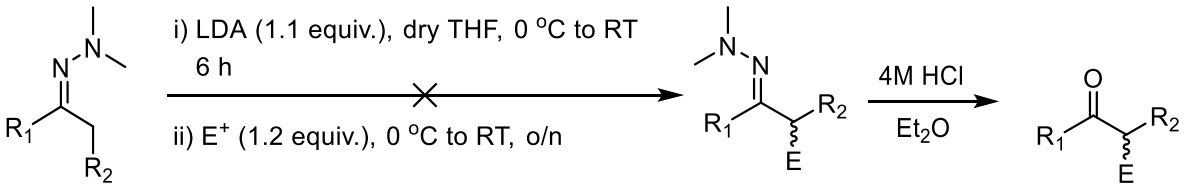
100
E^+ = PhSSPh
39%, racemic

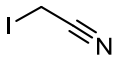
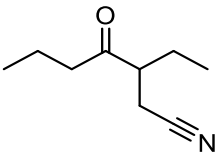
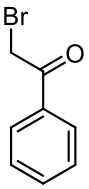
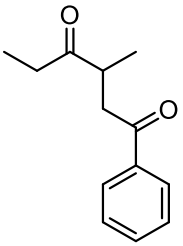
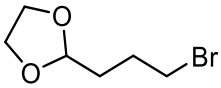
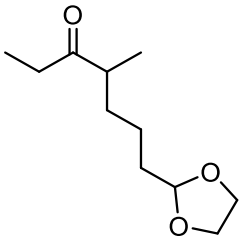
[a]3-pentanone DMH **60** was deprotonated using LDA and (+)-sp **37** was added post deprotonation.

Scheme 44. Enantioselective transformations

Attempts to further broaden the scope were unsuccessful. No α-functionalisation was observed using iodoacetonitrile, 2-bromoacetophenone and 2-(3-bromopropyl)-1,3-dioxolane as electrophiles **(Table 2, entries 1-3)**. Only starting material and electrophile was observed by ^{1}H NMR analysis in all cases respectively.

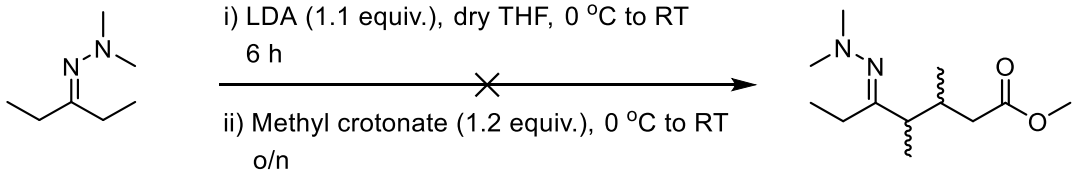
Table 2. Alkylation of DMHs with challenging electrophiles



Entry	E^+	Expected Product	Result
1			Unreacted SM and E^+
2			Unreacted SM and E^+
3			Unreacted SM and E^+

2.9.3 Michael reaction

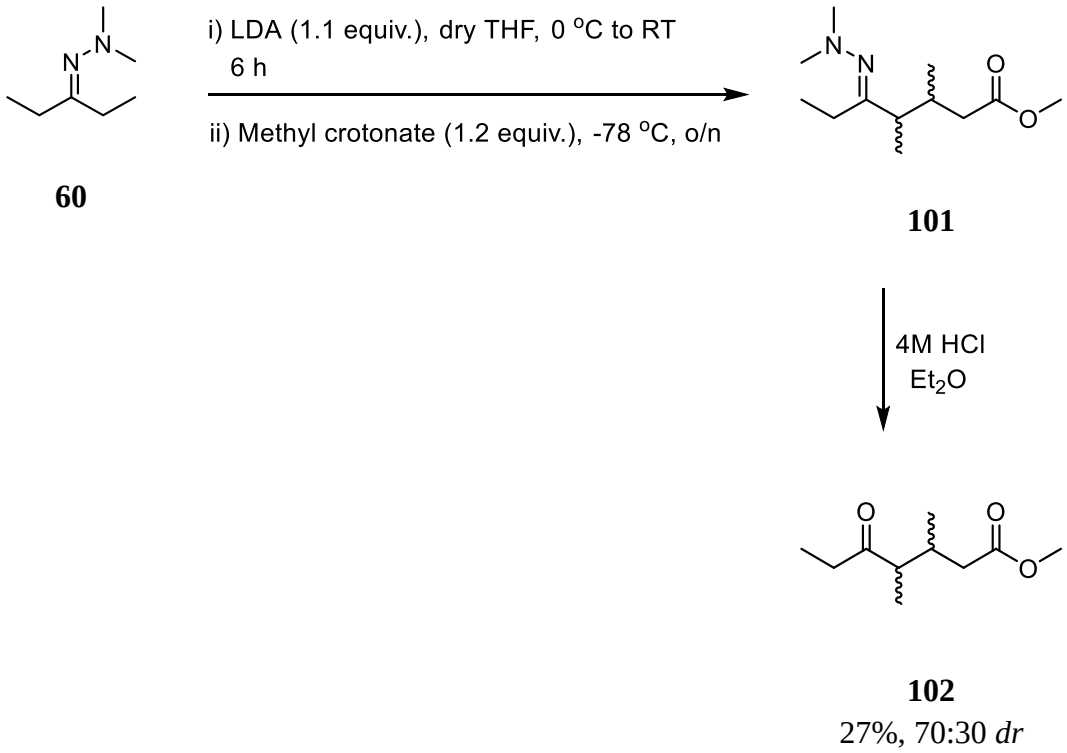
We were then curious to determine if this methodology could be extended to the synthesis of two chiral centres in one-pot. Of particular interest was the Michael reaction. Previous work within the group examined the use of *β*-nitrostyrene in an asymmetric Michael reaction with 3-pentanone DMH **60**. However, poor enantioselectivity was obtained (2% *ee*).[1a] For our investigation, initial attempts to alkylate 3-pentanone DMH **60** with methyl crotonate at room temperature failed and only a complex mixture was recovered **(Scheme 45)**.



60 **101**

Scheme 45. Alkylation at RT

The electrophile was then added at -78 °C and stirred at this temperature overnight **(Scheme 46)**. Pleasingly, a much cleaner ^{1}H NMR spectrum was observed following work-up. The diasteromeric ratio was calculated following hydrolysis and found to be 70:30 *dr* by ^{1}H NMR and GC analysis. A combined yield of 27% was obtained for the mixture following purification by column chromatography.



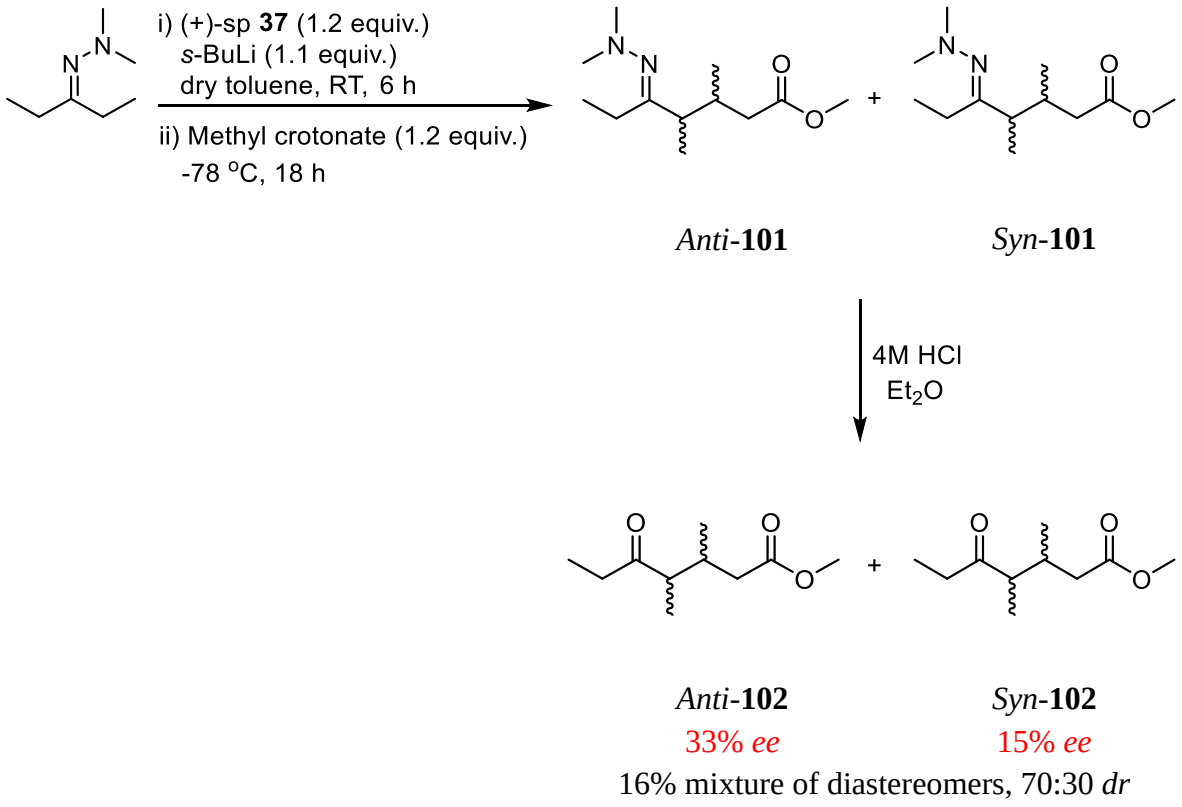
60

101

102
27%, 70:30 *dr*

Scheme 46. Alkylation at -78 °C overnight

The enantioselective synthesis of **102** was then carried out *via* our chiral ligand strategy **(Scheme 47)**. 3-pentanone DMH **60** was deprotonated in the presence of the *s*-BuLi/(+)-sp **37** complex and alkylated with methyl crotonate at -78 °C over 18 h. The crude α-alkylated hydrazones *anti*-**101** and *syn*-**101** were hydrolysed using 4M HCl in diethyl ether. The diastereomeric ratio was determined to be 70:30 by ^{1}H NMR and GC analysis. The enantiomeric ratio was found to be 15% for the *syn*-**102** and 33% for the *anti*-**102** product. The relative stereochemistry of the products was determined by comparison to ^{1}H NMR data in the literature.[29] Notably, a lower yield was obtained for the enantioselective variant of this transformation. The *syn*-**102** and *anti*-**102** diastereomers were isolated in a combined yield of 16% although a number of impurities remained (<10%) after several purification attempts by column chromatography.



Scheme 47. Enantioselective Michael reaction

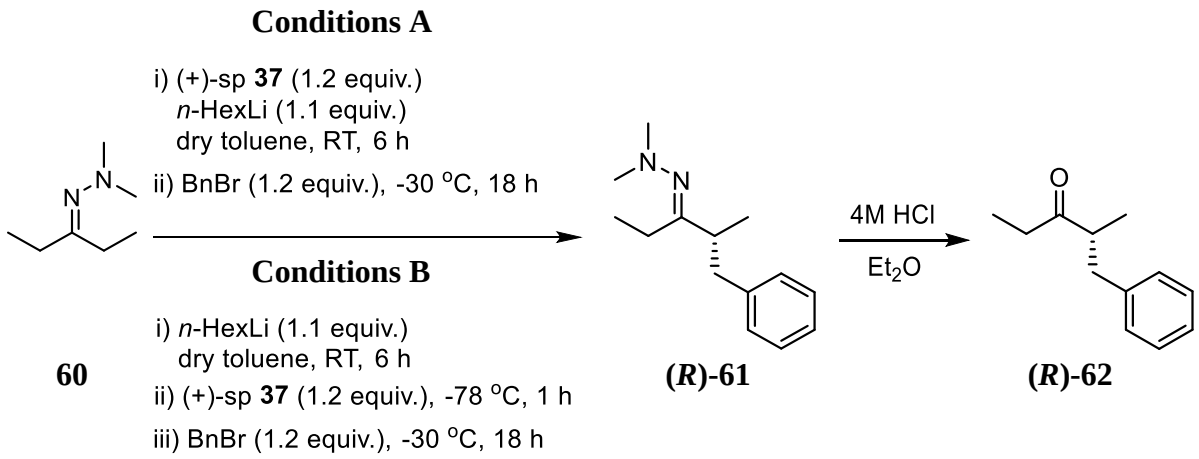
2.10 Variation of the alkyl lithium base

Previous optimisation studies within the McGlacken group established *s*-BuLi to be the optimum base for the asymmetric α-alkylation of DMHs.[1a] A range of alkyl lithium reagents were examined, with the enantioselectivity and yield varying considerably **(Table 3)**. This may be attributed to the different aggregate structures of the resulting alkyl lithium/(-)-sp **37** complexes. The reactivity and selectivity of carbanionic reagents depends on both the nature of the counterion as well as the structure of the relevant aggregates.[30]

Table 3. Previous investigations of alkylithium reagents

Entry	DMH	Ligand	Alkyl lithium reagent	Ketone	Yield (%)	*ee* (%)
1	**60**	(-)-sp **37**	PhLi	**(*S*)-62**	16	66
2	**60**	(-)-sp **37**	*n*-BuLi	**(*S*)-62**	44	44
3	**60**	(-)-sp **37**	*s*-BuLi	**(*S*)-62**	57	52
4	**60**	(-)-sp **37**	*t*-BuLi	**(*S*)-62**	35	52

Following on from this work, we decided to evaluate *n*-hexyl lithium as an alternative to *s*-BuLi as its use with (+)-sp **37** had not been previously reported **(Scheme 48)**. Firstly, 3-pentanone DMH **60** was deprotonated using *n*-hexyl lithium under the standard deprotonation and alkylation conditions **(Scheme 48, conditions A)**. Unfortunately, a significant decrease in enantioselectivity was observed in comparison to *s*-BuLi. Addition of (+)-sp **37** post deprotonation was also examined **(Scheme 48, conditions B)**. This resulted in a 20% improvement in enantioselectivity but again much lower than that obtained with *s*-BuLi. Overall the results of these reactions proved disappointing and no improvement in enantioselectivity was achieved using *n*-hexyl lithium as base.



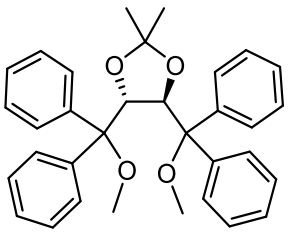
Conditions A: 42%[a], 10% *ee*
Conditions B: 23%[a], 29% *ee*

Scheme 48. Alternative base screen

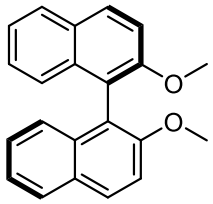
[a]Yield determined over two steps *via* ^{1}H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard.

2.11 Investigation of alternative chiral ligands

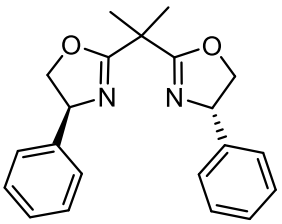
The next logical step in this project was to determine if better enantioselectivities could be achieved using an alternative chiral ligand. Previous studies conducted within the McGlacken group involved screening a range of chiral ligands in our asymmetric alkylation reaction **(Figure 11)**. Use of methylated TADDOL **(*R*,*R*)-103** and BINOL **(*R*)-104** ligands failed to induce enantioselectivity and only racemic mixtures were recovered.[1a] Surprisingly, BOX ligand **(*S*,*S*)-105** failed to promote any product formation.[1a] Poor conversions and very low enantioselectivities were observed for the diphenylethane derivatives **(*S*,*S*)-106** and **(*R*,*R*)-107** as well as the proline derived ligand **(*S*)-108**.[1a] A series of *trans*-diaminocyclohexane derivatives **109-115**, known and novel was also examined.[6] In all cases, enantioselectivities were lower than (+)-sp **37** despite extensive screening.



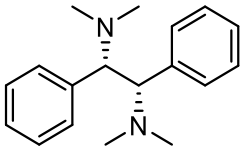
(*R*,*R*)-103



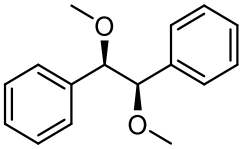
(*R*)-104



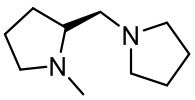
(*S*,*S*)-105



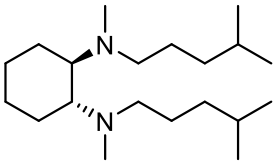
(*S*,*S*)-106



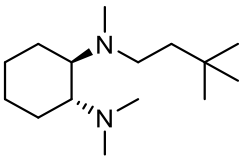
(*R*,*R*)-107



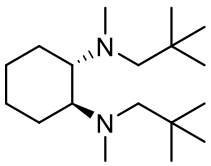
(*S*)-108



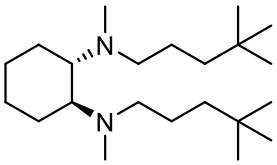
(*R*,*R*)-109



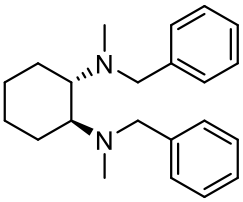
(*R*,*R*)-110



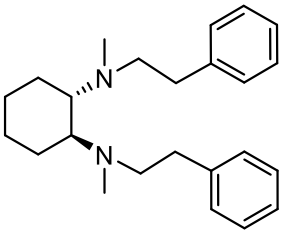
(*S*,*S*)-111



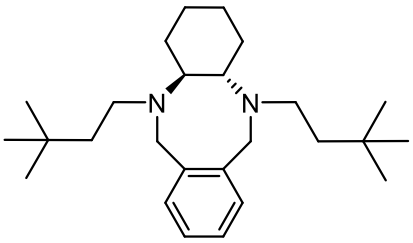
(*S*,*S*)-112



(*S*,*S*)-113



(*S*,*S*)-114



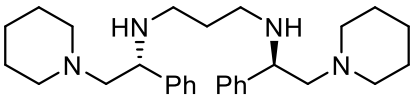
(*S*,*S*)-115

Figure 11. Previously tested chiral ligands

Due to the vast array of chiral ligands utilised in asymmetric transformations, we felt that there was scope for further work in this area. For our chiral ligand screen, we were primarily interested in identifying a ligand scaffold that was **i)** easy to modify **ii)** would allow for structural variability and **iii)** was commercially available or readily prepared.

2.11.1 Chiral tetramine

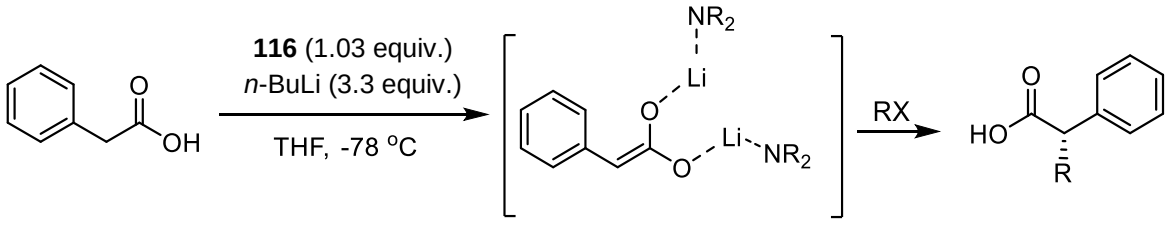
The first ligand examined in the asymmetric α-alkylation of ketones was the chiral tetramine **116 (Figure 12)**. This chiral tetramine was of particular interest as it is easy to prepare and can be readily modified.[31]



116

Figure 12. Chiral tetramine

In 2011, Zakarian and co-workers reported the highly enantioselective α-alkylation of arylacetic acids **117** *via* enediolates **118** using the C_2-symmetric amine **116 (Scheme 49)**.[31] Very high enantioselectivities and yields were achieved using a broad range of alkyl halides. Recently, this work has also been extended to the enantioselective alkylation of *β,γ*-unsaturated carboxylic acids.[32]



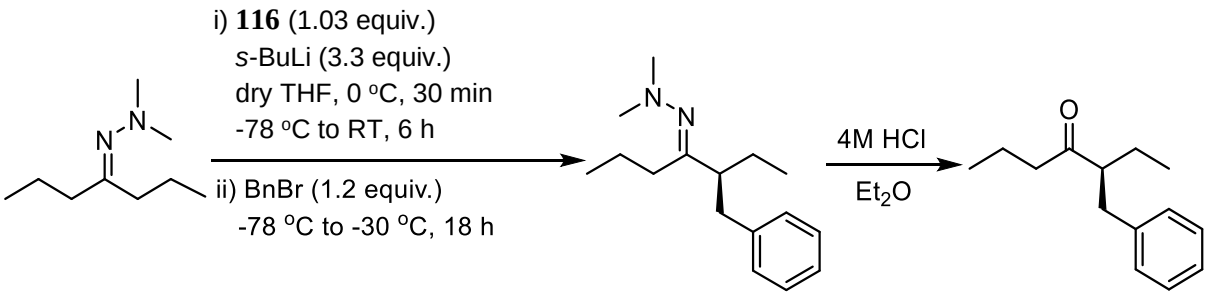
117 **118** **(*S*)-119**

High *ee*'s

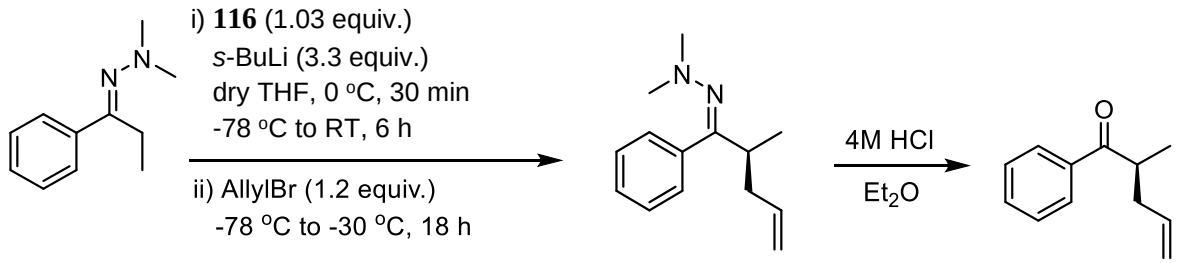
Scheme 49. Asymmetric α-alkylation of arylacetic acids **117**

Due to the high enantioselectivities reported for this ligand, we were curious as to whether similar levels of asymmetric induction could be achieved for our asymmetric α-alkylation reaction. The asymmetric α-alkylation of 4-heptanone DMH **71** with benzyl bromide and

propiophenone DMH **70** with allyl bromide were chosen for our investigation **(Scheme 50)**. Zakarian and co-workers have indicated that the stoichiometry of the chiral amine and BuLi are crucial reaction parameters to achieve high enantioselectivities.[31] They have stated that reproducibly high enantioselectivities have been achieved only when a slight excess of chiral amine is present. Thus, 1.03 equivalents of chiral tetramine **116** was utilised for these reactions. Zakarian has also emphasised that the level of asymmetric induction is also strongly dependent on the quality of BuLi. Therefore, for our reactions, a 1.40 M bottle of *s*-BuLi (3.3 equivalents) was titrated immediately prior to the deprotonation step. As is evident from the results **(Scheme 50)**, this ligand did not perform well in our system. In both cases, poor conversion and low *ee*'s were observed. However, a trace amount of product was detected by GC analysis which enabled us to determine the enantiomeric ratio. In both cases, the enantioselectivites were lower than those obtained with (+)-sp **37**.



71 **(*S*)-120** **(*S*)-69**
Trace, 11% *ee*



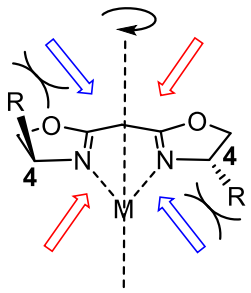
70 **(*S*)-121** **(*S*)-68**
Trace, 3% *ee*

Scheme 50. Evaluation of chiral tetramine **116** in the asymmetric α-alkylation of ketones

There is evidence to suggest that high stereocontrol correlates with control of aggregation. Zakarian's current model for his enediolate intermediate **118** is based on the formation of a well defined chiral aggregate composed of a lithium enediolate and the chiral dilithium amide. A complicating feature of our system is the potential formation of a number of azaenolate geometrical isomers as well as the unknown structure of the reactive aggregate in solution.

2.11.2 Investigation of bisoxazoline (BOX) ligands

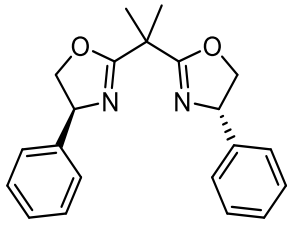
Bisoxazoline ligands represent an extraordinarily versatile class of chiral ligands that have been shown to be highly selective in a wide variety of transition metal catalysed asymmetric transformations.[33] There exists a vast library of commercially available BOX ligands. Moreover, these ligands can be easily derivatised allowing for high structural variability as well as fine tuning of the ligand scaffold. The R-groups located at the 4-position of the oxazoline ring **122** block one enantiotopic face leading to enantioselectivity in a variety of transformations **(Figure 13)**.[34]



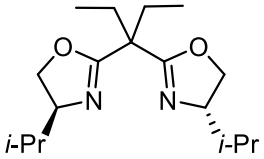
122

Figure 13. C_2-symmetric bis(oxazoline) ligand

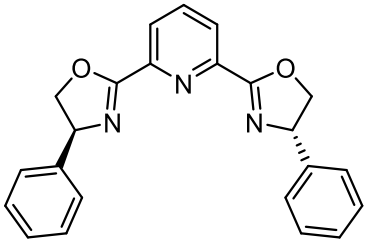
Despite previous unsuccessful attempts within the group to apply a BOX ligand to our asymmetric alkylation transformation, our aim was to evaluate a series of diverse BOX ligands. Thus, four commercially available BOX ligands were selected for our chiral ligand screen **(Figure 14)**.



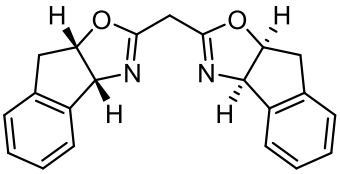
(*S*,*S*)-123



(*S*,*S*)-124



(*S*,*S*)-125



(*S*,*R*,*S*,*R*)-126

Figure 14. Chiral ligand screen

Traditionally, BOX ligands are complexed with copper[35] and other transition metals such as palladium[36] and rhodium.[37] Surprisingly, BOX ligands have rarely been used in combination with organolithium reagents and there are only limited examples. For instance, Hodgson has examined the enantioselective α-deprotonation-rearrangement of *cis*-cyclooctene oxide using *s*-BuLi and *i*-PrLi with BOX ligands.[38] Another example by Denmark describes the enantioselective addition of organolithium reagents to imines promoted by BOX ligands.[39]

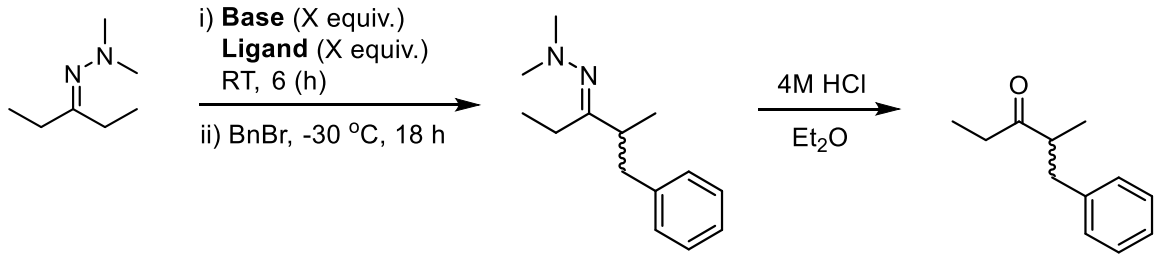
For our ligand screen, the α-benzylation of 3-pentanone DMH **60** was chosen as the model reaction **(Table 4)**. Firstly, we decided to re-examine ligand **(*S*,*S*)-123**, which previously failed to promote product formation in our system using *s*-BuLi as base. This time *n*-BuLi was utilised as base **(Table 4, entry 2)**. However, this also failed to promote product formation. Unfortunately, only a trace amount of desired product was observed *via* ^{1}H NMR and GC analysis.

We then turned our attention to increasing the steric bulk of the R-substituent at the 4-position of the oxazoline ring by introducing an *i*-propyl group. In the bisoxazoline scaffold, the two substituents at the stereogenic centres are located in close proximity to the metal centre.[40] Thus, we felt that increasing the steric bulk of the two substituents might exert a stronger influence on the selectivity of the reaction. Additionally, a number of research groups have demonstrated

a correlation between the ligand bite angle and enantioselectivity.[41] For example, Davies reported that increasing the bite angle of an indanol-based bisoxazoline resulted in an improvement in enantioselectivity in a copper catalysed Diels-Alder reaction.[42] Thus, we hoped that increasing the steric bulk of the R-substituent and the size of the bite angle might lead to an increase in enantioselectivity, although we were cognisant to the fact that very little product was formed in the previous case, using **(*S*,*S*)-123**. To examine this effect, **(*S*,*S*)-124** was subjected to our asymmetric α-alkylation reaction conditions using *s*-BuLi and *n*-BuLi as base **(Table 4, entry 3 and 4)**. For these reactions, we decided to use diethyl ether as solvent, as previous reactions using the BOX ligands indicated their low solubility in toluene. To our surprise, no trace of product was detected in either case.

pyBOX ligands are tridentate ligands that contain a pyridine spacer between the two oxazoline rings. Applying pyBOX ligand **(*S*,*S*)-125** in our standard reaction conditions and using *s*-BuLi as base resulted in no trace of product **(Table 4, entry 5)**. A second attempt using 2.0 equivalents of *s*-BuLi was then carried out **(Table 4, entry 6)**. While this did result in product formation, the reaction proceeded with low enantioselectivity (12% *ee*). Switching to *n*-BuLi resulted in erosion of enantioselectivity (6% *ee*) **(Table 4, entry 7)**. The indaBOX ligand **(*S*,*R*,*S*,*R*)-126** was also evaluated. With toluene as solvent and using 2.0 equivalents of *n*-BuLi, the desired product was afforded in 12% *ee* **(Table 4, entry 8)**.

Table 4. Chiral ligand screen



60 **61** **62**

Entry	Ligand	Base	Solvent	Equivalents (Base:Ligand)	Ketone	Result	*ee* (%)
1	**(+)-sp 37**	*s*-BuLi	Toluene	1.1:1.2	**(*R*)-62**	19%[a]	46
2	**(*S*,*S*)-123**	*n*-BuLi	Toluene	1.1:1.2	**62**	Trace	2
3	**(*S*,*S*)-124**	*s*-BuLi	Et_2O	1.1:1.2	**62**	No trace	-
4	**(*S*,*S*)-124**	*n*-BuLi	Et_2O	1.1:1.2	**62**	No trace	-
5	**(*S*,*S*)-125**	*s*-BuLi	Et_2O	1.1:1.2	**62**	No trace	-
6	**(*S*,*S*)-125**	*s*-BuLi	Et_2O	2:1	**(*S*)-62**	20%[b]	12
7	**(*S*,*S*)-125**	*n*-BuLi	Et_2O	2:1	**(*S*)-62**	22%[b]	6
8	**(*S*,*R*,*S*,*R*)-126**	*n*-BuLi	Toluene	2:1	**(*S*)-62**	17%[b]	12

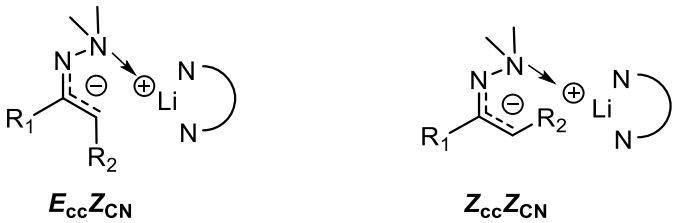
[a]Yield determined over two steps following purification by column chromatography.

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

In conclusion, BOX ligands are not suitable ligands for this asymmetric α-alkylation reaction. It is possible that the organolithium/BOX ligand complex failed to coordinate efficiently to the azaenolate species resulting in dramatically lower enantioselectivities. Denmark has previously described the weak chelating ability of BOX ligands to organolithium compounds, in particular for *n*-BuLi and PhLi.[39] Alternatively, the BOX ligand may have blocked the site of alkylation which may explain the observed poor yields in these reactions. Magnesium is a more commonly used metal with BOX ligands, thus, the formation of magnesium/BOX ligand complexes may warrant further investigation.

2.12 Further investigation of organolithium/(+)-sparteine 37 and (+)-sparteine surrogate 38 complexes

At this point in the project, despite efforts to further enhance the enantioselectivity of this chiral ligand protocol, little success had been achieved. As previously discussed, there are a number of factors that could potentially complicate this system. It is postulated that the presence of the dimethylamino group of the hydrazone enhances coordination of the *s*-BuLi/(+)-sp **37** complex resulting in the formation of a highly structured $E_{CC}Z_{CN}$ azaenolate **(Figure 15)**. DFT calculations support this speculation, however, one cannot rule out the $Z_{CC}Z_{CN}$ isomeric form.[1a]



Note: $R_1 > R_2$

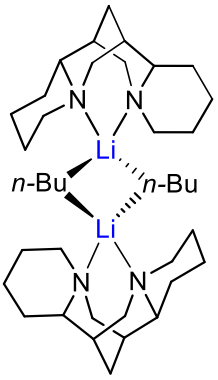
Figure 15. Formation of azaenolate geometrical isomers

Therefore, it is possible that a mixture of geometrical isomers are forming in this system. While one species may lead to high selectivity in the alkylation step, another azaenolate species may result in lower alkylation selectivity. Therefore, the moderate levels of enantioselectivity observed for this system may be due to poor selectivity in the alkylation step as a result of the formation of more than one azaenolate isomeric form.

Another complicating feature of this system relates to the organolithium/(-)-sp **37** complex. Despite the widespread use of organolithium/(-)-sp **37** complexes in asymmetric transformations, not much is currently known about their structure in solution and aggregation states.[43] As previously reported by Seebach, the structure of the relevant aggregate in addition to the nature of the counterion plays a crucial role in the reactivity and selectivity of carbanionic regents.[30] Organolithiums exhibit complex structural behaviour oftentimes consisting of aggregates and mixed aggregates. Complex homonuclear and heteronuclear aggregation can be expected for lithio-*N*,*N*-dimethylhydrazones.[44] In general, lower aggregates appear to be more reactive although the relative reactivity of different aggregates has rarely been

determined.[45] Organolithium/(-)-sp **37** adducts are also known to exist in a variety of aggregation states.[13] Therefore, gaining an understanding of the aggregation state is crucial to find the right balance between reactivity and selectivity. An excellent review on the solid-state and solution structures of organolithiums has been published by Strohmann and co-workers.[46] In general, aggregation of organolithium reagents is affected by three factors: **i)** the electrostatic interaction between the lithium atom and the carbanion **ii)** the coordination sphere of the lithium (solvent molecules or Lewis bases) and **iii)** the steric demand of the hydrocarbon and/or of the ligand.[46]

In relation to this work, we wanted to explore the effect of different organolithium/(+)-sp **37** complexes on the enantioselectivity in our asymmetric α-alkylation reaction. In particular, there exists very little information in the literature on the solution structure of organolithium/(-)-sp **37** complexes in toluene. Thus, the reactive (*s*-BuLi)$_x$/((+)-sp **37**)$_y$ aggregate in our system is unknown. The only characterized organolithium/(-)-sp **37** complex in toluene in the literature is the *n*-BuLi /(-)-sp **37** homodimer **127** which has been reported by Collum **(Figure 16)**.[47]

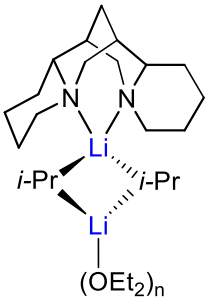


127

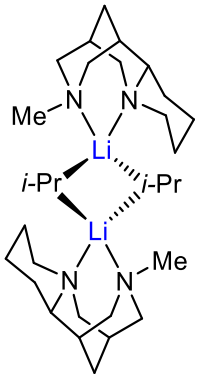
Figure 16. *n*-BuLi /(-)-sp **37** homodimer

Due to the formation of diastereomeric complexes for *s*-BuLi/(-)-sp **37** systems, *i*-PrLi is more commonly used instead of *s*-BuLi for NMR spectroscopic studies.[43,48] From ^{6}Li, ^{13}C and ^{1}H NMR spectroscopic studies, Beak established the structure of the *i*-PrLi/(-)-sp **37** complex in Et_2O as the unsymmetrical heterodimer **128** in which one of the lithium atoms is complexed to the (-)-sp **37** and the other is complexed by Et_2O **(Figure 17)**.[49] O'Brien and Hilmersson have also identified the solution strictures of *i*-PrLi/(-)-sp **37** and *i*-PrLi/(+)-sp surrogate **38** in Et_2O

and THF.[43] The *i*-PrLi/(+)-sp surrogate **38** in Et_2O was characterised as a head-to-tail homodimer **129 (Figure 17)**.



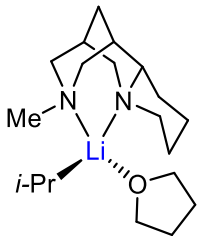
128



129

Figure 17. *i*-PrLi/(-)-sp **37** and *i*-PrLi/(+)-sp surrogate **38** solution structures in Et_2O

Interestingly, O'Brien and Hilmersson found that *i*-PrLi readily complexes to (+)-sp surrogate **38** in THF and observed a monomeric structure **130** in solution **(Figure 18)**.[43] In contrast, no complexation was observed using a 1:1 mixture of *i*-PrLi and (-)-sp **37** in THF. In fact, a similar monomeric structure was only identified when 6.0 equivalents of (-)-sp was present. *t*-BuLi is known to form a monomeric structure with (-)-sp **37** in the solid-state,[50] however, this is the first reported example of a simple organolithium/diamine monomer in solution. We were particularly interested in examining the use of the *i*-PrLi/(+)-sp surrogate **38** complex in THF in our asymmetric α-alkylation reaction.



130

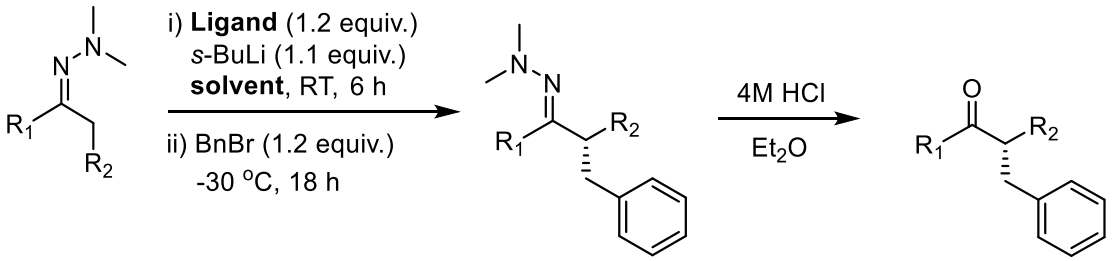
Figure 18. *i*-PrLi/(+)-sp surrogate **38** monomer in THF

Numerous reports have outlined that (-)-sp **37**-mediated asymmetric deprotonations in THF leads to the exclusive formation of racemates.[51] However, O'Brien and Hilmersson have demonstrated *via* ^{6}Li and ^{13}C NMR spectroscopic studies, that the (+)-sp surrogate **38** is

capable of out-competing THF for the generation of active organolithium aggregates/monomers.[43] Indeed, O'Brien and co-workers have shown that it is possible to carry out highly enantioselective transformations using *s*-BuLi/(+)-sp surrogate **38** and *i*-PrLi/(+)-sp surrogate **38** in THF. Examination of a series of asymmetric deprotonation reactions (asymmetric-lithiation trapping of *N*-Boc pyrrolidine, *O*-alkyl carbamates and phosphine boranes) showed that high enantioselectivities can be obtained using *s*-BuLi and *i*-PrLi/(+)-sp surrogate **38** in THF.[43] O'Brien was also able to show that *s*-BuLi and *i*-PrLi do indeed behave in a similar manner.

With this mind, we decided to examine the *s*-BuLi/(+)-sp surrogate **38** complex in THF in the α-benzylation of propiophenone DMH **70** and 3-pentanone DMH **60 (Table 5, entry 3 and 4)**. Due to the high reactivity of the (+)-sp surrogate **38**, the electrophile was added at -78 ^{o}C and held at this temperature over 18 h. To our surprise, no trace of desired product was detected *via* ^{1}H NMR or GC analysis. Previous work conducted within the group established that the *s*-BuLi/(+)-sp surrogate **38** complex in toluene could be used to promote enantioselectivity in the α-benzylation of 4-heptanone DMH **71**.[6] In fact, a slightly higher level of enantioselectivity was observed with the (+)-sp surrogate **38** than that with (-)-sp **37** (50% *ee* and 42% *ee* respectively).

Table 5. Evaluation of *s*-BuLi/(+)-sp surrogate **38** in THF

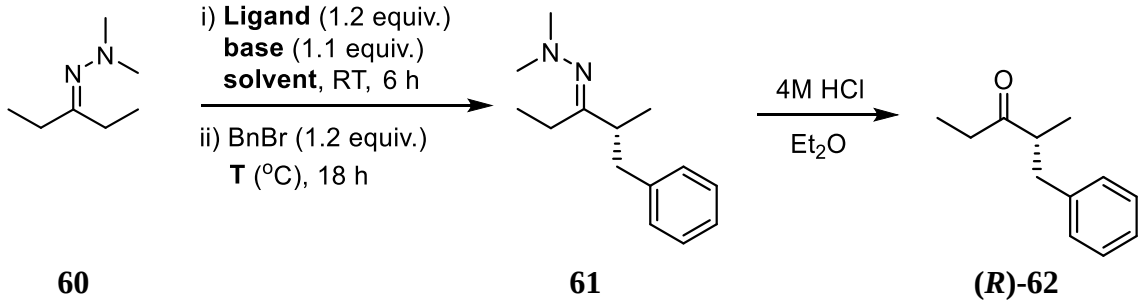


Entry	DMH	R_1	R_2	Ligand	Solvent	Ketone	E^+ (°C)	*ee* (%)	Result
1	**60**	CH_2CH_3	CH_3	(+)-sp **37**	Toluene	**(*R*)-62**	-30	46	19%[a]
2	**70**	Ph	CH_3	(+)-sp **37**	Toluene	**(*R*)-67**	-30	0	21%[a]
3	**60**	CH_2CH_3	CH_3	(+)-sp surrogate **38**	THF	**(*R*)-62**	-78	-	No trace
4	**70**	Ph	CH_3	(+)-sp surrogate **38**	THF	**(*R*)-67**	-78	-	No trace

[a]Yield determined over two steps following purification by column chromatography.

Next, the effect of *i*-PrLi as base was examined with (+)-sp **37** and the (+)-sp surrogate **38** in the α-benzylation of 3-pentanone DMH **60 (Table 6, entries 2-5)**. The *i*-PrLi/(+)-sp surrogate **38** complex in Et_2O produced the highest enantioselectivity (48% *ee*) **(Table 6, entry 2)**. However, ketone **(*R*)-62** was afforded in very poor yield (13%). Switching to toluene resulted in an improved yield but a drop off in enantioselectivity (35% *ee*) **(Table 6, entry 3)**. *i*-PrLi and (+)-sp **37** in Et_2O was also screened **(Table 6, entry 4)**. While a much improved yield (47%) was obtained in comparison to *i*-PrLi/(+)-sp surrogate **38** in Et_2O, ketone **(*R*)-62** was generated with a lower enantiomeric ratio. Using *i*-PrLi/(+)-sp **37** complex in toluene led to a marked increase in yield but the lowest enantioselectivity **(Table 6, entry 5)**.

Table 6. Evaluation of *i*-PrLi as base using (+)-sp **37** and (+)-sp surrogate **38**



60 **61** **(*R*)-62**

Entry	DMH	Base	Ligand	Solvent	Ketone	E^+ (ºC)	*ee* (%)	Yield (%)
1	**60**	*s*-BuLi	(+)-sp **37**	Toluene	**(*R*)-62**	-30	46	19[a]
2	**60**	*i*-PrLi	(+)-sp surrogate **38**	Et_2O	**(*R*)-62**	-78	48	13[b]
3	**60**	*i*-PrLi	(+)-sp surrogate **38**	Toluene	**(*R*)-62**	-78	35	34[b]
4	**60**	*i*-PrLi	(+)-sp **37**	Et_2O	**(*R*)-62**	-30	36	47[b]
5	**60**	*i*-PrLi	(+)-sp **37**	Toluene	**(*R*)-62**	-30	32	68[b]

[a]Yield determined over two steps following purification by column chromatography.

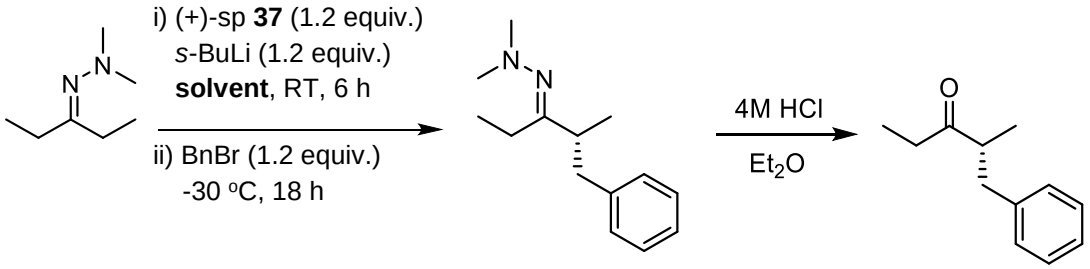
[b]Yield determined over two steps *via* ^{1}H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard.

Beak and co-workers have previously noted the crucial role solvents play on the selectivity of enantioselective transformations involving *s*-BuLi/(-)-sp **37**. Indeed, the enantioselectivity of our system showed a high solvent dependence and toluene was found to be the prime solvent. The use of THF as solvent afforded racemic mixtures, presumably due to competing

coordination of THF with (-)-sp **37**. As previously mentioned, the structure of the reactive (*s*-BuLi)$_x$/((+)-sp **37**)$_y$ aggregate in our system is currently unknown. However, it is likely that the presence of toluene as a non-coordinating solvent generates higher aggregates. With this in mind, we decided to investigate the addition of sub-stoichiometric amounts of THF as a deaggregating additive with the anticipation that we could influence the *s*-BuLi/(+)-sp **37** aggregation state. Hilmerson has previously demonstrated the deaggregation of a PhLi/(-)-sp **37** ladder tetramer complex to a THF-solvated dimer following the addition of sub-stoichiometric quantities of THF.[52] Stephenson and co-workers have also established that an improvement in enantioselectivity could be obtained upon addition of 1.5 equivalents of THF in a (-)-sp **37** mediated silylation of 7,8-dipropyltetrathis[7]helicene.[48] Previous examinations of metal salt additives (LiCl, LiBr, LiI) for this system were found to have a detrimental effect on both the yield and enantioselectivity.[1a] Under our standard reaction conditions and using toluene as solvent, the addition of 1.0 equivalent of THF was probed **(Table 7, entry 1)**. Disappointingly, the addition of THF had a detrimental effect on the enantioselectivity of this reaction and **(*R*)-62** was isolated as a racemic mixture and in 31% yield.

We were then interested to determine the effect of solvent combinations on the enantioselectivity of this system. A series of reactions were conducted using toluene in combination with Et_2O **(Table 7, entries 2-4)**. Interestingly, in relation to Denmark's work on the enantioselective addition of organolithium/BOX ligand complexes to imines,[39] an increase in yield and enantioselectivity was observed when toluene was used in combination with Et_2O. In all cases, the toluene/Et_2O solvent combination had an adverse effect on the enantioselectivity of this reaction. No improvement in selectivity was achieved using a toluene/Et_2O solvent combination. Similar selectivity was observed using a 4:1 and 2:1 ratio indicating that a general trend was not even apparent. However, this may be due to the capricious nature of Et_2O as a solvent in this system which has been previously observed within the group.

Table 7. Effect of solvent combinations



60 **(*R*)-61** **(*R*)-62**

Entry	DMH	Base	Ligand	Solvent	*ee* (%)	Yield (%)[a]
1	**60**	*s*-BuLi	(+)-sp **37**	Toluene, 1.0 equiv. THF	Racemic	31
2	**60**	*s*-BuLi	(+)-sp **37**	4:1, Toluene:Et_2O	37	44
3	**60**	*s*-BuLi	(+)-sp **37**	2:1, Toluene:Et_2O	25	58
4	**60**	*s*-BuLi	(+)-sp **37**	1:1, Toluene:Et_2O	38	38

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

With regards to our system, there are a number of potential factors which could influence the stereoselectivity. As mentioned, the structure of the reactive aggregate in solution is unknown. It is possible that the dominant aggregate in solution may be relatively unreactive, and it could be the presence of small quantities of a reactive aggregate that is responsible for the enantiodiscrimination in this system. For this asymmetric α-alkylation reaction, it is uncertain whether the reactive species in solution is a monomer formed as a result of aggregate-dissociation or if mixed aggregates are the actual reactive species. The formation of mixed-aggregates would even further complicate our efforts to elucidate a possible mechanism for this transformation. Contrary to the popular notion that aggregates first dissociate to form monomers which are the reactive species in organolithium reactions, reactive dimers and other aggregates have been reported.[46] It is difficult to ascertain the role that aggregates play in an enantioselective reaction. As recently highlighted by Collum and Zakarian "*for highly stereoselective reactions traced to specific solvation and aggregation effects, the control of aggregate structure appears to accompany and possibly be a prerequisite for high stereocontrol*."[53]

In addition, the formation of more than one azaenolate geometrical isomer may also be an important stereodetermining factor in this system. As previously discussed, the moderate *ee*'s achieved for this reaction may be due to the low alkylation selectivity of one of these azaenolate isomers. Furthermore, the different azaenolate species could generate several mixed-aggregates in solution.

2.13 Catalytic asymmetric α-alkylation of *N,N*-dimethylhydrazones using (+)-sparteine 37 and (+)-sparteine surrogate 38

The ultimate goal during the development of any enantioselective transformation is usually to develop a catalytic process. One and two ligand catalytic processes have been developed for asymmetric deprotonation reactions using (-)-sp **37** as a chiral ligand.[54] For our system, we were curious as to whether a one-ligand catalytic process could be applied to our asymmetric α-alkylation reaction **(Figure 19)**.

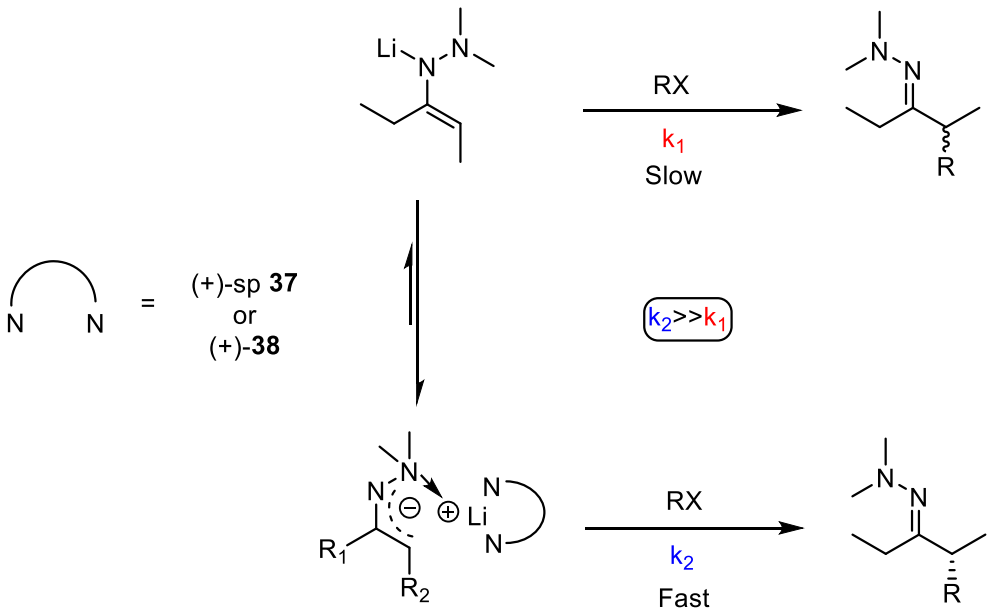


Figure 19. One ligand catalytic asymmetric α-alkylation of ketones.

Two criteria must be met to enable use of sub-stoichiometric amounts of (+)-sp **37**:

1. The rate of alkylation in the presence of chiral ligand (k_2) must be faster than the 'ligand free' reaction (k_1).
2. The chiral ligand must be able to reattach to the azaenolate in order to allow regeneration of the *s*-BuLi/(+)-sp **37** complex.

Previous work carried out within the group has established that the rate of alkylation (k_2) is in fact faster in the presence of *s*-BuLi/(-)-sp **37** than with *s*-BuLi alone (k_1).[1a] An investigation into the use of sub-stoichiometric amounts of ligand was also carried out using 0.4 equivalents of (-)-sp **37**. Only a slight decrease in enantioselectivity was observed in comparison to the stoichiometric reaction. However, there was a significant decrease in yield which perhaps indicates that (-)-sp **37** did not reattach to the azaenolate once alkylation occurred, and that the chiral ligand is required for efficient alkylation.

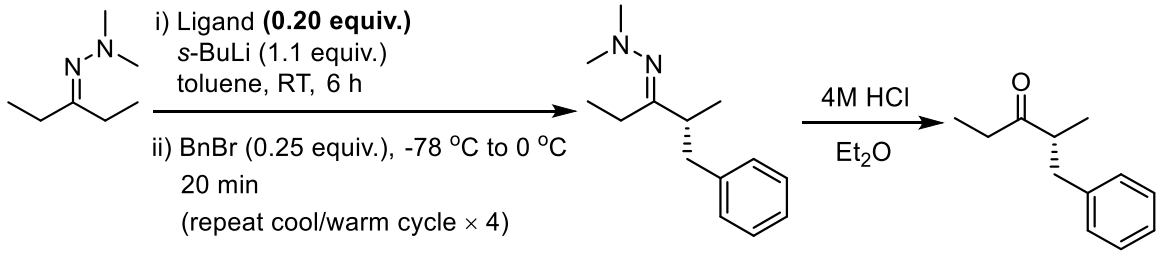
Following this work, we decided to re-examine the use of sub-stoichiometric amounts of (+)-sp **37**. Additionally, we wanted to investigate the effect of using sub-stoichiometric amounts of the (+)-sp surrogate **38**. O'Brien has previously highlighted that the *s*-BuLi/(+)-sp surrogate **38** complex appears to more reactive than the *s*-BuLi/(-)-sp **37** complex.[55] Furthermore, it was also established that the *s*-BuLi/(+)-sp surrogate **38** complex is more efficient than the *s*-BuLi/(-)-sp **37** complex in a one ligand catalytic asymmetric deprotonation of a ferrocene amide and a phosphine borane.[54b]

In relation to our system, we felt that if the enantiodetermining step was occurring after deprotonation i.e. asymmetric alkylation, sequential addition of the electrophile might facilitate more efficient turnover of the catalyst and therefore minimize background racemic alkylation. O'Brien has previously adopted a similar protocol involving the sequential addition of *s*-BuLi in a one-ligand catalytic asymmetric deprotonation of a phosphine borane using both (-)-sp **37** and the (+)-sp surrogate **38**.[56] This sequential addition approach delivered yields and enantioselectivities comparable to those obtained using stoichiometric amounts of chiral ligand. For our asymmetric α-alkylation reaction, we decided to investigate five sequential additions of electrophile over a period of approx. 2 h. Deprotonation of the DMH would be carried out using 0.2 equivalents of ligand and 1.1 equivalents of *s*-BuLi at room temperature. After 6 h, the solution would be cooled to -78 ^{o}C and 0.25 equivalents of electrophile would be added followed by stirring at 0 ^{o}C for 20 mins. This cool/warm cycle would then repeated a total of five times until 1.25 equivalents had been added to the reaction mixture.

To test our approach, deprotonation of 3-pentanone DMH **60** was carried using 0.20 equivalents of (+)-sp **37** and 1.1 equivalents of *s*-BuLi **(Table 8, entry 2)**. An identical reaction was conducted using the (+)-sp surrogate **38 (Table 8, entry 3)**. After 6 h, the solution was cooled to -78 ^{o}C and 0.25 equivalents of benzyl bromide was added and left warm to 0 ^{o}C for

20 mins. The solution was then re-cooled to -78 °C and 0.25 equivalents of benzyl bromide was added. Once again, the solution was left warm to 0 °C. This cool/warm cycle was repeated three more times after which 1.25 equivalents of benzyl bromide had been added. The reaction was then quenched with sat. aq. NH_4Cl solution at 0 °C after the final addition. Analogous to the stoichiometric conditions, an identical enantiomeric ratio of 46% was obtained using 0.2 equivalents of (+)-sp **37**. The desired product was isolated in a very poor yield (5%) which may be due to the inability of the ligand to reattach once alkylation has occurred. On the other hand, the reaction was quenched with sat. aq. NH_4Cl solution at 0 °C after just 20 minutes. A longer alkylation period may be required for higher conversion for this S_N2 reaction. Surprisingly, the (+)-sp surrogate **38** furnished the α-alkylated ketone **(*R*)-62** in lower enantioselectivity (28% *ee*). One might have expected this ligand to outperform (+)-sp **37** in a catalytic process, however, the high reactivity of the (+)-sp surrogate **38** may have required a lower alkylation quench for selectivity.

Table 8. Investigation of sub-stoichiometric amounts of chiral ligand



60 **(*R*)-61** **(*R*)-62**

Entry	DMH	Ligand	Conditions	Ketone	*ee* (%)	Yield (%)
1	**60**	(+)-sp **37**	Standard	**(*R*)-62**	46	19[a]
2	**60**	(+)-sp **37**	0.20 equiv.	**(*R*)-62**	46	5[b]
3	**60**	(+)-sp surrogate **38**	0.20 equiv.	**(*R*)-62**	28	9[b]

[a]Yield determined over two steps following purification by column chromatography.

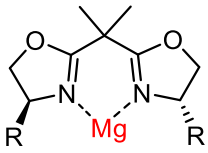
[b]Yield determined over two steps *via* ^1H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard.

2.14 Conclusions and future work

In summary, a range of symmetrical and unsymmetrical ketones were examined using a chiral ligand strategy. Racemic and enantioenriched α-alkylated ketones were prepared. The scope of this methodology was also expanded to include more diverse and challenging electrophiles resulting in the formation of an array of synthetically useful ketones. Overall, the enantioselectivities remain moderate for this system.

A number of reaction parameters were investigated in an effort to improve the enantioselectivity of this chiral ligand methodology. Attempts to utilise an oxime in place of the dimethylamino group proved unsuccessful.

A series of alternative chiral ligands was evaluated. Investigation of a range of versatile BOX ligands determined that these ligands were unsuitable for this asymmetric α-alkylation reaction using organolithium reagents. It should be noted that these ligands are usually used in tandem with other metals such as magnesium. Thus, future work will likely examine the use of Mg/BOX complexes in this transformation **(Figure 20)**.



Lithium/magnesium exchange *via* addition of $MgBr_2$

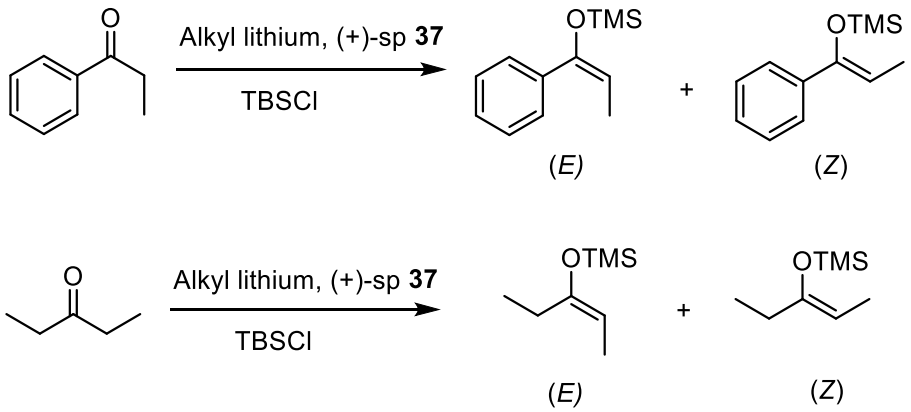
Figure 20. Mg/BOX complexes

The effect of different organolithium/(+)-sp **37** and (+)-sp surrogate **38** complexes on the enantioselectivity of this system was evaluated as well as different solvent combinations. Preliminary investigations using sub-stoichiometric amounts of (+)-sp **37** and the (+)-sp surrogate **38** were also conducted.

Future work

Future work within the group will likely focus on the direct asymmetric α-alkylation of ketones. Initial investigations in this area are currently been undertaken by another member of the group involving the use of trimethyl silyl enol ethers and chiral tetramines.

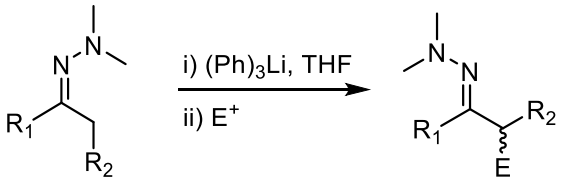
It would also be interesting to examine the *E*:*Z* enolization selectivity of 3-pentanone and propiophenone to determine the effect of enolate geometry on the stereoselectivity of this asymmetric α-alkylation reaction **(Scheme 51)**. This could be achieved using a variety of different alkyl lithium bases and trapping the resulting lithium enolates as silyl enol ethers in the presence of a chiral ligand such as (+)-sp **37**. For example, Xie and co-workers have shown that excellent *Z* selectivity can be obtained for 3-pentanone and propiophenone using amide bases with strong electron-withdrawing substituents such as lithium diphenyl amide.[57] High *E* selectivity was achieved using lithium *tert*-butyltrimethylsilylamide.



Scheme 51. *E*:*Z* enolization selectivity

Furthermore, future work in this project will be directed towards:

- The synthesis and investigation of other chiral ligand scaffolds.
- Examination of the use of triphenyl lithium as an alternative to *t*-BuLi as a non-nucleophilic base to deprotonate DMHs **(Scheme 52)**.



Scheme 52. Deprotonation of DMHs using triphenyl lithium

2.15 References

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Chapter 3

Experimental

for Chapter 2

3.1 General procedures

Solvents employed were either distilled prior to use: tetrahydrofuran (THF), toluene and diethyl ether (Et_2O) were distilled from sodium/benzophenone dianion under nitrogen. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Alternatively, solvents were dried and stored over flame dried 4 Å molecular sieves (10-15% w/v) in Young's flask. The concentration of *n*-BuLi, *s*-BuLi and *n*-HexLi was determined by titration with diphenylacetic acid. (+)-Sparteine was purchased from Beta Pharma and distilled prior to use using a Kugelrohr distillation apparatus. All other reagents were purchased from Sigma Aldrich, Fluorochem, Alfa Aesar and Acros unless otherwise noted. All non-aqueous reactions were carried out under oxygen-free nitrogen atmosphere using oven-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 and potassium permanganate staining. Melting points were measured in a Thomas Hoover Capillary Melting Point apparatus. Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrophotometer. Liquid samples were examined as thin films interspersed between NaCl plates.

NMR spectra were run in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard at 25 ^oC. ^1H NMR spectra were recorded at 300 MHz in proton decoupled mode on a Bruker Avance 300 spectrometer. ^{13}C NMR were recorded at 75.5 MHz on a Bruker Avance 300 instrument 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). Splitting patterns in ^1H NMR spectra are designated as s (singlet), *br* s (broad singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet), and m (multiplet). 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.

Low-resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water, containing 0.1%

formic acid as the mobile phase. Samples were made up in acetonitrile at a concentration of *ca*. 1mg/mL. High-resolution mass spectra were recorded on a Waters LCT Premier TOF LC-MS instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water, containing 0.1% formic acid as the mobile phase. Samples were made up in acetonitrile at a concentration of *ca*. 1 mg/mL.

Optical rotations were recorded on a DigiPol 781 TDV Polarimeter at 589 nm or on an Autopol V Plus Automatic Polarimeter in a 10 cm cell. Concentrations (c) are expressed in g/100 mL, $[\alpha]_D^T$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}. The specific rotations were recorded to indicate the direction of enantioselection and optically active samples are numbered with either (+)- or (-)- as prefix.

Gas chromatography analysis was carried out on an Agilent Technologies 7820A GC System using G4513A Series Injector and Astec Chiraldex^{TM} G-TA, fused silica capillary column, 20 m × 0.25 mm × 0.12 μm film thickness. All chiral columns were purchased from Sigma-Aldrich Supelco. Conditions for separation were determined using the following operating conditions as standard, flow rate: 1 mL/min, injection volume: 0.2 μL, split ratio: 10:1, front inlet temperature: 150 ^{o}C, detector temperature: 155 ^{o}C. Samples were prepared for GC analysis by dissolving in Et_2O to 2 mg/mL and passing through silica gel.

A Julabo FT902 cryocooler was used for low temperature reactions.

3.1.1 Analysis of known and novel compounds

^{1}H NMR spectra, ^{13}C NMR spectra, LRMS and IR analyses were recorded for all previously prepared compounds. For novel compounds, in addition to the previously mentioned analysis, HRMS was also obtained. For some compounds, only HRMS data is given due to the fact that the compound was not found using the LRMS instrument. Optical rotations were used to assign absolute stereochemistry for chiral compounds.

3.2 Synthesis of *N,N*-dimethylhydrazones

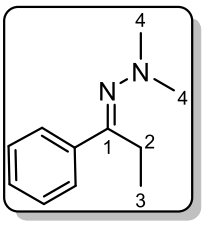
General procedure for the synthesis of *N,N*-dimethylhydrazones

Ketone (1.0 equiv.) was reacted neat with ***N,N*-dimethylhydrazine** (1.0-3.0 equiv.) and a few drops of acetic acid (6-8 drops). The reaction mixture was stirred at reflux temperature. The reaction progress was monitored by TLC analysis. On completion, the mixture was allowed cool to room temperature.

Work-up conditions as per 30 mmol of ketone

H_2O (10 mL) was added and the crude product was extracted with Et_2O (3 × 30 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude *N,N*-dimethylhydrazone which was purified *via* Kugelrohr distillation.

(*E*)-1,1-Dimethyl-2-(1-phenylpropylidene)hydrazine, 70

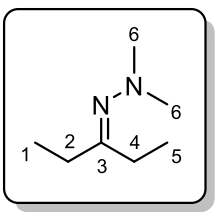


Compound **70** was prepared from the general procedure **3.2** outlined above using propiophenone (3.87 mL, 29 mmol) and *N,N*-dimethylhydrazine (6.62 mL, 87 mmol). The crude compound was purified *via* Kugelrohr distillation to give the title compound **70** as a bright yellow oil (4.4 g, 86%, 8:1 mixture of *E*:*Z* isomers).

Spectroscopic characteristics were consistent with previously reported data.[1]

IR ν_{max} (NaCl): 1608 (C=N stretch) cm^{-1}. ***E* isomer**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (3H, t, *J* = 7.6 Hz, H-3), 2.36 (6H, s, H-4), 2.91 (2H, q, *J* = 7.6 Hz, H-2), 7.33-7.39 (3H, m, Ar-H), 7.61-7.69 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.0 (C-3), 21.9 (C-2), 48.0 (C-4), 127.1 (2 × Ar-CH), 128.4 (2 × Ar-CH), 129.3 (Ar-CH), 137.9 (Ar-C), 169.5 (C-1) ppm. ***Z* isomer**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, t, *J* = 7.5 Hz, H-3), 2.56 (6H, s, H-4), 2.52 (2H, q, *J* = 7.5 Hz, H-2), 7.33-7.39 (3H, m, Ar-H), 7.61-7.69 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.8 (C-3), 32.5 (C-2), 47.2 (C-4), 127.1 (2 × Ar-CH), 128.4 (2 × Ar-CH), 129.3 (Ar-CH), 137.9 (Ar-C), 165.2 (C-1) ppm. MS (ESI) *m*/*z*: 177 $(M + H)^+$.

1,1-Dimethyl-2-(pentan-3-ylidene)hydrazine, 60

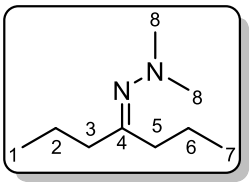


Compound **60** was prepared from the general procedure **3.2** outlined above using 3-pentanone (4.86 mL, 46 mmol) and *N,N*-dimethylhydrazine (7.00 mL, 92 mmol). The crude compound was purified *via* Kugelrohr distillation

to give the title compound **60** as a colourless oil (3.09 g, 52%). Spectroscopic characteristics were consistent with previously reported data.[2]

IR ν_{max} (NaCl): 1637 (C=N stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (6H, t, *J* = 7.6 Hz, H-1 and H-5), 2.23 (2H, q, *J* = 7.6 Hz, H-2), 2.41 (6H, s, H-6), 2.44 (2H, q, *J* = 7.6 Hz, H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.1 (C-1), 11.6 (C-5), 22.6 (C-2), 28.8 (C-4), 47.6 (C-6), 174.3 (C-3) ppm. MS (ESI) *m/z*: 129 $(M + H)^+$.

2-(Heptan-4-ylidene)-1,1-dimethylhydrazine, 71

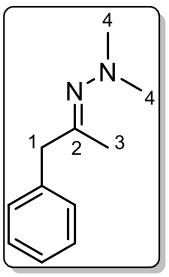


Compound **71** was prepared from the general procedure **3.2** outlined above using 4-heptanone (4.89 mL, 35 mmol) and *N*,*N*-dimethylhydrazine (7.99 mL, 105 mmol). The crude compound was purified *via* Kugelrohr distillation to give the title compound **71** as colourless oil (3.36 g, 62%).

Spectroscopic characteristics were consistent with previously reported data.[3]

IR ν_{max} (NaCl): 1633 (C=N stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90, 0.91 (2 × 3H, t, *J* = 7.4, H-1 and H-7), 1.40-1.57 (4H, m, H-2 and H-6), 2.10-2.17 (2H, m, H-3), 2.32-2.40 (2H, m, H-5), 2.36 (6H, s, H-8) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9 (C-1), 14.5 (C-7), 20.0 (C-2), 20.7 (C-6), 31.8 (C-3), 38.1 (C-5), 47.7 (C-8), 172.6 (C-4) ppm. MS (ESI) *m*/*z*: 157 $(M + H)^+$.

(*E*)-1,1-Dimethyl-2-(1-phenylproan-2-ylidene)hydrazine, 72

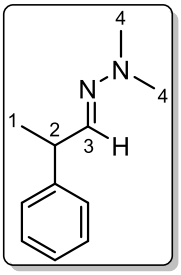


Compound **72** was prepared from the general procedure **3.2** outlined above using phenylacetone (3.21 mL, 24 mmol) and *N*,*N*-dimethylhydrazine (3.65 mL, 48 mmol). The crude compound was purified *via* Kugelrohr distillation to give the title compound **72** as a pale yellow oil (3.45 g, 82%, 3:1 mixture of *E*:*Z* isomers).

Spectroscopic characteristics were consistent with previously reported data.[4]

IR ν_{max} (NaCl): 1640 (C=N stretch) cm^{-1}. ***E* isomer**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (3H, s, H-3), 2.49 (6H, s, H-4), 3.51 (2H, s, H-1), 7.14-7.34 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.3 (C-3), 45.6 (C-1), 47.1 (C-4), 126.7 (Ar-CH), 128.7 (2 × Ar-CH), 129.0 (2 × Ar-CH), 137.6 (Ar-C), 166.5 (C-2) ppm. ***Z* isomer**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82 (3H, s, H-3), 2.48 (6H, s, H-4), 3.84 (2H, s, H-1), 7.14-7.34 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (C-3), 37.6 (C-1), 47.5 (C-4), 126.5 (Ar-CH), 128.7 (2 × Ar-CH), 129.2 (2 × Ar-CH), 137.3 (Ar-C), 167.5 (C-2) ppm. MS (ESI) *m*/*z*: 177 $(M + H)^+$.

(*E*)-1,1-Dimethyl-2-(2-phenylpropylidene)hydrazine, 73

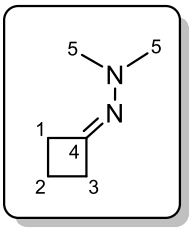


Compound **73** was prepared from the general procedure **3.2** outlined above using 2-phenylpropanal (5.00 mL, 37.3 mmol) and *N*,*N*-dimethylhydrazine (8.52 mL, 112 mmol). The crude compound was purified *via* Kugelrohr distillation to give the title compound **73** as a pale yellow oil (5.14 g, 78%).

Spectroscopic characteristics were consistent with previously reported data.[5]

IR ν_{max} (NaCl): 1604 (C=N stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (3H, d, *J* = 7.1 Hz, H-1), 2.73 (6H, s, H-4), 3.60-3.71 (1H, m, H-2), 6.67 (1H, d, *J* = 6.0 Hz, H-3), 7.17-7.34 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.8 (C-1), 43.1 (C-2), 43.4 (C-4), 126.4 (Ar-CH), 127.5 (2 × Ar-CH), 128.6 (2 × Ar-CH), 141.7 (Ar-C), 144.5 (C-3) ppm. MS (ESI) *m*/*z*: 177 $(M + H)^+$.

2-Cyclobutylidene-1,1-dimethylhydrazine, 74



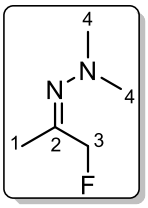
Compound **74** was prepared using cyclobutanone (0.75 mL, 10 mmol) and *N*,*N*-dimethylhydrazine (0.76 mL, 10 mmol) in the absence of acetic acid. The reaction mixture was stirred at room temperature. The reaction progress was monitored by TLC analysis. On completion, H_2O (5 mL) was added and the crude product was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude *N*,*N*-dimethylhydrazone. The crude product was used in the next step without purification (Pale yellow oil, 0.860 g, 77%).

Spectroscopic characteristics were consistent with previously reported data.[6]

IR ν_{max} (NaCl): 1660 (C=N stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89-2.03 (2H, m, H-2), 2.56 (6H, s, H-5), 2.84-3.02 (4H, m, H-1 and H-3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.6 (C-2), 35.3, 35.5 (C-1 and C-3), 47.0 (C-5), 160.8 (C-4) ppm. MS (ESI) *m*/*z*: 113 $(M + H)^+$.

COSY and HSQC were used to aid in assignment.

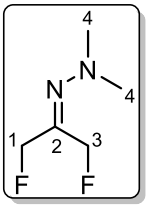
Fluoroacetone *N,N*-dimethylhydrazone, 75



To a two-neck round-bottomed flask under N_2 atmosphere containing Et_2O (2.5 mL) was added fluoroacetone (11.8 mmol, 0.85 mL) at -20 ^oC. *N,N*-dimethylhydrazine (35.4 mmol, 2.69 mL) was added slowly and the solution was warmed to room temperature overnight. The reaction progress was monitored by ^1H NMR analysis. On completion, the mixture was allowed cool to room temperature. The organic layer was extracted with Et_2O (10 mL). Product decomposed on exposure to air.

^1H NMR spectrum recorded during reaction monitoring. ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (3H, s, H-1), 2.49 (6H, s, H-4), 4.79 (2H, d, J = 47.2 Hz, H-3) ppm.

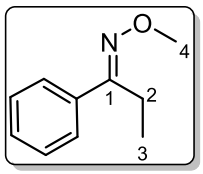
1,3-Difluoroacetone *N,N*-dimethylhydrazone, 76



To a two-neck round-bottomed flask under N_2 atmosphere containing Et_2O (2.5 mL) was added 1,3-difluoroacetone (4.89 mmol, 0.35 mL) at -20 ^oC. *N,N*-dimethylhydrazine (4.89 mmol, 0.37 mL) was added slowly and the solution was warmed to room temperature overnight. The reaction progress was monitored by ^1H NMR analysis. On completion, the mixture was allowed cool to room temperature. The organic layer was extracted with Et_2O (10 mL). Product decomposed on exposure to air.

^1H NMR recorded during reaction monitoring. ^1H NMR (300 MHz, $CDCl_3$) δ 2.51 (6H, s, H-4), 5.00 (2H, dd, J = 46.8, 1.8 Hz, H-1), 5.18 (2H, dd, J = 47.4, 1.5 Hz, H-3) ppm.

(*E*)-1-Phenylpropan-1-one-O-methyl oxime, 88



To a solution of propiophenone (14.9 mmol, 1.98 mL) and sodium hydroxide (14.9 mmol, 0.60 g) was added methoxyamine hydrochloride (14.9 mmol, 1.24 g) at room temperature. The reaction mixture was stirred at room temperature and the reaction progress was monitored by TLC analysis. Once the reaction had gone to completion, the reaction mixture was diluted with EtOAc (30 mL), washed with brine (10 mL) and extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude compound (1:0.4 mixture of *E*:*Z* isomers) was purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **88** as a colourless oil (0.900 g, 37% of *E* isomer).

Spectroscopic characteristics were consistent with previously reported data for the *E* isomer.[7] IR ν_{max} (NaCl): 1689 (C=N stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (3H, t, *J* = 7.6 Hz, H-3), 2.74 (2H, q, *J* = 7.6 Hz, H-2), 3.98 (3H, s, H-4), 7.32-7.42 (3H, m, Ar-H), 7.58-7.67 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3 (C-3), 20.2 (C-2), 70.0 (C-4), 126.4 (2 × Ar-CH), 128.9 (2 × Ar-CH), 129.1 (Ar-CH), 135.8 (Ar-C), 159.9 (C-1) ppm. MS (ESI) *m*/*z*: 164 $(M + H)^+$.

3.3 Synthesis of racemic α-alkylated ketones

Procedure A: General procedure for the synthesis of racemic compounds *via* alkylation of ketones

To a Schlenk tube under N_2 atmosphere containing anhydrous THF (5 mL/mmol of ketone) was added commercially available LDA (2.0 M, 1.1 equiv.) at -78 °C. **Ketone** (1.0 equiv.) was added slowly (neat), dropwise and the mixture was allowed to stir at this temperature for 1 h. **Electrophile** (1.2 equiv.) was added slowly (neat), dropwise and the mixture was allowed warm to room temperature overnight.

Work-up conditions as per 5 mmol of ketone

The reaction mixture was quenched with H_2O (0.5 mL). H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude α-alkylated ketone was purified using column chromatography on silica gel to give the pure α-alkylated ketone.

Procedure B: General procedure for the synthesis of racemic compounds *via* alkylation of *N,N*-dimethylhydrazones

To a Schlenk tube under N_2 atmosphere containing anhydrous THF (5 mL/mmol of hydrazone) was added commercially available LDA (2.0 M, 1.1 equiv.) at 0 ^oC. Distilled **hydrazone** (1.0 equiv.) was added slowly (neat), dropwise and the mixture was allowed to stir at room temperature over 6 h. The reaction mixture was cooled to 0 ^oC, **electrophile** (1.2 equiv.) was added slowly (neat), dropwise and allowed warm to room temperature overnight.

Work-up conditions as per 5 mmol of hydrazone

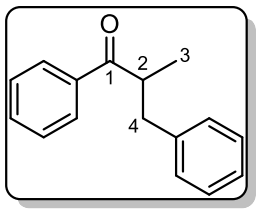
The reaction mixture was quenched with H_2O (0.5 mL). H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated *N*,*N*-dimethylhydrazones.

Hydrolysis Procedure

Method A: 4M HCl/diethyl ether

4M HCl (0.5 mL/mmol) was added to a vigorously stirred solution of crude α-alkylated *N*,*N*-dimethylhydrazone in Et_2O (5 mL/mmol). The reaction progress was monitored by TLC analysis. Once all the starting material had reacted, H_2O (5 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude α-alkylated ketone was purified using column chromatography on silica gel to afford the pure α-alkylated ketone.

2-Methyl-1,3-diphenyl-propan-1-one, 67



Compound **67** was prepared according to the general procedure **3.3 Procedure A** using propiophenone (0.66 mL, 5 mmol) and benzyl bromide (0.71 mL, 6 mmol). The crude compound was purified using column chromatography on silica gel (50:1 to 20:1, hexane:Et_2O) to give the title compound **67** as a pale yellow oil (0.156 g, 14%).

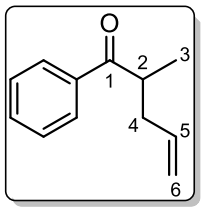
Spectroscopic characteristics were consistent with previously reported data.[8]

IR ν_{max} (NaCl): 1681 (C=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (3H, d, *J* = 6.9 Hz, H-3), 2.69 (1H, dd, *J* = 13.7, 7.8 Hz, H-4), 3.17 (1H, dd, *J* = 13.7, 6.3 Hz, H-4), 3.68-3.81 (1H, m, H-2), 7.11-7.31 (5H, m, Ar-H), 7.39-7.58 (3H, m, Ar-H), 7.88-7.97 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.5 (C-3), 39.5 (C-4), 42.9 (C-2), 126.3 (Ar-CH), 128.4

(2 × Ar-CH), 128.5 (2 × Ar-CH), 128.8 (2 × Ar-CH), 129.2 (2 × Ar-CH), 133.0 (Ar-CH), 136.6 (Ar-C), 140.1 (Ar-C), 203.8 (C-1) ppm. MS (ESI) *m*/*z*: 225 $[M + H]^+$.

GC analysis: t_R = 67.1 and 67.6 min (110 °C hold 45 min, ramp 2 °C/min to 140 °C, hold for 10 min).

2-Methyl-1-phenyl-4-pentan-3-one, 68



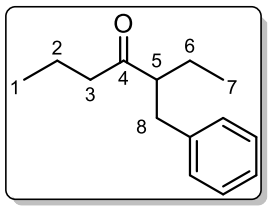
Compound **68** was prepared according to the general procedure **3.3 Procedure A** using propiophenone (0.66 mL, 5 mmol) and allyl bromide (0.52 mL, 6 mmol). The crude compound was purified using column chromatography on silica gel (50:1, hexane:Et_2O) to give the title compound **68** as a colourless oil (0.340 g, 39%).

Spectroscopic characteristics were consistent with previously reported data.[9]

IR ν_{max} (NaCl): 1683 (C=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (3H, d, *J* = 6.9 Hz, H-3), 2.08-2.18 (1H, m, one of H-4), 2.43-2.54 (1H, m, one of H-4), 2.64-2.79 (1H, m, H-2), 3.53-3.41 (1H, m, H-5), 4.91-5.02 (2H, m, H-6), 7.35-7.44 (2H, m, Ar-H), 7.45-7.53 (1H, m, Ar-H), 7.85-7.93 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.0 (C-3), 37.6 (C-4), 40.4 (C-2), 116.8 (C-6), 128.3 (2 × Ar-CH), 128.7, (2 × Ar-CH), 129.1 (Ar-CH), 135.8 (C-5), 136.4 (Ar-C), 203.7 (C-1) ppm. MS (ESI) *m*/*z*: 175 $(M + H)^+$.

GC analysis: t_R = 14.8 and 15.1 min (100 °C hold 17 min, ramp 5 °C/min to 140 °C, hold for 7 min).

3-Benzylheptan-4-one, 69



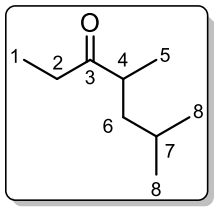
Compound **69** was prepared according to the general procedure **3.3 Procedure A** using 4-heptanone (0.70 mL, 5 mmol) and benzyl bromide (0.71 mL, 6 mmol). The crude compound was purified using column chromatography on silica gel (50:1 to 20:1, hexane:Et_2O) to give the title compound **69** as a colourless oil (0.142 g, 14%).

Spectroscopic characteristics were consistent with previously reported data.[10]

IR ν_{max} (NaCl): 1711 (C=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.79, 0.87 (2 × 3H, t, *J* = 7.4 Hz, H-1 and H-7), 1.39-1.75 (4H, m, H-2 and H-6), 2.11 (1H, ddd, *J* = 17.3, 7.5, 7.0 Hz, one of H-3), 2.28 (1H, ddd, *J* = 17.3, 7.5, 7.0 Hz, one of H-3), 2.60-2.79 (2H, m, H-5 and one of H-8), 2.87 (1H, dd, *J* = 12.3, 7.6 Hz, one of H-8), 7.08-7.30 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.9, 13.8 (C-1 and C-7), 16.8, 24.9 (C-2 and C-6), 37.8 (C-3),

45.7 (C-8), 55.6 (C-5), 126.3 (Ar-CH), 128.5 (2 × Ar-CH), 129.0 (2 × Ar-CH), 140.1 (Ar-C), 214.4 (C-4) ppm. HRMS (ESI) *m/z* calcd for $C_{14}H_{21}O$ $[M + H]^+$: 205.1592, found 205.1586.
GC analysis: t_R = 34.3 and 34.5 min (85 ^oC hold 20 min, ramp 2.5 ^oC/min to 140 ^oC, hold for 5 min).

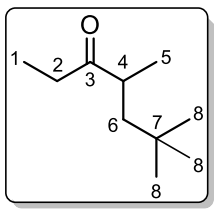
4,6-Dimethylheptan-3-one, 77



Compound **77** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.385 g, 3 mmol) and 1-iodo-2-methyl propane (0.41 mL, 3.6 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **77** as a pale yellow oil (0.057 g, 13% over two steps).
IR ν_{max} (NaCl): 1716 (C=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87, 0.90 (2 × 3H, d, *J* = 6.4 Hz, H-8), 1.04 (3H, d, *J* = 6.9 Hz, H-5), 1.05 (3H, t, *J* = 7.3 Hz, H-1), 1.46-1.62 (1H, m, H-7), 1.46-1.62 (2H, m, H-6), 2.47 (overlapping 2 × 1H, dq, *J* = 15.6, 7.3 Hz, one of each H-2), 2.56-2.68 (1H, m, H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.9 (C-1), 16.9 (C-5), 22.5, 23.0 (C-8), 25.9 (C-7), 34.2 (C-2), 42.4 (C-6), 44.2 (C-4), 215.8 (C-3) ppm. MS (ESI) *m/z*: 141 $[M - H]^-$.
GC analysis: t_R = 2.7 and 2.8 min (80 ^oC hold 10 min, ramp 10 ^oC/min to 140 ^oC, hold for 5 min).

Note: Compound **77** is a novel compound. No HRMS data was obtained due to the fact that no HRMS service was available during the synthesis of this compound.

4,6,6-Trimethylheptan-3-one, 78

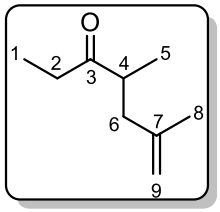


Compound **78** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.385 g, 3 mmol) and 1-iodo-2,2-dimethyl propane (0.48 mL, 3.6 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **78** as a pink oil (0.043 g, 9% over two steps).
Spectroscopic characteristics were consistent with previously reported data.[11]
IR ν_{max} (NaCl): 1717 (C=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (9H, s, H-8), 1.05 (3H, t, *J* = 7.3 Hz, H-1), 1.07 (3H, d, *J* = 7.1 Hz, H-5), 1.09 (1H, dd, *J* = 14.0, 7.2 Hz, one of

H-6), 1.89 (1H, dd, *J* = 14.1, 7.9 Hz, one of H-6), 2.38-2.70 (3H, m, H-2 and H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.1 (C-1), 20.0 (C-5), 29.8 (C-8), 31.0 (C-7), 34.3 (C-2), 42.7 (C-6), 46.7 (C-4), 215.8 (C-3) ppm. MS (ESI) *m*/*z*: 157 $[M + H]^+$.

GC analysis: t_R = 3.2 and 3.4 min (80 °C hold 10 min, ramp 10 °C/min to 140 °C, hold for 5 min).

4,6-Dimethylhept-6-en-3-one, 79



Compound **79** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.146 g, 1.14 mmol) and 3-bromo-2-methylprop-1-ene (0.14 mL, 1.37 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10 :1, hexane:Et_2O) to give the title compound **79** as a pale yellow oil (0.040 g, 25% over two steps).

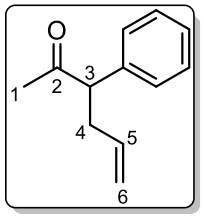
IR ν_{max} (NaCl): 1716 (C=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, t, *J* = 7.3 Hz, H-1), 1.06 (3H, d, *J* = 7.3 Hz, H-5), 1.71 (3H, s, H-8), 1.20 (1H, dd, *J* = 14.2, 7.7 Hz, one of H-6), 2.38 (1H, dd, *J* = 14.3, 6.7 Hz, one of H-6), 2.47 (overlapping 2 × 1H, dq, *J* = 14.8, 7.3 Hz, one of each H-2), 2.67-2.80 (1H, m, H-4), 4.63-4.69 (1H, m, one of H-9), 4.73-4.78 (1H, m, one of H-9) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8 (C-1), 16.5 (C-5), 22.4 (C-8), 34.4 (C-2), 41.3 (C-6), 44.2 (C-4), 112.3 (C-9), 143.2 (C-7), 214.9 (C-3) ppm. MS (ESI) *m*/*z*: 141 $[M + H]^+$.

GC analysis: t_R = 4.5 and 4.7 min (75 °C hold 11 min, ramp 10 °C/min to 140 °C, hold for 5 min).

COSY and HSQC were used to aid in assignment.

Note: Compound **79** is a novel compound. No HRMS data was obtained due to the fact that no HRMS service was available during the synthesis of this compound.

3-Phenylhex-5-en-2-one, 80



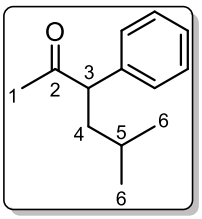
Compound **80** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **72** (0.441 g, 2.5 mmol) and allyl bromide (0.26 mL, 3 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **80** as a yellow oil (0.221g, 51% over two steps).

Spectroscopic characteristics were consistent with previously reported data.[12]

IR ν_{max} (NaCl): 1716 (C=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (3H, s, H-1), 2.74-2.86 (1H, m, one of H-4), 2.37-2.49 (1H, m, one of H-4), 3.70 (1H, t, *J* = 7.5 Hz, H-3), 4.92-5.05 (2H, m, H-6), 5.60-5.74 (1H, m, H-5), 7.17-7.37 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.1 (C-1), 36.1 (C-4), 59.4 (C-3), 116.6 (C-6), 127.4 (Ar-CH), 128.3 (2 × Ar-CH), 129.0 (2 × Ar-CH), 135.8 (C-5), 138.4 (Ar-C), 207.1 (C-2) ppm. MS (ESI) *m*/*z*: 175 $(M + H)^+$.

GC analysis: t_R = 9.0 and 9.4 min (100 ºC hold 11 min, ramp 10 ºC/min to 140 ºC, hold for 5 min).

5-Methyl-3-phenyl-2-hexanone, 81



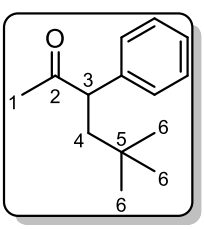
Compound **81** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **72** (0.441 g, 2.5 mmol) and 1-iodo-2-methylpropane (0.35 mL, 3 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **81** as a pale yellow oil (0.080g, 17% over two steps).

Spectroscopic characteristics were consistent with previously reported data.[13]

IR ν_{max} (NaCl): 1713 (C=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86, 0.88 (2 × 3H, d, *J* = 4.0 Hz, H-6), 1.30-1.46 (1H, m, H-5), 1.65 (1H, ddd, *J* = 13.9, 8.4, 5.9 Hz, one of H-4), 1.87 (1H, ddd, *J* = 13.8, 8.2, 6.7 Hz, one of H-4), 2.05 (3H, s, H-1), 3.72 (1H, dd, *J* = 8.3, 6.9 Hz, H-3), 7.17-7.39 (5H, m, Ar-CH) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1, 23.2 (C-6), 25.6 (C-5), 29.1 (C-1), 40.7 (C-4), 57.7 (C-3), 127.3 (Ar-CH), 128.4 (2 × Ar-CH), 129.0 (2 × Ar-CH), 139.2 (Ar-C), 208.8 (C-2) ppm. MS (ESI) *m*/*z*: 191 $(M + H)^+$.

GC analysis: t_R = 19.1 and 19.8 min (90 ºC hold 22 min, ramp 10 ºC/min to 140 ºC, hold for 5 min).

5,5-Dimethyl-3-phenyl-hexan-2-one, 82

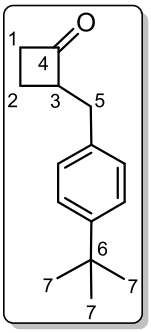


Compound **82** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **72** (0.441 g, 2.5 mmol) and 1-iodo-2,2-dimethylpropane (0.40 mL, 3 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **82** as an orange oil (0.158 g, 31% over two steps).

IR ν_{max} (NaCl): 1718 (C=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (9H, s, H-6), 1.50 (1H, dd, *J* = 14.1, 4.7 Hz, one of H-4), 2.09 (3H, s, H-1), 2.35 (1H, dd, *J* = 14.1, 7.5 Hz, one of H-4), 3.75 (1H, dd, *J* = 7.5, 4.7 Hz, H-3), 7.19-7.37 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 29.1 (C-1), 29.8 (C-6), 31.0 (C-5), 45.4 (C-4), 56.3 (C-3), 127.1 (Ar-CH), 128.4 (2 × Ar-CH), 129.0 (2 × Ar-CH), 140.9 (Ar-C), 208.3 (C-2) ppm. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{21}O$ $[M + H]^+$: 205.1592, found 205.1585.

Note: Enantiomers of **82** could not be successfully separated using GC.

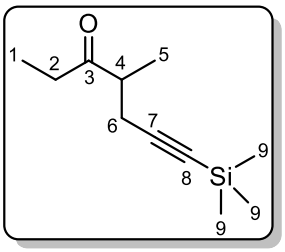
2-(4-(*Tert*-butyl)benzyl)cyclobutan-1-one, 83



Compound **83** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **74** (0.111 g, 1 mmol) and *t*-butyl benzyl bromide (0.22 mL, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (3:1, hexane:Et_2O) to give the title compound **83** as a pale yellow oil (0.083 g, 38% over two steps).
IR ν_{max} (NaCl): 1779 (C=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (9H, s, H-7), 1.75 (1H, ddt, *J* = 11.3, 9.6, 7.7 Hz, one of H-2), 2.17 (1H, dtd, *J* = 11.2, 10.3, 5.2 Hz, one of H-2), 2.77 (1H, dd, *J* = 14.6, 9.2 Hz, one of H-5), 2.87 (1H, dddd, *J* = 17.7, 9.7, 5.3, 2.7 Hz, one of H-1), 2.95-3.10 (2H, m, one of H-1 and one of H-5), 3.52-3.66 (1H, m, H-3), 7.08-7.15 (2H, m, Ar-H), 7.28-7.34 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.9 (C-2), 31.5 (C-7), 34.5 (C-6), 34.8 (C-5), 44.6 (C-1), 61.4 (C-3), 125.5 (2 × Ar-CH), 128.5 (2 × Ar-CH), 135.9 (Ar-C), 149.3 (Ar-C), 211.2 (C-4) ppm. HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}O$ $[M + H]^+$: 217.1587, found 217.1577.
COSY, HSQC and HMBC were used to aid in assignment.

Note: Enantiomers of **83** could not be successfully separated using GC.

4-Methyl-7-(trimethylsilyl)hept-6-yn-3-one, 97



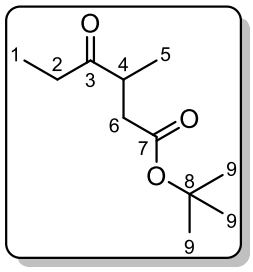
Compound **97** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.321 g, 2.5 mmol) and 3-bromo-1-(trimethylsilyl)-1-propyne (0.49 ml, 3 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **97** as a pale yellow oil (0.210 g, 43% over two steps).

IR ν_{max} (NaCl): 2177 (C≡C stretch), 1717 (C=O stretch), 1250 (C-Si stretch), 843 (C-Si stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (9H, s, H-9), 1.04 (3H, t, *J* = 7.2 Hz, H-1), 1.16 (3H, d, *J* = 7.0 Hz, H-5), 2.28 (1H, dd, *J* = 17.0, 7.6 Hz, one of H-6), 2.41-2.56 (3H, m, H-2 and one of H-6), 2.65-2.80 (1H, m, H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 0.2 (C-9), 7.8 (C-1), 16.4 (C-5), 23.5 (C-2), 35.0 (C-6), 45.2 (C-4), 86.4 (C-7), 104.9 (C-8), 213.5 (C-3) ppm. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{21}OSi$ $[M + H]^+$: 197.1356, found 197.1350.

GC analysis: t_R = 6.6 and 6.9 min (90 °C hold 10 min, ramp 10 °C/min to 140 °C, hold for 5 min).

COSY and HSQC were used to aid in assignment.

3-Methyl-4-oxo-1,1-dimethyl-hexanoate, 98



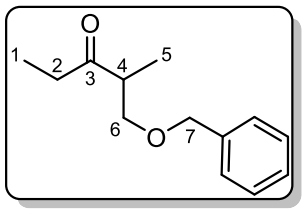
Compound **98** was prepared according to the general procedure **3.3 Procedure A** using 3-pentanone (0.431 g, 5 mmol) and *t*-butyl bromoacetate (0.89 mL, 6 mmol). The crude compound was purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **98** as a colourless oil (0.484 g, 48%).

Spectroscopic characteristics were consistent with previously reported data.[14]

IR ν_{max} (NaCl): 1729 (C=O stretch, one *br* peak), 1159 (C-O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.06 (3H, t, *J* = 7.3 Hz, H-1), 1.10 (3H, d, *J* = 7.2 Hz, H-5), 1.42 (9H, s, H-9), 2.23 (1H, dd, *J* = 16.5, 5.4 Hz, one of H-6), 2.50 (1H, dq, *J* = 17.9, 7.3 Hz, one of H-2), 2.59 (1H, dq, *J* = 17.9, 7.3 Hz, one of H-2), 2.69 (1H, dd, *J* = 16.5, 8.8 Hz, one of H-6), 2.88-3.04 (1H, m, H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8 (C-1), 16.9 (C-5), 28.2 (C-9), 34.4 (C-2), 38.6 (C-6), 42.0 (C-4), 80.7 (C-8), 171.7 (C-7), 213.7 (C-3) ppm. MS (ESI) *m*/*z*: 201 $[M + H]^+$. COSY and HSQC were used to aid in assignment.

Note: Enantiomers of **98** could not be successfully separated using GC.

1-Benzyloxy-2-methylpentan-3-one, 99



Compound **99** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.320 g, 2.5 mmol) and benzyloxymethyl chloride (0.42 mL, 3 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using

column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **99** as a colourless oil (0.242 g, 47% over two steps).

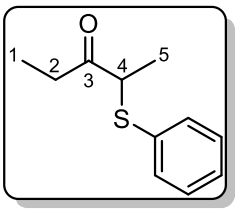
Spectroscopic characteristics were consistent with previously reported data.[15]

IR ν_{max} (NaCl): 1714 (C=O stretch), 1097 (C-O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (3H, t, *J* = 7.3 Hz, H-1), 1.07 (3H, d, *J* = 7.1 Hz, H-5), 2.51 (2H, q, *J* = 7.3 Hz, H-2), 2.82-2.95 (1H, m, H-4), 3.46 (1H, dd, *J* = 9.1, 5.5 Hz, one of H-6), 3.63 (1H, dd, *J* = 9.1, 7.8 Hz, one of H-6), 4.46, 4.50 (2H, ABq, J_{AB} = 12.1 Hz, H-7), 7.23-7.38 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.7 (C-1), 13.7 (C-5), 35.4 (C-2), 46.3 (C-4), 72.5 (C-6), 73.4 (C-7), 127.7 (3 × Ar-CH), 128.5 (2 × Ar-CH), 138.3 (Ar-C), 213.8 (C-3) ppm. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{18}O_2Na$ $[M + Na]^+$: 229.1199, found 229.1198.

GC analysis: t_R = 60.0 and 60.2 min (90 ºC hold 55 min, ramp 10 ºC/min to 140 ºC, hold for 5 min).

COSY and HSQC were used to aid in assignment.

2-(Phenylthiol)pentan-3-one, 100



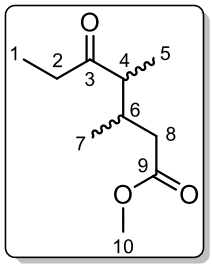
Compound **100** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.385 g, 3 mmol) and diphenyl disulfide (0.786 g, 3.6 mmol). Diphenyl disulfide was pre-dissolved in 1 mL of dry THF. The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (15:1, hexane:Et_2O) to give the title compound **100** as a colourless oil (0.154 g, 26% over two steps).

Spectroscopic characteristics were consistent with previously reported data.[16]

IR ν_{max} (NaCl): 1711 (C=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, t, *J* = 7.3 Hz, H-1), 1.41 (3H, d, *J* = 7.1 Hz, H-5), 2.55 (1H, dq, *J* = 17.7, 7.3 Hz, one of H-2), 2.73 (1H, dq, *J* = 17.7, 7.3 Hz, one of H-2), 3.78 (1H, q, *J* = 7.1 Hz, H-4), 7.22-7.41 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 8.3 (C-1), 16.4 (C-5), 32.5 (C-2), 51.4 (C-4), 128.1 (Ar-CH), 129.2 (2 × Ar-CH), 132.9 (2 × Ar-CH), 133.0 (Ar-C), 208.5 (C-3) ppm. MS (ESI) *m*/*z*: 193 $[M - H]^-$.

GC analysis: t_R = 10.0 and 10.6 min (120 ºC hold 20 min, ramp 10 ºC/min to 140 ºC, hold for 5 min).

Methyl 2,3-dimethyl-4-oxohexanoate, 102



Compound **102** was prepared according to the general procedure **3.3 Procedure B** using hydrazone **60** (0.128 g, 1 mmol) and methyl crotonate (0.13 mL, 1.2 mmol). **Alkylation temperature** was held at -78 ^{o}C over 18 h. The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (5:1, hexane:Et_2O) to give the title compound *syn*-**102** and *anti*-**102** as a colourless oil, isolated as a mixture of diastereomers (0.050 g, 27% over two steps, 70:30 *dr*). IR ν_{max} (NaCl): 1739 (C=O stretch), 1712 (C=O stretch) cm^{-1}.

***Syn* diastereomer**:

Spectroscopic characteristics were consistent with previously reported data.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88, 1.04 (2 × 3H, d, *J* = 7.0, 6.7 Hz, H-5 and H-7), 1.05 (3H, t, *J* = 7.2 Hz, H-1), 2.21 (1H, dd, *J* = 15.1, 7.8 Hz, one of H-8), 2.26-2.62 (5H, m, one of H-8, H-2, H-4 and H-6), 3.68 (3H, s, H-10) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.9 (C-1), 11.9, 16.0 (C-5 and C-7), 31.7 (C-10), 34.8 (C-2), 39.5 (C-8), 49.8 (C-6), 50.4 (C-4), 173.3 (C-9), 214.5 (C-3) ppm. MS (ESI) *m*/*z*: 186 $(M + H)^+$.

GC analysis: t_R = 22.5 and 23.0 min (80 ^{o}C hold 30 min, ramp 10 ^{o}C/min to 140 ^{o}C, hold for 5 min).

***Anti* diastereomer**:

Spectroscopic characteristics were consistent with previously reported data.[17]

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96, 1.04 (2 × 3H, d, *J* = 6.8, 7.0 Hz, H-5 and H-7), 1.05 (3H, t, *J* = 7.2 Hz, H-1), 2.10 (1H, dd, *J* = 14.4, 6.1 Hz, one of H-8), 2.26-2.62 (5H, m, one of H-8, H-2, H-4 and H-6), 3.67 (3H, s, H-10) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.8 (C-1), 13.1, 18.6 (C-5 and C-7), 32.3 (C-10), 35.3 (C-2), 37.7 (C-8), 50.6 (C-6), 51.7 (C-4), 173.4 (C-9), 214.6 (C-3) ppm. MS (ESI) *m*/*z*: 186 $(M + H)^+$.

GC analysis: t_R = 21.9 and 23.5 min (80 ^{o}C hold 30 min, ramp 10 ^{o}C/min to 140 ^{o}C, hold for 5 min).

3.4 Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using (+)-sparteine 37

Procedure C: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using LDA/(+)-sp 37

To a solution of dry diisopropylamine (1.2 equiv.) in anhydrous toluene (2 mL/mmol of hydrazone) in a nitrogen filled Schlenk tube was added *n*-BuLi (1.6 M, 1.1 equiv.) dropwise at 0 ^{o}C. The solution was allowed to stir for 20 min to generate a solution of LDA. The solution was cooled to -78 ^{o}C and distilled **hydrazone** (1.0 equiv.) was added slowly (neat), dropwise. The reaction mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -78 ^{o}C using an acetone/liq. nitrogen bath, **(+)-sp 37** (1.2 equiv.) was added dropwise and left to stir at room temperature for 1 h. The solution was cooled to -30 ^{o}C using a cryocooler, **electrophile** (1.2 equiv.) was added slowly (neat), dropwise at -30 ^{o}C and left to stir at this temperature over 18 h.

Work-up conditions as per 1 mmol of hydrazone

At -30 ^{o}C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.5 mL/mmol) and the mixture was allowed warm to room temperature. Et_2O (30 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification.

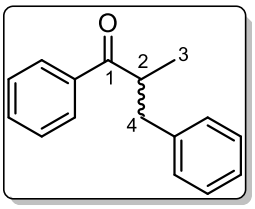
Procedure D: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using *s*-BuLi/(+)-sp 37

To a solution of **(+)-sp 37** (1.2 equiv.) in anhydrous toluene (2 mL/mmol of hydrazone) in a nitrogen filled Schlenk tube was added *s*-BuLi (1.4 M, 1.1 equiv.) dropwise at -78 ^{o}C. The solution was allowed to stir at -78 ^{o}C for 30 min. Distilled **hydrazone** (1.0 equiv.) was added slowly (neat), dropwise at -78 ^{o}C. The reaction mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -30 ^{o}C, **electrophile** (1.2 equiv.) was added slowly (neat), dropwise and left to stir at this temperature over 18 h.

Work-up conditions as per 1 mmol of hydrazone

At -30 ^{o}C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.5 mL/mmol) and the mixture was allowed warm to room temperature. Et_2O (30 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification.

2-Methyl-1, 3-diphenyl-propan-1-one, 67

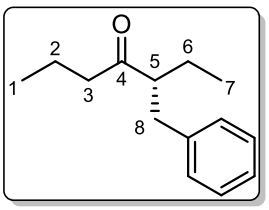


Compound **67** was prepared according to the general procedure **3.4 Procedure C** using hydrazone **70** (0.176 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (50:1 to 20:1, hexane:Et_2O) to give the title compound **67** as a pale yellow oil (0.048 g, 21% over two steps, 0% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **67** and previously reported data.[8]

Enantioselectivity was determined by GC analysis: t_R = 67.2 and 67.7 min (110 ^oC hold 45 min, ramp 2 ^oC/min to 140 ^oC, hold for 10 min).

(*R*)-3-Benzylheptan-4-one, (*R*)-69

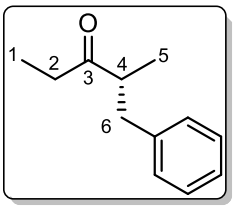


Compound **(*R*)-69** was prepared according to the general procedure **3.4 Procedure C** using hydrazone **71** (0.156 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (50:1, hexane:Et_2O) to give the title compound **(*R*)-69** as a colourless oil (0.035 g, 17% over two steps, 55% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **69** and previously reported data.[10]

$[\alpha]_D^{19}$ - 8.7 (c 1.0, $CHCl_3$) (lit.[10] $[\alpha]_D^{19}$ - 51.9 (c 1.01, $CHCl_3$) for 84% *ee*, *R*-enantiomer). Enantioselectivity was determined by GC analysis: t_R = 33.9 (*R*-enantiomer) and 34.1 min (*S* -enantiomer) (85 ^oC hold 20 min, ramp 2.5 ^oC/min to 140 ^oC, hold for 5 min).

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



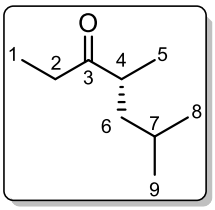
Compound **(*R*)-62** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **60** (0.192 g, 1.5 mmol) and benzyl bromide (0.21 mL, 1.8 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **(*R*)-62** as a pale yellow oil (0.050 g, 19% over two steps, 46% *ee*).

Spectroscopic characteristics were consistent with previously reported data.[18]

$[\alpha]_D^{20}$ - 40.4 (c 0.5, $CHCl_3$) (lit.[18] $[\alpha]_D^{20}$ - 65.1 (c 3.86, $CHCl_3$) for 93% *ee*, *R*-enantiomer).

IR ν_{max} (NaCl): 1713 (C=O) 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* = 6.9 Hz, H-5), 2.25 (1H, dq, *J* = 17.8, 7.3 Hz, one of H-2), 2.43 (1H, dq, *J* = 17.8, 7.3 Hz, one of H-2), 2.56 (1H, dd, *J* = 13.2, 7.2 Hz, one of H-6), 2.77-2.91 (1H, m, H-4), 2.97 (1H, dd, *J* = 13.2, 7.3 Hz, one of H-6), 7.09-7.33 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.7 (C-1), 16.7 (C-5), 35.3 (C-2), 39.4 (C-6), 48.0 (C-4), 126.3 (Ar-CH), 128.5 (2 × Ar-CH), 129.1 (2 × Ar-CH), 140.0 (Ar-C), 214.9 (C-3) ppm. MS (ESI) *m*/*z*: 177 $(M + H)^+$. Enantioselectivity was determined by GC analysis: t_R = 4.2 (*R*-enantiomer) and 4.4 min (*S*-enantiomer) (120 °C hold min, ramp 10 °C/min to 140 °C, hold for 5 min).

(*R*)-4,6-Dimethylheptan-3-one, (*R*)-77



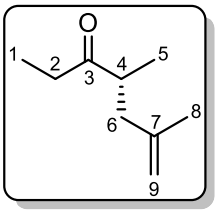
Compound **(*R*)-77** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **60** (0.192 g, 1.5 mmol) and 1-iodo-2-methyl propane (0.21 mL, 1.8 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10 :1, hexane:Et_2O) to give the title compound **(*R*)-77** as a pale yellow oil (0.039 g, 18% over two steps, 20% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **77**.

$[\alpha]_D^{25}$ - 211.7 (c 0.25, $CHCl_3$).

Enantioselectivity was determined by GC analysis: t_R = 2.9 (*R*-enantiomer) and 3.1 min (*S*-enantiomer) (80 °C hold 10 min, ramp 10 °C/min to 140 °C, hold for 5 min).

(*R*)-4,6-Dimethylhept-6-en-3-one, (*R*)-79



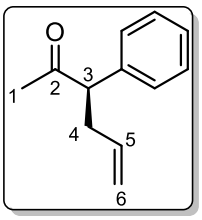
Compound **(*R*)-79** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **60** (0.192 g, 1.5 mmol) and 3-bromo-2-methylprop-1-ene (0.18 mL, 1.8 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (10:1, hexane:Et_2O) to give the title compound **(*R*)-79** as a pale yellow oil (0.041 g, 20% over two steps, 39% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **79**.

$[\alpha]_D^{25}$ - 28.9 (c 0.25, $CHCl_3$).

Enantioselectivity was determined by GC analysis: t_R = 4.2 (*R*-enantiomer) and 4.5 min (*S*-enantiomer) (75 °C hold 11 min, ramp 10 °C/min to 140 °C, hold for 5 min).

(*R*)-3-Phenylhex-5-en-2-one, (*R*)-80



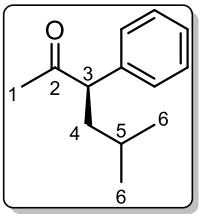
Compound **(*R*)-80** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **72** (0.176 g, 1 mmol) and allyl bromide (0.10 mL, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **(*R*)-80** as a yellow oil (0.033 g, 19% over two steps, 22% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **80** and previously reported data.[12]

$[\alpha]_D^{25}$ - 23.8 (c 0.25, $CHCl_3$).

Enantioselectivity was determined by GC analysis: t_R = 9.0 (*R*-enantiomer) and 9.4 min (*S*-enantiomer) (100 ºC hold 11 min, ramp 10 ºC/min to 140 ºC, hold for 5 min).

(*R*)-5-Methyl-3-phenyl-2-hexanone, (*R*)-81



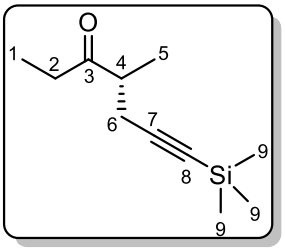
Compound **(*R*)-81** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **72** (0.176 g, 1 mmol) and 1-iodo-2-methyl propane (0.14 mL, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **(*R*)-81** as a pale yellow oil (0.078 g, 41% over two steps, 10% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **81** and previously reported data.[13]

$[\alpha]_D^{25}$ - 31.6 (c 0.25, $CHCl_3$).

Enantioselectivity was determined by GC analysis: t_R = 19.1 (*R*-enantiomer) and 19.8 min (*S*-enantiomer) (90 ºC hold 22 min, ramp 10 ºC/min to 140 ºC, hold for 5 min).

(*R*)-4-Methyl-7-(trimethylsilyl)hept-6-yn-3-one, (*R*)-97



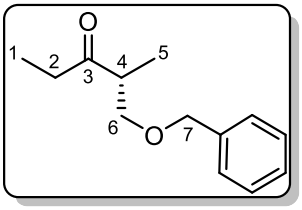
Compound **(*R*)-97** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **60** (0.128 g, 1 mmol) and 3-bromo-1-(trimethylsilyl)-1-propyne (0.20 ml, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **(*R*)-97** as a pale yellow oil (0.072 g, 37% over two steps, 19% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **97**.

$[\alpha]_D^{25}$ - 7.3 (c 1.0, $CHCl_3$).

Enantioselectivity was determined by GC analysis: t_R = 7.0 (*R*-enantiomer) and 7.3 min (*S*-enantiomer) (90 ^oC hold 10 min, ramp 10 ^oC/min to 140 ^oC, hold for 5 min).

(*R*)-1-Benzyloxy-2-methylpentan-3-one, (*R*)-99



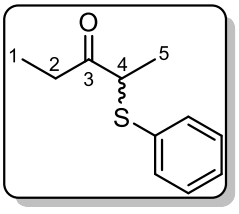
Compound **(*R*)-99** was prepared according to the general procedure **3.4 Procedure C** using hydrazone **60** (0.128 g, 1 mmol) and benzyloxymethyl chloride (0.17 ml, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (20:1, hexane:Et_2O) to give the title compound **(*R*)-99** as a colourless oil (0.072 g, 35% over two steps, 34% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **99** and previously reported data.[15]

$[\alpha]_D^{20}$ - 33.9 (c 1.0, $CHCl_3$) (lit.[18] $[\alpha]_D^{20}$ - 65.1 (c 3.86, $CHCl_3$) for 93% *ee*, *R*-enantiomer).

Enantioselectivity was determined by GC analysis: t_R = 60.0 (*R*-enantiomer) and 60.1 min (*S*-enantiomer) (90 ^oC hold 55 min, ramp 10 ^oC/min to 140 ^oC, hold for 5 min).

2-(Phenylthiol)pentan-3-one, 100

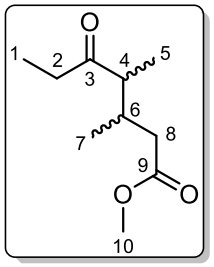


Compound **100** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **60** (0.192 g, 1.5 mmol) and diphenyl disulfide (0.393 g, 1.8 mmol). Diphenyl disulfide was pre-dissolved in 1 mL of dry toluene. The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (15:1, hexane:Et_2O) to give the title compound **100** as a colourless oil (0.113 g, 39% over two steps).

Spectroscopic characteristics were consistent with that reported for racemic **100** and previously reported data.[16]

Enantioselectivity was determined by GC analysis: t_R = 10.0 and 10.5 min (120 °C hold 20 min, ramp 10 °C/min to 140 °C, hold for 5 min).

Methyl 2,3-dimethyl-4-oxohexanoate, 102



Compound **102** was prepared according to the general procedure **3.4 Procedure D** using hydrazone **60** (0.064 g, 0.5 mmol) and methyl crotonate (0.06 mL, 0.6 mmol). **Alkylation temperature** was held at -78 °C over 18 h. The crude α-alkylated hydrazone was hydrolysed using **Method A** and purified using column chromatography on silica gel (5:1, hexane:Et_2O) to give the title compound as a colourless oil, isolated as a mixture of diastereomers (0.015 g, 16% over two steps, 70:30 *dr*, *syn* 15% *ee*, *anti* 33% *ee*).

Spectroscopic characteristics were consistent with that reported for racemic **102** and previously reported data.[17]

***Syn* diastereomer**: Enantioselectivity was determined by GC analysis: t_R = 22.5 (major enantiomer) and 23.0 min (minor enantiomer) (80 °C hold 30 min, ramp 10 °C/min to 140 °C, hold for 5 min).

***Anti* diastereomer**: Enantioselectivity was determined by GC analysis: t_R = 21.9 (major enantiomer) and 23.5 min (minor enantiomer) (80 °C hold 30 min, ramp 10 °C/min to 140 °C, hold for 5 min).

3.5 Investigation of *n*-hexyl lithium as base

Procedure E: Addition of (+)-sp 37 post deprotonation

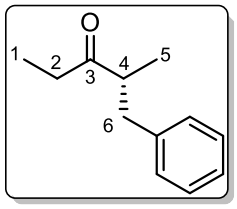
To a stirred solution of *n*-hexyl lithium (1.1 mmol) in anhydrous toluene (2 mL/mmol of hydrazone) in a N_2 filled Schlenk tube was added distilled **hydrazone** (1 mmol) slowly (neat), dropwise at -78 °C. The reaction mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -78 °C using an acetone/liq. nitrogen bath, **(+)-sp 37** (1.2 mmol) was added dropwise and left to stir at room temperature for 1 h. The solution was cooled to -30 °C using a cryocooler, **electrophile** (1.2 mmol) was added slowly (neat), dropwise and left to stir at this temperature over 18 h. At -30 °C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.5 mL) and the mixture was allowed warm to room temperature. Et_2O (30 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under

reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification.

Procedure F: *n*-hexyl lithium/(+)-sp 37 deprotonation

To a stirred solution of **(+)-sp 37** (1.2 mmol) in anhydrous toluene (2 mL/mmol of hydrazone) in a N_2 filled Schlenk tube was added *n*-hexyl lithium (1.1 mmol) at -78 ^oC. Distilled **hydrazone** (1 mmol) was added slowly (neat), dropwise at -78 ^oC. The reaction mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -30 ^oC, **electrophile** (1.2 mmol) was added slowly (neat), dropwise and left to stir at this temperature over 18 h. At -30 ^oC, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.5 mL) and the mixture was allowed warm to room temperature. Et_2O (30 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification.

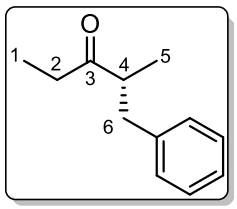
(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



Compound **(*R*)-62** was prepared according to the general procedure **3.5 Procedure E** using hydrazone **60** (0.128 g, 1 mmol) and benzyl bromide (0.14 mL, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A**. Yield was determined *via* ^1H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard (23% over two steps, 28% *ee*).

Enantioselectivity was determined by GC analysis: t_R = 33.2 (*R*-enantiomer) and 33.7 min (*S*-enantiomer) (75 ^oC hold min, ramp 10 ^oC/min to 140 ^oC, hold for 5 min).

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



Compound **(*R*)-62** was prepared according to the general procedure **3.5 Procedure F** using hydrazone **60** (0.128 g, 1 mmol) and benzyl bromide (0.14 ml, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A**. Yield was determined *via* ^1H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard (42% over two steps, 10% *ee*).

Enantioselectivity was determined by GC analysis: t_r = 33.3 (*R*-enantiomer) and 33.7 min (*S*-enantiomer) (75 ^oC hold min, ramp 10 ^oC/min to 140 ^oC, hold for 5 min).

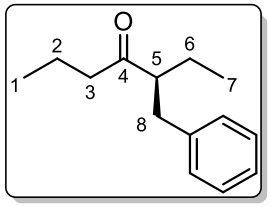
Note: Difference in GC retention times and conditions due to use of older column for product **(*R*)-62**.

3.6 Chiral ligand screen for the asymmetric α-alkylation of *N*,*N*-dimethylhydrazones

Procedure G: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using chiral tetramine 116

To a stirred solution of *s*-BuLi (1.4 M, 3.3 equiv.) in anhydrous **THF** (5 mL) in a nitrogen filled Schlenk tube was added **chiral amine 116** (1.03 equiv.) at 0 °C. The reaction mixture was allowed to stir at this temperature for 30 min and then cooled to -78 °C. Distilled **hydrazone** (1.0 equiv.) was added slowly (neat), dropwise. The solution was warmed to room temperature and allowed to stir at this temperature over 6 h. The reaction mixture was cooled to -78 °C, **electrophile** (4 equiv.) was added slowly (neat), dropwise and left to gradually warm to -30 °C over 18 h. At -30 °C, the reaction mixture was quenched with THF (0.49 mL):MeOH (0.16 mL). After 4 min, H_2O was added (5 mL) followed by Et_2O (30 mL). The organic layers were subsequently washed with H_2O (3 × 20 mL) and brine (10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification.

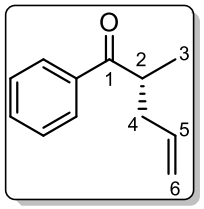
(*S*)-3-Benzylheptan-4-one, (*S*)-69



Compound **(*S*)-69** was prepared according to the general procedure **3.6 Procedure G** using hydrazone **71** (0.078 g, 0.50 mmol) and benzyl bromide (0.24 ml, 2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** (Trace amount of product detected by GC and MS analysis, 11% *ee*).

Enantioselectivity was determined by GC analysis: t_R = 33.3 (*R*-enantiomer) and 33.5 min (*S*-enantiomer) (85 °C hold 20 min, ramp 2.5 °C/min to 140 °C, hold for 5 min).

(*R*)-2-Methyl-1-phenylpent-4-en-1-one, (*R*)-68

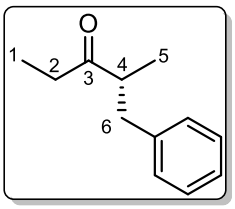


Compound **(*R*)-68** was prepared according to the general procedure **3.6 Procedure G** using hydrazone **70** (0.088 g, 0.50 mmol) and allyl bromide (0.17 ml, 2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A** (Trace amount of product detected by GC and MS analysis, 3% *ee*).

Enantioselectivity was determined by GC analysis: t_R = 12.95 (*R*-enantiomer) and 13.3 min (*S*-enantiomer) (100 °C hold 17 min, ramp 5 °C/min to 140 °C, hold for 7 min).

Procedure H: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using BOX ligands

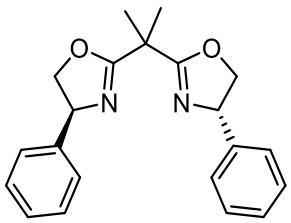
(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



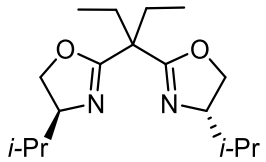
To a solution of **ligand** (1.0-1.2 equiv.) in anhydrous **solvent** (1 mL/0.5 mmol of hydrazone) in a nitrogen filled Schlenk tube was added **base** (1.1-2 equiv.) dropwise at -78 °C. The solution was allowed to stir at -78 °C for 30 min. Distilled **hydrazone** (1.0 equiv.) was added slowly (neat), dropwise at -78 °C, the mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -30 °C, **electrophile** (1.2 equiv.) was added slowly (neat), dropwise and left to stir over 18 h.

Work-up conditions as per 0.5 mmol of hydrazone

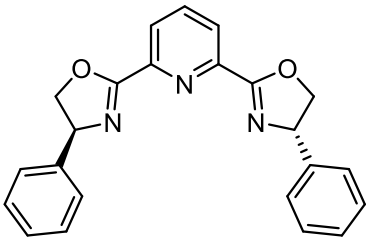
At -30 °C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.25 mL/0.5 mmol) and warmed to room temperature. Et_2O (15 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification. The crude α-alkylated hydrazone was hydrolysed using **Method A**.



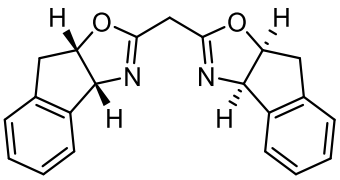
(*S*,*S*)-123



(*S*,*S*)-124



(*S*,*S*)-125



(*S*,*R*,*S*,*R*)-126

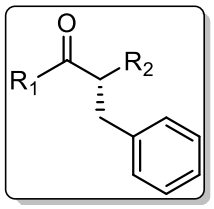
Table 9. BOX ligand screen

Entry	Ligand	Base	Solvent	Equivalents (Base:Ligand)	Ketone	Result[a]	*ee* (%)
1	**(*S*,*S*)-123**	*n*-BuLi	Toluene	1.1:1.2	**62**	Trace	2
2	**(*S*,*S*)-124**	*s*-BuLi	Et_2O	1.1:1.2	**62**	No trace	-
3	**(*S*,*S*)-124**	*n*-BuLi	Et_2O	1.1:1.2	**62**	No trace	-
4	**(*S*,*S*)-125**	*s*-BuLi	Et_2O	1.1:1.2	**62**	No trace	-
5	**(*S*,*S*)-125**	*s*-BuLi	Et_2O	2:1	**(*S*)-62**	20%[a]	12
6	**(*S*,*S*)-125**	*n*-BuLi	Et_2O	2:1	**(*S*)-62**	22%[a]	6
7	**(*S*,*R*,*S*,*R*)-126**	*n*-BuLi	Toluene	2:1	**(*S*)-62**	17%[a]	12

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

3.7 Base and solvent variations using (+)-sparteine 37 and (+)-sparteine surrogate 38

Procedure I: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using *s*-BuLi/(+)-sp surrogate 38 in THF



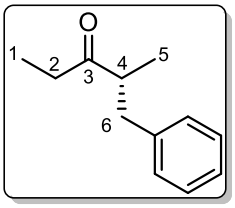
To a solution of **(+)-sp surrogate 38** (0.26 mmol) in anhydrous **THF** (1 mL) in a nitrogen filled Schlenk tube was added *s*-BuLi (1.09 M, 0.24 mmol) dropwise at -78 °C. The solution was allowed to stir at -78 °C for 30 min. Distilled **hydrazone** (0.21 mmol) was added slowly (neat), dropwise at -78 °C, the mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -78 °C, **electrophile** (0.26 mmol) was added slowly (neat), dropwise and left to stir at -78 °C over 18 h. At -78 °C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.25 mL) and warmed to room temperature. Et_2O (10 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification. The crude α-alkylated hydrazone was hydrolysed using **Method A**.

Table 10. *s*-BuLi/(+)-sp surrogate **38** in THF experiment

Entry	DMH	R_1	R_2	Ligand	Solvent	Ketone	E^+ (°C)	*ee* (%)	Result
1	**60**	CH_2CH_3	CH_3	(+)-sp surrogate **38**	THF	**(*R*)-62**	-78	-	No trace
2	**70**	Ph	CH_3	(+)-sp surrogate **38**	THF	**(*R*)-67**	-78	-	No trace

Procedure J: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using *i*-PrLi/(+)-sp surrogate 38

(*R*)-2-methyl-1-phenylpentan-3-one, (*R*)-62



To a solution of **(+)-sp surrogate 38** (0.46 mmol) in anhydrous **solvent** (1 mL) in a nitrogen filled Schlenk tube was added *i*-PrLi (0.62 M, 0.42 mmol) dropwise at -78 °C. The solution was allowed to stir at -78 °C for 30 min. Distilled **hydrazone** (0.38 mmol) was added slowly (neat), dropwise at -78 °C, the mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -78 °C, **electrophile** (0.46 mmol) was added slowly (neat), dropwise and left to stir at -78 °C over 18 h. At -78 °C, the reaction mixture was quenched with sat. NH_4Cl solution (0.25 mL) and warmed to room temperature. Et_2O (15 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification. The crude α-alkylated hydrazone was hydrolysed using **Method A**.

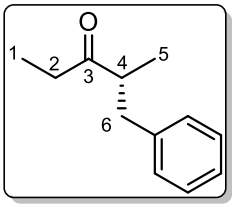
Table 11. *i*-PrLi/(+)-sp surrogate **38** experiments

Entry	DMH	Base	Ligand	Solvent	Ketone	*ee* (%)	Yield[a] (%)
1	**60**	*i*-PrLi	(+)-sp surrogate **38**	Et_2O	**(*R*)-62**	48	13
2	**60**	*i*-PrLi	(+)-sp surrogate **38**	Toluene	**(*R*)-62**	35	34

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

Procedure K: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using *i*-PrLi/(+)-sp 37

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



To a solution of **(+)-sp 37** (0.6 mmol) in anhydrous **solvent** (1 mL) in a nitrogen filled Schlenk tube was added *i*-PrLi (0.62 M, 0.55 mmol) dropwise at -78 °C. The solution was allowed to stir at -78 °C for 30 min. Distilled **hydrazone** (0.5 mmol) was added slowly (neat), dropwise at -78 °C, the mixture was warmed to room temperature and left to stir over 6 h. The solution was cooled to -30 °C, **electrophile** (0.6 mmol) was added slowly (neat), dropwise and left to stir at -30 °C for 18 h. At -30 °C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.25 mL) and warmed to room temperature. Et_2O (15 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification. The crude α-alkylated hydrazone was hydrolysed using **Method A**.

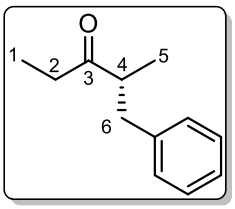
Table 12. *i*-PrLi/(+)-sp **37** experiments

Entry	DMH	Base	Ligand	Solvent	Ketone	*ee* (%)	Yield[a] (%)
1	**60**	*i*-PrLi	(+)-sp **37**	Et_2O	**(*R*)-62**	36	47
2	**60**	*i*-PrLi	(+)-sp **37**	Toluene	**(*R*)-62**	32	68

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

Procedure L: Solvent combination investigation using *s*-BuLi/(+)-sp 37

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



To a solution of **(+)-sp 37** (0.60 mmol) in anhydrous **solvent** (1 mL) in a nitrogen filled Schlenk tube was added *s*-BuLi (1.09 M, 0.55 mmol) dropwise at -78 ^{o}C. The solution was allowed to stir at -78 ^{o}C for 30 min. Distilled **hydrazone** (0.50 mmol) was added slowly (neat), dropwise at -78 ^{o}C, allowed warm to room temperature and left to stir over 6 h. The solution was cooled to -30 ^{o}C, **electrophile** (0.60 mmol) was added slowly (neat), dropwise and left to stir at -30 ^{o}C over 18 h. At -30 ^{o}C, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.25 mL) and warmed to room temperature. Et_2O (15 mL) was added and the reaction mixture was washed with sat. aq. NH_4Cl (3 × 5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification. The crude α-alkylated hydrazone was hydrolysed using **Method A**.

Table 13. Solvent combination experiments

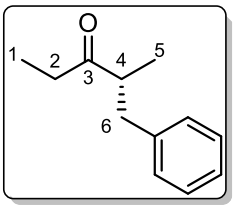
Entry	DMH	Base	Ligand	Solvent	Ketone	*ee* (%)	Yield[a] (%)
1	**60**	*s*-BuLi	(+)-sp **37**	Toluene, 1.0 equiv. THF	**(*R*)-62**	Racemic	31
2	**60**	*s*-BuLi	(+)-sp **37**	4:1, Toluene:Et_2O	**(*R*)-62**	37	44
3	**60**	*s*-BuLi	(+)-sp **37**	2:1, Toluene:Et_2O	**(*R*)-62**	25	58
4	**60**	*s*-BuLi	(+)-sp **37**	1:1, Toluene:Et_2O	**(*R*)-62**	38	38

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

3.8 Catalytic use of chiral ligand

Procedure M: Asymmetric α-alkylation of *N*,*N*-dimethylhydrazones using catalytic amounts of (+)-sp 37 and (+)-sp surrogate 38

(*R*)-2-Methyl-1-phenylpentan-3-one, (*R*)-62



To a stirred solution of **ligand** (0.20 mmol) in anhydrous **toluene** (2 mL) in a N_2 filled Schlenk tube was added *s*-BuLi (1.4 M, 1.1 mmol) at -78 ^oC. Distilled **hydrazone** (1 mmol) was added slowly (neat), dropwise, the solution was warmed to room temperature and left to stir over 6 h. The reaction mixture was cooled to -78 ^oC, **electrophile** (0.25 mmol) was added slowly (neat), dropwise. The solution was warmed to 0 ^oC and stirred for 20 mins. The solution was then cooled to -78 ^oC and **electrophile** (0.25 mmol) was added slowly (neat), dropwise. The solution was warmed to 0 ^oC and stirred for 20 mins. The cool/warm cycle was repeated an additional three more times until 1.25 equiv. of electrophile was added. At 0 ^oC, the reaction mixture was quenched with sat. aq. NH_4Cl solution (0.5 mL) and the mixture was allowed warm to room temperature. Et_2O (30 mL) was added and the mixture was washed with sat. aq. NH_4Cl (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification. The crude α-alkylated hydrazone was hydrolysed using **Method A**.

Table 14. Catalytic use of chiral ligand

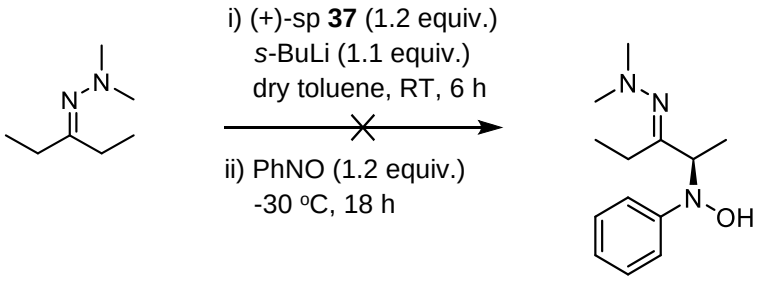
Entry	DMH	Base	Ligand	Ketone	*ee* (%)	Yield [a] (%)
1	**60**	*s*-BuLi	(+)-sp **37** 0.20 equiv.	**(*R*)-62**	46	5
2	**60**	*s*-BuLi	(+)-sp surrogate **38** 0.20 equiv.	**(*R*)-62**	28	9

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

3.9 Additional work

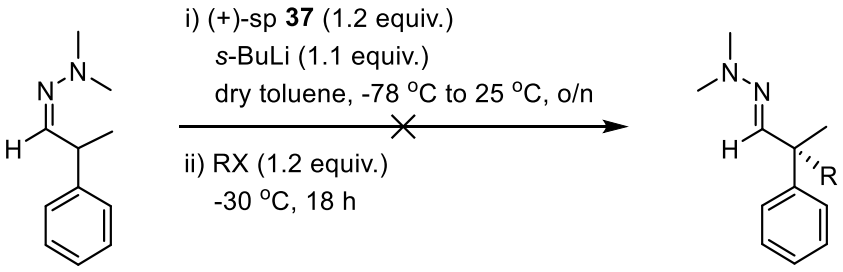
A number of other transformations were also attempted using our chiral ligand methodology including the use of alternative metal azaenolates. The results of these reactions are summarized below. Unfortunately, no encouraging results were obtained.

Asymmetric α-alkylation reactions



60 **131**

Scheme 53. Asymmetric nitroso aldol reaction



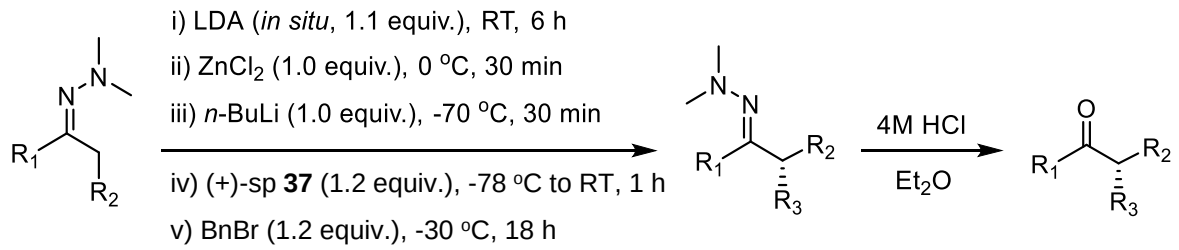
73

132a, R = Allyl, complex mixture
132b, R = D, complex mixture

Scheme 54. Asymmetric α-alkylation of an aldehyde DMH

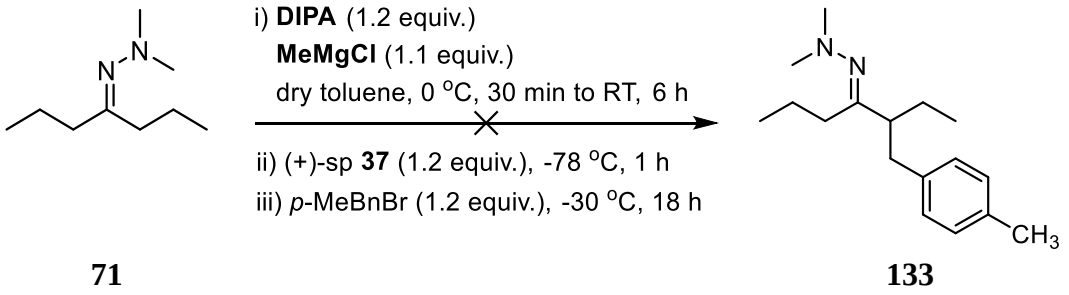
Investigation of alternative metal azaenolates

Table 15. Investigation of zinc azaenolates



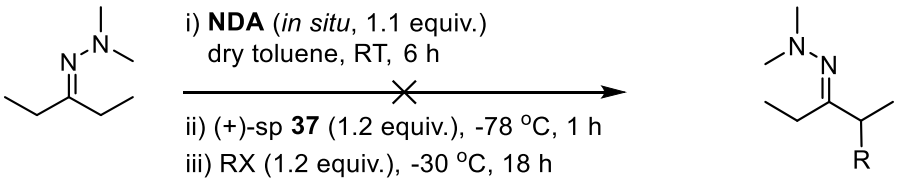
Entry	DMH	R_3X	Ketone	*ee* (%)	Yield[a] (%)
1	**71**	BnBr	**(*R*)-69**	18	25
2	**70**	BnBr	**67**	Racemic	24

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



71 **133**

Scheme 55. Investigation of magnesium azaenolates



60

134a, R = Allyl, no reaction
134b, R = Pentyl, no reaction

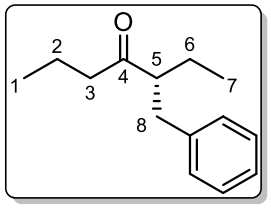
Scheme 56. Investigation of sodium azaenolates

3.10 Alternative azaenolates

Procedure N: Preparation and alkylation of zinc azaenolates

To a stirred solution of dry diisopropylamine (1.2 equiv.) in anhydrous toluene (2 mL/mmol of hydrazone) in a nitrogen filled Schlenk tube was added *n*-BuLi (1.1 equiv.) at 0 °C. The solution was left to stir for 20 min to generate a solution of LDA. The solution was cooled to -78 °C, distilled **hydrazone** (1.0 equiv.) was added slowly (neat), dropwise. The reaction mixture was allowed warm to room temperature and left to stir over 6 h. The solution was cooled to 0 °C and **zinc chloride** (1.0 equiv.) was added and left to stir for 30 min. The reaction was cooled to -70 °C, ***n*-BuLi** (1.0 equiv.) was then added slowly, dropwise. After 30 min, **(+)-sp 37** (1.2 equiv.) was added dropwise at -78 °C and left to stir at room temperature for 1 h. The solution was cooled to -30 °C, **electrophile** (1.2 equiv.) was added slowly (neat), dropwise and left to stir at this temperature over 18 h. At -30 °C, sat. aq. NH_4Cl solution (0.5 mL) was added and the mixture was left warm to room temperature. Et_2O (30 mL) was added and the mixture was washed with sat. aq. NH_4Cl (3 × 20 mL) and 1/15 N phosphate buffer solution (3 × 10 mL). The combined organic layers were washed with sat. aq. sodium bicarbonate (10 mL) and sat. aq. sodium chloride (10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude α-alkylated hydrazone which was used in the next step without purification.

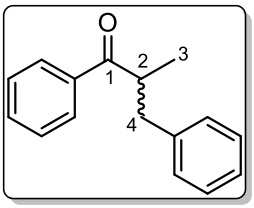
(*R*)-3-Benzylheptan-4-one, (*R*)-69



Compound **(*R*)-69** was prepared according to the general procedure **3.10 Procedure N** using hydrazone **71** (0.156 g, 1 mmol) and benzyl bromide (0.14 ml, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A**. Yield was determined *via* ^1H NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard (25% over two steps, 18% *ee*).

Enantioselectivity was determined by GC analysis: t_R = 33.8 (*R*-enantiomer) and 34.1 min (*S*-enantiomer) (85 °C hold 20 min, ramp 2.5 °C/min to 140 °C, hold for 5 min).

2-Methyl-1,3-diphenyl-propan-1-one, 67



Compound **67** was prepared according to the general procedure **3.10 Procedure N** using hydrazone **70** (0.176 g, 1 mmol) and benzyl bromide (0.14 ml, 1.2 mmol). The crude α-alkylated hydrazone was hydrolysed using **Method A**. Yield was determined *via* ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard (24% over two steps, 0% *ee*).

Enantioselectivity was determined by GC analysis: t_R = 65.2 and 65.7 min (110 ^{o}C hold 45 min, ramp 2 ^{o}C/min to 140 ^{o}C, hold for 10 min).

Procedure O: Preparation of sodium diisopropylamide

Prepared according to a literature procedure.[19] To a stirred solution of dry diisopropylamine (3.0 mmol) in anhydrous hexane (7 mL) in a nitrogen filled Schlenk tube was added *n*-BuLi (2.8 mmol) at 0 ^{o}C. The solution was left to stir for 20 min to generate a solution of LDA. *t*-BuONa (2.2 mmol) was added in one portion, the solution was warmed to room temperature and stirred for 3 h. After 3 h of stirring, the solid white precipitate was allowed to sit for 30 min and settle to the bottom of the flask. The hexanes (and soluble LDA and *t*-BuOLi) were then removed *via* syringe. Dry hexane (2 mL) was then added, the solution was stirred for 10 min and allowed to sit for 30 min and settle to the bottom of the flask. The washing process was repeated three times. The hexane was removed under vacuum and a solution of NDA was prepared following the addition of 1 mL of dry hexane.

3.11 References

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“The best view comes after the hardest climb, so give that climb all you’ve got and take in the view on the other side”

II

The Asymmetric Aldol-Tishchenko Reaction of (*S*)-*tert*-butanesulfinyl Imines for the Introduction of 2, 3, 4 and 5 New Chiral Centres in One Pot

Chapter 4

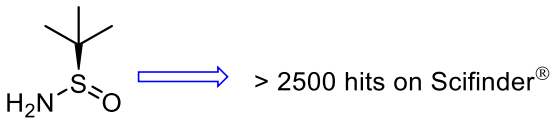
The Asymmetric Aldol-Tishchenko Reaction of (*S*)-*tert*-butanesulfinyl Imines for the Introduction of 2, 3, 4 and 5 New Chiral Centres in One Pot

Introduction

4. Introduction

4.1 *N-tert*-butanesulfinyl imines

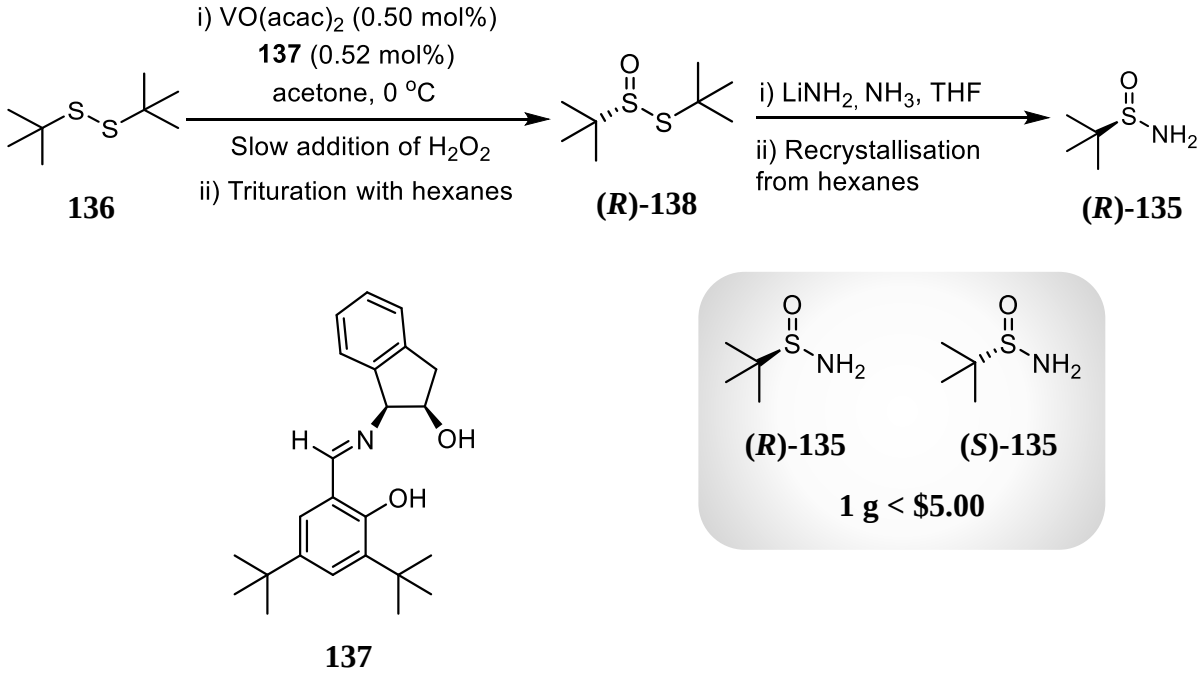
Chiral amines are key structural components of many bioactive molecules including pharmaceuticals and amino acids.[1] Currently, it is estimated that 40-45% of small molecule pharmaceuticals contain this important structural feature.[2] The *tert*-butanesulfinamide **135** first pioneered by the Ellman lab has proven to be an extremely valuable synthetic intermediate in the synthesis of a diverse range of enantioenriched amines **(Figure 21)**.[3]



135

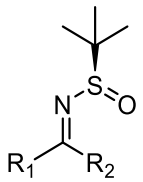
Figure 21. Ellman's *tert*-butanesulfinamide

Moreover, this chiral ammonia synthon is a stable, crystalline solid that can now be prepared on a kilogram scale in a practical two-step catalytic method as outlined in **Scheme 57**.[4] Oxidation of the very inexpensive oil waste product di-*tert*-butane disulfide **136** *via* the slow addition of H_2O_2 over 20 h at 0 ^oC in the presence of $VO(acac)_2$ and the chiral Schiff base **137** provides thiosulfinate **(*R*)-138**, which can be used in the next step without purification. Addition of $LiNH_2$ in liquid ammonia affords the optically pure *tert*-butanesulfinamide **(*R*)-135** in good overall yield (68%, >99% *ee*) following recrystallisation from hexanes. Furthermore, both enantiomers are also commercially available at a low cost which further highlights the synthetic practicality of this reagent **(Scheme 57)**.



Scheme 57. Ellman's synthesis of *tert*-butanesulfinamide and current commercial cost

In 1997, Ellman first introduced the enantiopure *tert*-butanesulfinamide **135** as a versatile chiral auxiliary for the asymmetric synthesis of *N*-*tert*-butanesulfinyl imines (*t*BS) **139 (Figure 22)**.[5] Since then, *N*-*tert*-butanesulfinyl imines **139** have now become one of the most extensively used compounds in asymmetric synthesis.[6]



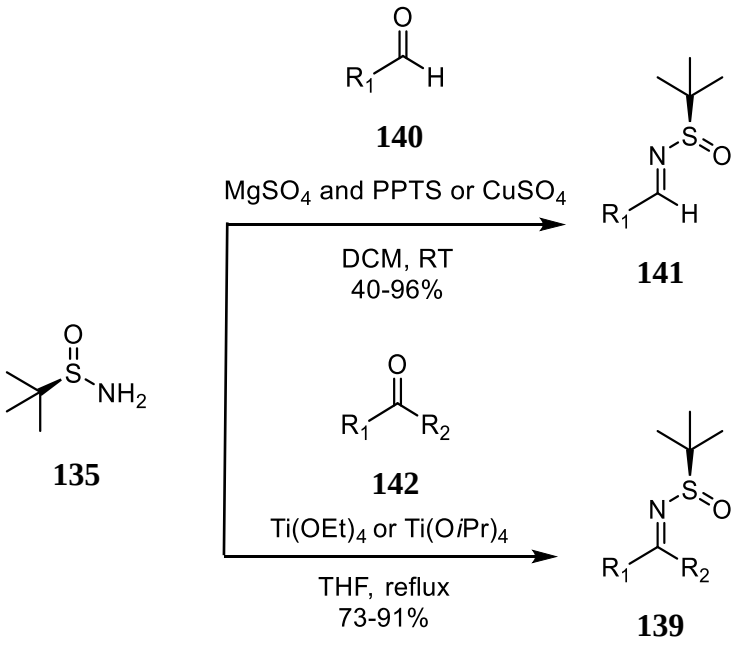
139

Figure 22. *N*-*tert*-butanesulfinyl imines

The *N*-*tert*-butanesulfinyl imines are a highly attractive class of imines: **i)** The bulky *tert*-butyl group acts as a powerful chiral directing group **ii)** The configurationally stable stereocentre and metal-coordinating ability of the sulfinyl group provides diastereofacial selectivity for nucleophilic addition **iii)** The steric bulk of the *tert*-butyl group prevents competitive nucleophilic attack at the sulfur atom **iv)** *N*-*tert*-butanesulfinyl imines are much more hydrolytically stable and less prone to tautomerization compared to *N*-alkyl, aryl, acyl, or carbamoyl imines **v)** The *N*-*tert*-butanesulfinyl group parallels the reactivity of the *tert*-

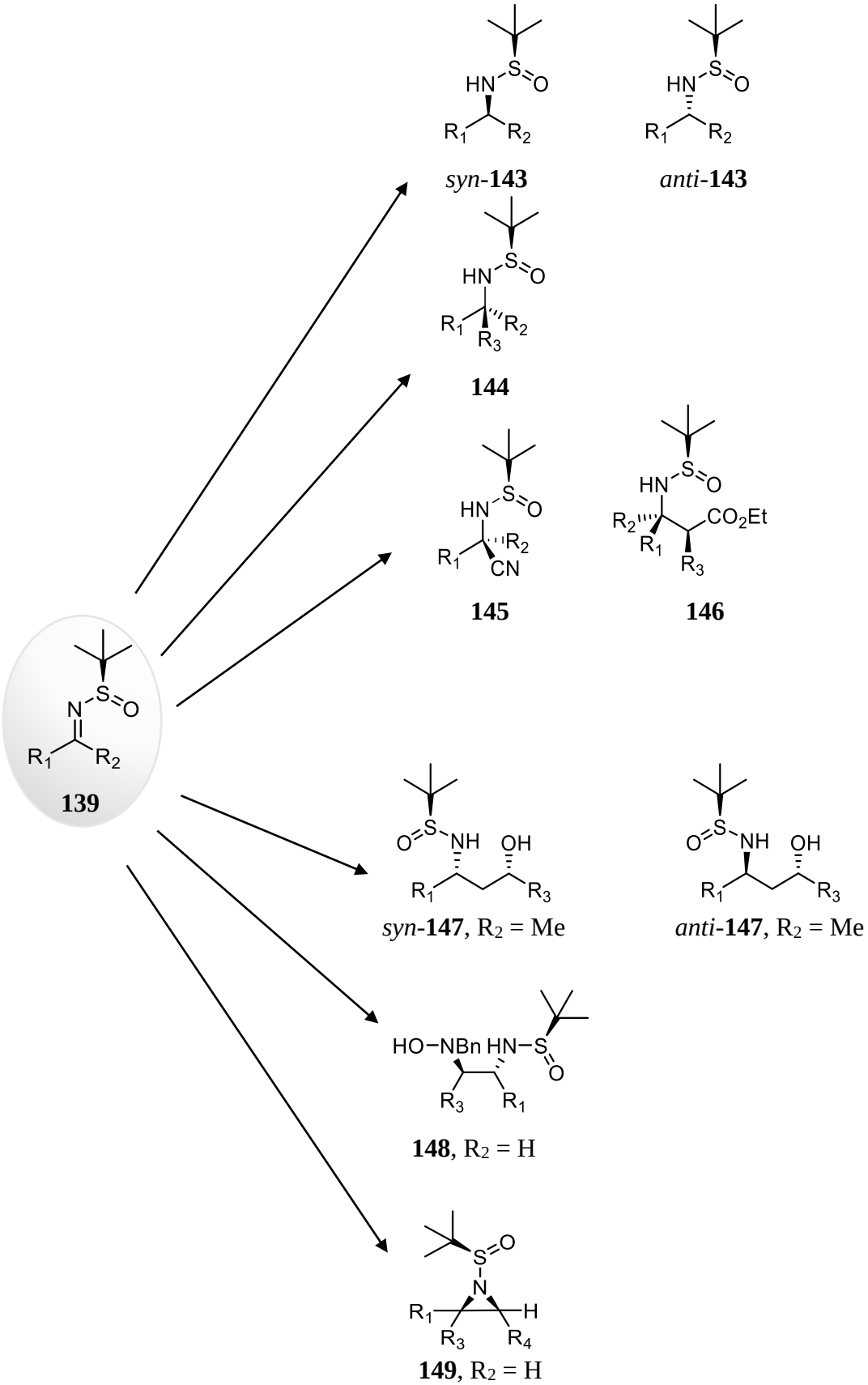
butyloxycarbonyl (Boc)- protecting group. Therefore, it is stable to strong bases, nucleophiles as well as many transition metal-catalysed processes.[7] However, it can be easily cleaved in the presence of conc. HCl in a protic solvent.

N-*tert*-butanesulfinyl imines **139** and **141** can be readily synthesised in one-step by direct condensation with carbonyl compounds **(Scheme 58)**.[8] The Lewis acidic dehydrating agents $MgSO_4$ and PPTS or $CuSO_4$ enable the one step preparation of *N*-*tert*-butanesulfinyl aldimines **141** in high yields (40-96%). In contrast, the condensation of the less electrophilic and more sterically demanding ketone substrates require the use of titanium alkoxides, $Ti(OEt)_4$ or $Ti(OiPr)_4$. Heating the resulting mixture generates *N*-*tert*-butanesulfinyl ketimines **139** in very good yields (73-91%). *N*-*tert*-butanesulfinyl imines **139** and **141** can be handled in air, purified *via* column chromatography and stored dry at -5 ^oC for extended periods of time.



Scheme 58. Synthesis of *N*-*tert*-butanesulfinyl imines

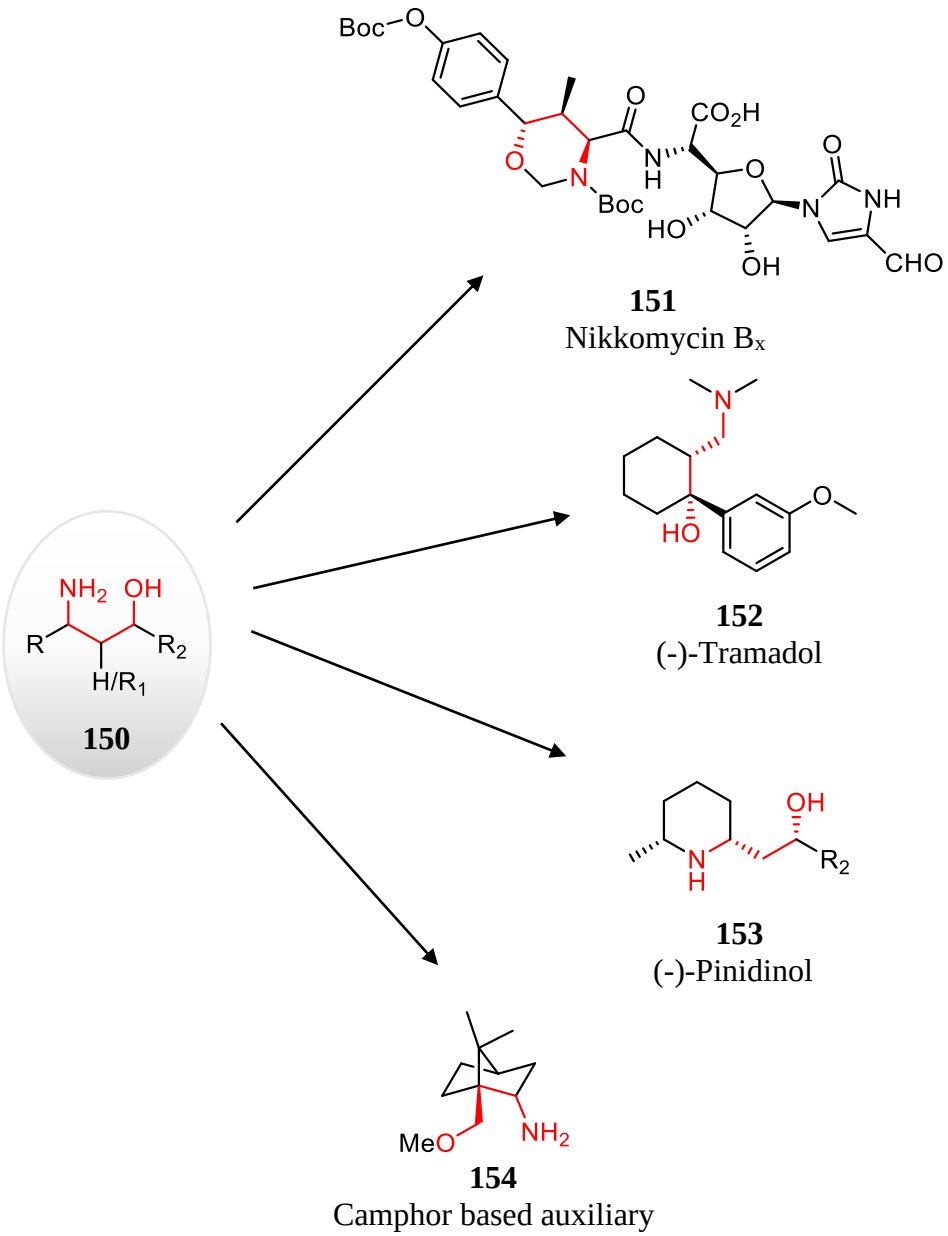
Since Ellman's seminal paper, a variety of enantioselective transformations have been achieved utilising *N*-*tert*-butanesulfinyl imines including the synthesis of α-branched amines *syn*-**143** and *anti*-**143**,[5] α,α-dibranched amines **144**,[8b] α- and β-amino acids **145**[9] and **146**,[10] γ -amino alcohols *syn*-**147** and *anti*-**147**,[11] vicinal diamines **148**[12] and aziridines **149**[13] **(Scheme 59)**.



Scheme 59. Summary of products derived from *N*-*tert*-butanesulfinyl imines

4.2 1,3-Amino alcohols

1,3-Amino alcohols **150** are key structural motifs found in many natural products and potent drugs,[14] including antibiotics such as nikkomycin B_x **151**,[15] the opioid pain reliever (-)-tramadol **152**[16] and the sedum alkaloid (-)-pinidinol **153**.[17] They have also been used extensively as chiral ligands in asymmetric catalysis and chiral auxiliaries in asymmetric synthesis, for example, **154 (Scheme 60)**.[18] Despite the prevalence of 1,3-amino alcohols, there exists few general methods for their stereoselective synthesis.[17] Thus, the desire to pursue new strategies to produce chiral 1,3-amino alcohols *via* operationally simple, economic and stereoselective methods remains a top priority for organic chemists.



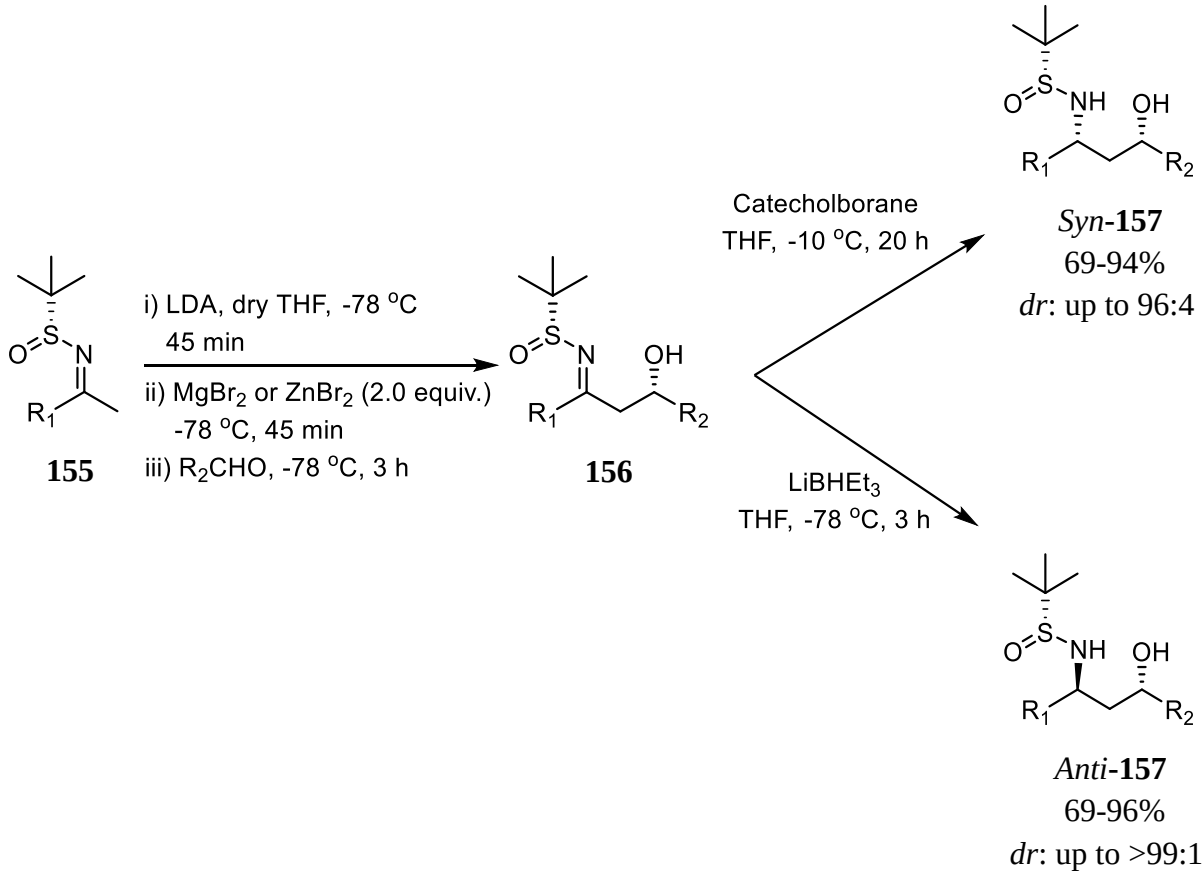
Scheme 60. Prevalence of the 1,3-amino alcohol structural motif

4.2.1 Modern methods for the stereoselective synthesis of 1,3-amino alcohols

4.2.1.1 Diastereoselective reduction

Currently, the stereoselective synthesis of 1,3-amino alcohols is tedious and in many cases step-intensive.[19] The most common methods involve the diastereoselective reduction of enantiomerically pure substrates derived from Mannich[17,20] and aldol reactions.[11] In 2002, Ellman and Kochi developed a general two step method for the asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols.[11a] This method involves the diastereoselective addition of metalloenamines derived from *N*-*tert*-butanesulfinyl imines **155** to a range of aromatic and aliphatic aldehydes in the presence of metal salts. External reduction of the *β*-hydroxy *N*-sulfinyl imines **156** with catecholborane and $LiBHEt_3$ provides the *syn*-**157** and *anti*-**157** 1,3-amino alcohols respectively with very high diastereomeric ratios (*dr*: up to >99:1) **(Scheme 61)**. The reaction proceeds efficiently with a variety of substrates incorporating both aromatic and aliphatic substituents.

Ellman's Methodology



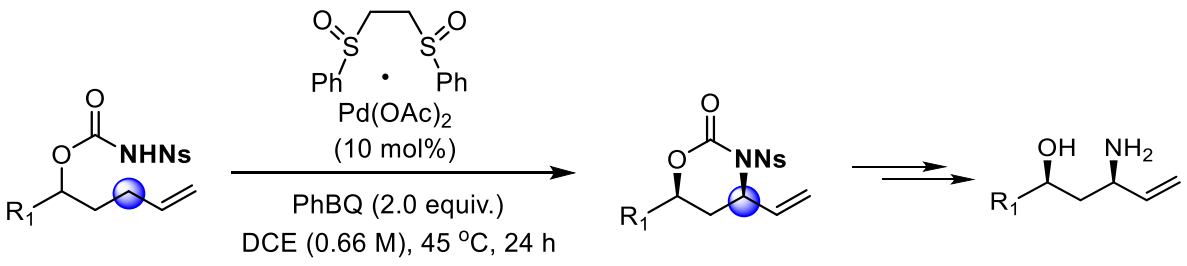
Scheme 61. Ellman's synthesis of *syn*- and *anti*-1,3-amino alcohols

While this methodology can furnish both *syn*- and *anti*-1,3-amino alcohols, there are limitations to Ellman's protocol. Firstly, the use of excess additives (2.0 equivalents) such as $MgBr_2$ and $ZnBr_2$ is necessary to achieve high levels of diastereoselectivity. The presence of the salt additive is presumed to lead to the formation of a tightly chelated aldol complex between the oxygen lone pair and the Lewis acid. Secondly, expensive superhydride reagents (catecholborane and lithium triethyl borohydride) are required for the diastereoselective reduction step. Finally, this method has so far only been applied to methyl ketones which limits its potential for the synthesis of 1,3-amino alcohols containing a maximum of two stereogenic centres.

4.2.1.2 Metal catalysed C-H amination

In recent years, transition metal catalysed aliphatic C-H amination with nitrenes[21] and allylic C-H amination reactions[22] have provided an atom-economical approach for the construction of 1,3-amino alcohols. In 2009, White's group reported a highly stereoselective method for the preparation of *syn*-1,3-amino alcohols.[22b] This strategy employs an electron deficient *N*-nosyl carbamate **158** as a nucleophile which enables a mild Pd(II)/sulfoxide-catalysed C-H allylic amination reaction to furnish *syn*-1,3-amino alcohols precursors **159** in good yields and diastereoselectivity **(Scheme 62)**. Subsequent cleavage of the *syn*-oxazinanones **159** provides the desired *syn*-1,3-amino alcohols **160**.

White's Methodology



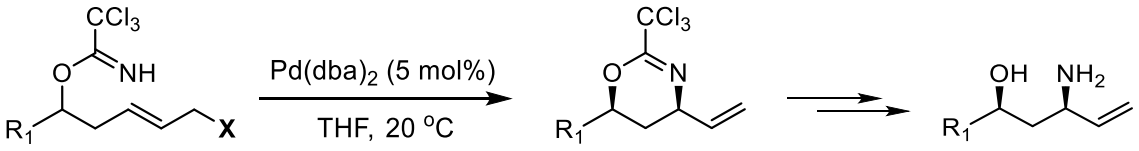
158 **159** 50-65% *dr*: up to 6.8:1 **160**

Scheme 62. White's synthesis of *syn*-1,3 amino alcohols

More recently, Gu and co-workers have demonstrated a palladium catalysed cyclisation of homoallyic trichloroacetimidates **161** to give *syn*-1,3-amino alcohols **160 (Scheme 63)**.[22d] This system involves cyclisation of trichloroacetimidates **161** in the presence of $Pd(dba)_2$ to furnish 5,6-dihydro-1,3-oxazines **162** which are suitable precursors to 1,3-amino alcohols. 2-

Substituted phenyl rings and 1-naphthalene derivatives afforded the desired products **162** in excellent yields and diastereoselectivity. The reaction also proved applicable when an aliphatic group was employed. The resulting 5,6-dihydro-1,3-oxazine **162** can be easily hydrolysed to the free 1,3-amino alcohol **160** with 1M HCl followed by treatment with a 1M aqueous solution of NaOH.

Gu's Methodology



161
X = OBoc

162
77-95%
dr: up to >20:1

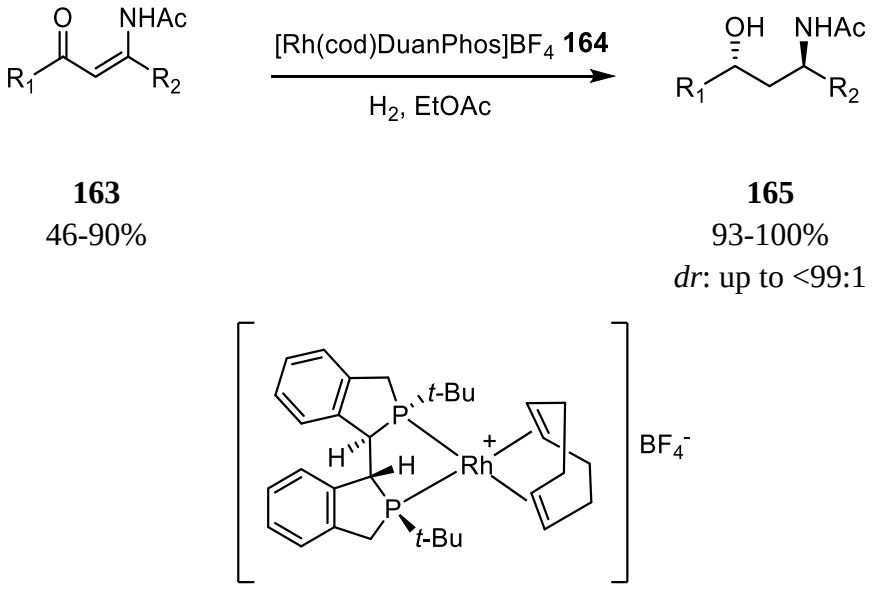
160

Scheme 63. Gu's synthesis of *syn*-1,3-amino alcohols

4.2.1.3 *Anti*-1,3-amino alcohols

To date, there exists very few methods for the preparation of *anti*-1,3 amino alcohols. In 2009, Zhang demonstrated an elegant catalytic approach for the preparation of *anti*-1,3-amino alcohols.[23] This protocol utilises an efficient rhodium-catalysed enantio- and diastereoselective hydrogenation of readily prepared *β*-ketoenamides **163** to afford *anti*-1,3-amino alcohols **165 (Scheme 64)**. It is also the first reported asymmetric catalytic method for the preparation of these substrates. While excellent yields and diastereoselectivity was obtained for the majority of substrates, an *ortho*-methyl substituted (R_1) aryl substrate afforded slightly lower levels of diastereoselectivity (*dr*:14:86).

Zhang's Methodology



163
46-90%

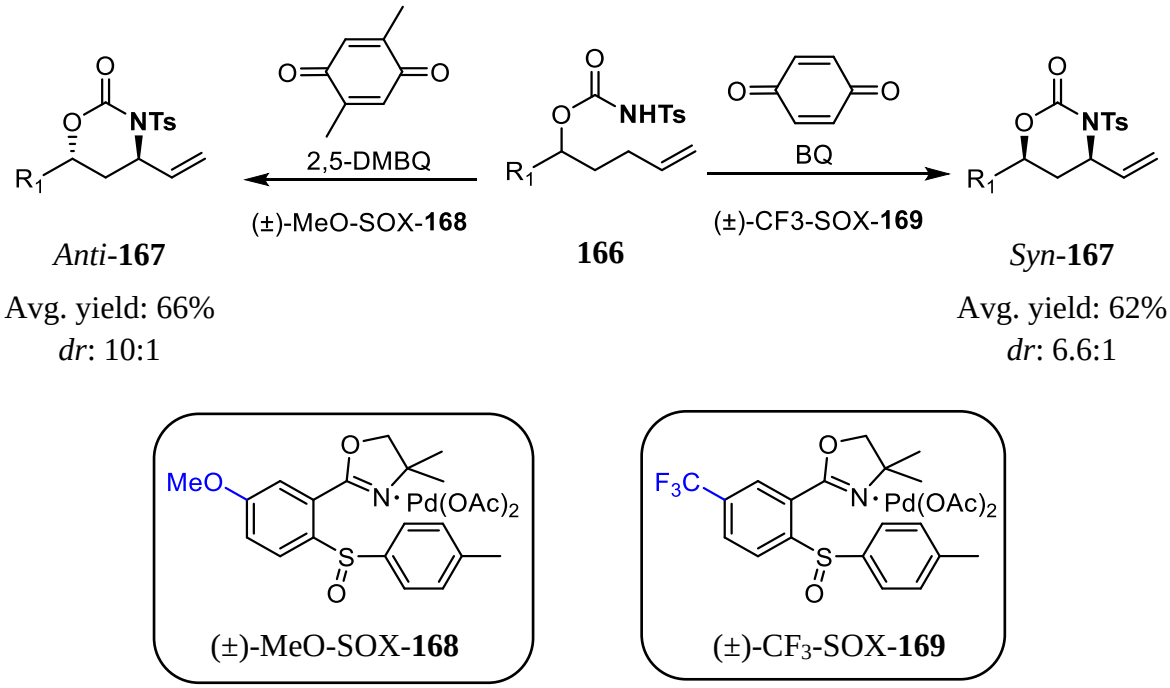
165
93-100%
dr: up to <99:1

[Rh(cod)DuanPhos]BF_4, **164**

Scheme 64. Rhodium catalysed asymmetric hydrogenation of *β*-ketoenamides

Very recently, White has reported the synthesis of both *syn*- and *anti*-1,3-amino alcohols *via* Pd(II)/SOX catalysed C-H amination of *N*-tosyl carbamates **166 (Scheme 65)**.[24] Most impressively, the diastereoselectivity in this system is tunable *via* combination of both the quinone oxidant and SOX ligand. The *anti*-1,3-amino alcohol motif **167** is accessible through the use of a Pd(II)/(±)-MeO-SOX catalyst **168** with the sterically hindered 2,5-dimethylbenzoquinone oxidant. Mechanistic studies have indicated that both Pd(II)/(±)-MeO-SOX **168** and Pd(II)/(±)-CF_3-SOX **169** catalysis promote the formation of the kinetic *syn*-oxazinanone product **167**. However, Pd(0)-catalysed isomerization to the more thermodynamically favoured *anti*-oxazinanone **167** occurs only for the (±)-MeO-SOX ligand and not for the (±)-CF_3-SOX system. The *anti*-1,3-amino alcohol derivatives **167** are afforded in good yields with high selectivities over a broad substrate scope. Analogously, the *syn*-1,3-amino alcohol precursors **167** can be accessed in comparable yields and selectivity.

White's Methodology

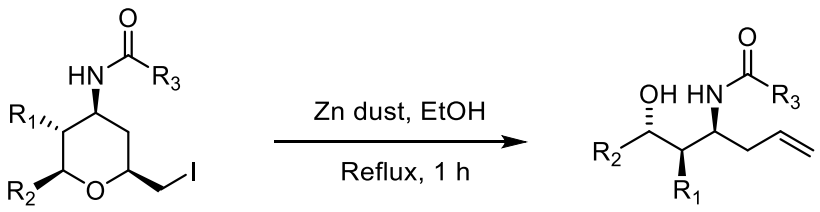


Scheme 65. Allylic C-H amination for the synthesis of *syn*- and *anti*-1,3-amino alcohol motifs

4.2.1.4 Three chiral centres

Methods to furnish 1,3-amino alcohols simultaneously with the introduction of three chiral centres are not widely reported. However, one example has been described by Yadav and co-workers.[25] This indirect approach generates the *anti*-1,3-amino alcohol motif *via* the reductive ring opening of 4-amidotetrahydropyrans **170** through a sequential Prins-Ritter reaction **(Scheme 66)**. An attractive feature of this strategy is that the resulting ring opening reaction provides access to three chiral centres in one synthetic step. The reaction sequence demonstrated a wide substrate scope and the *anti*-1,3-amino alcohols **171** were formed in high yields and excellent diastereoselectivity. However, five synthetic steps are required to access the 4-amidotetrahydropyrans **170** motif which limits the general applicability of this methodology.

Yadav's Methodology

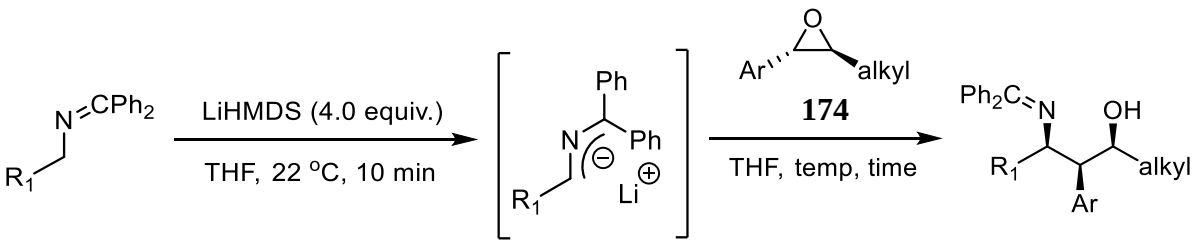


170 **171**
83-89%
dr: up to 99:1

Scheme 66. Synthesis of *anti*-1,3-amino alcohols through reductive ring opening of 4-amidotetrahydropyrans

A more recent report has been disclosed by Malcolmson, who demonstrated the direct preparation of *syn*-1,3-amino alcohols *via* an umpolung strategy involving the coupling of imines and epoxides **(Scheme 67)**.[26] Notably, this method generates three chiral centres in one step without the need for further redox manipulation. The 2-azaallyl anions **173** derived from imines **172** undergo exclusive benzylic addition to disubstituted epoxides **174** to afford the *syn*-1,3-amino alcohol derivatives **175** with the simultaneous introduction of three contiguous stereocentres in high yields and diastereoselectivity.

Malcolmson's Methodology



172 **173** **175**
2-azaallyl anion
57-98%
dr: up to >20:1

Scheme 67. Umpolung synthesis of *syn*-1,3-amino alcohols

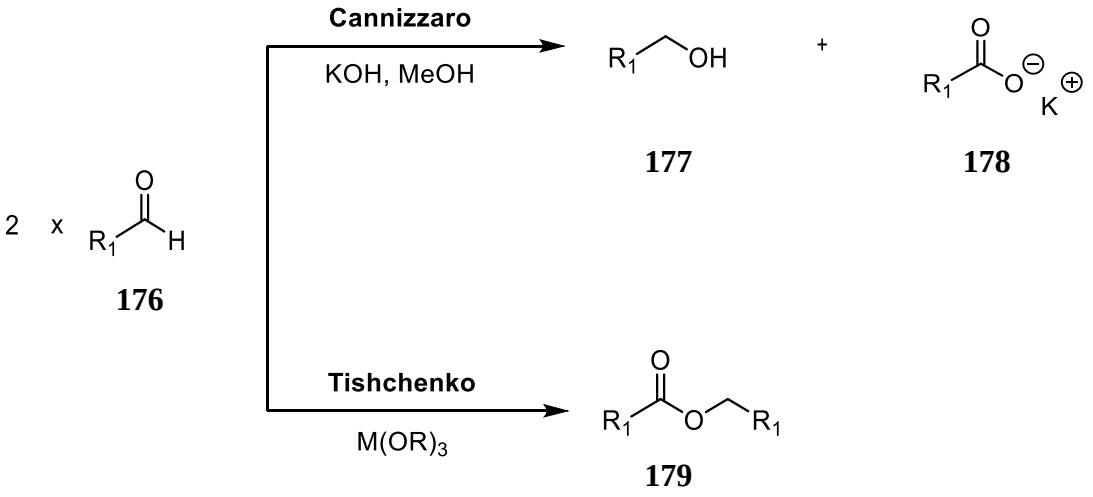
4.2.1.5 Limitations of current methods

While important advances have been made over the past two decades, there are clear limitations to the available methods. Currently, many of the existing strategies are multi-step routes and do not generate the amino alcohol framework directly. Furthermore, in many cases an

additional reduction step is required to produce the free 1,3-amino alcohol. Additionally, rarely do these strategies generate three consecutive chiral centres in one-pot. Hence, exploring new routes and addressing some of the challenges in accessing these valuable motifs is an attractive goal for synthetic chemists.

4.3 Early hydride reductions

In 1853, Cannizzaro reported the first *in situ* hydride reduction of an aldehyde **176**.[27] This transformation involved the base induced disproportionation of non-enolisable aldehydes to form an equimolar amount of alcohol **177** and carboxylate salt **178 (Scheme 68)**. Over fifty years later, an interesting variant of the Cannizzaro reaction was reported by Tishchenko.[28] The classic Tishchenko reaction entails the dimerization of two aldehydes to form an ester **179** in the presence of a Lewis acid catalyst (e.g. aluminium and magnesium ethoxides). The oxidation-reduction sequence involves a hydride shift from one aldehyde to another, and proceeds smoothly with both aromatic and aliphatic aldehydes in moderate to good yields.

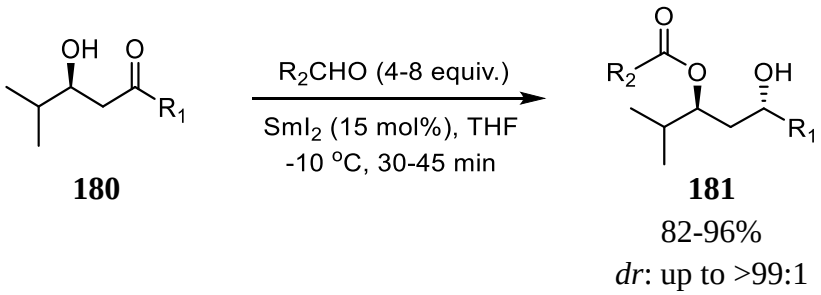


Scheme 68. Early *in situ* hydride reductions

4.3.1 Evans-Tishchenko reaction

In 1990, an important variant of the Tishchenko reaction was established by Evans and Hoveyda which has subsequently become known as the Evans-Tishchenko reaction.[29] This reaction sequence provides access to *anti*-1,3-diol monoesters *via* the Tishchenko reduction of *β*-hydroxy ketones. The initial report outlined a samarium-catalysed Tishchenko reduction of preformed *β*-hydroxy ketones **180** and 4-8 equivalents of aldehyde to generate *anti*-1,3-diol monoesters **181** in excellent yields and diastereoselectivity **(Scheme 69)**. A plausible mechanism suggested by the authors involves coordination of the aldehyde and hydroxy ketone

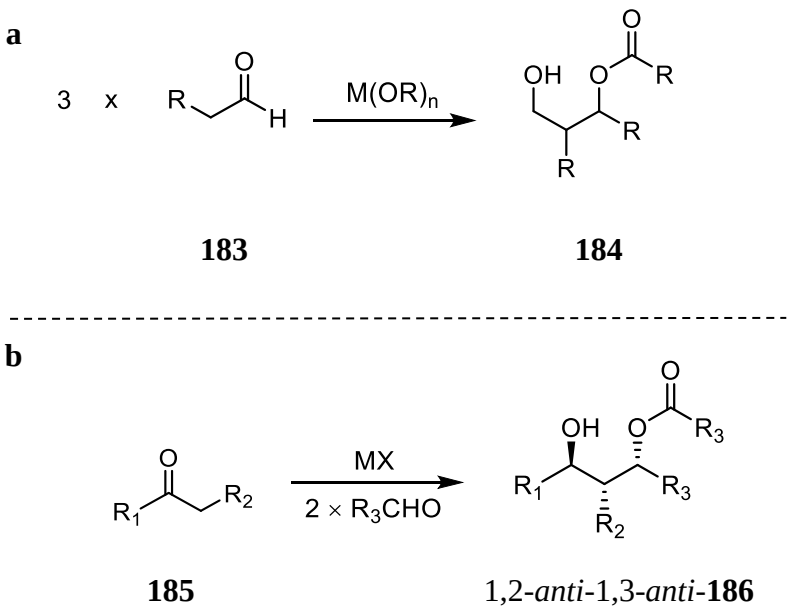
to the samarium catalyst resulting in hemiacetal formation **182** followed by intramolecular hydride transfer. While the Evans-Tishchenko reaction has provided a mild and reliable method for the stereoselective generation of *anti*-1,3-diol monoesters, a widely applicable asymmetric variant is currently lacking.[30]



Scheme 69. Evans-Tishchenko synthesis of *anti*-1,3-diol monoesters

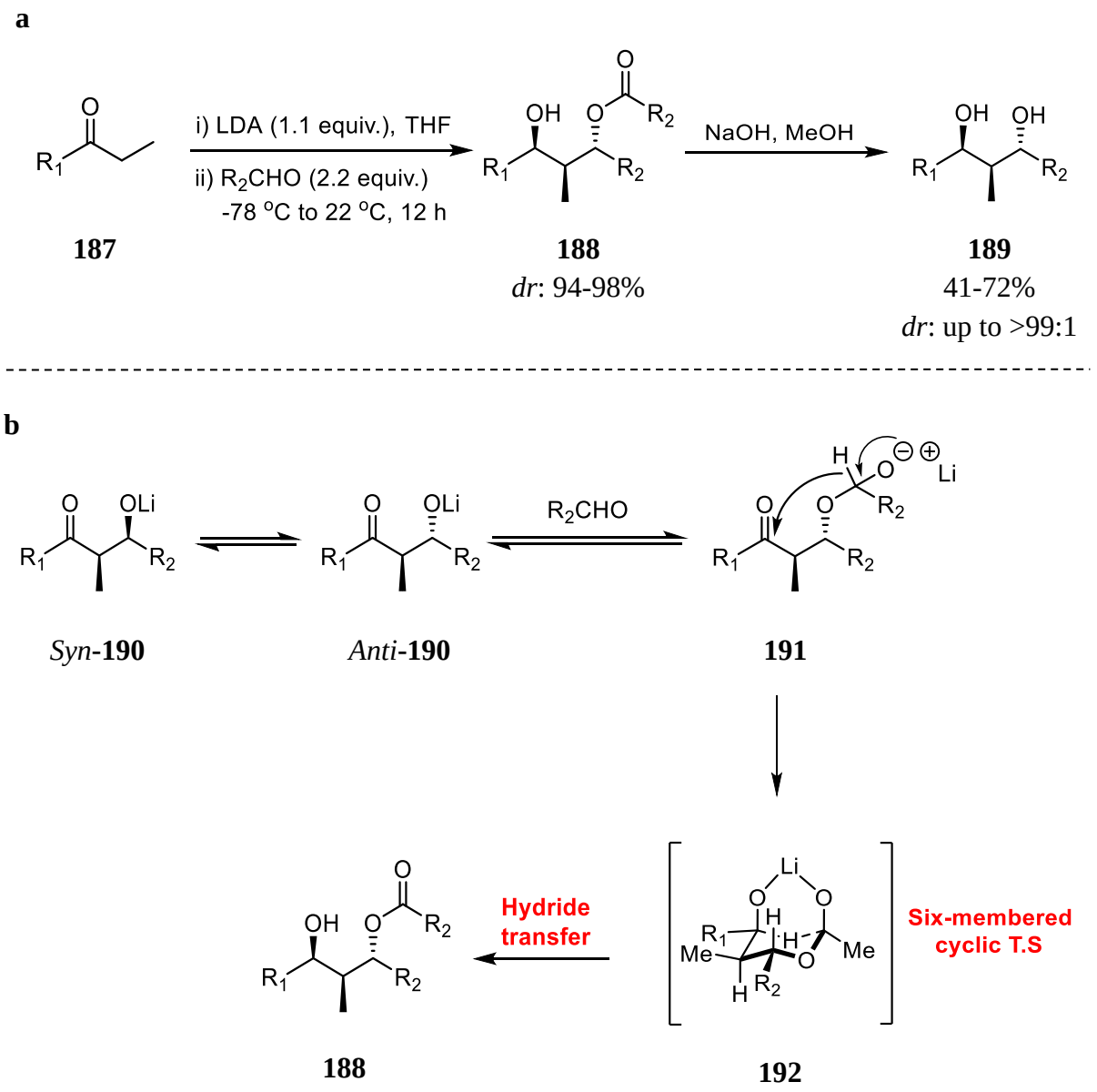
4.3.2 The aldol-Tishchenko reaction

Modification of the Tishchenko reaction led to the discovery of the aldol-Tishchenko reaction in 1943 by Nord.[31] The classic aldol-Tishchenko reaction involves the self-condensation of enolisable aldehydes **183** to generate 1,3-diol monoesters **184 (Scheme 70a)**. Later on, cross aldol-Tishchenko reactions were also developed in which metal enolates derived from ketones **185** were shown to react with 2.0 equivalents of aldehyde to form *anti*-1,3-diol monoesters **186** in a stereoselective manner **(Scheme 70b)**.[32] Most importantly, this research demonstrated the potential of the aldol-Tishchenko reaction as a highly effective method for the stereoselective synthesis of 1,3-diol monoesters.[32,33]



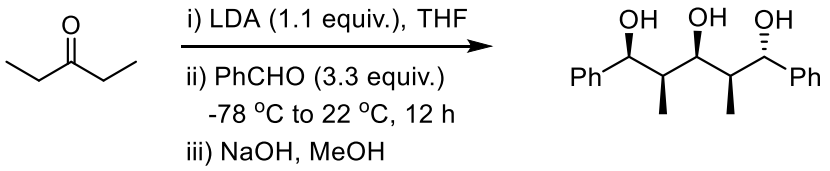
Scheme 70. a) Classic aldol-Tishchenko reaction **b)** Cross aldol-Tishchenko with ketone enolates

The generality of this transformation was not fully investigated until 1997 when Woerpel reported a highly stereoselective tandem aldol-Tishchenko reaction of lithium enolates to generate polyoxygenated compounds.[34] This simple method enables up to five stereocentres to be created in one synthetic step with excellent diastereoselectivity. Treatment of lithium enolates derived from ketones **187** with 2.2 equivalents of aldehyde at 22 ^{o}C over a period of 12 h resulted in the formation of *anti*-1,3-diol monoester **188** in high diastereomeric ratios **(Scheme 71a)**. Subsequent hydrolysis afforded the *anti*-1,3-diols **189** in moderate to good yields. The authors determined that the stereochemical relationship of the final product was independent of the stereochemical nature of the aldolate **190**. The proposed mechanism involves a reversible aldolization step which precedes a rate-determining and stereodefining hydride transfer step underpinned by a cyclic six-membered transition state **192** as outlined in **Scheme 71b**.



Scheme 71. a) Bodnar and Woerpel's tandem aldol-Tishchenko reaction of ketone enolates **b)** Proposed mechanism for the aldol-Tishchenko reaction

Interestingly, initial attempts by the authors to extend this reaction to 3-pentanone **86** failed under the aforementioned conditions.[34] However, reaction of 3-pentanone **86** with 3.3 equivalents of benzaldehyde provided access to a 1,3,5-triol monoester product **193** and enabled the introduction of five chiral centres in one synthetic step **(Scheme 72)**. The authors described this to be a tandem sequence of two aldol reactions followed by proton transfer and finally an intramolecular Tishchenko reduction step.



86

193
64%
dr: 86:6:5:3 (triol monoester)

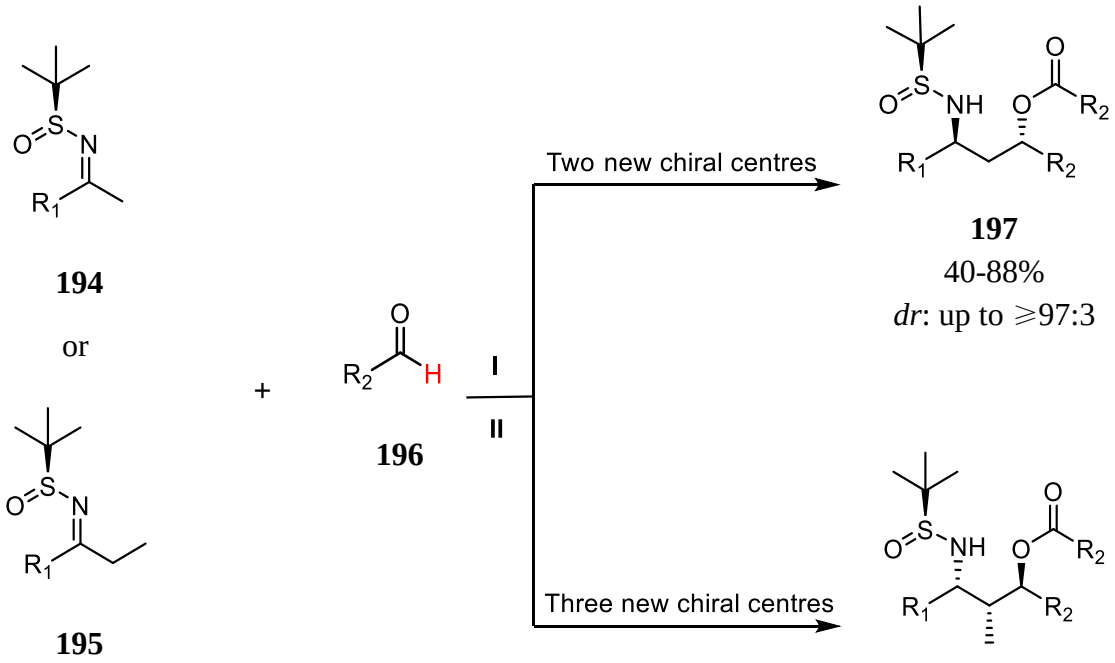
Scheme 72. Synthesis of five chiral centres in one-pot

4.4 Asymmetric aldol-Tishchenko reaction of *N-tert*-butanesulfinyl imines

The aldol-Tishchenko reaction has proven to be an extremely valuable tool in asymmetric synthesis to access 1,3-diol monoesters, due to good atom economy and operational simplicity. Prior to 2015, there had been no such reports of a tandem aldol-Tishchenko reaction using an imine derivative. However, in 2016 our research group demonstrated a novel protocol for the highly diastereoselective synthesis of *anti*-1,3-amino alcohol derivatives *via* a tandem aldol-Tishchenko reaction using *N-tert*-butanesulfinyl imines.[35] This work represents the first reported intramolecular diastereoselective reduction of a C=N bond and describes a rare example of the concomitant introduction of two and three chiral centres in one pot **(Scheme 73)**.

This protocol has shown to be highly stereoselective and tolerates a broad range of substrates. Aryl and alkyl methyl sulfinyl imines **194** afforded *anti*-1,3-amino alcohols **197** with two chiral centres in good to excellent yields and diastereoselectivity using pivaldehyde as an aldol acceptor. Enolizable aldehydes such as isobutyraldehyde, cyclohexane carboxaldehyde and isovaleraldehyde also proved applicable for acetophenone based sulfinyl imines **194**. For the propiophenone based sulfinyl imines **195**, aryl aldehydes worked best and produced the desired products **198** in very good yields and diastereoselectivity.

McGlacken Methodology

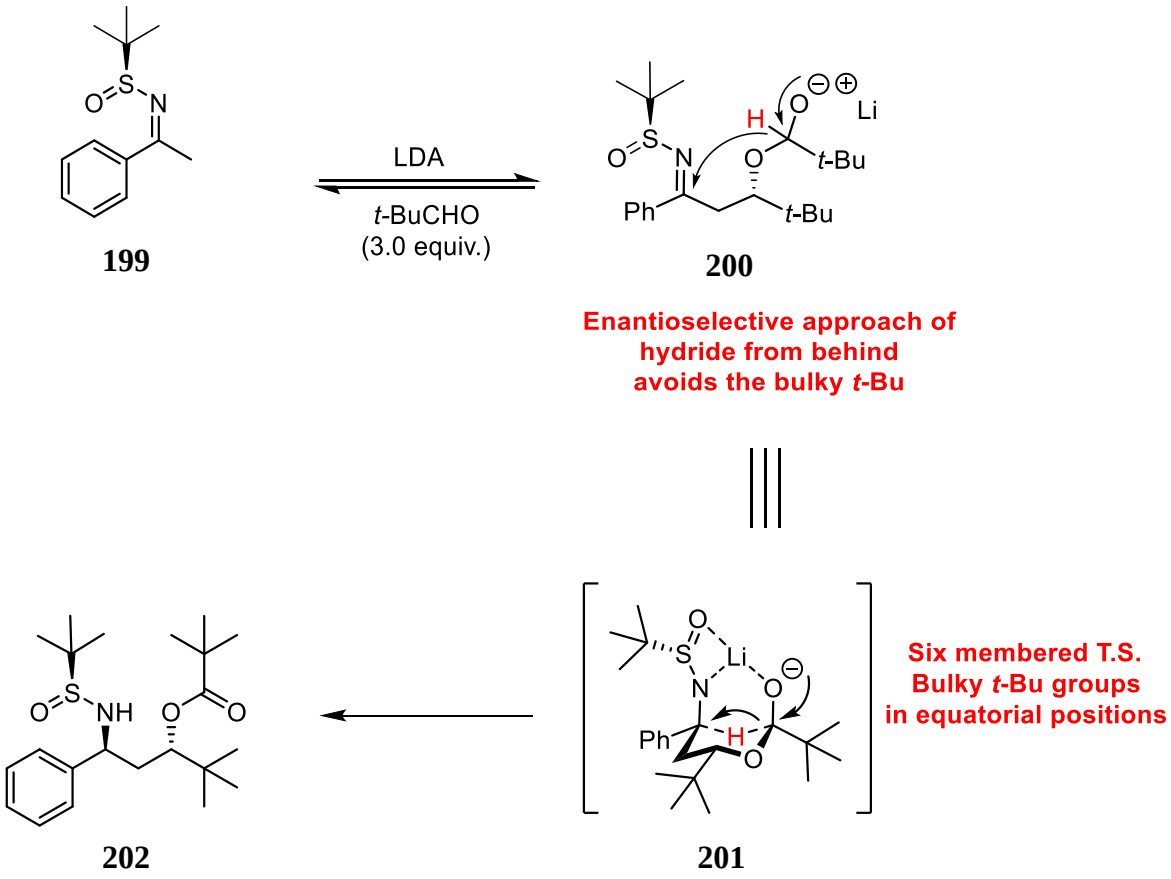


I) LDA, -78 °C/0 °C, 1 h **II)** R_2CHO (2.2-3.0 equiv.), -78 °C to -20 °C, 16 h

Scheme 73. McGlacken's aldol-Tishchenko reaction of chiral *N-tert*-butanesulfinyl imines

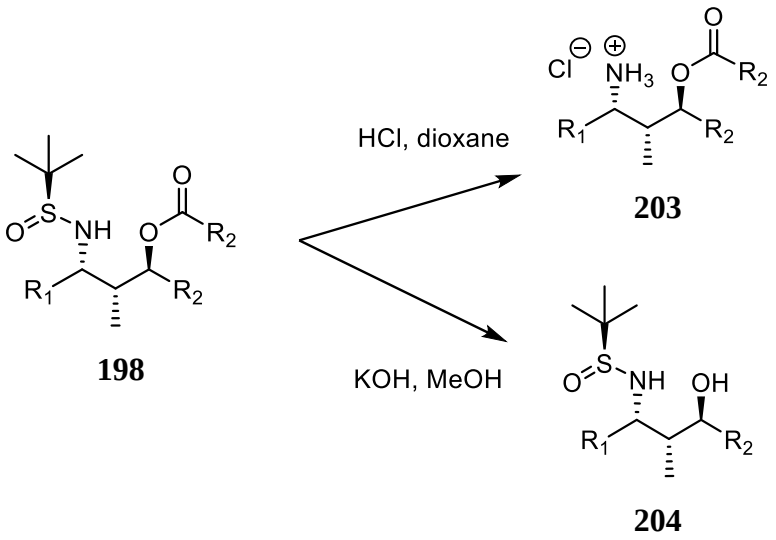
A similar mechanism for the classic aldol-Tishchenko transformation of ketones is proposed to be operating for the aldol-Tishchenko reaction of *N-tert*-butanesulfinyl imines.[35] This involves a reversible aldol addition step followed by intramolecular hydride transfer **(Scheme 74)**. Deprotonation of **199** with LDA followed by the addition of 3.0 equivalents of aldehyde results in the formation of alkoxide **200**. Mechanistic studies have established that the reaction proceeds *via* a reversible aldol reaction followed by an irreversible diastereo- and enantioselective hydride transfer. The highly organised six-membered transition state adopted by **201**, is analogous to that previously proposed by Bodnar and Woerpel.[34] Hydride transfer is facilitated only when the bulky *t*-Bu groups are positioned at the equatorial position, thus avoiding unfavourable 1,3-diaxial interactions, yielding **202** as the major diastereomer. Crucially, the formation of the six-membered transition state leads to a highly diastereoselective reaction while the use of the chiral auxiliary induces the enantioselectivity.

Proposed Mechanism



Scheme 74. McGlacken's proposed mechanism for stereochemical induction

Furthermore, facile cleavage of each ancillary is also possible using HCl in dioxane to generate **203** and KOH in MeOH to give **204 (Scheme 75)**.



Scheme 75. Selective cleavage of each ancillary

The McGlacken methodology represents a convenient two-step approach for the stereoselective preparation of *anti*-1,3-amino alcohols. This protocol offers considerable advantages over previously reported methods:

1. Crucially, additional external reductants are avoided through the use of an extra equivalent of aldehyde.
2. It is the first reported example of a stereoselective intramolecular hydride transfer to a C=N bond.
3. This work demonstrates a very rare example of the concomitant introduction of two and three chiral centres in one pot.
4. Significantly, ethyl ketones which are perceived as difficult substrates can also be successfully utilised under the reaction conditions.

4.5 References

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Chapter 5

The Asymmetric Aldol-Tishchenko Reaction of (*S*)-*tert*-butanesulfinyl Imines for the Introduction of 2, 3, 4 and 5 New Chiral Centres in One Pot

Results and Discussion

Chapter 5. Asymmetric Aldol-Tishchenko Reaction of (*S*)-*tert*-butanesulfinyl imines for the Synthesis of Multiple Chiral Centres in One Pot.

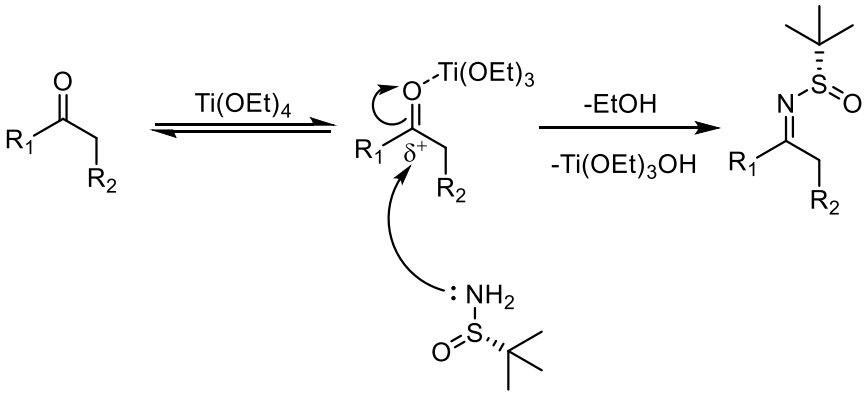
5.1 Aims and objectives

In this chapter, the asymmetric aldol-Tishchenko reaction of (*S*)-*tert*-butanesulfinyl imines will be investigated. One of the key aims of this project is to further explore the potential of this novel methodology. As part of this research a number of objectives were followed:

- Symmetrical and unsymmetrical cyclic and acyclic (*S*)-*tert*-butanesulfinyl imines will be examined.
- *N*-sulfinyl aldimine equivalents will be investigated as potential aldol donors.
- A number of aldehydes will also be employed as hydride donors, including a formaldehyde equivalent.
- Additionally, attempts to utilise aldimines as aldol acceptors will be explored as a novel approach to synthesise *anti*-1,3 diamines.
- An alternative quench method to form *N*-alkylated 1,3-amino alcohols will be examined in the synthesis of chiral secondary amines.
- Scale-up of the aldol-Tishchenko reaction will be evaluated.
- Extension of this methodology to the synthesis of four and five chiral centres will be performed enabling the synthesis of 3-amino-1,5-diol derivatives *via* a tandem double aldol-Tishchenko reaction.
- Density Functional Theory (DFT) calculations will be carried out as part of a collaboration to gain an insight into the double aldol-Tishchenko reaction mechanism.
- Finally, attempts to further functionalise cyclopentanone and cycloheptanone 3-amino-1,5-diol derivatives will be explored.

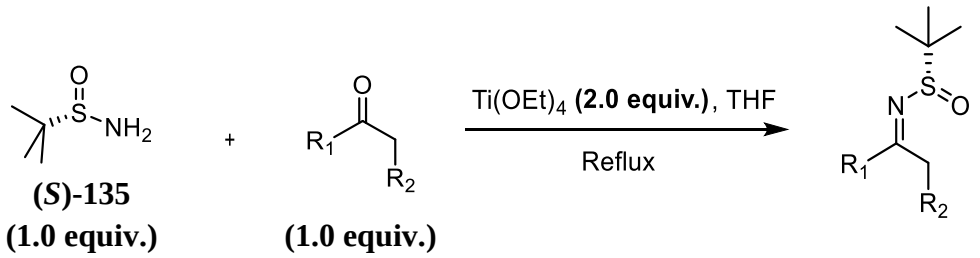
5.2 Synthesis of (*S*)-*tert*-butanesulfinyl imines

Research in this project began with the synthesis of a range of (*S*)-*tert*-butanesulfinyl imines. (*S*)-*tert*-butanesulfinyl imines are easily prepared *via* condensation of the parent ketone and (*S*)-*tert*-butanesulfinamide **(*S*)-135** in the presence of $Ti(OEt)_4$ **(Scheme 76)**. The $Ti(OEt)_4$ imparts a dual role in the reaction behaving both as a Lewis acid to activate the carbonyl moiety and as a water scavenger.



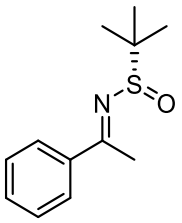
Scheme 76. Mechanism for the formation of (*S*)-*tert*-butanesulfinyl imines

An array of versatile (*S*)-*tert*-butanesulfinyl imines were synthesised in good to excellent yields (33-83%) **(Scheme 77)**. The sulfinyl imines were found to be stable to flash column chromatography and could be stored at -18 ^{o}C over long periods of time without any observable decomposition or hydrolysis. Unsymmetrical sulfinyl imines have been shown to exist as rapidly equilibrating *E*:*Z* mixtures.[1] However, in most cases, the sulfinyl imines were observed exclusively as the *E* isomer presumably due to the decreased steric interactions. Acetophenone derived sulfinyl imine **(*S*)-199** as well as substituted and unsubstituted propiophenone based sulfinyl imines **(*S*)-205-207** were isolated in very good yields (74-87%). The 2-thiophene analogue **(*S*)-208** was prepared in a lower yield of 39%. A moderate yield of 58% was obtained for alkyl sulfinyl imine **(*S*)-209**. Additionally, cyclic and fused cyclic sulfinyl imines **(*S*)-210** and **(*S*)-211** were also prepared *via* this method. Attempts to synthesize **(*S*)-212-214** proved futile.

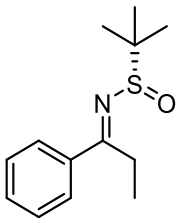


(*S*)-135
(1.0 equiv.)

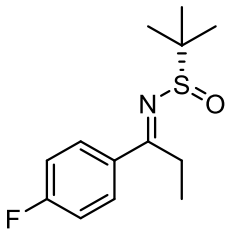
(1.0 equiv.)



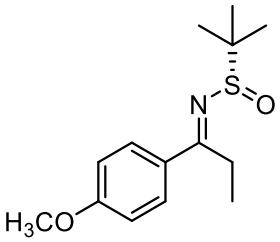
(*S*)-199, 74%



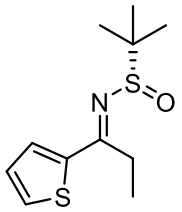
(*S*)-205, 76%



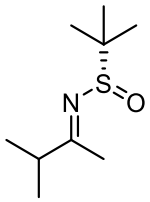
(*S*)-206, 87%



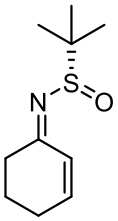
(*S*)-207, 79%



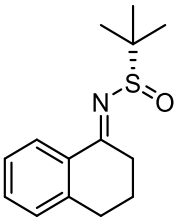
(*S*)-208, 39%



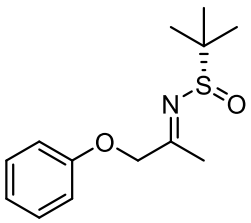
(*S*)-209, 58%



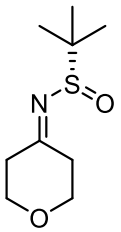
(*S*)-210, 55%



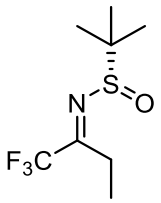
(*S*)-211, 33%



(*S*)-212, yield n.d



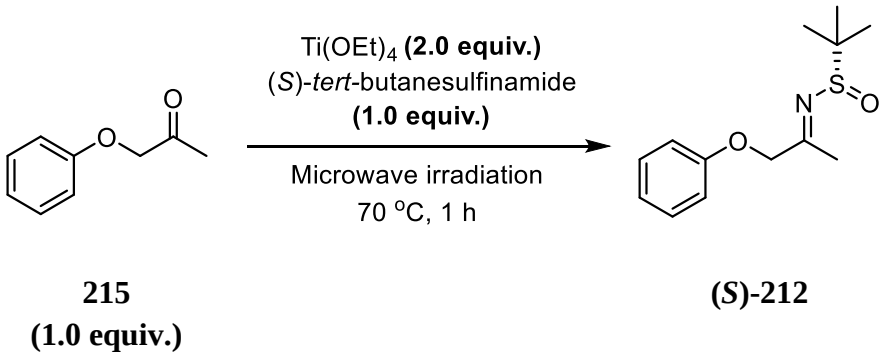
(*S*)-213, yield n.d



(*S*)-214, yield n.d.

Scheme 77. Synthesis of (*S*)-*tert*-butanesulfinyl imines

The synthesis of phenoxy sulfinyl imine **(*S*)-212** proved to be very challenging. Reaction of the parent ketone **215** with 2.0 equivalents of $Ti(OEt)_4$ under reflux conditions was unsuccessful. Microwave irradiation also resulted in no desired product **(Scheme 78)**. TLC analysis of the crude reaction mixture indicated that the starting material **215** had in fact been consumed. However, no characteristic signals corresponding to the sulfinyl imine **(*S*)-212** could be identified in the ^1H NMR spectrum of the crude reaction mixture.



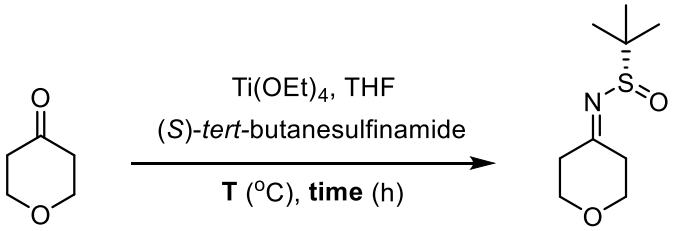
215
(1.0 equiv.)

(*S*)-212

Scheme 78. Attempted synthesis of **(*S*)-212**

The synthesis of tetrahydro-4*H*-pyran-4-one derived sulfinyl imine **(*S*)-213** was also attempted using a number of reaction procedures. Poor conversion to product was observed under standard reflux conditions **(Table 16**, **Entry 1)**. Lowering the reaction temperature to 20 °C and utilising 4.0 equivalents of $Ti(OEt)_4$ resulted in only a slight improvement in product conversion **(Table 16**, **Entry 2)**. The highest conversion was obtained using 3.0 equivalents of $Ti(OEt)_4$ under reflux conditions **(Table 16**, **Entry 3)**. However, a number of side-products were also present in the crude reaction mixture. Thus, isolation of the product *via* column chromatography was problematic due to co-elution of the product with the starting material **216** and the additional side-products.

Table 16. Attempted synthesis of **(*S*)-213**



216 **(*S*)-213**

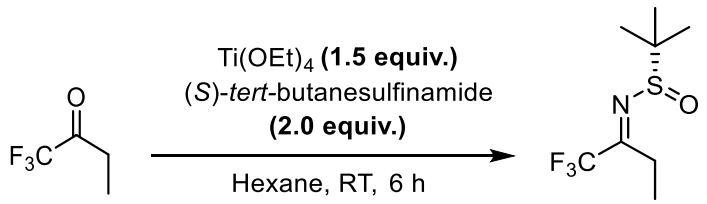
Entry	Ti(OEt)$_4$ (Equiv.)	Ketone (Equiv.)	Sulfinamide (Equiv.)	Temperature (°C)	Time (h)	Conversion[b] (%)
1	2.0	1.0	1.0	Reflux	22[a]	19
2	4.0	1.0	1.0	20 °C	3	23
3	3.0	1.0	1.0	Reflux	46[a]	46

[a]Reaction progress monitored by TLC analysis.

[b]Conversion calculated from ratio of starting material to product in the ^{1}H NMR spectrum of the crude reaction mixture.

Sulfinyl imines **(*S*)-212** and **(*S*)-213** were particularly challenging substrates. Overall, the reactions were sluggish and poor conversion to product was observed. This may be due to the presence of the additional oxygen atom on the carbon chain of **215** and **216** which could present additional coordination sites for the titanium.

Efforts to further expand our scope to the α-CF_3-substituted sulfinyl imine **(*S*)-214** were unsuccessful. Following a literature procedure,[2] a complex mixture of products was obtained after careful reaction monitoring by ^{1}H NMR analysis **(Scheme 79)**. Attempted isolation of the desired product **(*S*)-214** by column chromatography proved difficult as α-CF_3-substituted (*S*)-*tert*-butanesulfinyl imines are readily hydrolysed upon prolonged standing on silica gel.[2] Unfortunately, only one isolated fraction from the column contained minor amounts of product **(*S*)-214**. However, this fraction also contained additional side-products. Thus, the problems encountered with isolating this sulfinyl imine prompted us to no longer pursue the synthesis of α-CF_3-substituted (*S*)-*tert*-butanesulfinyl imines.



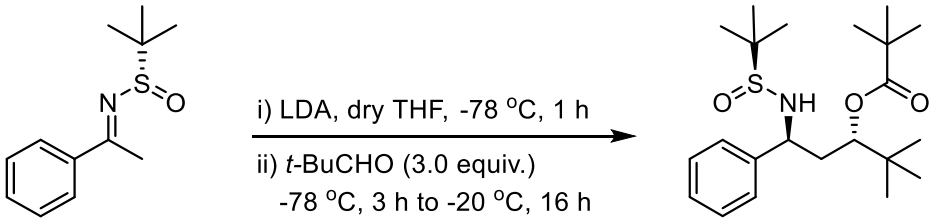
217
(1.0 equiv.)

(*S*)-214

Scheme 79. Attempted synthesis of α-CF_3-substituted (*S*)-*tert*-butanesulfinyl imine **(*S*)-214**

5.3 Expansion of substrate scope

With a range of (*S*)-*tert*-butanesulfinyl imines in hand, we proceeded to apply these substrates to our aldol-Tishchenko reaction conditions. Firstly, a test reaction was performed to generate compound **(*S*,*S*,*S*)-202** which had been previously synthesised within the group **(Scheme 80)**.[3] Acetophenone sulfinyl imine **(*S*)-199** was deprotonated at -78 °C for 1 h followed by the slow addition of 3.0 equivalents of pivaldehyde and warming to -20 °C over a period of 16 h. Pleasingly, the desired 1,3-amino alcohol derivative **(*S*,*S*,*S*)-202** was formed in moderate yield and excellent diastereoselectivity.

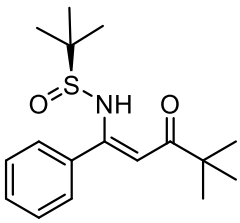


(*S*)-199

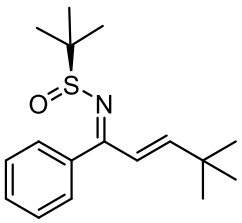
(*S*,*S*,*S*)-202
55%, 93:7 *dr*

Scheme 80. Test reaction

It should be noted that for the aldol-Tishchenko reaction of acetophenone derived sulfinyl imines, two competing side-reactions are known to exist resulting in the formation of two impurities, **218** and **219 (Figure 23)**. These impurities have been identified and characterised by a previous member of the group.[4]



218



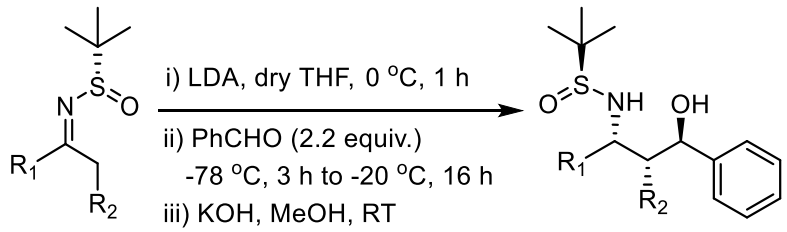
219

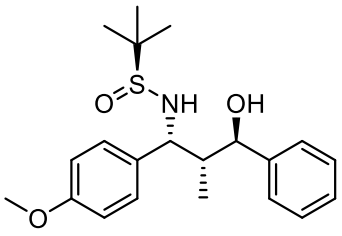
Figure 23. Impurities formed during the aldol-Tishchenko reaction

Next, the synthesis of 1,3-amino alcohol derivatives with three chiral centres was examined **(Scheme 81)**. For these substrates, deprotonation with LDA was performed at 0 ^{o}C for 1 h followed by subsequent treatment with 2.2 equivalents of benzaldehyde. In all cases, the Tishchenko esters were hydrolysed to the corresponding 1,3-amino alcohols directly by stirring in a methanolic solution of potassium hydroxide prior to purification by column chromatography on silica gel. This step was necessary in order to prevent problematic purification procedures due to partial cleavage of the ester on the silica gel which had been previously observed by another member of the group.[3]

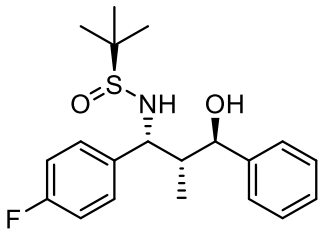
A series of the propiophenone derived sulfinyl imines were subjected to our aldol-Tishchenko conditions. Good levels of diastereoselectivity were obtained for the *p*-methoxy **(*S*,*R*,*R*,*R*)-220** and *p*-fluoro **(*S*,*R*,*R*,*R*)-221** derivatives, although a drop in selectivity was observed overall for the propiophenone based substrates. Noticeably, a significant decrease in diastereoselectivity was observed for the 2-thiophene analogue **(*S*,*R*,*R*,*R*)-222**. Furthermore, the less electrophilic sulfinyl imines containing the methoxy and thiophene moieties afforded the aldol-Tishchenko products **(*S*,*R*,*R*,*R*)-220** and **(*S*,*R*,*R*,*R*)-222** in lower yields of 48 and 41% respectively.

The substrate scope was then further challenged to include cyclic and α-substituted cyclic sulfinyl imines. Attempts to form the corresponding products **223** and **224** by reacting cyclohex-2-ene-1-one and α-tetralone sulfinyl imines, **(*S*)-210** and **(*S*)-211** failed under the reaction conditions. Unfortunately, in both cases, only degraded starting material along with benzyl alcohol and benzaldehyde were recovered following work-up.

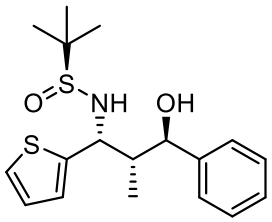




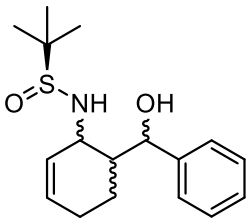
(*S*,*R*,*R*,*R*)-220
48%, 80:10:10 *dr*



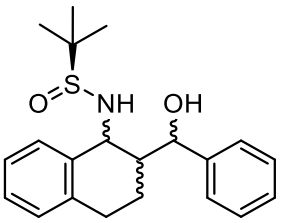
(*S*,*R*,*R*,*R*)-221
53%, 82:13:5 *dr*



(*S*,*R*,*R*,*R*)-222
41%, 62:38 *dr*



223
No product formation

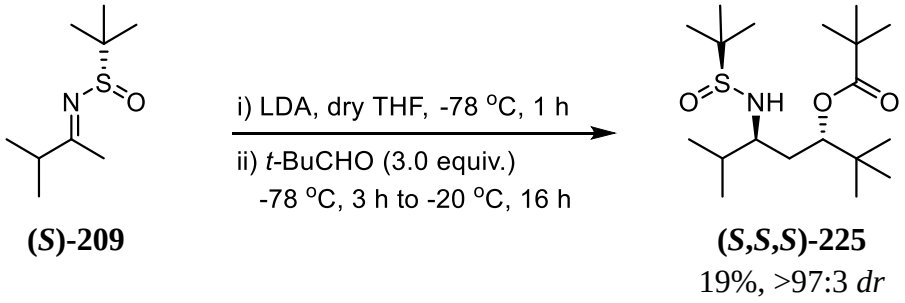


224
No product formation

Scheme 81. Substrate scope for propiophenone derived sulfinyl imines

We then proceeded to attempt to scale-up one of our previously published aldol-Tishchenko reactions utilising alkyl sulfinyl imine **(*S*)-209** and pivaldehyde **(Scheme 82)**. Overall, this proved to be a challenging process. The reaction was scaled up by a factor of 30 and conducted on a 30 mmol scale. It was decided to perform the reaction using the established reaction conditions. Pleasingly, excellent diastereoselectivity was maintained (>97:3 *dr*). However, isolation of the major diastereomer **(*S*,*S*,*S*)-225** *via* column chromatography resulted in a low yield of 19%. For comparison, isolation of this compound on a 1 mmol scale by another member of the group generated **(*S*,*S*,*S*)-225** in a very good yield of 76%.[5] Noticeably, the ^{1}H NMR spectrum of the crude reaction mixture from the scale-up indicated the formation of a

number of impurities, including **218** and **219**, in addition to other unidentified side-products. Thus, this presented us with great difficulty in isolating the major diastereomer **(*S*,*S*,*S*)-225**. Future work on scaling up the aldol-Tishchenko reaction will involve modification of reaction conditions and will be discussed thoroughly in **Section 5.3.5**.



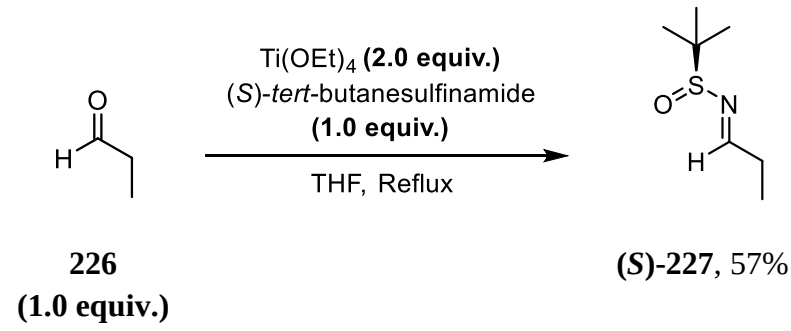
(*S*)-209

(*S*,*S*,*S*)-225
19%, >97:3 *dr*

Scheme 82. Scale-up of aldol-Tishchenko reaction

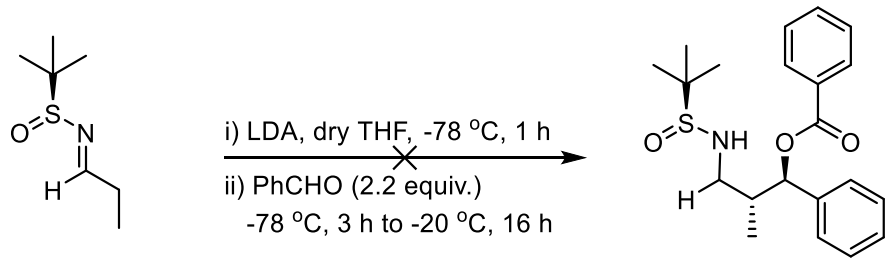
5.3.1 α-Functionalisation of (*S*)-*tert*-butanesulfinyl aldimines

Having examined a series of (*S*)-*tert*-butanesulfinyl ketimines, the next step was to apply our methodology to (*S*)-*tert*-butanesulfinyl aldimines which are perceived as much more challenging aldol donors. Firstly, (*S*)-*tert*-butanesulfinyl aldimine **(*S*)-227** was prepared in a moderate yield of 57%, following our previously outlined reaction conditions **(Scheme 83)**. We then proceeded our investigation by reacting **(*S*)-227** with benzaldehyde under our standard aldol-Tishchenko conditions **(Scheme 83)**. Disappointingly, ^{1}H NMR analysis of the crude reaction mixture showed a complex mixture of products including unreacted starting material and a number of unidentified products. This was to be expected as direct α-functionalisation of *N*-sulfinylaldimines is difficult due to competing auto-condensation during the deprotonation step.[6]



226
(1.0 equiv.)

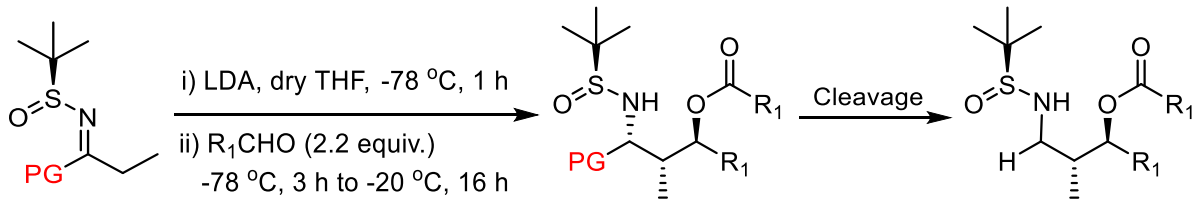
(*S*)-227, 57%



(*S*)-227 **228**

Scheme 83. Investigation of **(*S*)-227** as an aldol donor

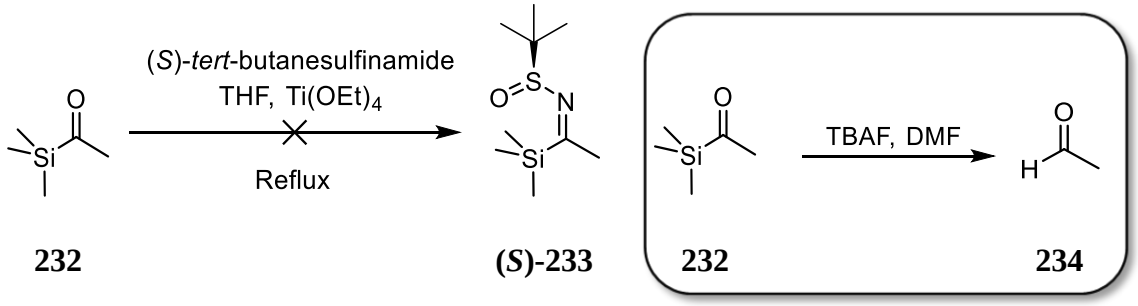
One way of overcoming this problem would be to use a protecting group strategy **(Scheme 84)**. A search of the literature identified two protecting groups which we felt could be applied under our conditions.



229 **230** **231**

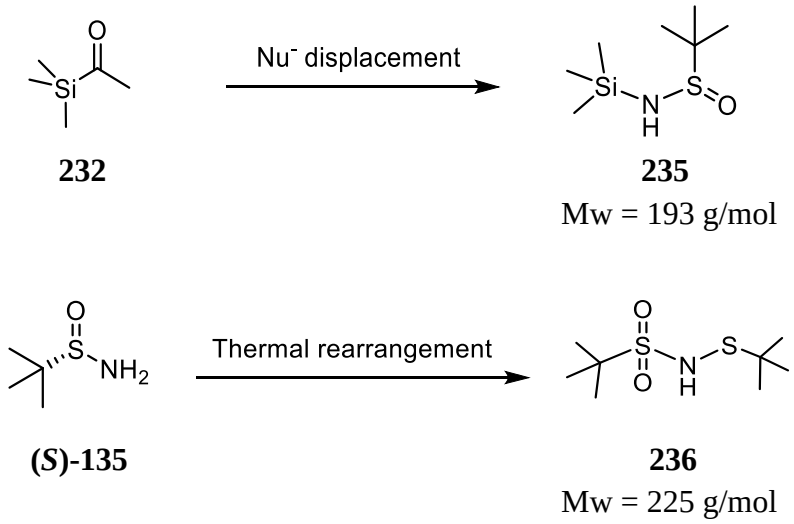
Scheme 84. Protecting group strategy

The first protecting group employed was the trimethylsilyl derivative of formaldehyde **232 (Scheme 85)**. After treatment with *n*-tetrabutylammonium fluoride (TBAF), the desilyated product **234** can be readily obtained.[7] Unfortunately, attempts to form the (*S*)-*tert*-butanesulfinyl imine **(*S*)-233** of acetyltrimethyl silane failed. The crude reaction mixture showed a complex mixture of products and attempts to isolate **(*S*)-233** from this mixture proved unsuccessful.



Scheme 85. TMS protecting group

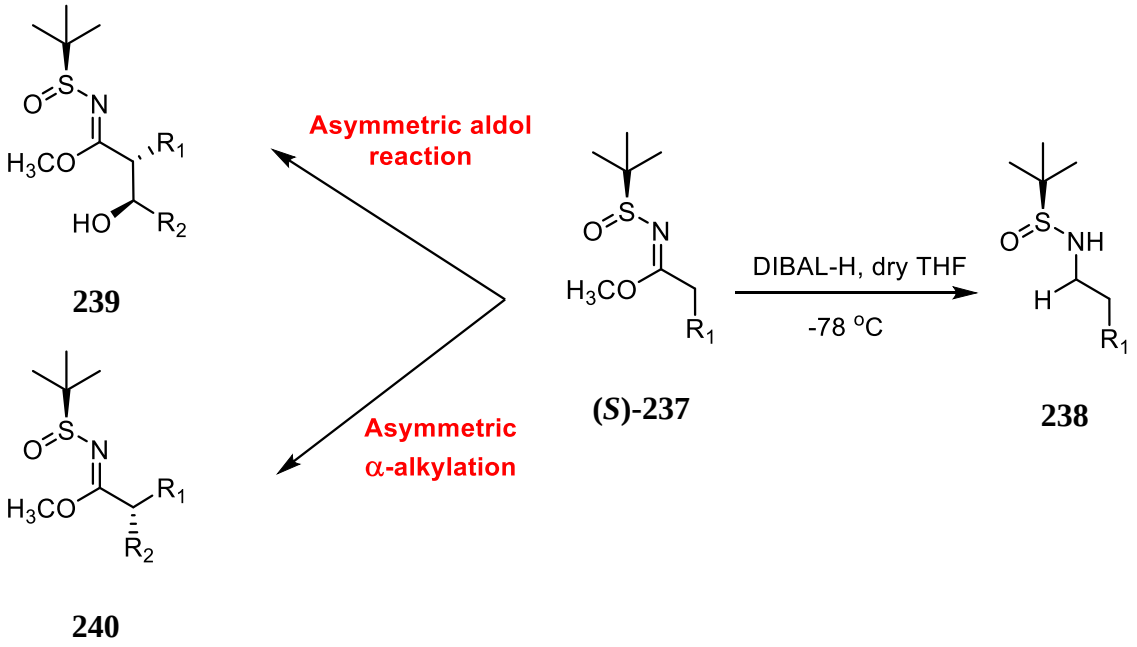
It was evident that a number of side-products had formed. Evidence in the literature suggests that acyl silanes and *C*-silyl imines are susceptible to thermal rearrangements.[8] Formation of **235** can also occur *via* nucleophilic attack on **232** at Si **(Scheme 86)**. Additionally, *tert*-butane sulfinamide **(*S*)-135** is unstable above room temperature and is known to undergo rearrangement to form the more stable *N*-(*tert*-butylthio)-*tert*-butylsulfonamide **236**.[9] **235** was tentatively assigned by ^{1}H NMR and mass spectrometry analysis following column chromatography. Due to this disappointing result, it was decided to search for an alternative protecting group.



Scheme 86. Possible side-products generated during the reaction

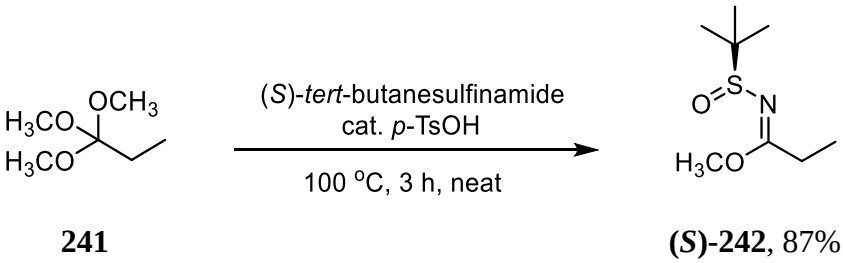
Other useful *N*-sulfinylaldimine equivalents include *N*-sulfinylimidates **(*S*)-237**. The synthetic potential of *N*-sulfinylimidates **(*S*)-237** has been highlighted in a number of publications **(Scheme 87)**. In relation to our work, diastereoselective α-functionalisation of *N*-sulfinylimidates **(*S*)-237** *via* aldol additions[10] and α-alkylations[11] have been reported. In particular, Liu and co-workers have demonstrated the use of *N*-sulfinylimidate **(*S*)-237** as a

suitable aldol donor under basic conditions.[10a] *N*-sulfinylimidates **(*S*)-237** can be deprotected by treatment with DIBAL-H to yield **238**.[10a]



Scheme 87. α-functionalisation of *N*-sulfinylimidates **(*S*)-237**

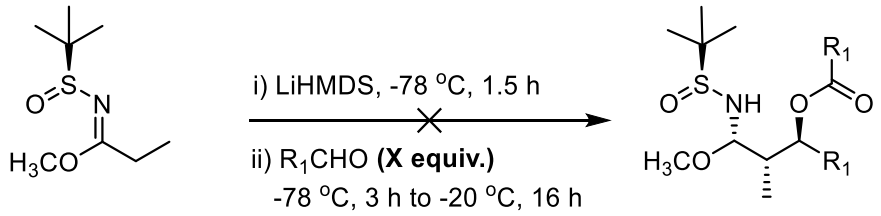
Following a literature procedure,[11] condensation of (*S*)-*tert*-butanesulfinamide and ortho ester **241** with a catalytic amount of *p*-TsOH afforded *N*-sulfinyl imidate **(*S*)-242** in an excellent yield of 87% **(Scheme 88)**.



Scheme 88. Synthesis of *N*-sulfinyl imidate **(*S*)-242**

Previous work by De Kimpe and co-workers identified LiHMDS as being the most efficient base for deprotonation of *N*-sulfinylimidates.[11] They observed incomplete conversion to desired product when LDA was utilised as base in the asymmetric α-alkylation of *N*-sulfinyl imidates due to the formation of unidentified side products. Thus, *N*-sulfinylimidate **(*S*)-242** was subjected to our aldol-Tishchenko reaction conditions using LiHMDS as base **(Scheme**

89). Previous work within our group has shown that comparable levels of diastereoselectivity and yields are achieved using LiHMDS and LDA.[4] Unfortunately, **(*S*)-242** failed to undergo a Tishchenko reaction with both pivaldehyde and benzaldehyde as aldol acceptors. In each case, only aldol product was obtained. A repeat reaction was then carried out using benzaldehyde in which the reaction mixture was warmed to room temperature over 16 h, in an attempt to promote the Tishchenko step. The ^{1}H NMR spectrum exhibited only aldol product, starting material and a number of unidentified product peaks.

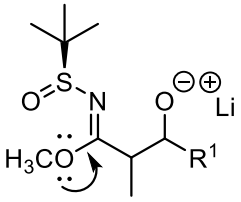


(*S*)-242 **243**

R_1 = *t*-Bu **(3.0 equiv.)**, aldol product.
R_1 = Ph **(2.2 equiv.)**, aldol product.
R_1 = Ph **(2.2 equiv.)** at RT:
Aldol product, starting material and unidentified products

Scheme 89. Aldol-Tishchenko reaction of **(*S*)-242**

It is likely that *N*-sulfinylimidates are less susceptible to hydride attack in comparison to (*S*)-*tert*-butanesulfinyl imines. The electron donating character of the methoxy group results in a much less electrophilic species **(Figure 24)**. Thus, while it is possible to generate the aldol product, the significantly less electrophilic *N*-sulfinylimidate intermediate **244** is likely to prevent hydride transfer to the C=N moiety. After failing to obtain aldol-Tishchenko product utilising both the TMS protecting group and *N*-sulfinylimidate **(*S*)-242**, we decided to no longer pursue the use of (*S*)-*tert*-butanesulfinyl aldimines as aldol donors.

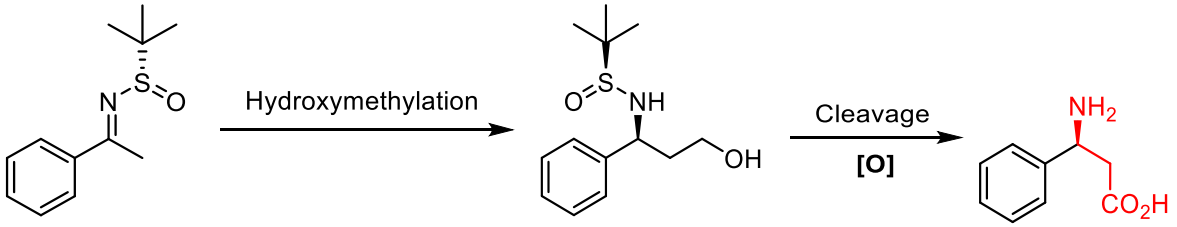


244

Figure 24. Electron donating effect of methoxy group

5.3.2 α-Hydroxymethylation of (*S*)-*tert*-butanesulfinyl imines

Hydroxymethylation reactions represent one of the most useful one-carbon extension methods in organic synthesis.[12] The hydroxymethyl group is not only of great importance due to its prevalence in many natural products and biologically important compounds,[13] but it can also undergo a range of synthetic transformations.[14] Primarily, we were interested to see if we could use the hydroxymethyl group to access *β*-amino acids. We envisaged that the our aldol-Tishchenko methodology could provide a novel route to *β*-amino acids **246** *via* simple oxidation of hydroxymethylated aldol-Tishchenko product **245 (Scheme 90)**.

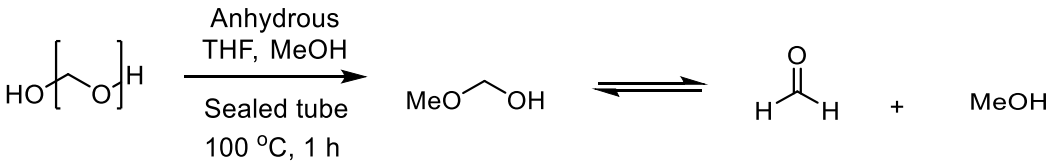


(*S*)-199 **245** **246**

Scheme 90. Access to *β*-amino acid precursors

The most common reagent to introduce the hydroxymethyl group is formaldehyde. Due to the difficulties in the preparation and handling of anhydrous gaseous formaldehyde, we sought to find an appropriate alternative. A solution of anhydrous monomeric formaldehyde is unstable in THF and readily polymerises upon handling. Thus, it was essential that the formaldehyde source was prepared *in situ* shortly before application. Suna and co-workers have identified methoxy methanol, a stable and easy-to handle hemiacetal of formaldehyde, as a convenient source of monomeric formaldehyde **(Scheme 91)**.[15] The authors have demonstrated the applicability of using methoxy methanol as a formaldehyde source in the diastereoselective hydroxymethylation of cyclic (*S*)-*tert*-butanesulfinyl imines to form *syn*- and *anti*-1,3-amino alcohols. Therefore, we were optimistic that we would be able to perform a Tishchenko reaction utilising methoxy methanol as a formaldehyde source.

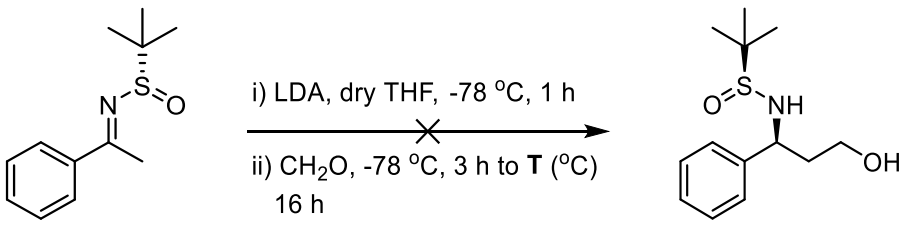
Methoxy methanol was readily prepared by heating a solution of paraformaldehyde in anhydrous THF and methanol in a pressure tube for 1 hour **(Scheme 91)**. Once cooled, the solution was then adjusted to 10 mL by the of THF. This 2M solution of methoxy methanol in THF could then be stored in the sealed vessel for up to two weeks.



Scheme 91. Preparation of methoxy methanol

With the formaldehyde source in hand, we applied our aldol-Tishchenko conditions to acetophenone sulfinyl imine **(*S*)-199** and methoxy methanol **(Table 17)**. Notably, Suna and co-workers observed that a five fold excess of methoxy methanol was necessary to achieve high yields and diastereoselectivity in their enantioselective aldol reaction.[15] Thus, the aldol-Tishchenko reaction was conducted using 10 equivalents of methoxy methanol. However, the desired hydroxy methylated product **245** was not observed after warming the mixture to -20 °C over 16 h **(Table 17, entry 1)**. Under these conditions, the ^{1}H NMR spectrum revealed a complex mixture of products and starting material. Aldol-Tishchenko product **245** and aldol-product were tentatively assigned by mass spectrometry analysis. Isolation of either of these products was not pursued. Warming the aldol-Tishchenko reaction mixture to room temperature over 16 h resulted in no improvement **(Table 17, entry 2)**. This unsuccessful result deterred us from further studies with this aldol acceptor.

Table 17. Attempted hydroxymethylation of **(*S*)-199**

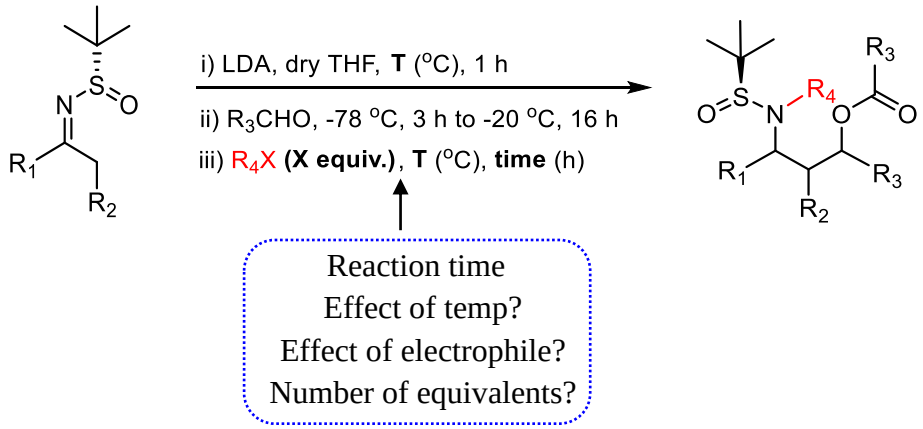


(*S*)-199 **245**

Entry	Sulfinyl imine (Equiv.)	Methoxy methanol (Equiv.)	Temperature (°C)	Time (h)	Result
1	**(*S*)-199**	10	-20	16 h	No product formation
2	**(*S*)-199**	10	RT	16 h	No product formation

5.3.3 Synthesis of *N*-alkylated 1,3-amino alcohols

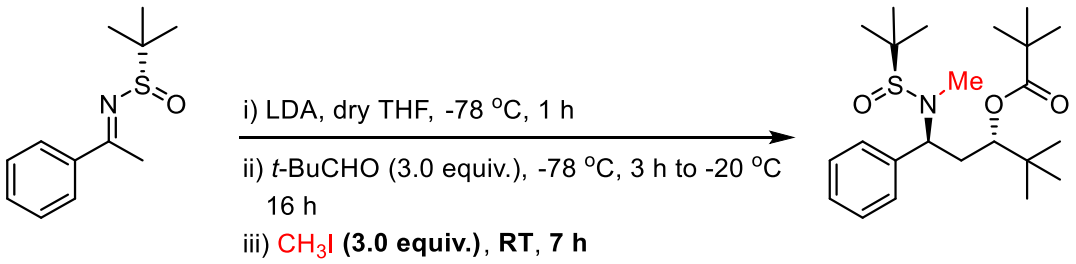
Next, we wanted to explore the possibility of using an alternative quench procedure in the synthesis of *N*-alkylated 1,3-amino alcohol derivatives **(Scheme 92)**. By quenching the lithiated aldol-Tishchenko product **247** with alkyl halides such as methyl iodide and allyl bromide, a new C-N bond in addition to two or three new chiral centres could be formed in one synthetic step. Cleavage of the ancillaries would then provide access to chiral secondary amines **248**. Secondary amines are ubiquitous structural motifs and serve as valuable synthons for pharmaceuticals[16] and functionalized materials.[17]



247 **248**

Scheme 92. Potential route to chiral secondary amines

A number of reaction parameters including alkylation temperature, time and electrophiles were evaluated through a series of reactions. The reaction of acetophenone sulfinyl imine **(*S*)-199** with pivaldehyde was chosen as our model reaction. Investigations began by quenching the reaction mixture with 3.0 equivalents of methyl iodide at -20 °C after 16 hours, followed by slowly warming to room temperature **(Scheme 93)**. After a period of 7 hours, we were pleased to observe a 39% conversion to the desired *N*-methylated product **(*S*,*S*,*S*)-249**, as determined by ^{1}H NMR analysis.



(*S*)-199

(*S*,*S*,*S*)-249
39% conversion

Scheme 93. Attempted *N*-methylation

The % conversion was calculated from the ratio of the *N*-H and *N*-Me products **(*S*,*S*,*S*)-202** and **(*S*,*S*,*S*)-249** along with two of the previously discussed impurities **218** and **219** from the ^{1}H NMR spectrum of the crude reaction mixture **(Figure 25)**. The 1H dd corresponding to H-1 of **(*S*,*S*,*S*)-249** and the *N*-H doublet corresponding to **(*S*,*S*,*S*)-202** with no interfering overlapping signals proved to be the most discernible peaks in the ^{1}H NMR spectrum. Thus, these signals were used to calculate the % conversion throughout this study. Following purification by column chromatography, the desired *N*-Me product **(*S*,*S*,*S*)-249** was isolated in a yield of 37%.

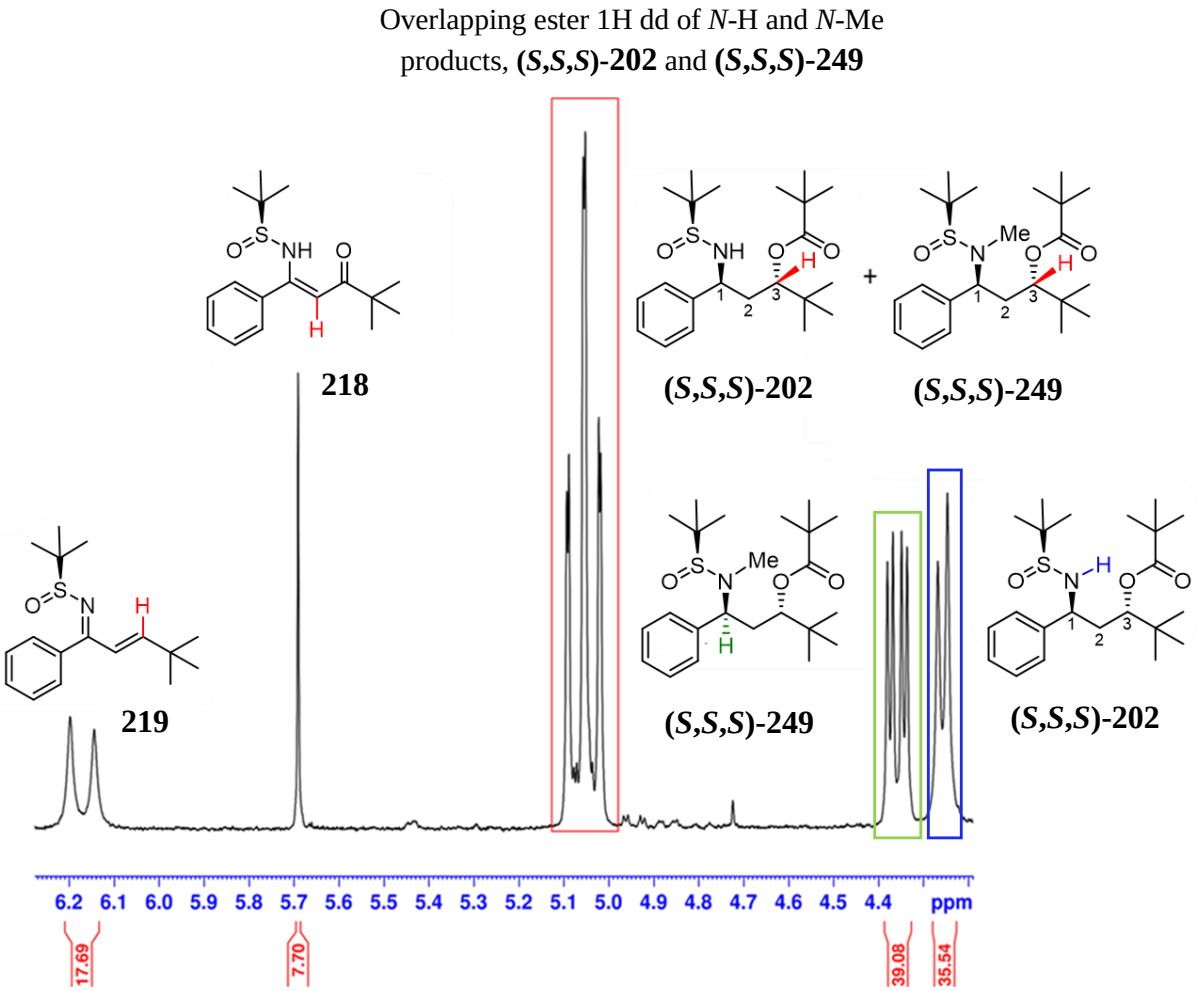


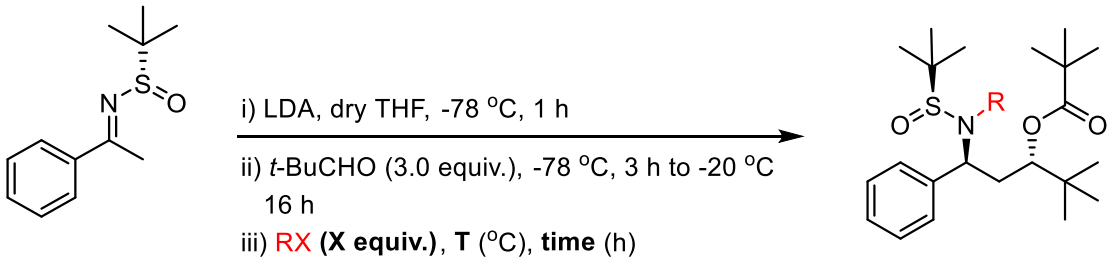
Figure 25. ^{1}H NMR spectrum showing 39% conversion to *N*-methylated aldol-Tishchenko product **(*S*,*S*,*S*)-249**

We then felt that we could improve on this result *via* modification of the reaction conditions. Thus, we decided to increase the number of equivalents of methyl iodide to 5.0 equivalents. The quench was also performed at -40 ^{o}C **(Table 18, entry 2)**. However, this proved unsuccessful and only a 26% conversion to desired product was observed. Consequently, the temperature was then increased following addition of the electrophile in the hope that we could drive the reaction to completion. However, warming to 25 ^{o}C overnight only resulted in a slight increase in conversion **(Table 18, entry 3)**. Increasing the temperature to 45 ^{o}C resulted in no further improvement **(Table 18, entry 4)**.

Next, the effect of quenching the reaction with a more reactive electrophile was examined. Employing allyl bromide afforded only 10% conversion to **250 (Table 18, entry 5)**. Additionally, no product was detected utilising TMSCl **(Table 18, entry 6)**. After having

investigated a number of reaction variables, we found that no further improvement in conversion could be obtained.

Table 18. Alternative quench method with acetophenone sulfinyl imine **(*S*)-199** and pivaldehdye



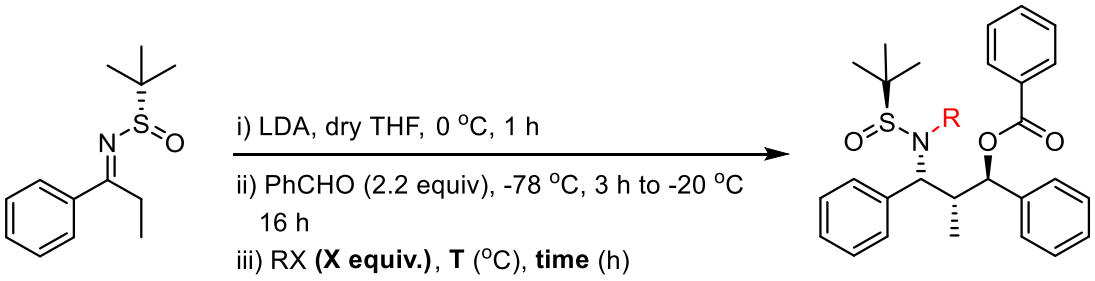
(*S*)-199 **250**

Entry	SM	RX (Equiv.)	Temperature (°C)	Time (h)	Conversion (%)	Yield[a] (%)
1	**(*S*)-199**	CH_3I (3.0)	-20 to RT	7	39	37[a]
2	**(*S*)-199**	CH_3I (5.0)	-40 to RT	7	26	n.d.
3	**(*S*)-199**	CH_3I (5.0)	-20 to 25	o/n	41	n.d.
4	**(*S*)-199**	CH_3I (5.0)	-20 to 45	o/n	39	n.d.
5	**(*S*)-199**	AllylBr (3.0)	-20 to RT	7	<10	n.d.
6	**(*S*)-199**	TMSCl (5.0)	-20 to 25	o/n	0	n.d.

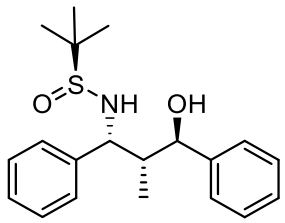
[a]Isolated yield following purification by column chromatography.

A small study using propiophenone sulfinyl imine **(*S*)-205** and benzaldehyde was also conducted **(Table 19)**. Unfortunately, attempts to form the *N*-methylated product **251** using 5.0 equivalents of methyl iodide and allyl bromide proved unsuccessful. In fact, in each case we failed to see any conversion to desired product. ^{1}H NMR analysis indicated that significant ester hydrolysis **(252)** had occurred in both cases.

Table 19. Alternative quench method with propiophenone sulfinyl imine **(*S*)-205** and benzaldehyde



(*S*)-205 **251**

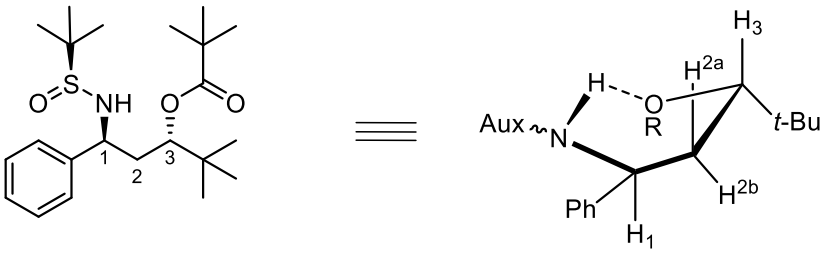


252
Cleaved alcohol product

Entry	SM	RX (Equiv.)	Temperature (°C)	Time (h)	Conversion (%)	Yield (%)
1	**(*S*)-205**	CH_3I (5.0)	-20 to RT	o/n	0	n.d.
2	**(*S*)-205**	AllylBr (5.0)	-20 to RT	o/n	0	n.d.

In summary, limited success was achieved using this alternative quench protocol. The highest conversion was obtained when acetophenone sulfinyl imine **(*S*)-199** was treated with pivaldehdye and subsequently quenched with 3.0 or 5.0 equivalents of methyl iodide at -20 °C. Warming the mixture to room temperature over 7 hours resulted in a 39% conversion to the *N*-methylated product **(*S*,*S*,*S*)-249** giving a 37% isolated yield. A similar result was obtained when the reaction mixture was left warm to 45 °C overnight. Unfortunately, only poor conversion to desired product was observed using allyl bromide while no product formation was observed with TMSCl. Attempts to promote product formation by warming the reaction mixture over an extended period of time also failed to improve the results. Investigations utilising propiophenone sulfinyl imine **(*S*)-205** proved unsuccessful.

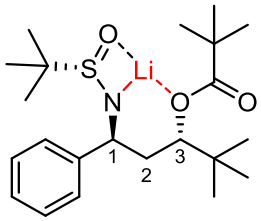
The poor reactivity of the *N*-lithiated aldol-Tishchenko intermediate may be attributed to a number of factors. Firstly, the reaction of the *N*-lithiated intermediate with methyl iodide would be expected to occur *via* an S_N2 mechanism. In general, S_N2 reactions are sensitive to steric effects including the size of the approaching nucleophile. Thus, the *N*-lithiated intermediate may not serve as an efficient nucleophile. This may also be the case for allyl bromide although allylic halides can react *via* S_N1 or S_N2 mechanisms. Nucleophilic substitution of the *N*-lithiated intermediate with TMSCl as an electrophile resulted in no desired product formation. Substitution reactions with TMSCl proceed through a pentacoordinated intermediate which in this case would be disfavoured due to steric interactions. While the aforementioned reaction mechanisms may explain the poor results obtained, it is possible that the poor reactivity of the *N*-lithiated intermediate may be related to the structure of the preliminary Tishchenko product in solution. Previous work carried out within the group suggested that the structure of **(*S*,*S*,*S*)-202** lies in a boat conformation in solution whereby a hydrogen-bonding interaction exists between the N-H proton and the pivalate O-atom **(Figure 26)**.[4]



(*S*,*S*,*S*)-202

Figure 26. Structure of aldol-Tishchenko product in solution

Therefore, it is likely that an intramolecular interaction exists between the lithiated nitrogen atom (N-Li) and that of the pivalate O-atom **(Figure 27)**. In addition, the lithium atom could also interact with the sulfoxide O-atom. This would result in a highly congested intermediate **253** that would most likely be relatively unreactive towards an electrophile.

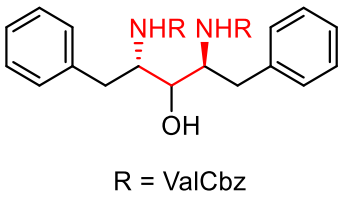


253

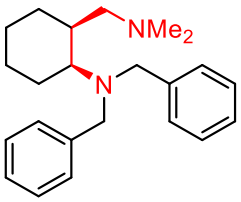
Figure 27. *N*-lithiated intermediate **253**

5.3.4 Synthesis of 1,3-diamines

We were then interested if we could synthesize 1,3-diamines through our aldol-Tishchenko methodology. Compounds possessing the 1,3-diamine structural motif are prevalent in many natural products and pharmaceuticals.[18] In particular, chiral 1,3-diamines are key building blocks in the synthesis of bioactive compounds such as the HIV-1 protease inhibitor, A-74704 **254 (Figure 28)**.[19] Moreover, they have also been used as efficient chiral ligands in asymmetric transition metal catalysis **255 (Figure 28)**.[20]



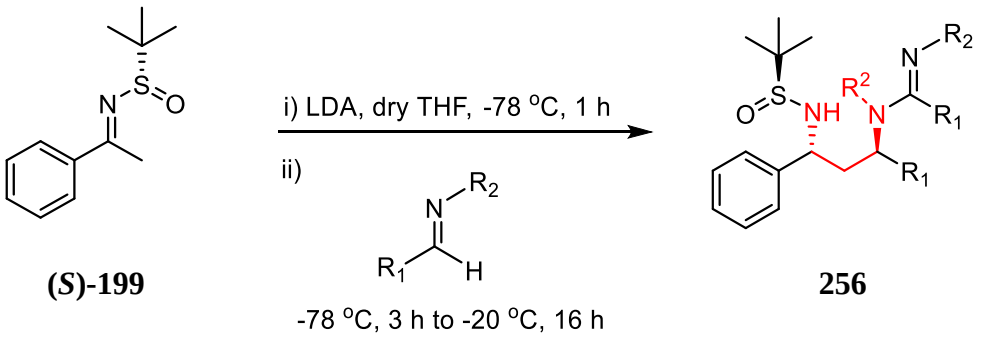
254



255

Figure 28. Pharmaceuticals and chiral ligands containing the 1,3-diamine motif

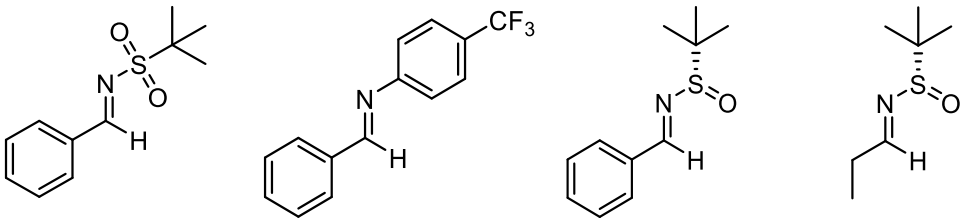
By substituting an aldehyde for an aldimine as an aldol acceptor, we anticipated that we could form 1,3-diamines in a diastereo- and enantioselective fashion **(Scheme 94)**. This would provide a novel approach to access these synthetically useful building blocks.



(*S*)-199 **256**

Scheme 94. Synthesis of 1,3-diamine derivatives

To begin, a number of aldimines varying in both steric and electronic properties were identified as potential aldol acceptors **(Figure 29)**. It was imperative that the aldimine was sufficiently electron withdrawing in order to facilitate an aldol reaction. The relatively low electrophilicity of imines means that an electron withdrawing *N*-substituent is often required to enhance their reactivity.[21]

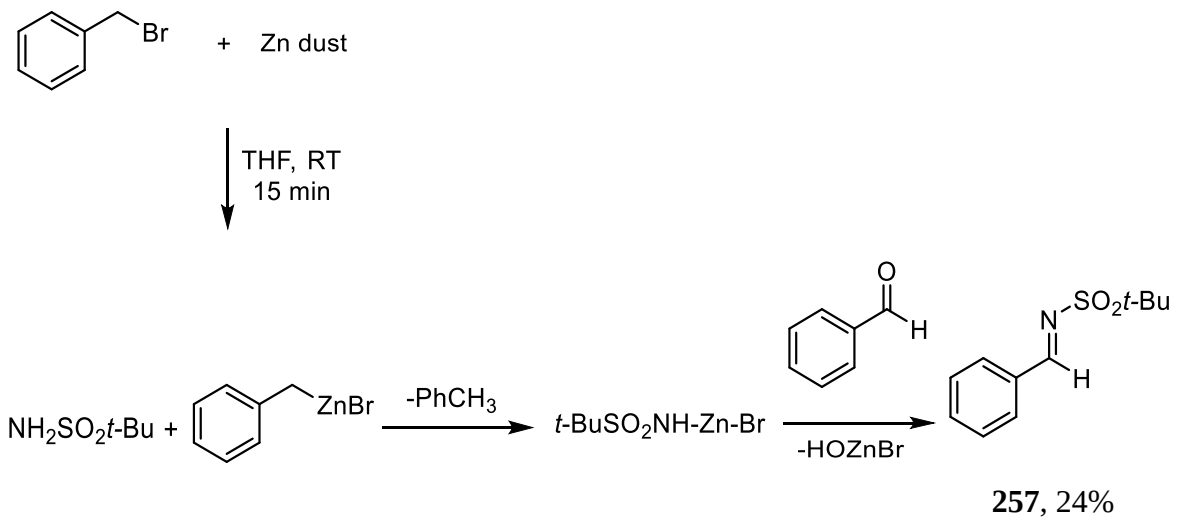


257 **258** **(*S*)-259** **(*S*)-227**

Figure 29. Potential aldol acceptors

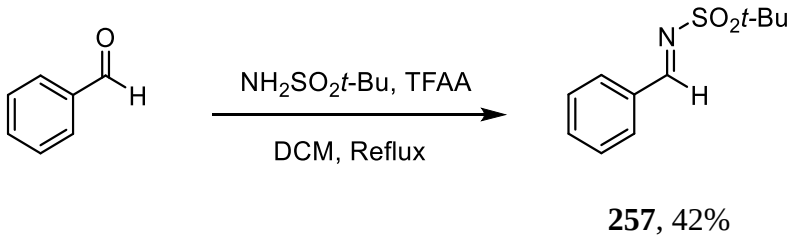
A publication by Lanter and co-workers has demonstrated the application of *N*-*tert*-butanesulfonyl imine **257** in an aza-Mannich reaction with acetophenone sulfinyl imine **(*S*)-199**.[22] Thus, we were intrigued if we could apply this aldimine to our aldol-Tishchenko conditions. Firstly, we wanted to see if we could synthesise **257** under mild conditions and using readily available reagents. Thus, we attempted to prepare **257** using a simple procedure outlined by Fan and co-workers.[23] This was accomplished *via* condensation of benzaldehyde and *tert*-butylsulfonamide in the presence of zinc dust and benzyl bromide at room temperature under Barbier-type conditions **(Scheme 95)**. Examination of the ^{1}H NMR spectrum of the crude reaction mixture indicated low conversion to **257**. Purification of the crude product by

recrystallisation in EtOH gave **257** in a poor yield of 24%. We then decided to search for an alternative procedure to see if we could improve the conversion.



Scheme 95. Synthesis of **257** under Barbier-type reaction conditions

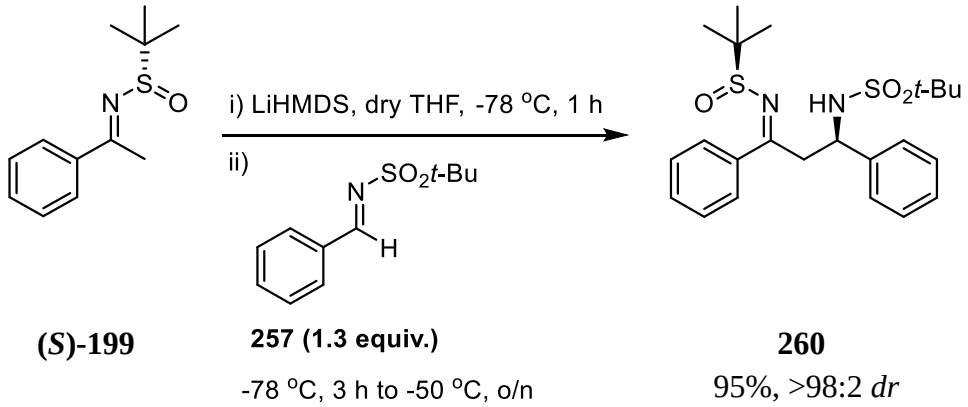
A search of the literature identified a practical synthesis of **257** using trifluoracetic anhydride as a dehydrating agent **(Scheme 96)**.[24] Thus, the synthesis of **257** was achieved by reaction of benzaldehyde and *tert*-butylsulfonamide in dichloromethane in the presence of trifluoracetic anhydride. The reaction progress was monitored by TLC analysis. Although the authors reported an 88% yield, we failed to replicate this result. Following purification by column chromatography, aldimine **257** was isolated in a yield of 42%.

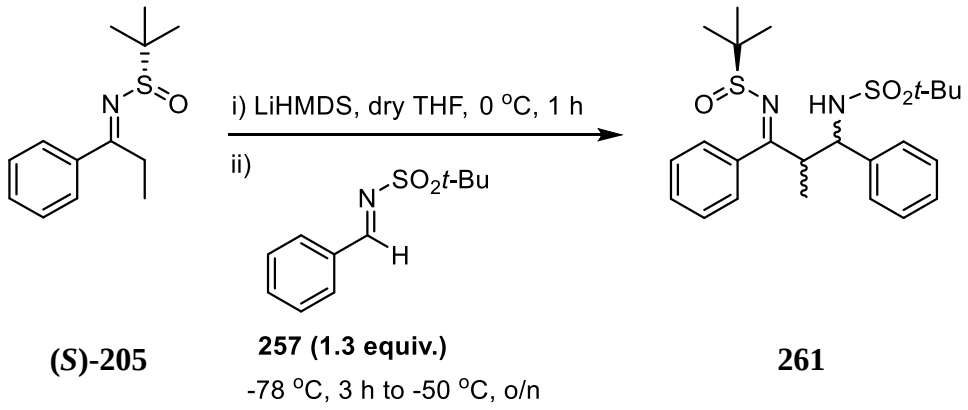


Scheme 96. Improved synthesis of **257**

We initiated our study by attempting to reproduce the aza-Mannich reaction reported by Lanter and co-workers in which acetophenone sulfinyl imine **(*S*)-199** was utilised as the nucleophile and *N*-*tert*-butanesulfonyl imine **257** as an aldol acceptor.[22] Notably, a general procedure for this transformation was absent in the paper, thus, we wanted to establish reaction conditions

for the aldol addition step prior to attempting the aldol-Tishchenko transformation. Additionally, the authors utilised LiHMDS as base for these reactions. As previously mentioned, comparable yields and diastereoselectivity are achieved using LDA and LiHMDS under our established reactions conditions. Thus, the azaenolate of **(*S*)-199** was generated using LiHMDS **(Scheme 97)**. Pleasingly, aldol product **260** was isolated in excellent diastereoselectivity (>98:2 *dr*) and a yield of 95% was achieved following purification by column chromatography. Attempts to apply propiophenone sulfinyl imine **(*S*)-205** to these reaction conditions resulted in poor conversion to aldol product **261**. Unreacted starting material as well as decomposition of aldimine **257** was observed by ^{1}H NMR analysis of the crude material.

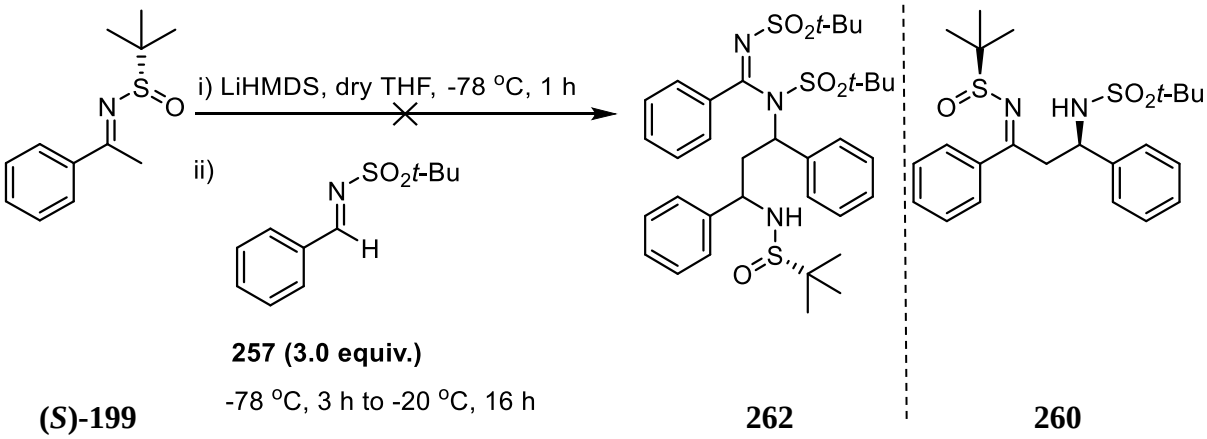




Scheme 97. Aldol reactions using aldimine **257**

The next logical step was to subject acetophenone sulfinyl imine **(*S*)-199** and aldimine **257** to our standard aldol-Tishchenko conditions **(Scheme 98)**. Unfortunately, no aldol-Tishchenko product **262** was detected. Examination of the ^{1}H NMR spectrum indicated the presence of

aldol product **260**. Due to the reversibility of the aldol reaction, starting materials (**(*S*)-199** and **257**) in addition to decomposition products of **257** (benzaldehyde and *tert*-butylsulfonamide) were also detected.

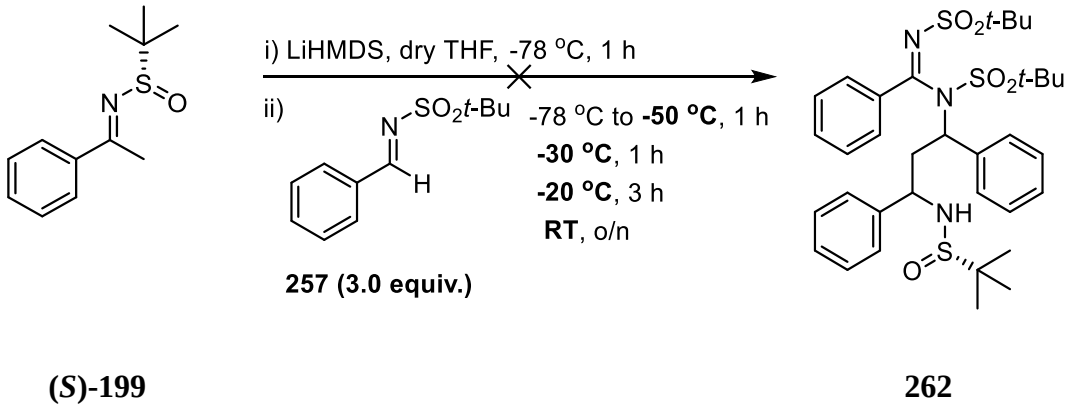


Scheme 98. Aldol-Tishchenko reaction utilising aldimine **257**

In an attempt to gain an insight into this process, we decided to carefully monitor the progress of the reaction following addition of the aldol acceptor **(Figure 30)**. Firstly, the reaction mixture was slowly warmed to room temperature overnight and a sample of the mixture was examined *via* ^{1}H NMR spectroscopy at different temperatures. At -50 °C, aldol product **260** as well as *N*-*tert*-butanesulfonyl imine **257**, benzaldehyde and *tert*-butylsulfonamide were present, and complete consumption of acetophenone sulfinyl imine **(*S*)-199** was noted. After stirring for 1 hour at -30 °C, another sample of the reaction mixture was taken and examined *via* ^{1}H NMR spectroscopy. At -30 °C, no desired aldol-Tishchenko formation was observed and only aldol product **260**, *N*-*tert*-butanesulfonyl imine **257** and products formed from the decomposition of *N*-*tert*-butanesulfonyl imine **257** were detected. Disappointingly, increasing the temperature to -20 °C also showed no evidence of the Tishchenko product.

We then decided to warm the mixture to room temperature overnight to see if we could promote the Tishchenko step. However, retro-aldolisation of the lithium aldolate generated the acetophenone sulfinyl imine **(*S*)-199** enolate and *N*-*tert*-butanesulfonyl imine **257**. Subsequently, warming the reaction mixture to room temperature resulted in degradation of acetophenone sulfinyl imine **(*S*)-199** and *N*-*tert*-butanesulfonyl imine **257**. Thus, no aldol product was detected once the mixture was warmed to room temperature overnight. Only

benzaldehyde and *tert*-butylsulfonamide along with degraded sulfinyl imine were recovered following work-up.



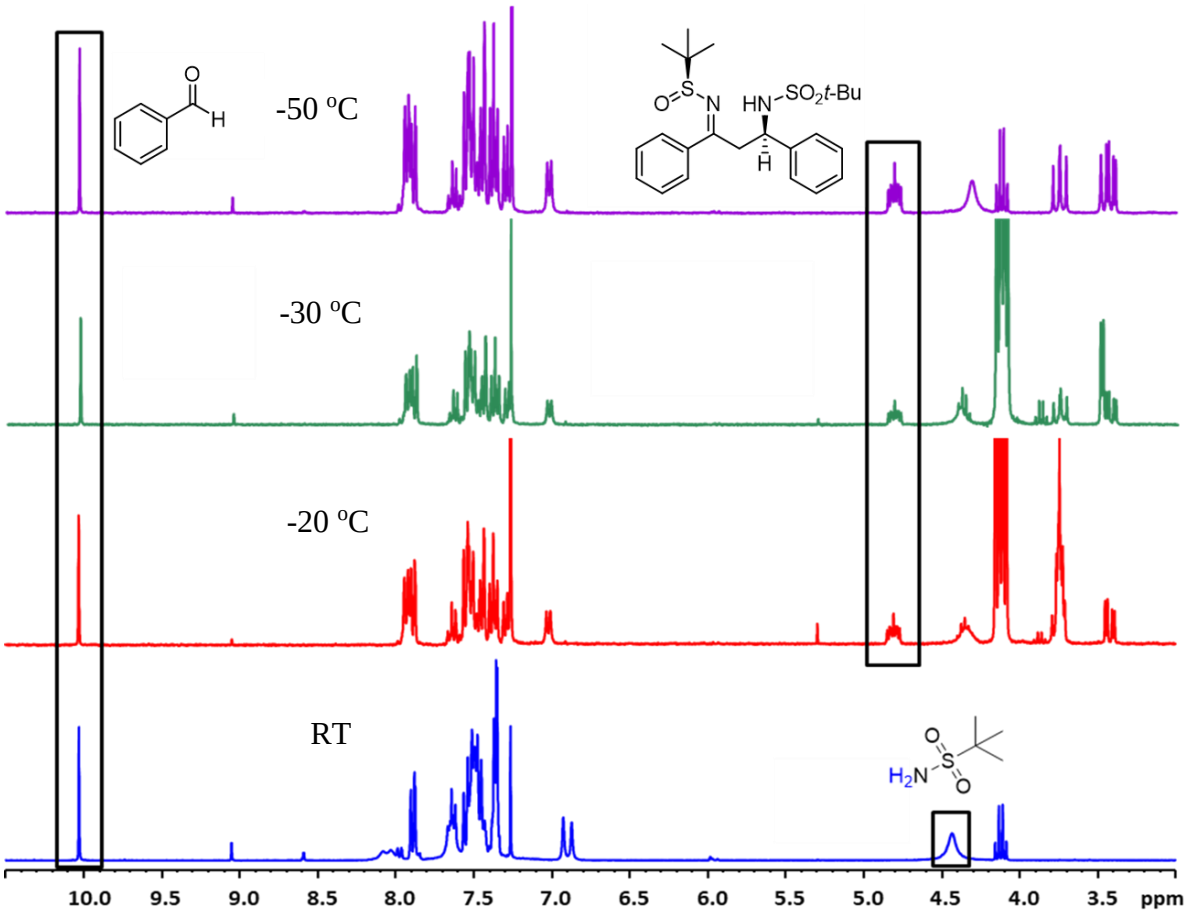
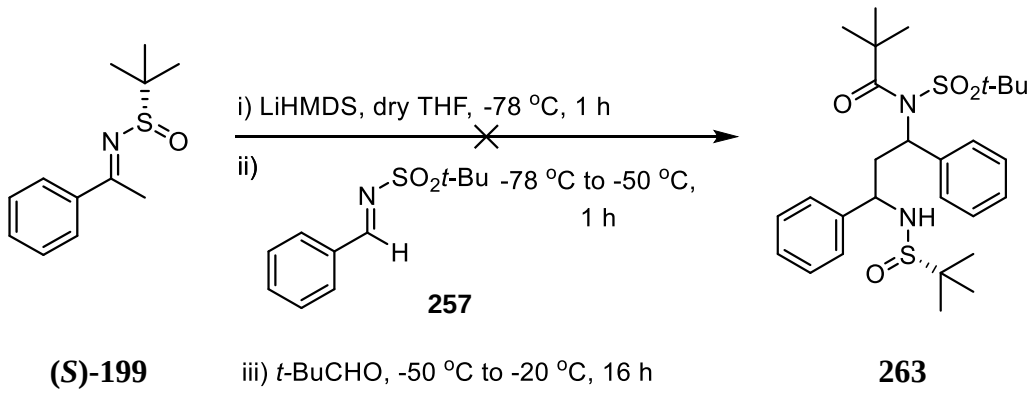


Figure 30. Reaction monitoring *via* ^{1}H NMR spectroscopy and overlay of ^{1}H NMR spectra recorded at different temperatures

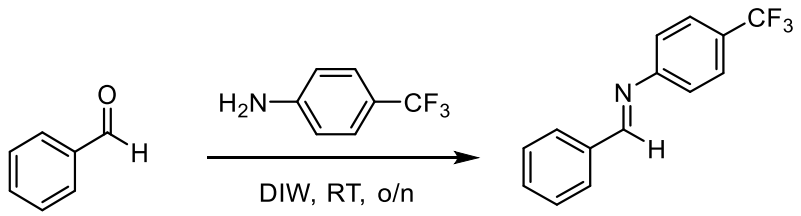
Application of *N*-*tert*-butanesulfonyl imine **257** in our aldol-Tishchenko reaction proved unsuccessful. The results from the aforementioned reactions demonstrate that while this imine does undergo aldol addition, it does not facilitate a Tishchenko reaction. However, we were interested to determine if we could use a second aldol acceptor to promote the Tishchenko step. Therefore, we decided to investigate the use of a sacrificial aldehyde which had been previously shown to provide the hydride necessary for the Tishchenko step. Thus, we attempted to carry out the Tishchenko step using 1.0 equivalent of pivaldehyde **(Scheme 99)**.

Firstly, the aldol step was performed using acetophenone sulfinyl imine **(*S*)-199** and 1.0 equivalent of aldimine **257**. After 1 hour at -50 ^{o}C, 1.0 equivalent of pivaldehyde was added with the anticipation that this aldehyde would undergo a Tishchenko reaction with the preformed lithium aldolate. The reaction mixture was then slowly warmed to -20 ^{0}C over a period of 16 h. Unfortunately, this strategy proved unsuccessful. ^{1}H NMR analysis revealed a mixture of products including aldol product **260** and imine decomposition products (benzaldehyde and *tert*-butylsulfonamide). In addition, a minor amount of aldol product formed from the reaction between acetophenone sulfinyl imine **(*S*)-199** and pivaldehyde was also detected which is most likely due to the reversibility of the aldol step.



Scheme 99. Investigation of a sacrificial aldehyde to promote a Tishchenko reaction

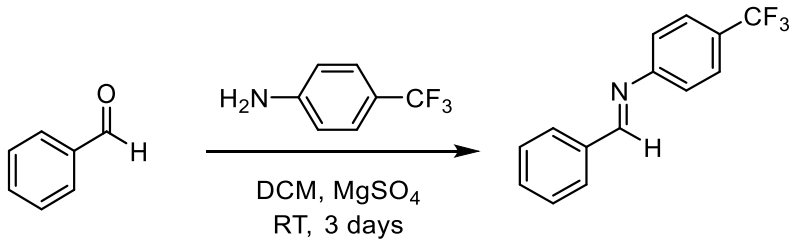
Having achieved little success with *N*-*tert*-butanesulfonyl imine **257**, we decided to alter the *N*-substituent. Hence, *N*-aryl aldimine **258** containing a strongly electron withdrawing substituent was chosen as a potential aldol acceptor. Following a literature procedure,[25] **258** was prepared by stirring equimolar amounts of benzaldehyde and *p*-trifluoromethylaniline in deionized water at room temperature overnight **(Scheme 100)**. Purification by recrystallisation in dichloromethane furnished the product in a poor isolated yield of 16%.



258, 16%

Scheme 100. Synthesis of **258**

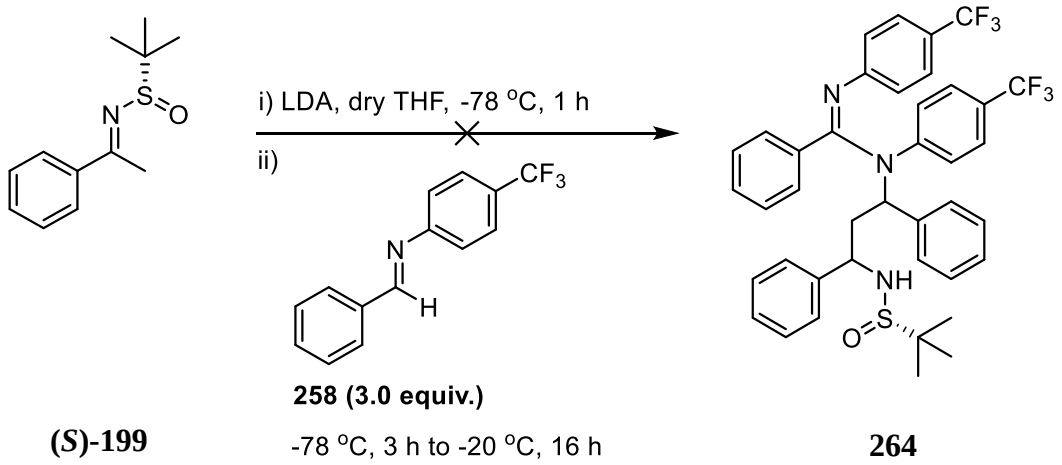
An alternative procedure was then sought in order to improve the yield. Utilising a procedure optimised by a member within our group, equimolar amounts of benzaldehyde and *p*-trifluoromethylaniline were stirred vigorously in the presence of anhydrous $MgSO_4$ and dichloromethane at room temperature over a period of three days **(Scheme 101)**. Gratifyingly, this procedure furnished **258** in an improved yield of 80%.



258, 80%

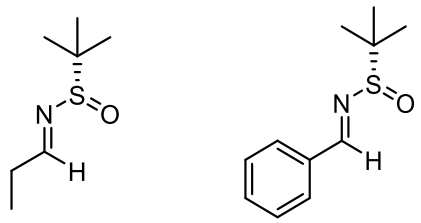
Scheme 101. Improved synthesis of **258**

Aldimine **258** was then subjected to our aldol-Tishchenko conditions with acetophenone sulfinyl imine **(*S*)-199 (Scheme 102)**. However, only unreacted starting material and aldimine **258** were recovered from the crude reaction mixture.



Scheme 102. Aldol-Tishchenko reaction utilising aldimine **258**

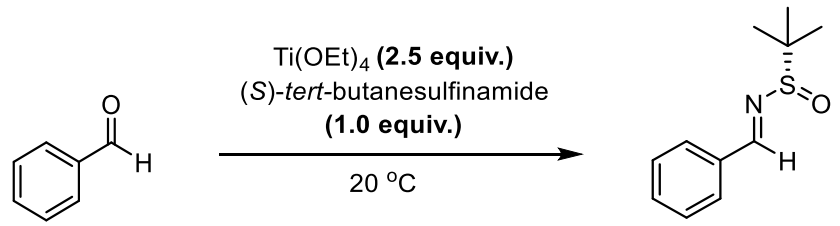
Finally, we made one last attempt to substitute an aldimine for an aldehyde by replacing the aldol donor with a ketone. We reasoned that the absence of the steric bulk of the *t*-Bu group on the sulfinyl imine might favour hydride transfer from the aldimine to the ketone. For this purpose, two chiral sulfinyl imines **(*S*)-227** and **(*S*)-259** were chosen as potential aldol acceptors and hydride donors to enable enantio- and diastereoselective transformations **(Figure 31).**



(*S*)-227 **(*S*)-259**

Figure 31. Chiral sulfinyl imines

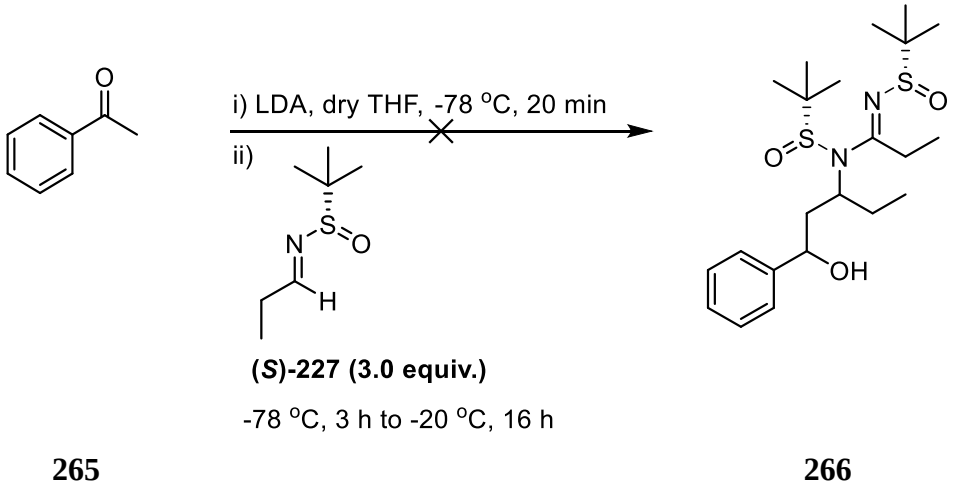
Ellman has demonstrated the utility of **(*S*)-227** as an aldol acceptor in a self-condensation reaction.[6] This aldimine had been previously prepared earlier in the project **(Section 5.3.1)**. Following a literature procedure, (*S*)-*tert*-butanesulfinyl imine **(*S*)-259** was isolated in an excellent yield of 91% **(Scheme 103)**.[26]



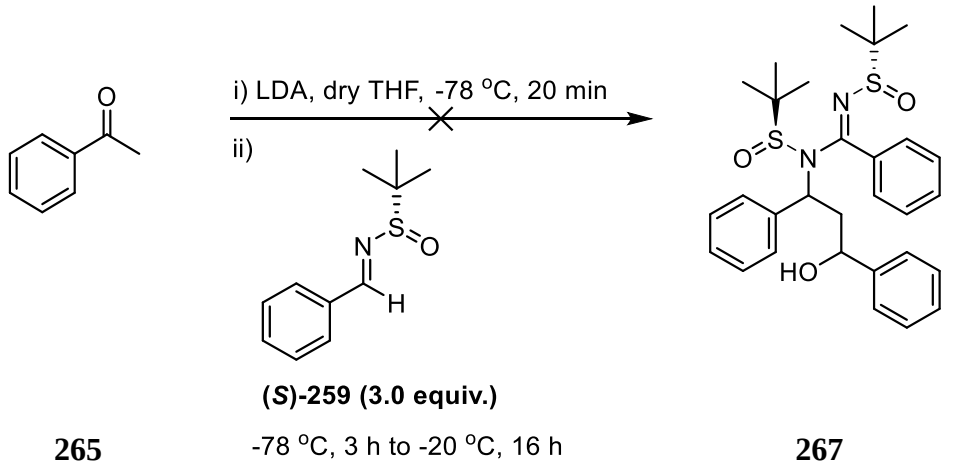
(1.1 equiv.) **(*S*)-259**, 91%

Scheme 103. Preparation of **(*S*)-259**

Attempts to react acetophenone **265** with **(*S*)-227** and **(*S*)-259** under our aldol-Tishchenko reaction conditions proved unsuccessful. In both cases, only starting materials and minor amounts of aldol product were recovered following work-up **(Scheme 104)**.



265 **266**



265 **267**

Scheme 104. Attempted aldol-Tishchenko reactions using aldimines **(*S*)-227** and **(*S*)-259**

In summary, investigations into utilising aldimines as aldol acceptors and hydride donors proved unsuccessful. Disappointingly, no desired product formation was observed in any of these reactions. While a few of the aldimines proved reactive and underwent aldol reactions, it was found that in most cases, only unreacted starting materials and decomposition of aldimine was observed. Perhaps, the presence of the *N*-substituent on the imine results in the formation of an unfavoured intermediate **269** which does not facilitate hydride transfer **(Figure 32)**. The R groups on the aldimine are likely to disfavour reaction of aldolate **268** with a second equivalent of imine. As is evident from the intermediates **269a** and **269b**, a number of sterically unfavoured interactions would disfavour a Tishchenko reaction.

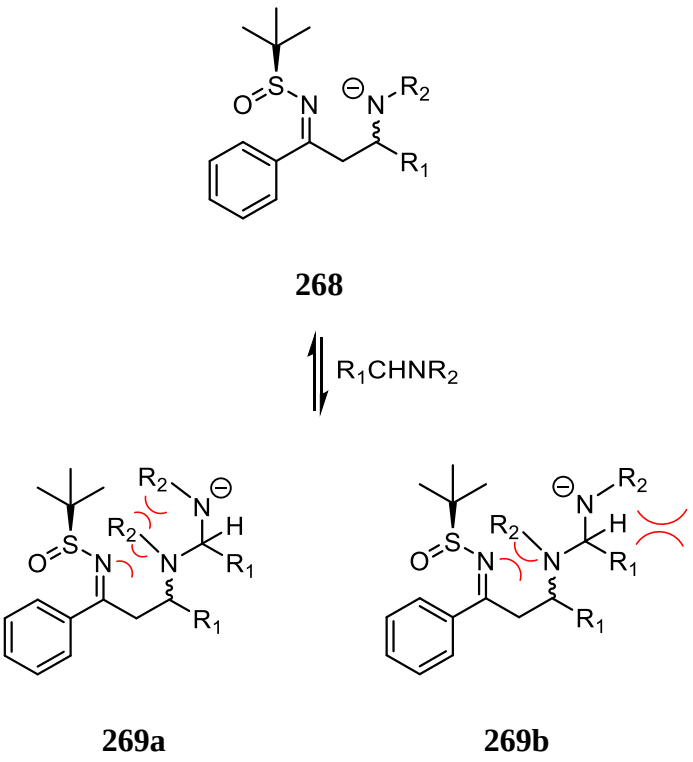


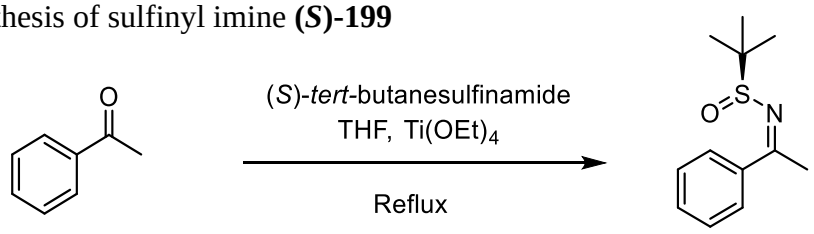
Figure 32. Unfavoured steric interactions

5.3.5 Aldol-Tishchenko scale-up

Following an invitation from the board of editors from the journal Organic Syntheses, we were delighted to get the opportunity to demonstrate the reproducibility of our aldol-Tishchenko methodology.[27] Organic Syntheses provides reliable and detailed procedures for the synthesis of organic compounds. One of the key objectives of this journal is to provide the chemistry community with important synthetic methods for general utility. Our challenge would be to scale-up 1,3-amino alcohol derivative **(*S*,*S*,*S*)-271** from our previously published aldol-Tishchenko reactions **(Scheme 105)**.[3]

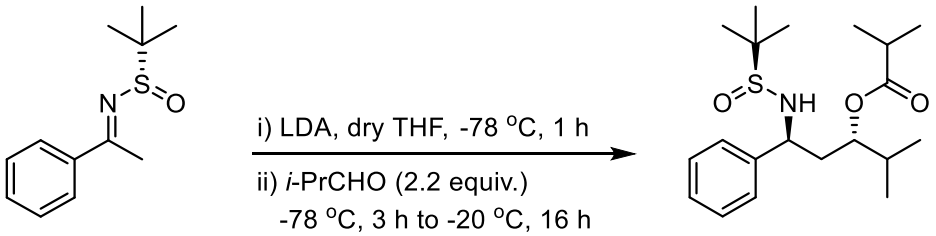
Published work

Step 1: Synthesis of sulfinyl imine **(*S*)-199**



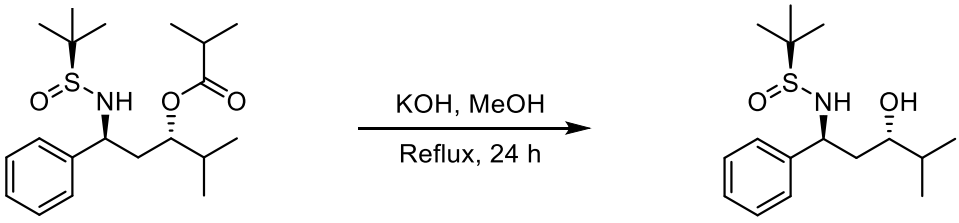
265 **(*S*)-199**, 75%

Step 2: Aldol-Tishchenko reaction



(*S*)-199 **(*S*,*S*,*S*)-270**
61%, 98:2 *dr*

Step 3: Cleavage of ancillary



(*S*,*S*,*S*)-270 **(*S*,*S*,*S*)-271**, 70%

Scheme 105. Three step synthesis of **(*S*,*S*,*S*)-271**

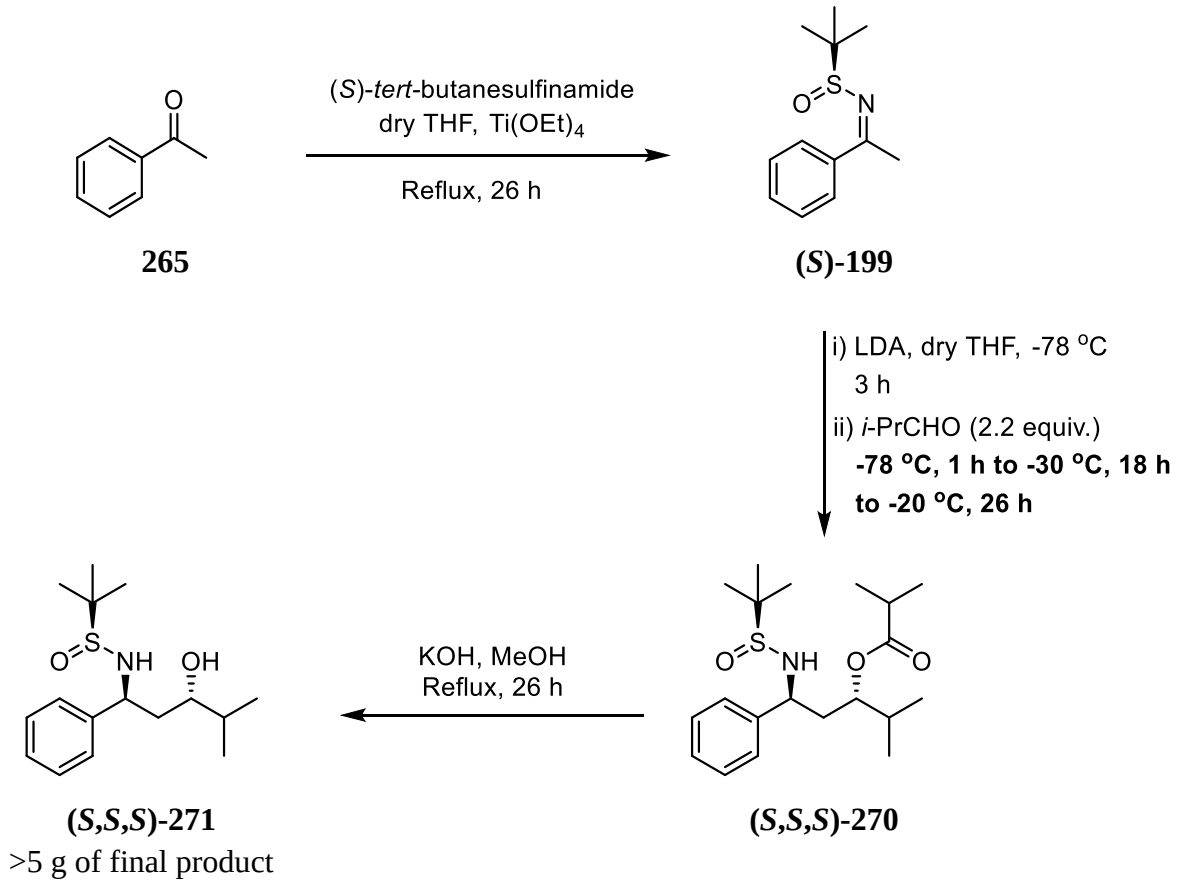
The aim of the scale-up was to prepare >5 g of final product **(*S*,*S*,*S*)-271**. Thus, it was necessary to scale-up the reaction by a factor of 60 from the previously published conditions. A detailed account of all experimental procedures is required for the Organic Syntheses journal. Furthermore, photographs exemplifying key reaction elements are also required. An additional prerequisite is that the scale-up reaction must be performed at least twice in order to ensure reproducibility of the process. Following completion of the scale-up, the results were then submitted to the journal Organic Syntheses. Finally, each reaction was then carefully checked in the laboratory of a member of the Board of Editors.

Scaling up a chemical process can provide the synthetic chemist with a number of challenges.[28] Thus, several factors need to be addressed when performing a reaction on scale-up which can affect both the yield and quality of the product:

1. As the scale increases, it is likely that the time required to carry out each synthetic operation will increase. In addition, increased addition times are required for each reagent.
2. Cooling the reaction mixture on a large scale may lead to increased viscosity of the solvent as well as lower solubility of the reactants and products. This can lead to problems in mixing and a non-homogenous reaction mixture.
3. For asymmetric syntheses, the selectivity of the process may also be affected.
4. Problems can also be encountered during the extraction process. The separation efficiency may be impacted due to increased separation times and possible formation of emulsions. This can affect yield as well as product quality.
5. Purification of the product can also be problematic, for example, the formation of different polymorphs and additional impurities may affect the recrystallisation process.
6. Finally, evaluation of all safety aspects and undertaking a sufficient risk assessment is of paramount importance for scaling up a laboratory process.

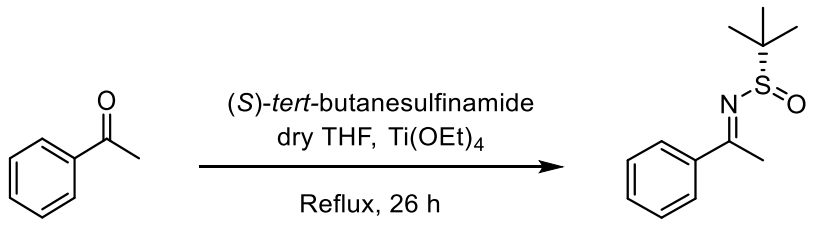
Our scale-up reaction would involve a linear three step synthesis of 1,3-amino alcohol derivative **(*S*,*S*,*S*)-271 (Scheme 106)**.

Objective



Scheme 106. Aldol-Tishchenko scale-up reaction

The three step synthesis of the desired 1,3-amino alcohol derivative **(*S*,*S*,*S*)-271** was conducted following our aldol-Tishchenko conditions accompanied by minor modifications to facilitate the larger scale. The first step of the scale-up reaction involved preparation of acetophenone sulfinyl imine **(*S*)-199**. Condensation of acetophenone **265** with (*S*)-*tert*-butanesulfinamide in the presence of $Ti(OEt)_4$ provided 9.443 g of **(*S*)-199** in a yield of 67% **(Scheme 107)**. The purity of the product was calculated to be 97% *via* quantitative ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

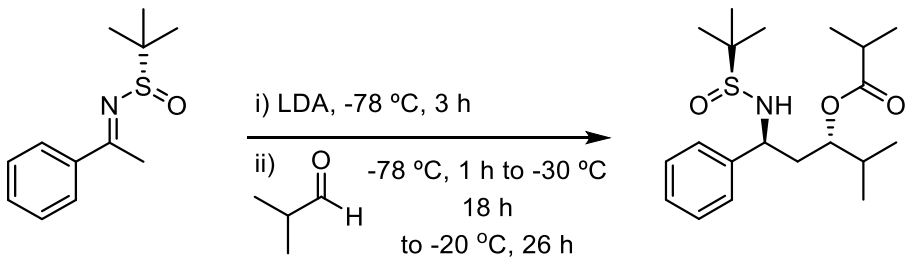


265

(*S*)-199
Yield: 9.443 g, 67%
Purity: 97%

Scheme 107. Synthesis of acetophenone sulfinyl imine **(*S*)-199**

The next step was to subject acetophenone sulfinyl imine **(*S*)-199** to our aldol-Tishchenko reaction conditions **(Scheme 108)**. Due to the fact that the reaction was being conducted on a much larger scale, both the rate of reaction and rate of cooling had to be considered. Therefore, we decided to perform the initial deprotonation step at -78 ^{o}C for 3 h. The aldehyde addition step was also slightly modified to ensure that the reaction would go to completion. Following deprotonation, isobutyraldehyde was added slowly over a period of 30 mins at -78 ^{o}C. The reaction mixture was held at this temperature for 1 hour. It was then slowly warmed to -30 ^{o}C through the use of a cryocooler. The mixture was then kept at -30 ^{o}C for 18 h. Finally, the temperature was increased to -20 ^{o}C for an additional 26 h. Following work-up, **(*S*,*S*,*S*)-270** was obtained with very high diastereoselectivity (98:2 *dr*). We decided not to isolate the sulfinyl ester due to concerns over loss of material during column chromatography. Instead, the reaction was telescoped through the ester cleavage step and **(*S*,*S*,*S*)-270** was subsequently used in the next step without further purification.



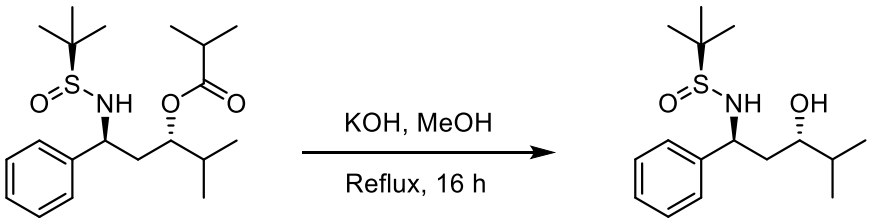
(*S*)-199

(*S*,*S*,*S*)-270
98:2 *dr*

Scheme 108. Step 2

The final step of the scale-up involved cleavage of the ester moiety to give the 1,3-amino alcohol product **(*S*,*S*,*S*)-271 (Scheme 109)**. The removal of the *tert*-butanesulfinyl group was

carried out by heating **(*S*,*S*,*S*)-270** at reflux temperature under basic conditions. Over 3.3 g of final product **(*S*,*S*,*S*)-271** was isolated following recrystallisation of the crude material to give an overall yield of 26%. The purity of the final product was determined to be 97% by NMR spectroscopy.



(*S*,*S*,*S*)-270 **(*S*,*S*,*S*)-271**
Overall yield: 26%
Purity: 97%

Scheme 109. Step 3

The absolute configuration of the major diastereomer was determined to be **(*S*,*S*,*S*)** by X-ray crystallographic analysis **(Figure 33)**.

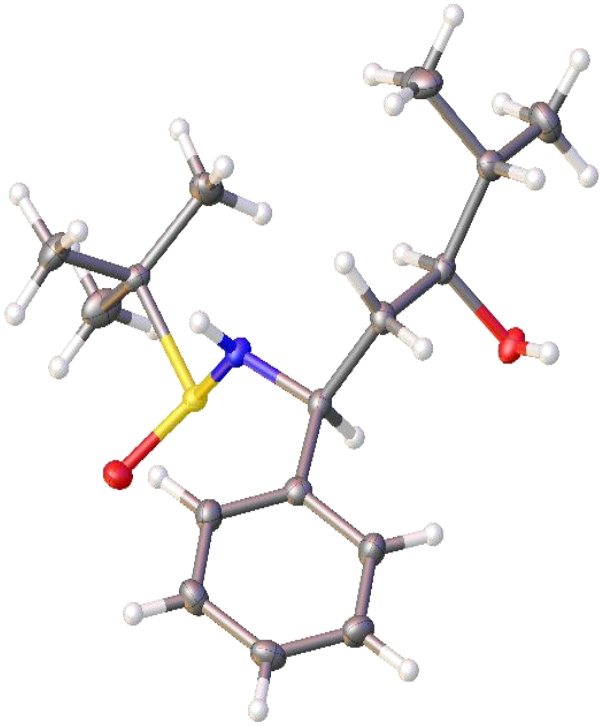
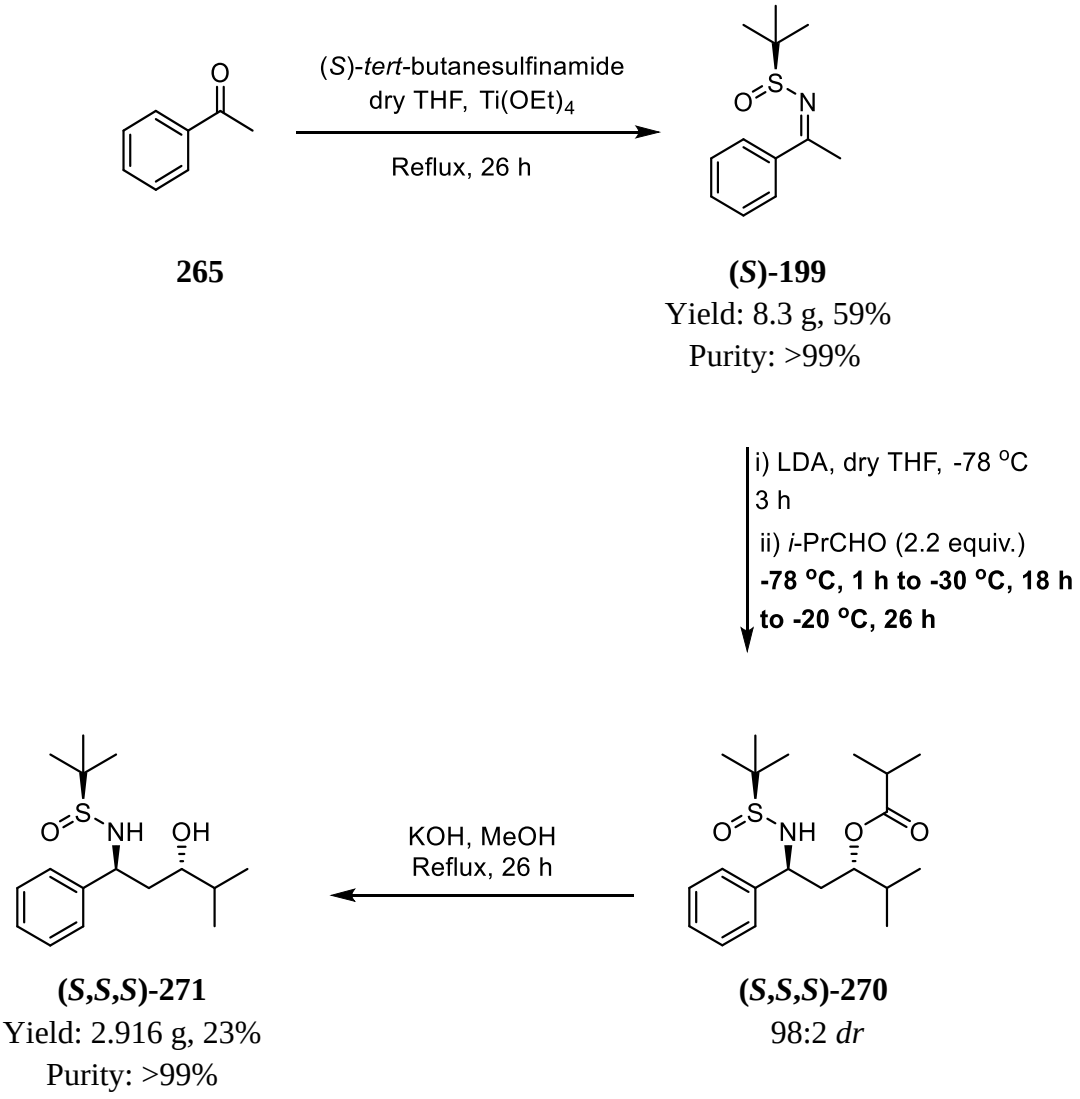


Figure 33. Crystallographic structure of **(*S*,*S*,*S*)-271**

A second run was also carried out for reproducibility purposes. Pleasingly, 2.916 g of final product **(*S*,*S*,*S*)-271** was isolated as a pure diastereomer to give an overall yield of 23% for the second run **(Scheme 110)**.



Scheme 110. Second run of aldol-Tishchenko scale-up reaction

In conclusion, the scale-up process enabled the synthesis of 1,3-amino alcohol precursor **(*S*,*S*,*S*)-271**. Two new chiral centres (C-N and C-O) in addition to three new bonds (C-N, C-C and C-O) were formed in one synthetic step. In terms of reproducibility, both runs produced similar yields (26 and 23% respectively). In addition, the reaction was telescoped through the ester cleavage step, thereby avoiding silica chromatography purification. This enabled sulfinyl

ester **(*S*,*S*,*S*)-270** to be used in the next step without further purification. Finally, the results were published in the journal Organic Syntheses.[27]

There were however some limitations to the scale-up process. The aim was to prepare >5 g of final product. We were unable to accomplish this target which may be due to a number of factors:

- In comparison to our small-scale synthesis, a lower yield was obtained for the (*S*)-*tert*-butanesulfinyl imine **(*S*)-199**.
- Longer reaction times were required for both the aldol and Tishchenko steps.
- The larger scale impacts the rate of stirring and may have led to less efficient mixing of the reaction mixture.
- Slower cooling rate meant that it was more difficult to control the overall cooling rate of the reaction mixture.
- During the work-up procedure, ethyl acetate was used as the extraction solvent. In general, ethyl acetate can be regarded as a poor extraction solvent for scale-up due to the high solubility of ethyl acetate in water.

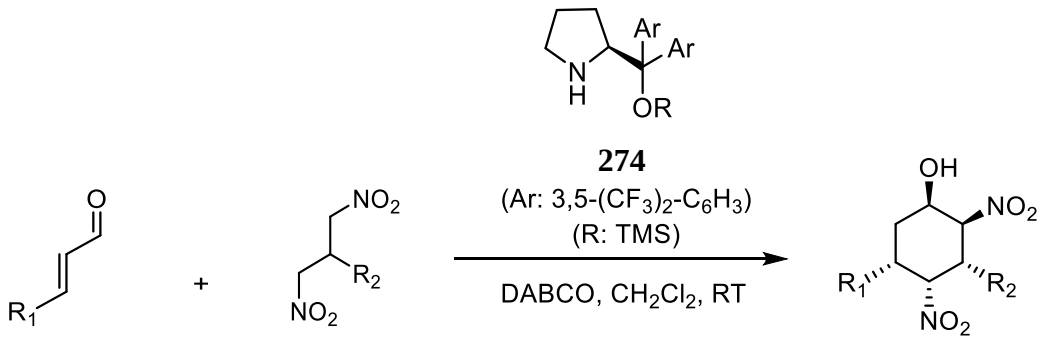
5.4 Tandem Double aldol-Tishchenko Reaction for the Formation of 3-Amino-1,5-Diols with Four and Five Contiguous Chiral Centres

5.4.1 Background

The asymmetric synthesis of enantiomerically enriched compounds bearing multiple chiral centres is a challenging task for synthetic chemists.[29] This process is usually difficult to achieve *via* conventional stepwise processes.[30] Asymmetric tandem reactions constitute a powerful approach to furnish multiple new bonds and chiral centres in a single-pot operation.[31] Moreover, this can provide a very convenient route to build up stereogenic complexity.[32]

The success of the one-pot approach lies in the ability to perform multiple chemical transformations sequentially in a single reaction vessel.[33] Additionally, these one-pot reactions often require only a single reaction solvent, work-up procedure and purifications steps, thus simultaneously reducing time, labour and costs.[32]

Consequently, there has been an rapid growth in the field of asymmetric tandem reactions over the past decade. In the field of organocatalysis, Jørgensen has described the synthesis of five contiguous stereocentres in one-pot *via* an intermolecular two component reaction of nitroalkanes to *α,β*-unsaturated aldehydes **(Scheme 111)**.[34] This transformation enables the synthesis of substituted cyclohexanols **275** with five contiguous stereocentres *via* the addition of nitroalkanes **273** to *α,β*-unsaturated aldehydes **272** followed by an intramolecular Henry reaction.



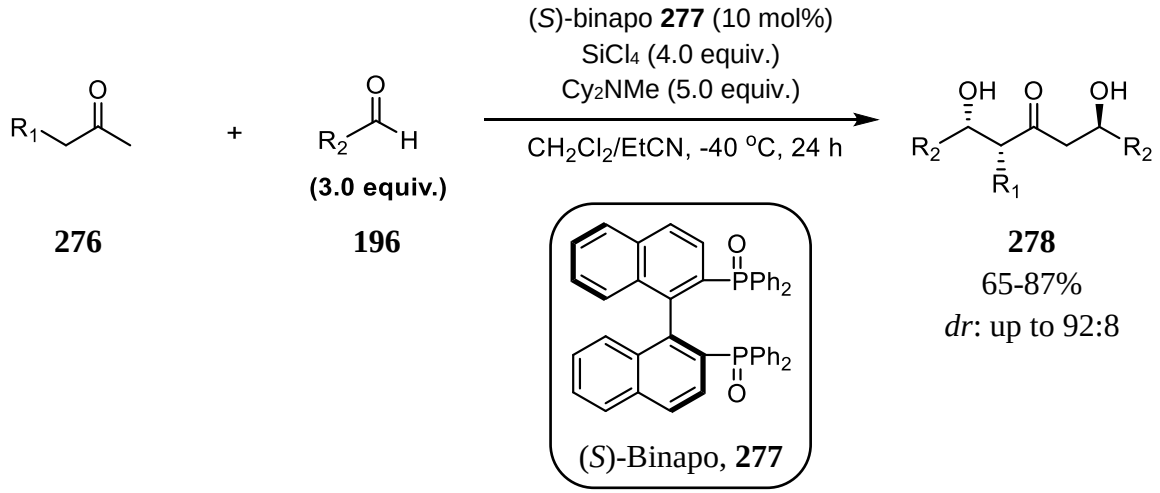
272 + **273** → **275**

38-65%

dr: up to 12:3:2

Scheme 111. Formation of substituted cyclohexanols **275** with five contiguous chiral centres

Nakajima has also reported the stereoselective construction of three chiral centres in a single operation *via* an enantioselective double-aldol reaction using silicon tetrachloride and a chiral phosphine oxide (*S*)-Binapo, as an organocatalyst **(Scheme 112)**.[35] This novel enantioselective double-aldol reaction of methyl ketones **276** with various aldehydes **196** provides access to 1,2-*syn*-1,5-*anti*-1,5-dihdroxy-3-pentanones **278** in high yields and enantio- and diastereoselectivity. In 2017, Nakajima and co-workers expanded on this work to achieve the synthesis of four chiral centres in one pot with ethyl ketones such as 3-pentanone, using (*S*)-Binapo **277** and trichlorosilyl triflate.[36]



Scheme 112. Nakajima's stereoselective synthesis of three chiral centres using a double-aldol reaction

5.4.4.1 Double aldol-Tishchenko reaction

The enantioselective aldol reaction is a fundamental reaction for the construction of multiple bonds and chiral centres.[37] In recent years, the enantioselective aldol-Tishchenko reaction has also emerged as an underutilised tool for the construction of defined adjacent stereogenic centres.[38] Thus, a consecutive enantioselective double aldol-Tishchenko reaction could serve as a versatile tandem process to build molecular diversity in a stereoselective fashion **(Figure 34)**.

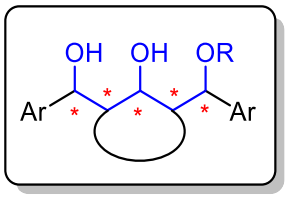
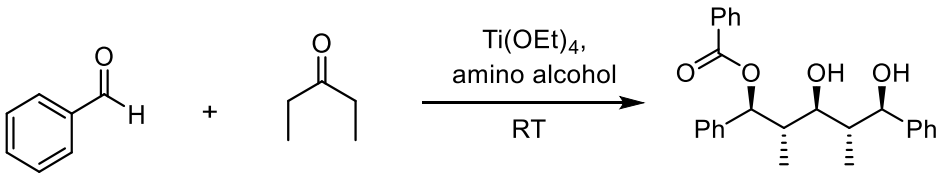


Figure 34. Access to chiral stereopentads

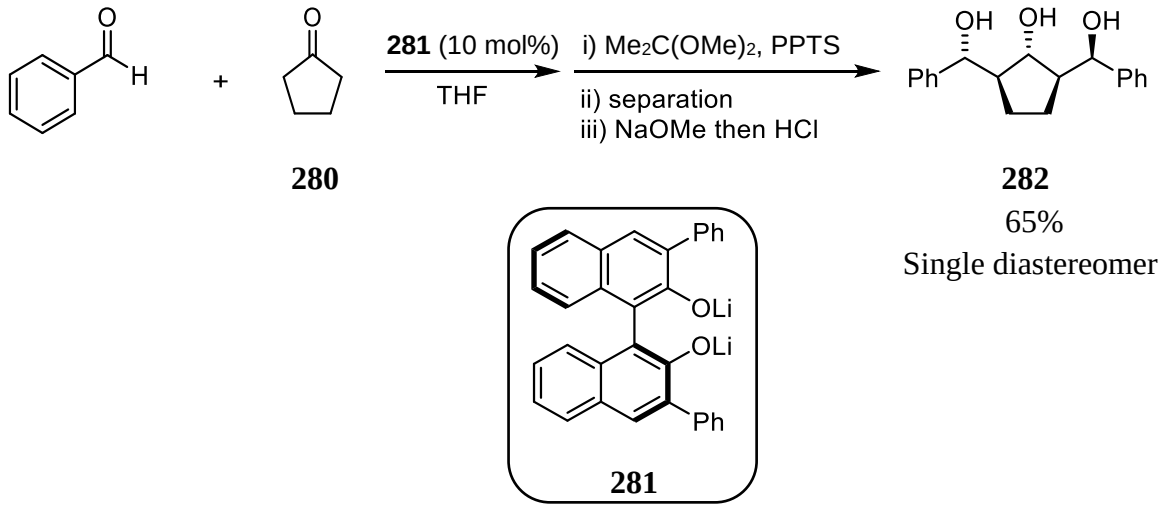
To date, the synthetic potential of this transformation has been highlighted in only a few publications. In 2005, Mahrwald demonstrated for the first time, the enantioselective synthesis of a chiral 1,3,5-triol monoester *via* a double aldol-Tishchenko reaction.[39] Stereopentad **279** was synthesised *via* a double aldol-Tishchenko reaction in the presence of $Ti(OEt)_4$ and an amino alcohol **(Scheme 113)**. The authors reported that a high degree of stereoselectivity was obtained for this adduct although no specific value was given in the paper.



86 **279**

Scheme 113. Enantioselective synthesis of a chiral 1,3,5-triol monoester

More recently, Nakajima reported a successive double aldol-Tishchenko reaction utilising chiral lithium diphenylbinaphtholate **281** as an effective catalyst to furnish a 1,3,5-diol monoester derivative.[35] In the case of cyclopentanone **280** as an aldol donor, 3.5 equivalents of benzaldehyde was employed to afford triol **282** as a single diastereomer with five consecutive chiral centres **(Scheme 114)**.

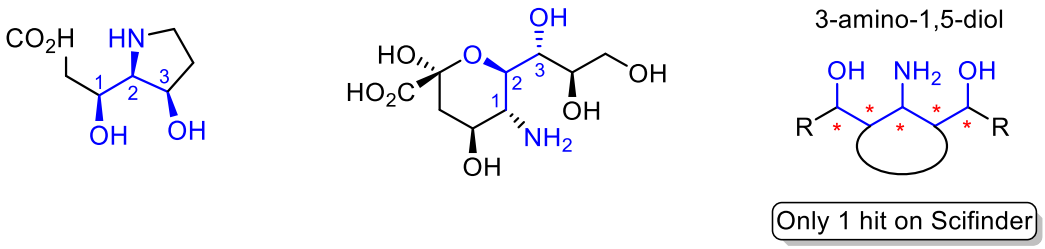


Scheme 114. Double aldol-Tishchenko reaction catalysed by chiral lithium diphenylbinaphthalate **281**

The research outlined by Nakajima and Mahrwald has indeed highlighted the synthetic utility of this transformation in terms of atom and chiral economy. Thus, the development of a tandem double aldol-Tishchenko reaction with (*S*)-*tert*-butanesulfinyl imines as aldol donors could provide a novel route to access amine containing stereopentads.

5.4.2 Amino diols

Enantiomerically pure amino diols are key structural elements that are prevalent in a diverse array of biologically active compounds.[40] In particular, the 2-amino-1,3-diol and 1-amino-2,3-diol moieties are found in many natural products and pharmaceuticals, for example, detoxinine **283** and Neuraminic acid **284 (Figure 35)**.[41] In contrast, there is very little precedent for the 3-amino-1,5-diol scaffold.

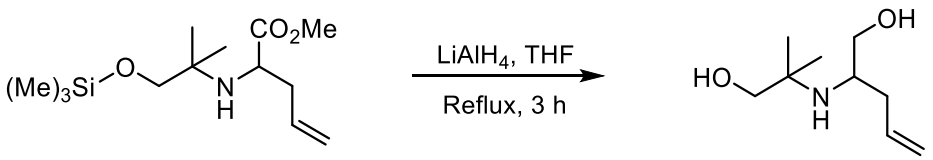


283
Detoxinine

284
Neuraminic acid

Figure 35. Bioactive molecules containing the amino diol framework and the 3-amino-1,5-diol subunit

A search of the literature identified only one publication describing the synthesis and utility of racemic 3-amino-1,5-diols. In 1996, Courtois and co-workers reported the synthesis of racemic 3-amino-1,5-diols **286** *via O*-silyated *α*-aminoesters **285 (Scheme 115)**.[42]



285 **286**

Scheme 115. Synthesis of racemic 3-amino-1,5-diols

At present, there is no reported enantioselective synthesis of 3-amino-1,5-diols. These highly functionalised scaffolds could serve as versatile synthetic building blocks to access a wide variety of potentially important medicinal scaffolds and chiral ligands **(Figure 36)**.

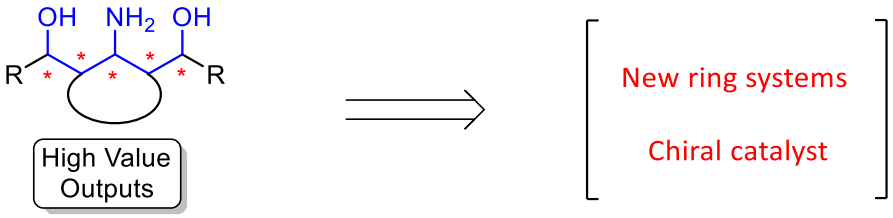
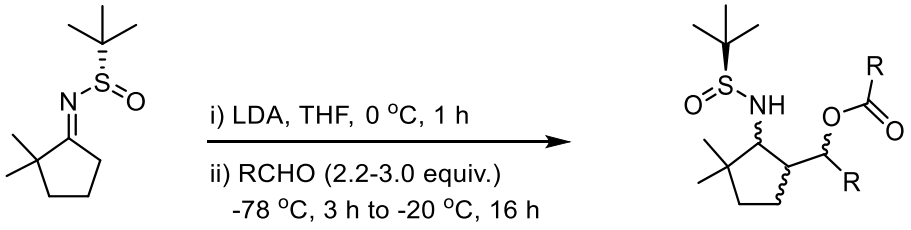


Figure 36. Valuable synthetic building block

5.4.3 Results and discussion

The aldol-Tishchenko reaction of chiral sulfinyl imines has been shown to be a highly diastereoselective method for the synthesis of *anti*-1,3-amino alcohol derivatives with the simultaneous formation of two and three chiral centres in one pot. Previous work conducted within our group has demonstrated successful application of the aldol-Tishchenko reaction conditions to an α-cyclic sulfinyl imine **(*S*)-287** utilising both pivaldehyde and benzaldehyde **(Scheme 116)**.[3] Excellent yields and diastereoselectivities were obtained for both substrates.

Previous work



(*S*)-287

288
R = Ph, 82%, >98:2 *dr*
R = *t*-Bu, 78%, 91:9 *dr*

Absolute stereochemistry not determined

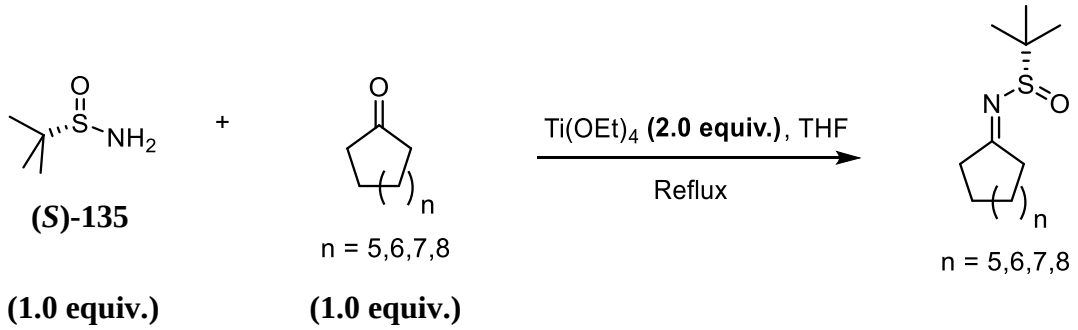
Scheme 116. Aldol-Tishchenko reaction utilising an α-cyclic sulfinyl imine

One of the objectives of this project was to examine a series of symmetric cyclic sulfinyl imines for use in our aldol-Tishchenko reaction. These substrates would present an additional challenge due to the possibility of side reactions as there are two possible sites for deprotonation.

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

Work in this area of the project began with the synthesis of a series of cyclic sulfinyl imines **(Scheme 117)**. Overall, the preparation of these sulfinyl imines proved to be a lot more challenging in comparison to the acetophenone and propiophenone based sulfinyl imines previously prepared in this project. Initially, we attempted to synthesise sulfinyl imines **(*S*)-289-292** using the previously reported reaction conditions. Under these conditions, cyclopentanone sulfinyl imine **(*S*)-289** was prepared in a very good yield of 80%. Overall however, poor yields were obtained for the six-, seven- and eight- membered cyclic sulfinyl

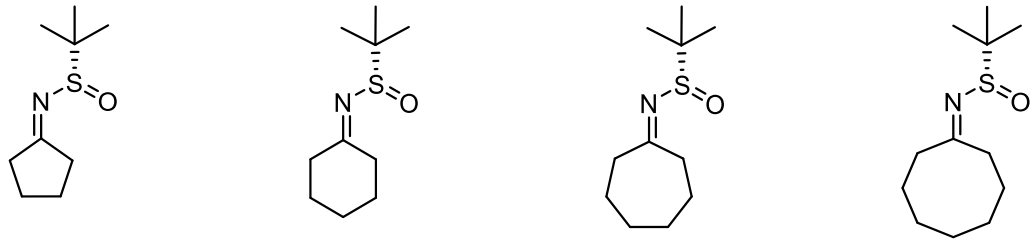
imines. Although the synthesis of *N*-*tert*-butanesulfinyl ketimines is known to be accelerated at elevated temperatures,[43] reports have indicated that ketimines are susceptible to thermal decomposition.[44]



(*S*)-135

(1.0 equiv.)

(1.0 equiv.)



(*S*)-289, 80%

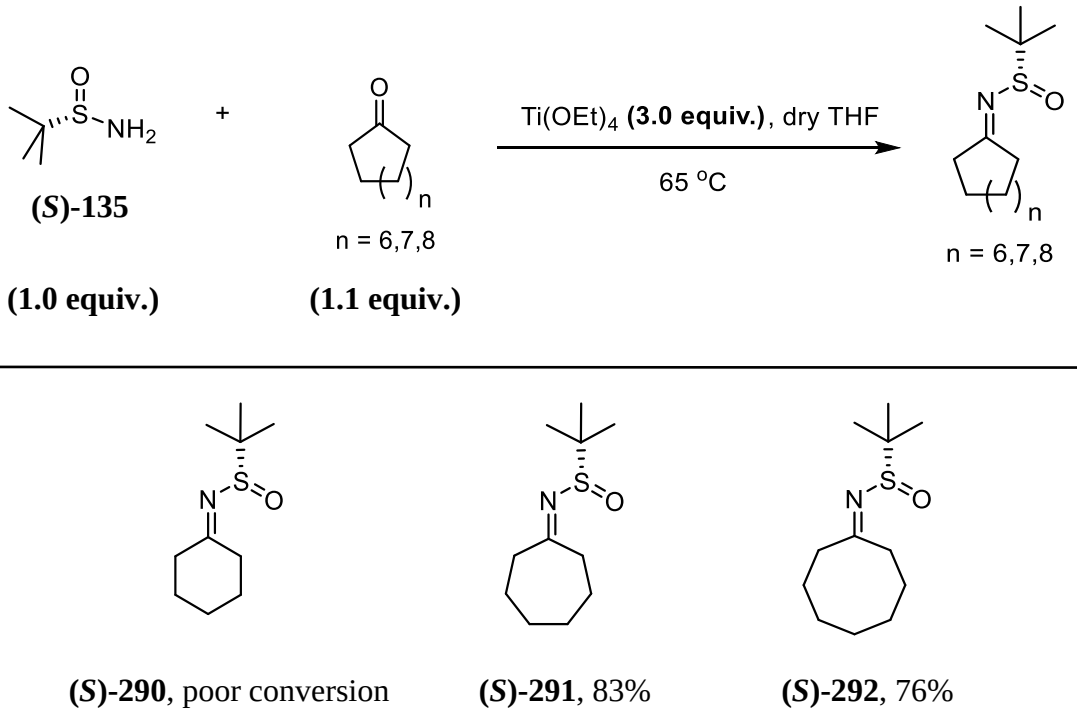
(*S*)-290, ~16% conversion

(*S*)-291, 40%

(*S*)-292, 43%

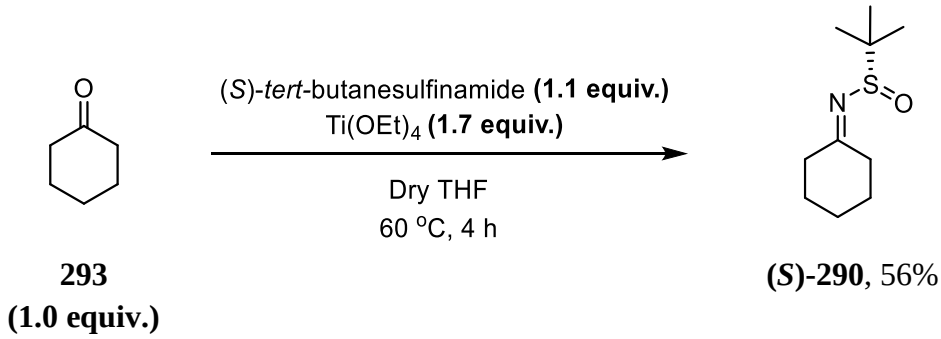
Scheme 117. Yields obtained using standard reaction conditions

Thus, we decided to reduce the temperature of the reaction for substrates **(*S*)-290-292** and follow a procedure by Stockman and co-workers.[45] This involved careful monitoring of the reaction mixture at 65 ^{o}C by TLC analysis. Pleasingly, this resulted in a significant improvement in yield for **(*S*)-291** and **(*S*)-292 (Scheme 118)**. Unfortunately, the synthesis of cyclohexanone sulfinyl imine **(*S*)-290** continued to prove difficult and only poor conversion was observed.



Scheme 118. Synthesis of cyclic (*S*)-*tert*-butanesulfinyl imines

Finally, after several manipulations of reaction conditions, **(*S*)-290** was isolated in a yield of 56% utilising a procedure previously described by Ellman **(Scheme 119)**.[43]

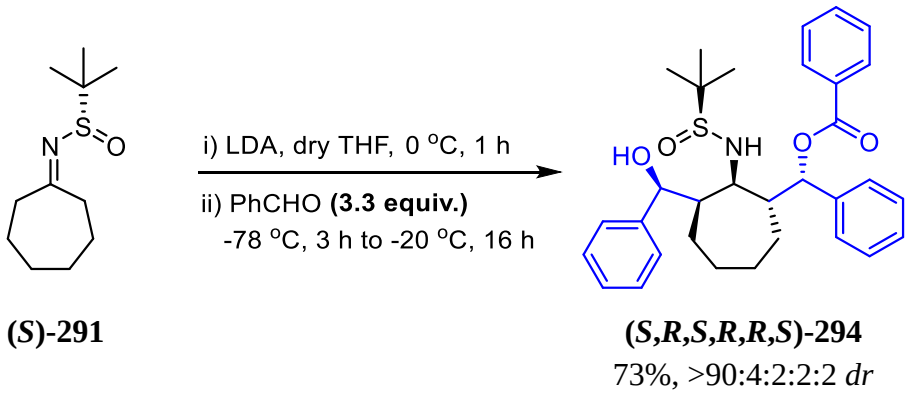


Scheme 119. Ellman's procedure

5.4.3.2 Substrate scope

Having synthesised a series of cyclic sulfinyl imines, we then proceeded to apply these substrates in our aldol-Tishchenko methodology. At first, we were interested in challenging our aldol-Tishchenko reaction using symmetric cyclic sulfinyl imine **(*S*)-291**. However, through our method development we discovered that use of 3.3 equivalents of aldehyde (as

opposed to 2.2) gave a double aldol-Tishchenko product **(*S*,*R*,*S*,*R*,*R*,*S*)-294** in a yield of 73% with excellent diastereoselectivity (>90:4:2:2:2 *dr*) **(Scheme 120)**. Remarkably, only one diastereomer was formed almost exclusively (from a possible 32).



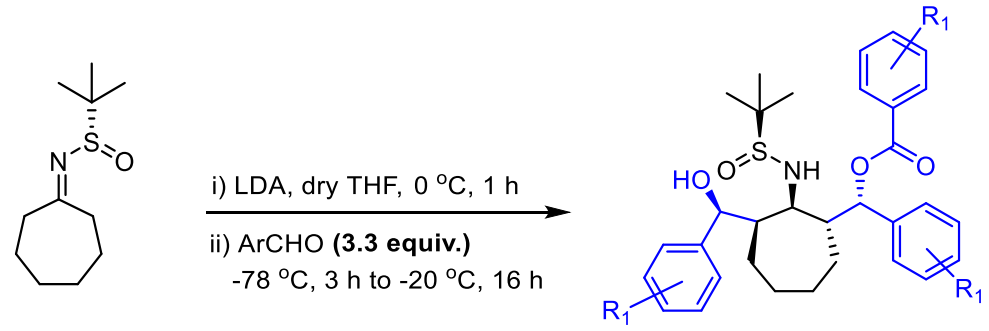
(*S*)-291

(*S*,*R*,*S*,*R*,*R*,*S*)-294
73%, >90:4:2:2:2 *dr*

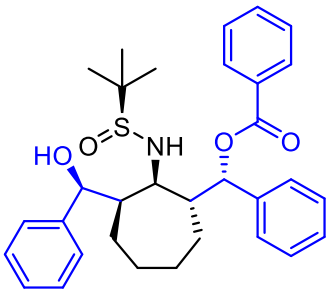
Scheme 120. Double aldol-Tishchenko reaction

Inspired by this result, we next explored the substrate scope of this transformation. A range of substituted benzaldehydes were examined under the reaction conditions **(Scheme 121** and **Scheme 122)**. Pleasingly, both electron-donating and electron-withdrawing substituents proved to be successful. In each case, the reaction was found to be highly diastereoselective. For example, the *p*-fluoro analogue **(*S*,*R*,*S*,*R*,*R*,*S*)-299** was formed in 66% yield with excellent diastereoselectivity (>98:2 *dr*). The *p*-*tert*-Bu and *p*-OCF_3 substituted benzaldehydes also afforded the corresponding products **(*S*,*R*,*S*,*R*,*R*,*S*)-298** and **(*S*,*R*,*S*,*R*,*R*,*S*)-304** with very high levels of diastereoselectivity. Good yield (62%) and very good diastereoselectivity (95:3:2 *dr*) was also obtained for **(*S*,*R*,*S*,*R*,*R*,*S*)-295** which contained the *p*-methyl substituent.

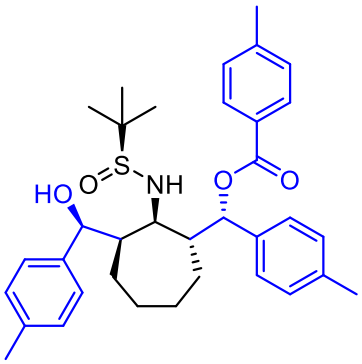
Meta-substituted benzaldehydes provided the products in slightly better yields. For example, the *m*-methyl **(*S*,*R*,*S*,*R*,*R*,*S*)-296** and *m*-fluoro **(*S*,*R*,*S*,*R*,*R*,*S*)-300** products and were isolated in 76 and 73% yields respectively. Interestingly, the sterically bulky *p*-*iso*-Pr benzaldehyde furnished the corresponding product **(*S*,*R*,*S*,*R*,*R*,*S*)-297** in very good yield but with slightly lower diastereoselectivity. Use of *p*-chlorobenzaldehyde gave the product **(*S*,*R*,*S*,*R*,*R*,*S*)-301** in good yield and high diastereoselectivity. The *p*-thiomethoxy **(*S*,*R*,*S*,*R*,*R*,*S*)-302** and *m*-methoxy **(*S*,*R*,*S*,*R*,*R*,*S*)-303** adducts were generated in lower yields, but excellent levels of diastereoselectivity were maintained. The *p*-CF_3-double aldol-Tishchenko product **(*S*,*R*,*S*,*R*,*R*,*S*)-305** was isolated in a slightly lower yield but very good diastereoselectivity was achieved.



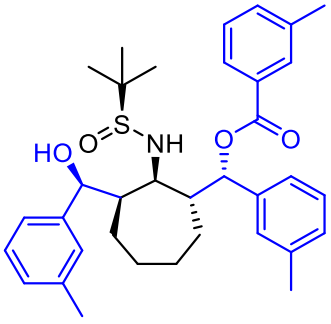
(*S*)-291



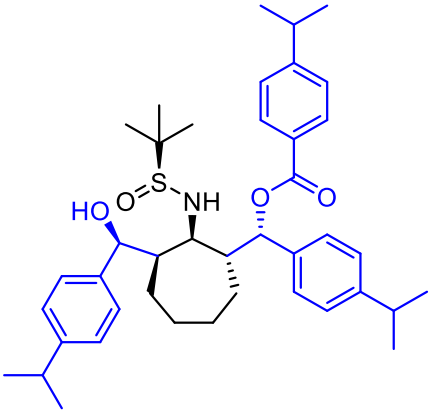
(*S*,*R*.*S*,*R*,*R*,*S*)-294
>90:4:2:2:2 *dr*, 73%



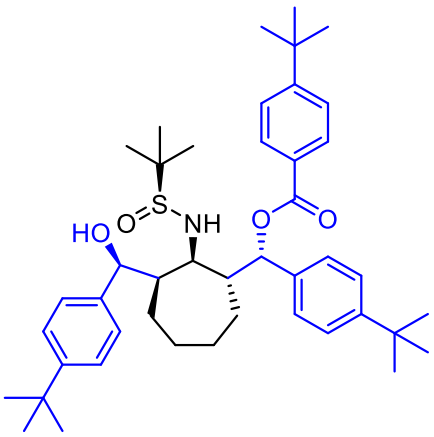
(*S*,*R*,*S*,*R*,*R*,*S*)-295
95:3:2 *dr*, 62%



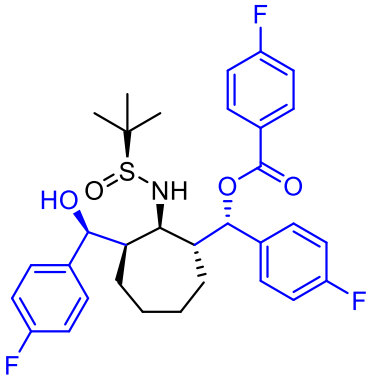
(*S*,*R*,*S*,*R*,*R*,*S*)-296
94:3:3 *dr*, 76%



(*S*,*R*,*S*,*R*,*R*,*S*)-297
<91:4:3:2 *dr*, 70%

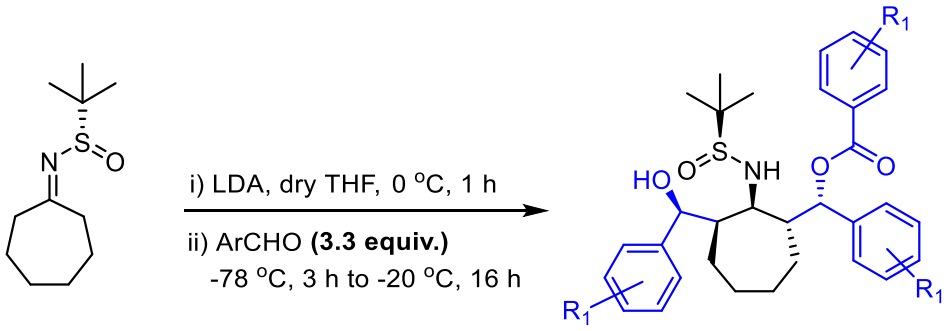


(*S*,*R*,*S*,*R*,*R*,*S*)-298
97:2:1 *dr*, 59%

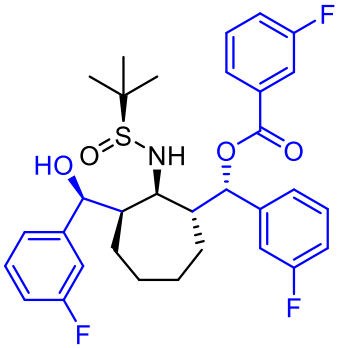


(*S*,*R*,*S*,*R*,*R*,*S*)-299
>98:2 *dr*, 66%

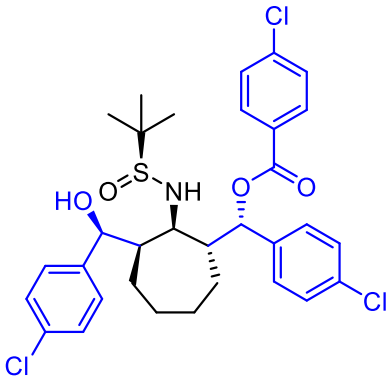
Scheme 121. Substrate scope for double aldol-Tishchenko reaction of cycloheptanone sulfinyl imine **(*S*)-291** with substituted benzaldehydes



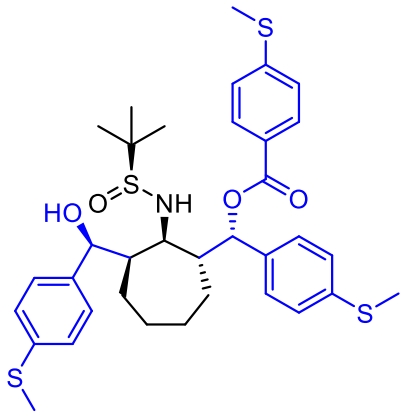
(*S*)-291



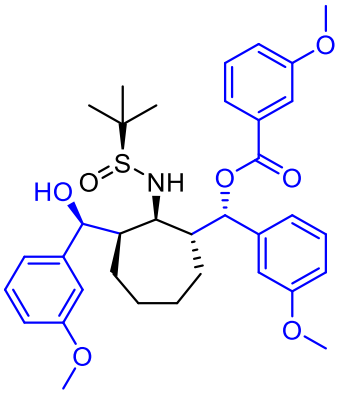
(*S*,*R*,*S*,*R*,*R*,*S*)-300
>97:3 *dr*, 73%



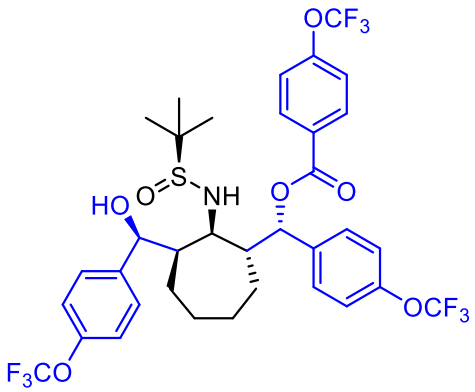
(*S*,*R*,*S*,*R*,*R*,*S*)-301
98:2 *dr*, 61%



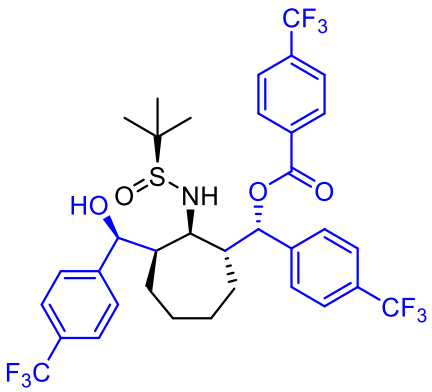
(*S*,*R*,*S*,*R*,*R*,*S*)-302
96:4 *dr*, 46%



(*S*,*R*,*S*,*R*,*R*,*S*)-303
98:2 *dr*, 36%



(*S*,*R*,*S*,*R*,*R*,*S*)-304
97:3 *dr*, 70%



(*S*,*R*,*S*,*R*,*R*,*S*)-305
93:4:3 *dr*, 44%

Scheme 122. Substrate scope for double aldol-Tishchenko reaction of cycloheptanone sulfinyl imine **(*S*)-291** with substituted benzaldehydes

In all cases, the diastereomeric ratio was calculated from the characteristic ester doublet identified in the ^{1}H NMR spectrum of the crude reaction mixtures **(Figure 37)**.

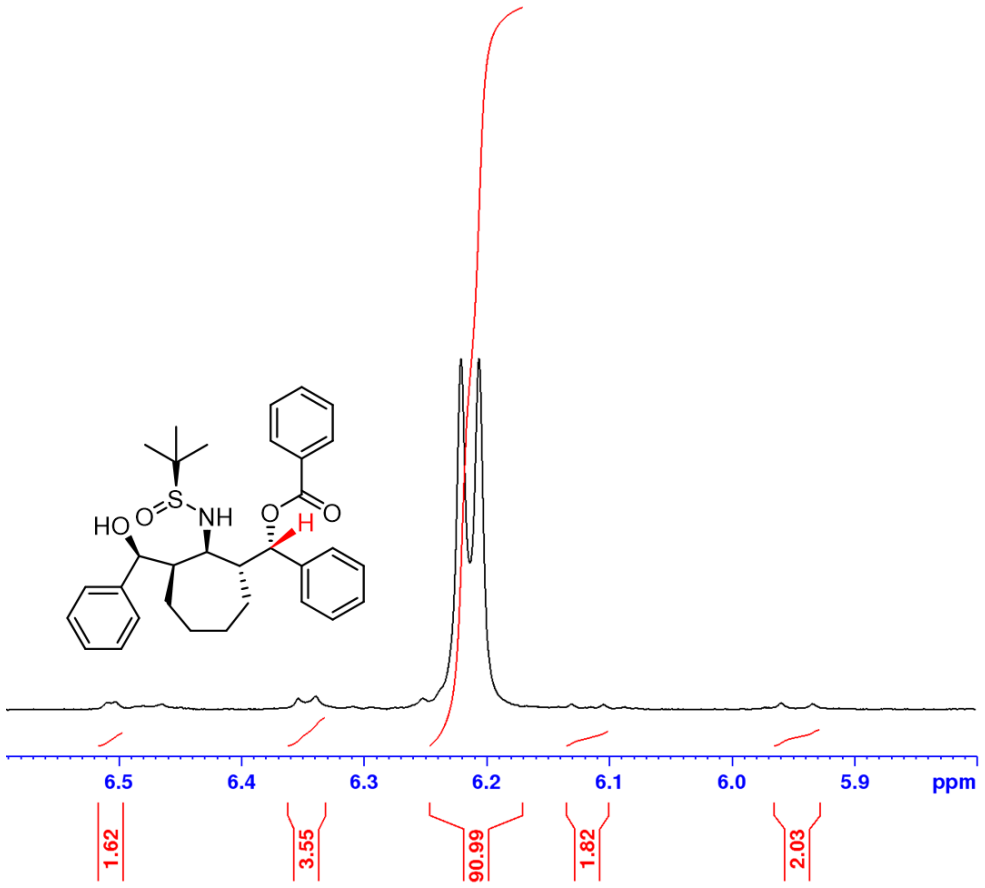
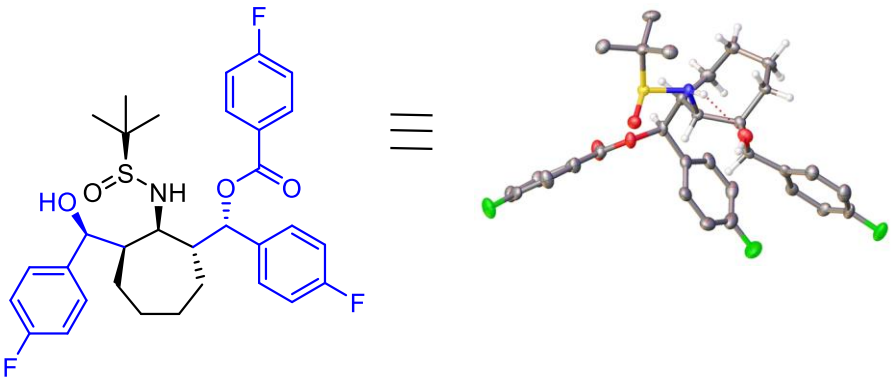


Figure 37. Calculation of diastereomeric ratio

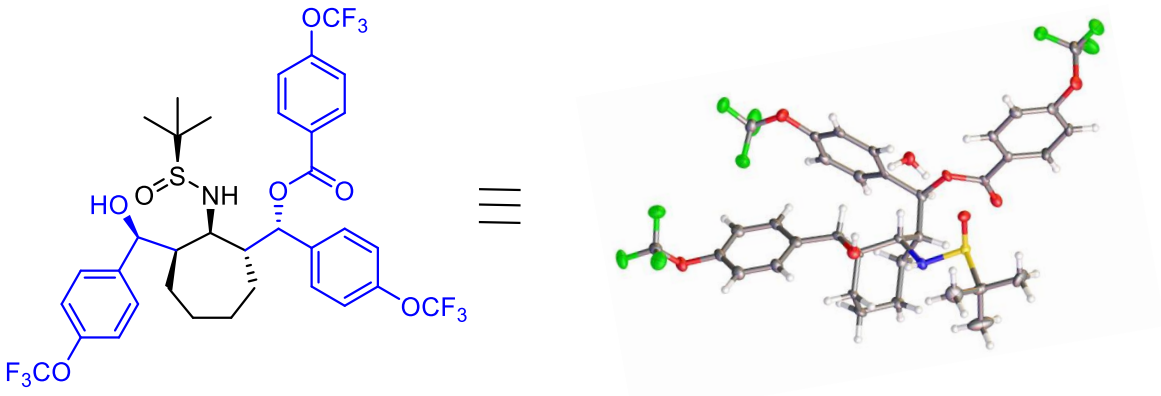
The absolute stereochemistry of the major diastereomer was determined by x-ray crystallographic analysis of **(*S*,*R*,*S*,*R*,*R*,*S*)-299** and **(*S*,*R*,*S*,*R*,*R*,*S*)-304 (Figure 38** and **Figure 39)**.



(*S*,*R*,*S*,*R*,*R*,*S*)-299

Figure 38. Crystal structure of **(*S*,*R*,*S*,*R*,*R*,*S*)-299**

The crystal structure of **(*S*,*R*,*S*,*R*,*R*,*S*)-299** displays a hydrogen-bonding interaction between the amine proton and the oxygen atom of the hydroxyl group (N-H···O-H). Due to the polarity of the sulfoxide functional group, hydrogen atoms α to the sulfur moiety can act as hydrogen bond donors.[46]

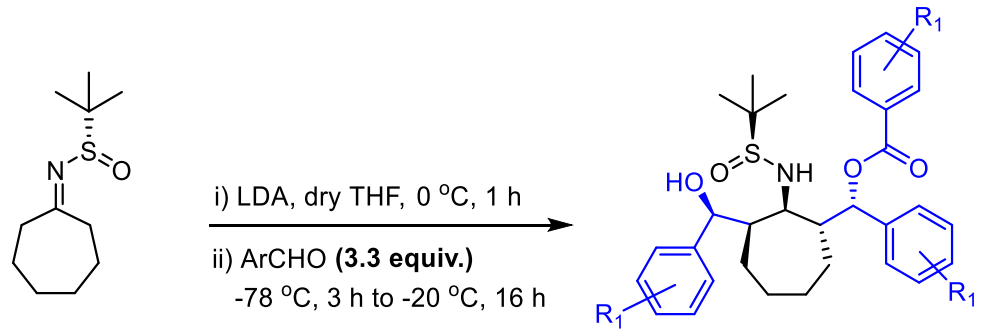


(*S*,*R*,*S*,*R*,*R*,*S*)-304

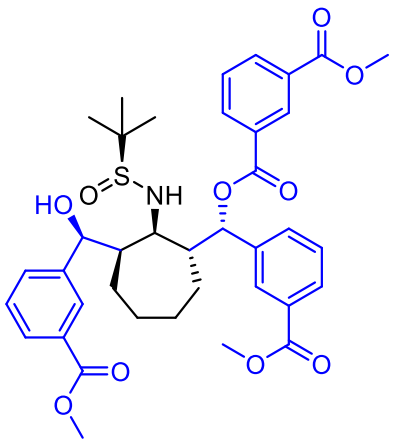
Figure 39. Crystal structure of **(*S*,*R*,*S*,*R*,*R*,*S*)-304**

A number of challenging aldol acceptors were also examined using the reaction conditions **(Scheme 123)**. Notably, the *in situ* intramolecular Tishchenko hydride transfer enables the

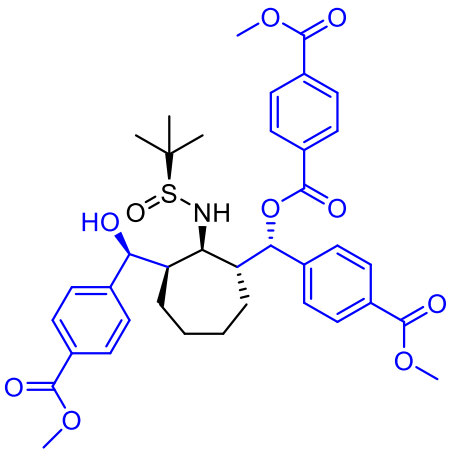
formation of 3-amino-1,5-diol derivatives **(*S*,*R*,*S*,*R*,*R*,*S*)-306-309** containing an ester, nitro and nitrile substituent. These functionalities would otherwise be susceptible to reduction if an external reductant was used.[47] Excellent diastereoselectivities were obtained for all of these substrates. Pleasingly, 4-pyridine carboxaldehyde was also employed affording product **(*S*,*R*,*S*,*R*,*R*,*S*)-310** in good yield and selectivity. The pyridine subunit is an appealing moiety present in many natural products and biologically important compounds.[48]



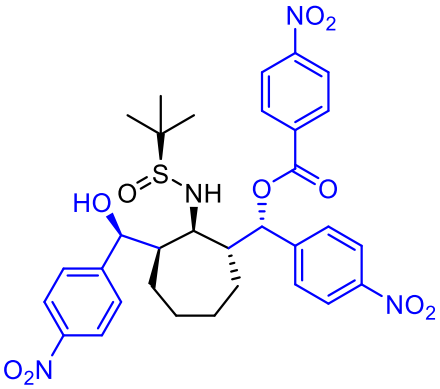
(*S*)-291



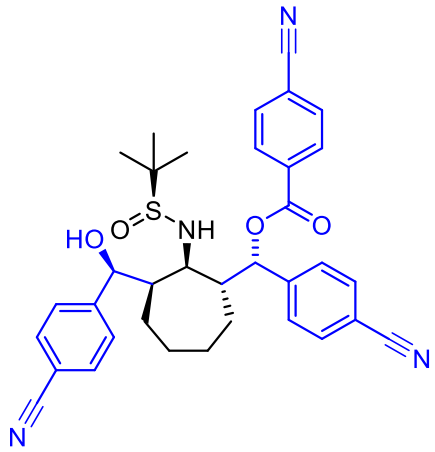
(*S*,*R*,*S*,*R*,*R*,*S*)-306
97:3 *dr*, 53%



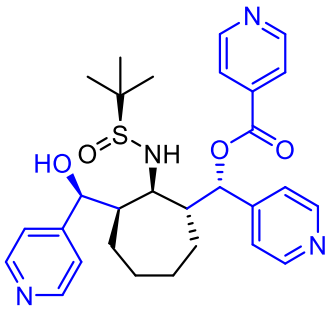
(*S*,*R*,*S*,*R*,*R*,*S*)-307
98:2 *dr*, 51%



(*S*,*R*,*S*,*R*,*R*,*S*)-308
>95:5 *dr*, 36%



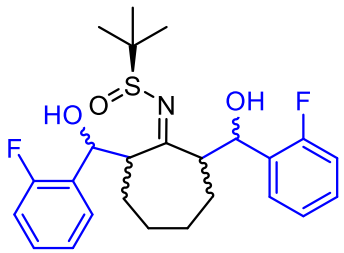
(*S*,*R*,*S*,*R*,*R*,*S*)-309
98:2 *dr*, 36%



(*S*,*R*,*S*,*R*,*R*,*S*)-310
90:6:4 *dr*, 45%

Scheme 123. Challenging aldol-acceptors

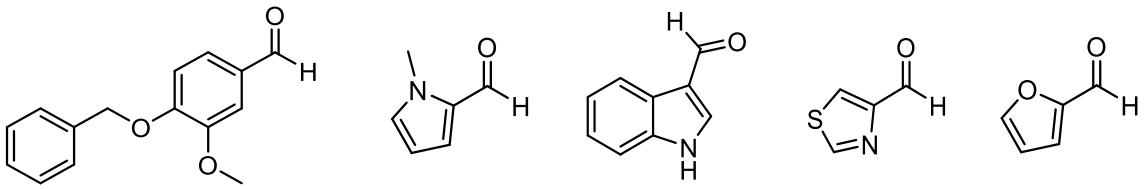
Ortho-substituted benzaldehydes were also tested under the reaction conditions. Unfortunately, no product formation was observed utilising *o*-tolualdehyde as an aldol acceptor. This is likely due to the steric hinderance at the ortho position of the aryl ring. However, *o*-fluoro benzaldehyde did afford the double aldol product **311** in a moderate yield of 55% with very good diastereoselectivity (91:9 *dr*) **(Figure 40)**.



311
91:9 *dr*, 55%

Figure 40. Double aldol product

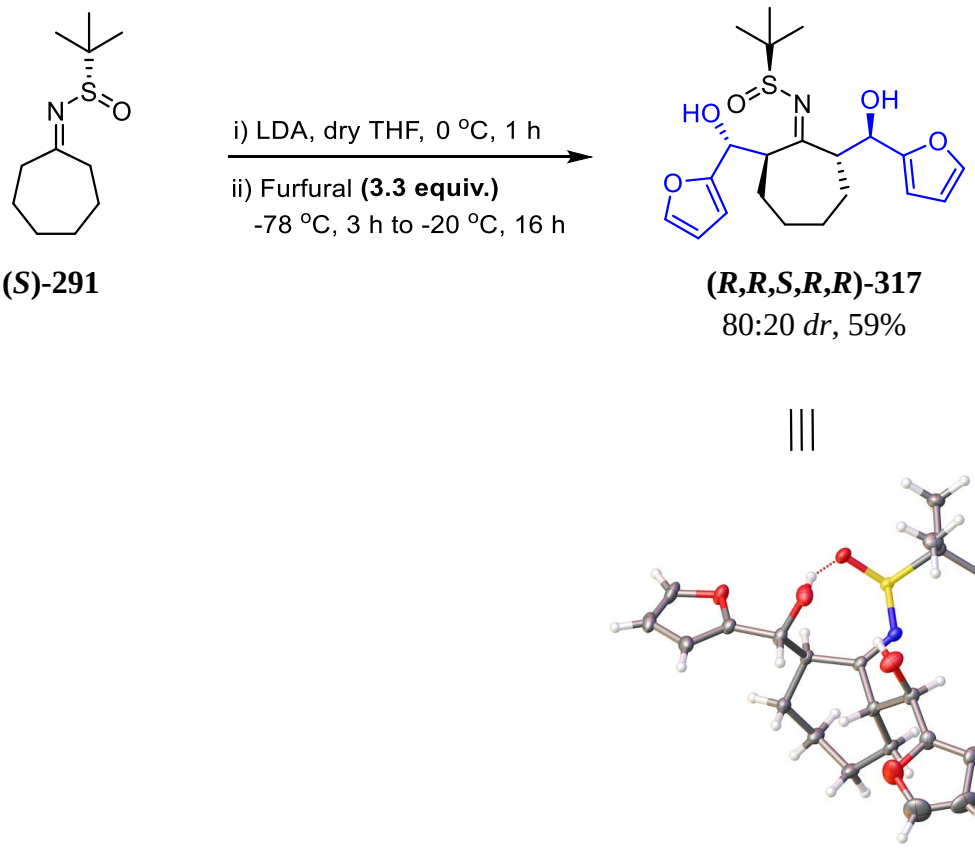
In an attempt to further extend our substrate scope, we then examined the reaction of **312** and a range of heteroaryl aldehydes as aldol acceptors **(Figure 41)**. Aldehydes **312-315** failed to generate any desired product with only starting material being recovered in each case.



312 **313** **314** **315** **316**

Figure 41. Diverse aldehydes

Interestingly, although the reaction of furfural **316** failed to give the desired double aldol-Tishchenko product, the double aldol adduct **(*R*,*R*,*S*,*R*,*R*)-317** was successfully isolated in a yield of 59% with a *dr* value of 80:20 **(Scheme 124)**. In this case, the crystal structure shows an intramolecular hydrogen-bonding interaction between the sulfinyl oxygen and the hydroxyl proton (S-O···H). This type of hydrogen-bonding interaction has also been observed in the crystal structure of Ellman's *β*-hydroxy sulfinyl imines.[49]

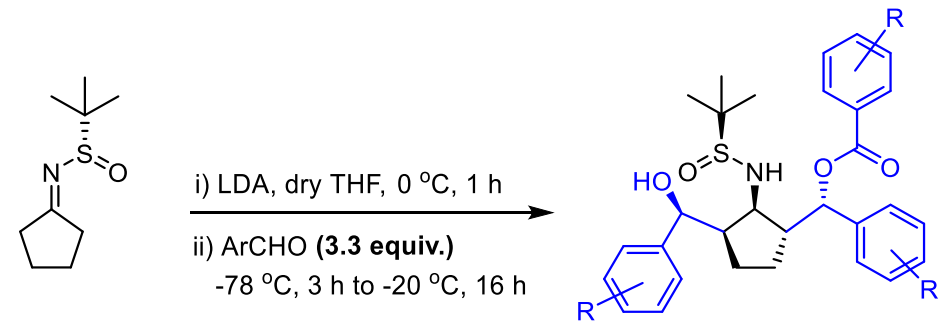


(*S*)-291

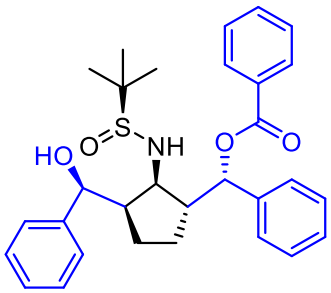
(*R*,*R*,*S*,*R*,*R*)-317
80:20 *dr*, 59%

Scheme 124. Crystallographic structure of double aldol product **(*R*,*R*,*S*,*R*,*R*)-317**

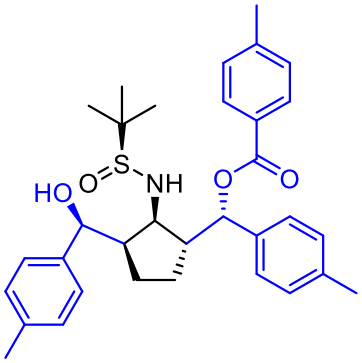
Our next objective was to explore the diversity of this transformation by expanding the scope to five-membered cyclic (*S*)-*tert*-butanesulfinyl imines. Gratifyingly, reaction of cyclopentanone sulfinyl imine **(*S*)-289** with benzaldehyde generated the 3-amino-1,5-diol derivative **(*S*,*R*,*S*,*R*,*R*,*S*)-318** in excellent diastereoselectivity (90:6:4 *dr*), although a decrease in chemical yield was observed in comparison to the cycloheptanone substrates **(Scheme 125)**. Use of *p*-methyl benzaldehyde furnished the product **(*S*,*R*,*S*,*R*,*R*,*S*)-319** in a moderate yield of 49%. In this case, the diastereoselectivity could not be determined due to the complexity of the ^{1}H NMR spectrum of the crude reaction mixture. However, a single diastereomer was isolated. Further increasing the steric bulk of the *para*-substituent furnished products in high diastereoselectivity. Excellent diastereoselectivity was obtained for *p*-ethyl and *p*-*iso*-Pr benzaldehydes affording the corresponding products **(*S*,*R*,*S*,*R*,*R*,*S*)-320** and **(*S*,*R*,*S*,*R*,*R*,*S*)-321**.



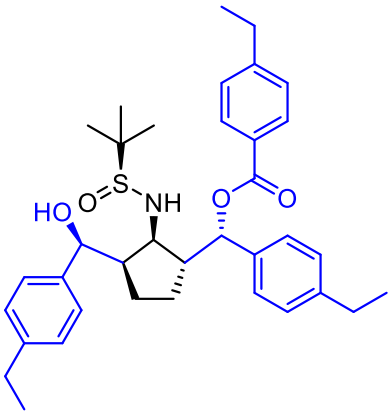
(*S*)-289



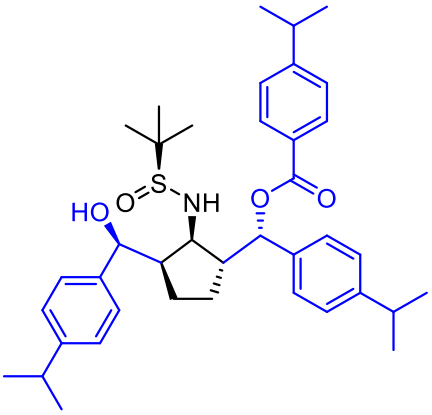
(*S*,*R*,*S*,*R*,*R*,*S*)-318
90:6:4 *dr*, 48%



(*S*,*R*,*S*,*R*,*R*,*S*)-319
49%, single diastereomer
dr not determined



(*S*,*R*,*S*,*R*,*R*,*S*)-320
94:6 *dr*, 45%



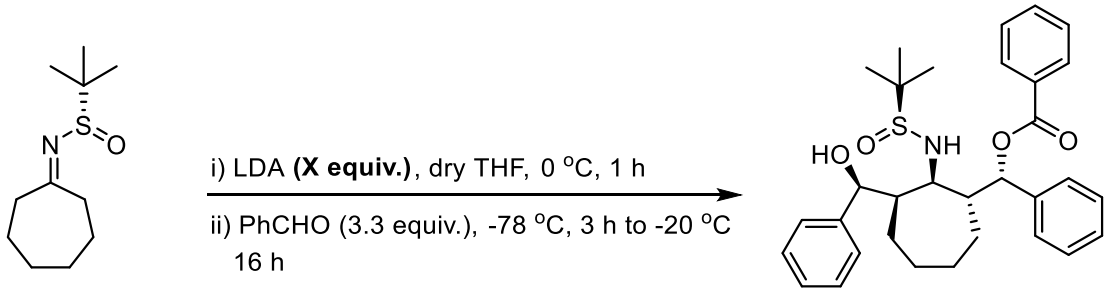
(*S*,*R*,*S*,*R*,*R*,*S*)-321
93:7 *dr*, 48%

Scheme 125. Cyclopentanone derived 3-amino-1,5-diol derivatives

5.4.3.3 Further optimisation of reaction conditions

During the course of this research, an important observation was made. We noticed that excess LDA seemed to be detrimental to reaction progress. Under the standard conditions, 1.1 equivalents of LDA was used to carry out the deprotonation step. Theoretically, it would be expected that two equivalents of base would be required to deprotonate both the α and α′ positions of, for example, cycloheptanone sulfinyl imine **(*S*)-291**. However, we found that using 2.0 equivalents of LDA had a detrimental impact on the reaction **(Table 20, entry 2)**. In fact, the major products present in the ^{1}H NMR spectrum were identified as benzyl alcohol and a double aldol product.

Table 20. LDA equivalents



(*S*)-291 **(*S*,*R*,*S*,*R*,*R*,*S*)-294**

Entry	LDA (Equiv.)	Temperature (ºC)	Time (h)	^{1}H NMR ratios[a] (AAT:AA:Alcohol)
1	1.1	-20	16	1.0:0.26:0.31
2	2.0	-20	16	1.0:4.5:4.1

[a]Ratio of **i)** aldol-aldol-Tishchenko product **ii)** aldol-aldol product and **iii)** benzyl alcohol determined from the ^{1}H NMR spectrum of the crude reaction mixture.

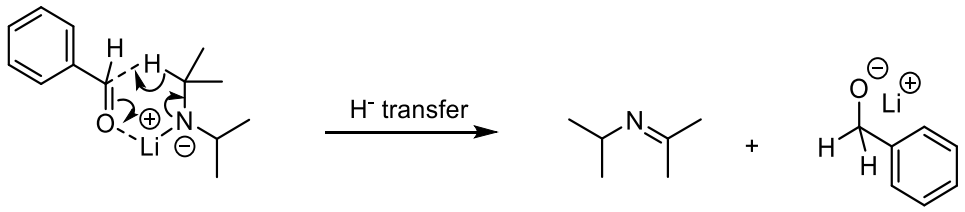
AAT: aldol-aldol-Tishchenko

AA: aldol-aldol

Alcohol: benzyl alcohol

An additional problem which appeared to be associated with excess LDA was the reduction of benzaldehyde *via* a suspected Meerwein-Ponndorf-Verley-type hydride transfer.[50] It was observed that use of 2.0 equivalents of LDA resulted in an increase in the amount of benzyl alcohol formed during the course of the reaction. This was evident from the ^{1}H NMR singlet

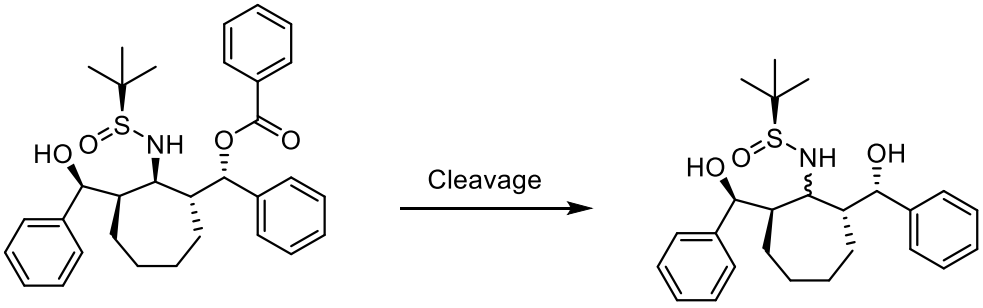
present at 4.6 ppm which is characteristic of the reduction of the C=O group to the corresponding alcohol. It is likely that the benzaldehyde is being reduced *in situ* in the presence of excess base. Evidence in the literature suggests that LDA can reduce aldehydes and ketones to the corresponding alcohols.[50] Aldehydes in particular are much more prone to reduction than their ketone counterparts. It is postulated that the *β*-hydrogen is transferred from the lithium amide to the aldehyde *via* a six-membered transition state **(Scheme 126)**. This is analogous to a Meerwein-Ponndorf-Verley hydride transfer mechanism. During the reaction the lithium amide is subsequently oxidised to the corresponding imine **323**.



322 **323** **324**

Scheme 126. Mechanism for the reduction of benzaldehyde to benzyl alcohol *via* hydride transfer from LDA

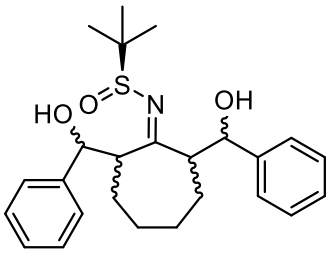
During these optimisation studies, we also made another important observation. Throughout this work, it became apparent that the yield was dependent on the presence of an unknown side-product. This side-product was present in the ^{1}H NMR spectra of the crude reaction mixtures for both the cyclopentanone and cycloheptanone substrates and was identified by a ^{1}H NMR doublet present at ~5.00 ppm. Initially, on analysis of the crude reaction mixture, we suspected that this product had been as a result of hydrolysis of the ester functionality affording diol **325 (Scheme 127)**. As previously discussed, cleavage of this functionality had been observed for the propiophenone derived 1,3-amino alcohol substrates **(Section 5.3)**.



(*S*,*R*,*S*,*R*,*R*,*S*)-294 **325**

Scheme 127. Hydrolysis of the ester moiety forming diol **325**

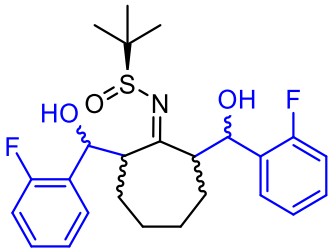
However, examination of the ^{1}H NMR spectrum of the crude reaction mixture of **(*S*,*R*,*S*,*R*,*R*,*S*)-294** (cycloheptanone sulfinyl imine **(*S*)-291** and benzaldehyde) indicated that this side-product was in fact the double aldol product **326 (Figure 42)**.



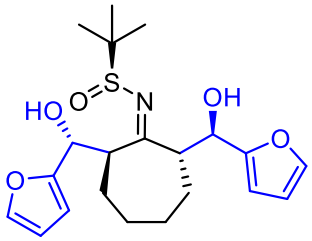
326

Figure 42. Double aldol product

This was further confirmed following isolation of double aldol products **311** and **(*R*,*R*,*S*,*R*,*R*)-317** formed from the reaction of cycloheptanone sulfinyl imine **(*S*)-291** with furfural and *o*-fluoro benzaldehyde **(Figure 43)**.



311



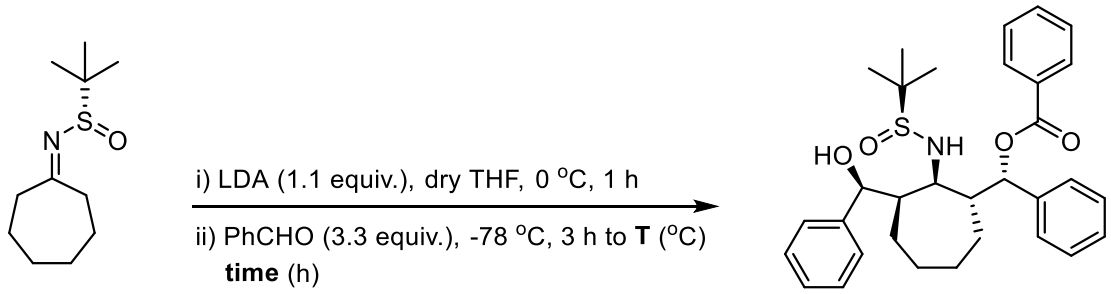
(*R*,*R*,*S*,*R*,*R*)-317

Figure 43. Previously isolated double-aldol products

After thoroughly examining the ^{1}H NMR spectra of the crude reaction mixtures obtained from all substrates, it was determined that the side-product was the double aldol product. We also observed that the amount of double aldol product in the crude reaction mixtures varied with each aldehyde.

We then felt that further optimisation of the reaction conditions could drive our double aldol-Tishchenko reaction to completion and thus increase the yield. For this purpose, we chose to investigate the reaction of cycloheptanone sulfinyl imine **(*S*)-291** and benzaldehyde. We began our investigation by warming the reaction mixture to 0 ^{o}C over 16 h **(Table 21, entry 2)**. This resulted in a slight improvement in comparison to the standard reaction conditions **(Table 21, entry 1)**. The temperature was then increased to -10 ^{o}C over a period of 24 h **(Table 21, entry 3)**. Pleasingly, a further decrease in double aldol product was observed in the ^{1}H NMR spectrum of the crude reaction mixture. However, in both cases, it was determined *via* ^{1}H NMR analysis that as the temperature increased, a concomitant increase in benzyl alcohol (*via* benzaldehyde reduction), was observed.

Table 21. Tishchenko temp/time screen



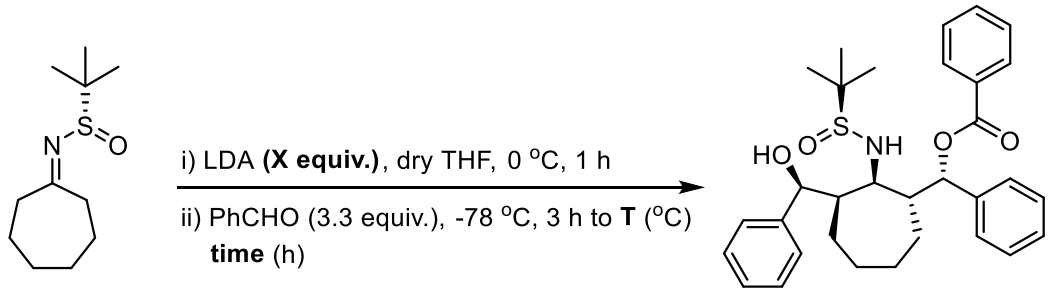
(*S*)-291 **(*S*,*R*,*S*,*R*,*R*,*S*)-294**

Entry	LDA (Equiv.)	Temperature (°C)	Time (h)	^{1}H NMR ratios[a] (AAT:AA:Alcohol)
1	1.1	-20	16	1.0:0.26:0.31
2	1.1	0	16	1:0.21:1.11
3	1.1	-10	24	1:0.19:0.73

[a]Ratio of **i)** aldol-aldol-Tishchenko product **ii)** aldol-aldol product and **iii)** benzyl alcohol determined from the ^{1}H NMR spectrum of the crude reaction mixture.

Further optimisation work revealed that use of sub-stoichiometric amounts of LDA could help progress the reaction even further by possibly facilitating reversible aldol steps. A range of temperatures and times for the Tishchenko step was screened using 0.8 equivalents of LDA **(Table 22, entries 1-4)**. Holding the temperature at -20 °C over 24 h did improve the conversion slightly, while also reducing the amount of benzyl alcohol **(Table 22, entry 1)**. The best result was obtained utilising 0.8 equivalents of LDA and increasing the temperature to -15 °C over 24 h **(Table 22, entry 2)**. Notably, while the latter two entries **(Table 22, entries 3 and 4)** demonstrated similar results, a drop off in diastereoselectivity was observed, particularly when the amount of base was reduced to 0.5 equivalents.

Table 22. Investigation of sub-stoichiometric amounts of LDA

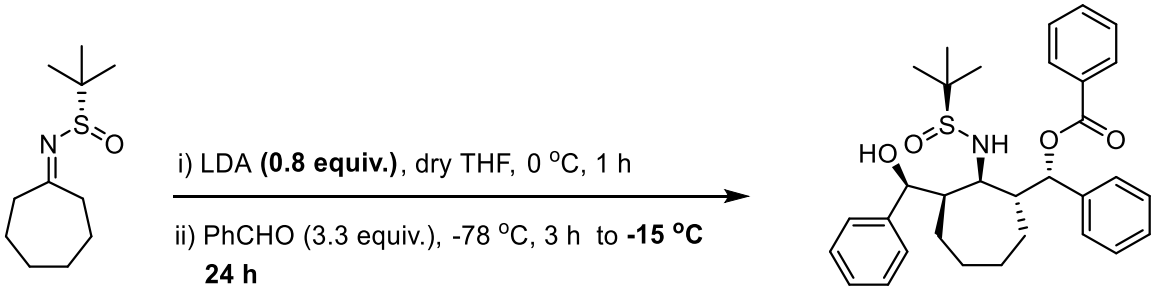


(*S*)-291 **(*S*,*R*,*S*,*R*,*R*,*S*)-294**

Entry	LDA (Equiv.)	Temperature (ºC)	Time (h)	^{1}H NMR ratios[a] (AAT:AA:Alcohol)
1	0.8	-20	24	1:0.22:0.36
2	0.8	-15	24	1:0.08:~0.40
3	0.8	-10	24	1:0.07:0.42
4	0.5	-20	24	1:0.09:0.11

[a]Ratio of **i)** aldol-aldol-Tishchenko product **ii)** aldol-aldol product and **iii)** benzyl alcohol determined from the ^{1}H NMR spectrum of the crude reaction mixture.

Overall, we found that the yield could be improved (80%) utilising 0.8 equivalents of LDA and increasing the temperature of the Tishchenko step to -15 ºC over 24 h. These conditions also led to the highest level of diastereoselectivity **(Scheme 128)**.



(*S*)-291

(*S*,*R*,*S*,*R*,*R*,*S*)-294
dr: >90% major diastereomer
80% isolated yield

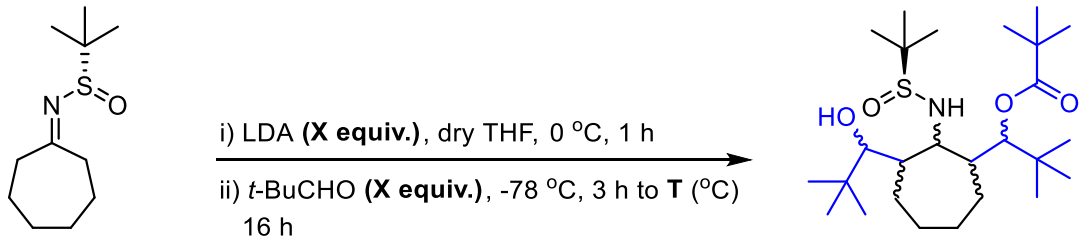
Scheme 128. Improved yield of **(*S*,*R*,*S*,*R*,*R*,*S*)-294** in the presence of 0.8 equivalents of LDA

5.4.3.4 Aliphatic aldehydes

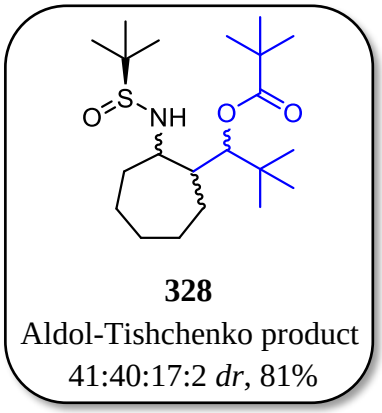
Previous work conducted within the group has demonstrated the use of aliphatic aldehydes as suitable aldol acceptors and hydride donors with acetophenone derived sulfinyl imines. Thus, it was decided to test our methodology using an aliphatic aldehyde such as pivaldehyde with cycloheptanone sulfinyl imine **(*S*)-291**. Unfortunately, this aldehyde did not promote a double aldol-Tishchenko reaction under the standard conditions utilising 1.1 equivalents of LDA **(Table 23, entry 1)**. The only observable products appeared to be aldol-Tishchenko product **328**. Due to overlapping signals, it was not possible to calculate an exact diastereomeric ratio. However, it was evident that the selectivity was depleted.

We then investigated the use sub-stoichiometric amounts of LDA (0.8 equivalents) and an excess of aldehyde (4.5 equivalents) **(Table 23, entry 2)**. In addition, the reaction mixture was warmed to 0 ^{o}C over 16 h. Under these conditions, the aldol-Tishchenko product **328** was once again found to be the major product. In this case, it was possible to calculate the diastereomeric ratio from the ^{1}H NMR spectrum of the crude reaction mixture. Much depleted selectivity was again observed for this aldol-Tishchenko reaction (41:40:17:2 *dr*). Four diastereomers were identified in the ^{1}H NMR spectrum. This was confirmed following purification of the crude material *via* column chromatography. Three fractions were isolated from the column and were all found to contain aldol-Tishchenko product. It was possible to isolate and individually characterise the two major diastereomers. A third fraction was also isolated from the column and contained a mixture of the two major diastereomers and the minor diastereomers. The absolute and relative stereochemistry of this aldol-Tishchenko product was not confirmed. In this case, the lithium aldolate formed during the first aldol reaction maybe more conducive to a Tishchenko reaction. Thus, once the aldol-Tishchenko product has formed it would no longer be susceptible to a second aldol addition.

Table 23. Investigation of pivaldehyde as an aldol acceptor



(*S*)-291 **327**



328
Aldol-Tishchenko product
41:40:17:2 *dr*, 81%

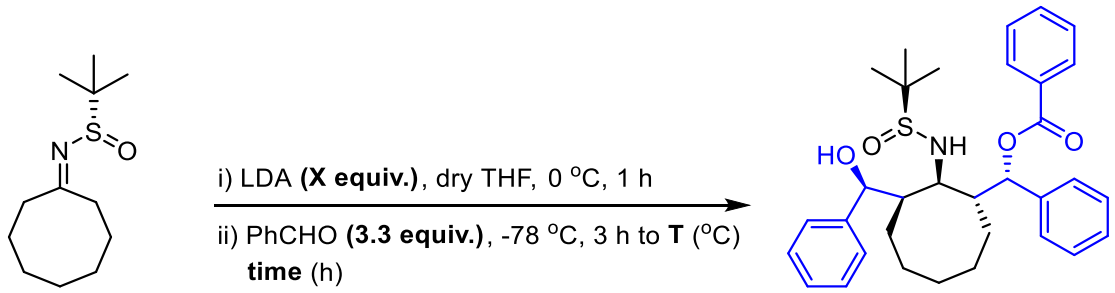
Entry	LDA (Equiv.)	Aldehyde (Equiv.)	Temperature (°C)	Time (h)	Product	Yield	*dr*
1	1.1	3.3	-20	16	Aldol-Tishchenko	n.d	n.d
2	0.8	4.5	0	16	Aldol-Tishchenko	81	41:40:17:2

5.4.3.5 Application of double aldol-Tishchenko methodology to six- and eight-membered cyclic sulfinyl imines

Having applied our reaction conditions to five- and seven-membered cyclic sulfinyl imines, we next sought to further extend the scope to six- and eight-membered cyclic sulfinyl imines. Overall, the results of these reactions proved disappointing. Cyclooctanone sulfinyl imine **(*S*)-292** was initially subjected to our standard double aldol-Tishchenko conditions utilising 1.1 equivalents of LDA and benzaldehyde **(Table 24, entry 1)**. Unfortunately, a complex mixture including **i)** double aldol-Tishchenko and **ii)** double aldol products was recovered following work-up in addition to a number of other side-products. We then examined the use of sub-stoichiometric amounts of LDA. Treatment of **(*S*)-292** with 0.8 equivalents of LDA and warming the mixture to -20 °C over 24 h resulted in no improvement in results **(Table 24,**

entry 2). The reaction mixture was then warmed to 0 °C over 16 h in an effort to promote the Tishchenko step **(Table 24, entry 3)**. However, ^{1}H NMR analysis revealed a complex mixture of products.

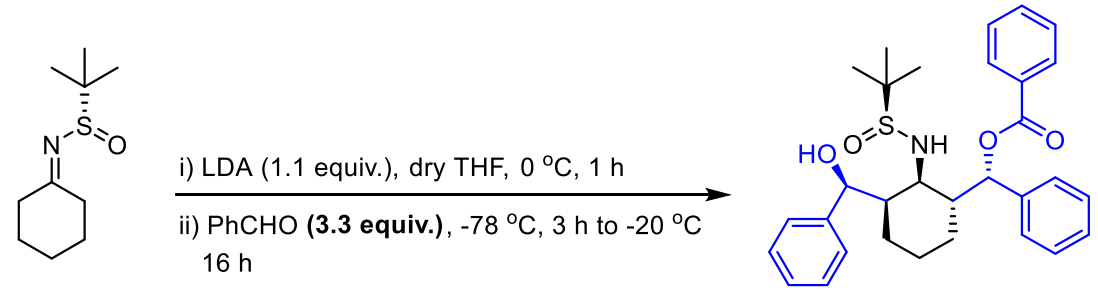
Table 24. Investigation of cyclooctanone sulfinyl imine **(*S*)-292** as an aldol donor



(*S*)-292 **329**

Entry	LDA (Equiv.)	Temperature (°C)	Time (h)	Result
1	1.1	-20	16	Complex mixture
2	0.8	-20	16	Complex mixture
3	0.8	0	16	Complex mixture

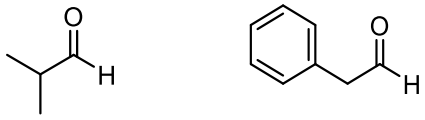
Given the lack of success with the eight-membered ring, we hoped that we would achieve better results with cyclohexanone sulfinyl imine, **(*S*)-290**. In particular, compounds containing six-membered rings are common structural motifs present in hundreds of drug molecules.[51] When cyclohexanone sulfinyl imine **(*S*)-290** was utilised as the aldol donor, poor conversion to the desired product **330** was observed following ^{1}H NMR analysis **(Scheme 129)**.



(*S*)-290 **330**
Complex mixture

Scheme 129. Investigation of cyclohexanone sulfinyl imine **(*S*)-289** as an aldol donor

We then felt that perhaps using an alternative aldol acceptor might facilitate the double aldol-Tishchenko reaction. With this mind, we chose to examine two very different aldehydes, **331** and **332** under the standard conditions **(Figure 44)**.

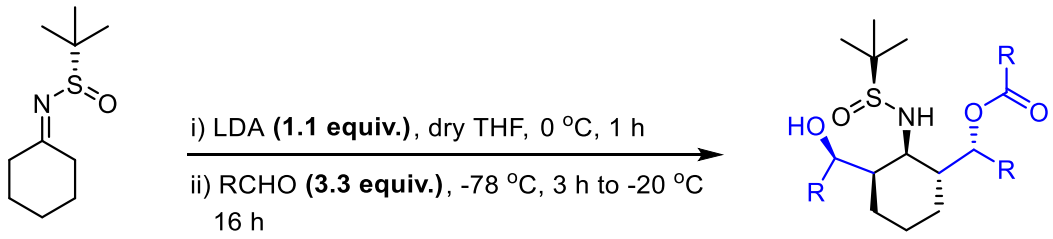


331 **332**

Figure 44. Alternative aldehydes

However, neither of these aldehydes produced any encouraging results. In the case of isobutyraldehyde, the crude material showed a complex mixture of products and degraded starting material **(Table 25, entry 1)**. The benzyl aldehyde **332**, also generated a complex mixture of products **(Table 25, entry 2)**.

Table 25. Effect of varying the aldol-acceptor



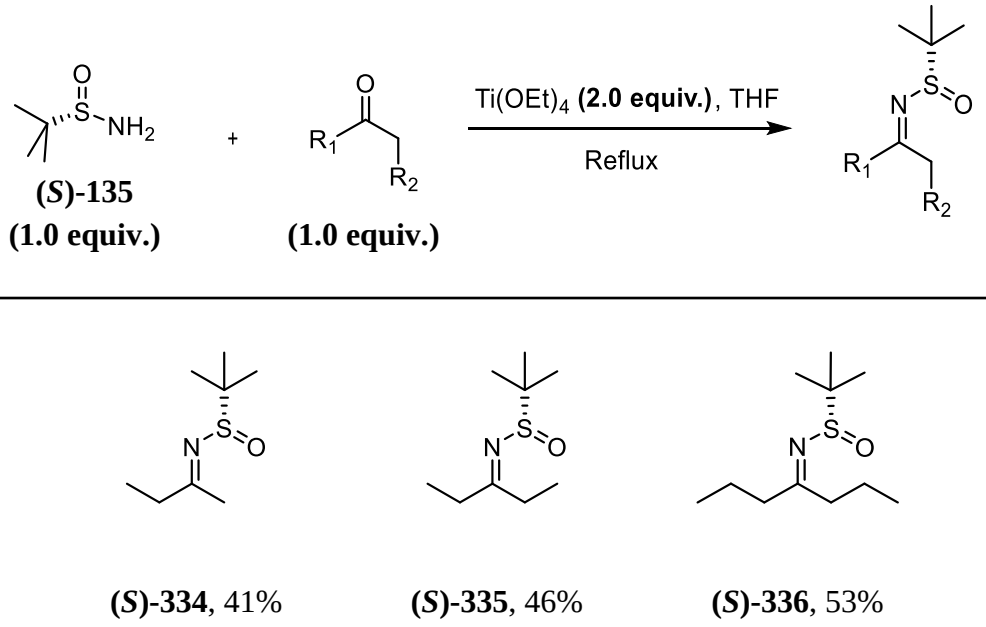
(*S*)-290 **333**

Entry	Aldehyde	Result
1	**331**	Complex mixture
2	**332**	Complex mixture

Given this result, no further investigations were carried out using sulfinyl imines **(*S*)-290** and **(*S*)-292**.

5.4.3.6 Application of double aldol-Tishchenko methodology to acyclic alkyl sulfinyl imines

Next, we turned our attention towards applying our methodology to acyclic alkyl sulfinyl imines. Acyclic carbon frameworks bearing contiguous chiral centres are useful building blocks in the synthesis of many biologically important compounds.[52] Firstly, a series of acyclic alkyl sulfinyl imines was easily prepared following the standard reaction conditions of heating the reaction mixture at reflux temperature overnight in the presence of 2.0 equivalents of $Ti(OEt)_4$ **(Scheme 130)**. Due to the volatility of the final products, the acyclic sulfinyl imines were isolated in slightly lower yields in comparison to the previously prepared sulfinyl imines (41-53%).

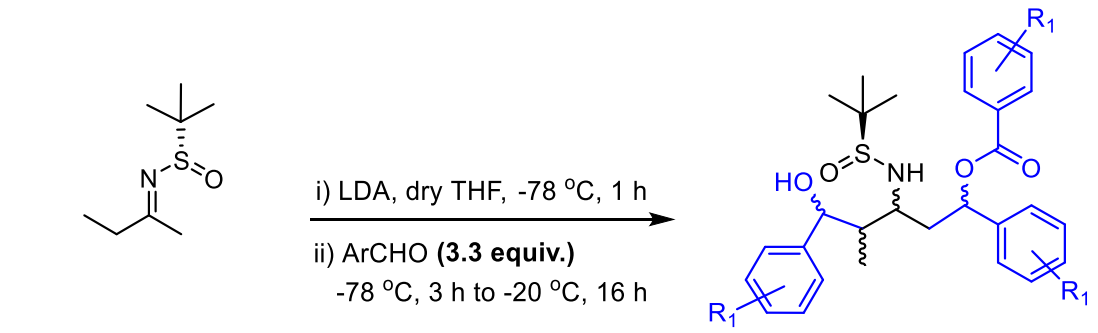


Scheme 130. Synthesis of acyclic (*S*)-*tert*-butanesulfinyl imines

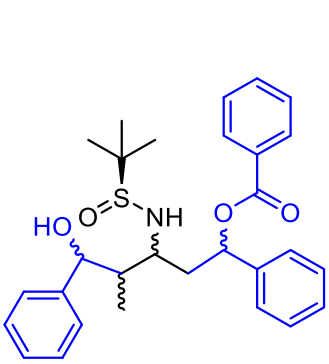
We initiated our investigation with 2-butanone sulfinyl imine **(*S*)-334**. This substrate has two potential sites for deprotonation, the kinetically favoured methyl site and the thermodynamically favoured methylene site. Previous work within the McGlacken group demonstrated that the aldol-Tishchenko reaction was completely regioselective for the least sterically hindered methyl position.[3] Thus, we were pleased that reaction of **(*S*)-334** with 3.3 equivalents of benzaldehyde in our double aldol-Tishchenko reaction showed no evidence for the presence of regioisomers **(Scheme 131)**. In all cases, the Tishchenko step was regioselective for the least sterically hindered site.

High diastereoselectivity was maintained for the majority of substrates. However, a noticeable drop in chemical yield was observed for substrates **337-340**. Increasing the number of equivalents of aldehyde to 4.5 for the *p*-methyl derivative **338** resulted in no improvement in yield. The presence of an electron-withdrawing substituent at the *meta*-position for **341** did result in a slight improvement in yield. For this substrate, the diastereoselectivity could not be determined due to the complexity of the ^{1}H NMR spectrum of the crude reaction mixture. However, a single diastereomer was isolated in 47% yield. The highest selectivity was achieved using benzaldehyde and the sterically hindered *p-iso*-Pr benzaldehyde affording the

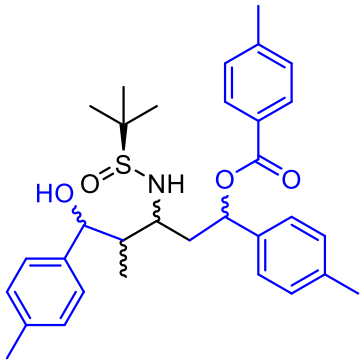
corresponding products **337** and **340** almost exclusively as pure diastereomers (>98:2 *dr*). However, depleted yields were obtained for both of these substrates.



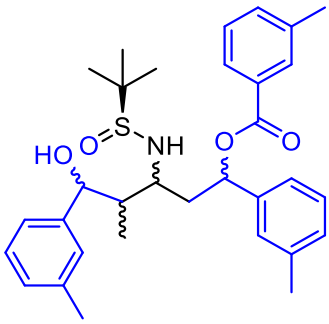
(*S*)-334



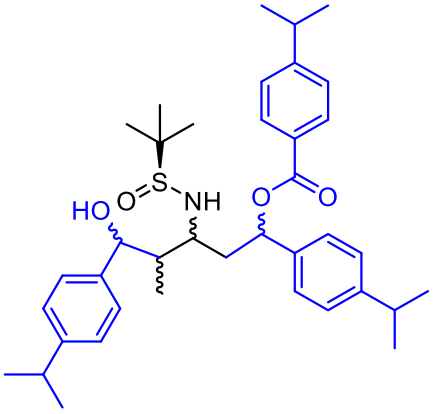
337
>98:2 *dr*, 32%



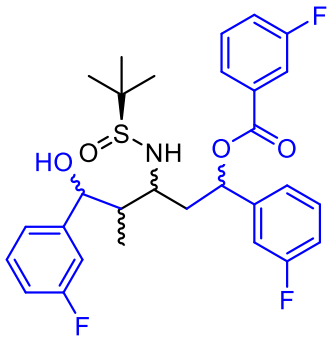
338
<97:3 *dr*, 44%



339
<90:10 *dr*, 38%



340
>98:2 *dr*, 25%



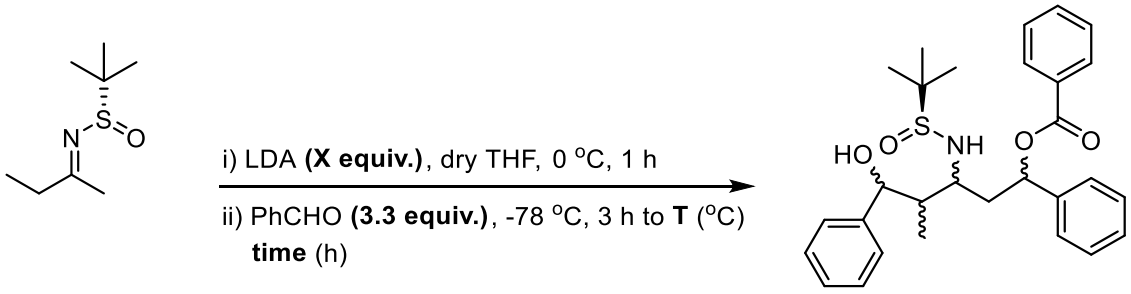
341
47%, single diastereomer
dr not determined

Scheme 131. Synthesis of four chiral centres in one-pot

Next, aliphatic aldehydes, pivaldehyde and isobutyraldehyde were examined as suitable aldol acceptors and hydride donors. Both of these aldehydes proved ineffective. While pivaldehyde did promote the aldol-Tishchenko reaction, this product had been previously isolated by another member of the group.[3] Increasing the equivalents of aldehyde to 4.5 had no positive effect. A complex mixture was recovered when isobutyraldehyde was utilised.

Having examined the number of equivalents of base with previous substrates, we were again able to demonstrate: **a)** the detrimental effect of using 2.0 equivalents of LDA and **b)** that an improved yield could be obtained using sub-stoichiometric amounts of base. The effect of using 2.0 equivalents of LDA was first probed **(Table 26, entry 2)**. Similar to previous investigations, while complete consumption of starting material was observed, a complex mixture of products was identified in the ^{1}H NMR spectrum of the crude reaction mixture. Only a trace amount of desired double aldol-Tishchenko product was detected. Deprotonation was then carried out in the presence of 0.8 equivalents of LDA. Pleasingly, this resulted in an improved yield of 45% **(Table 26, entry 3)**.

Table 26. Investigation of sub-stoichiometric amounts of base



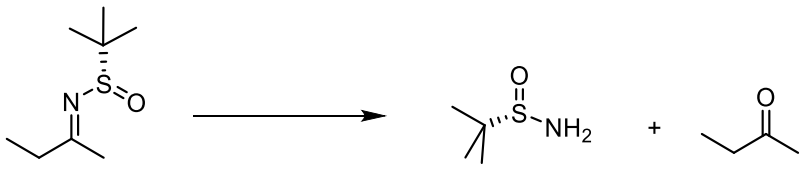
(*S*)-334 **337**

Entry	LDA (Equiv.)	Temperature (°C)	Time (h)	Yield[a] (%)	^{1}H NMR ratios[b] (AAT:Alcohol)
1	1.1	-20	16	32	1 : 2.8
2	2.0	-20	16	n/a	n/a
3	0.8	-15	16	45	1 : 1.1

[a]Isolated yield following purification by column chromatography.

[b]Ratio of aldol-aldol-Tishchenko product to benzyl alcohol determined from the ^{1}H NMR spectrum of the crude reaction mixture.

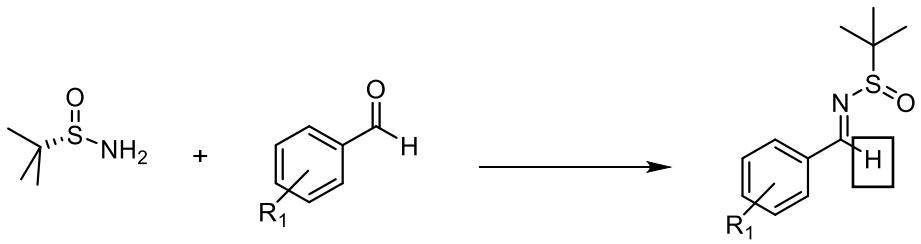
For this series of substrates, it was observed that little or no double-aldol product was detected in the crude reaction mixtures, as was previously observed for the cyclopentanone and cycloheptanone series. Despite this, lower yields were obtained for the 2-butanone derived double aldol-Tishchenko products. During the compilation of this thesis, it was postulated that the reduced yields may be due to degradation of 2-butanone sulfinyl imine **(*S*)-334**, as the reaction mixture is warmed to -20 °C during the Tishchenko step **(Scheme 132)**.



(*S*)-334 **(*S*)-135** **342**

Scheme 132. Degradation of sulfinyl imine **(*S*)-334**

Analysis of all the ^{1}H NMR spectra of the crude reaction mixtures for the 2-butanone series showed the presence of a singlet at ~8.5 ppm (a doublet was identified for the *m*-fluoro benzaldehyde double aldol-Tishchenko derivative **341**, **Scheme 131**). Due to the reversible nature of the aldol reaction, it is postulated that this singlet is due to the formation of sulfinyl aldimine **(*S*)-344**. We believe that this product is formed during the course of the reaction as a result of degradation of the 2-butanone sulfinyl imine **(*S*)-334** and subsequent reaction of the (*S*)-*tert*-butane sulfinamide **(*S*)-135** with the corresponding aldehyde **343 (Scheme 133)**.



(*S*)-135 **343** **(*S*)-344**

Scheme 133. Formation of sulfinyl aldimine **(*S*)-344**

There is evidence to support this theory on examination of the ^{1}H NMR spectra of the crude reaction mixtures for the 2-butanone derived substrates **(Figure 45)**. In particular, for the reaction of 2-butanone sulfinyl imine **(*S*)-334** with *p-i*so-Pr benzaldehyde which proceeded to

give the lowest yield, the ^{1}H NMR spectrum of the crude material showed the presence of a large singlet at 8.56 ppm. Furthermore, similar to previous substrates, reduction of the aldehyde to the corresponding alcohol was also detected.

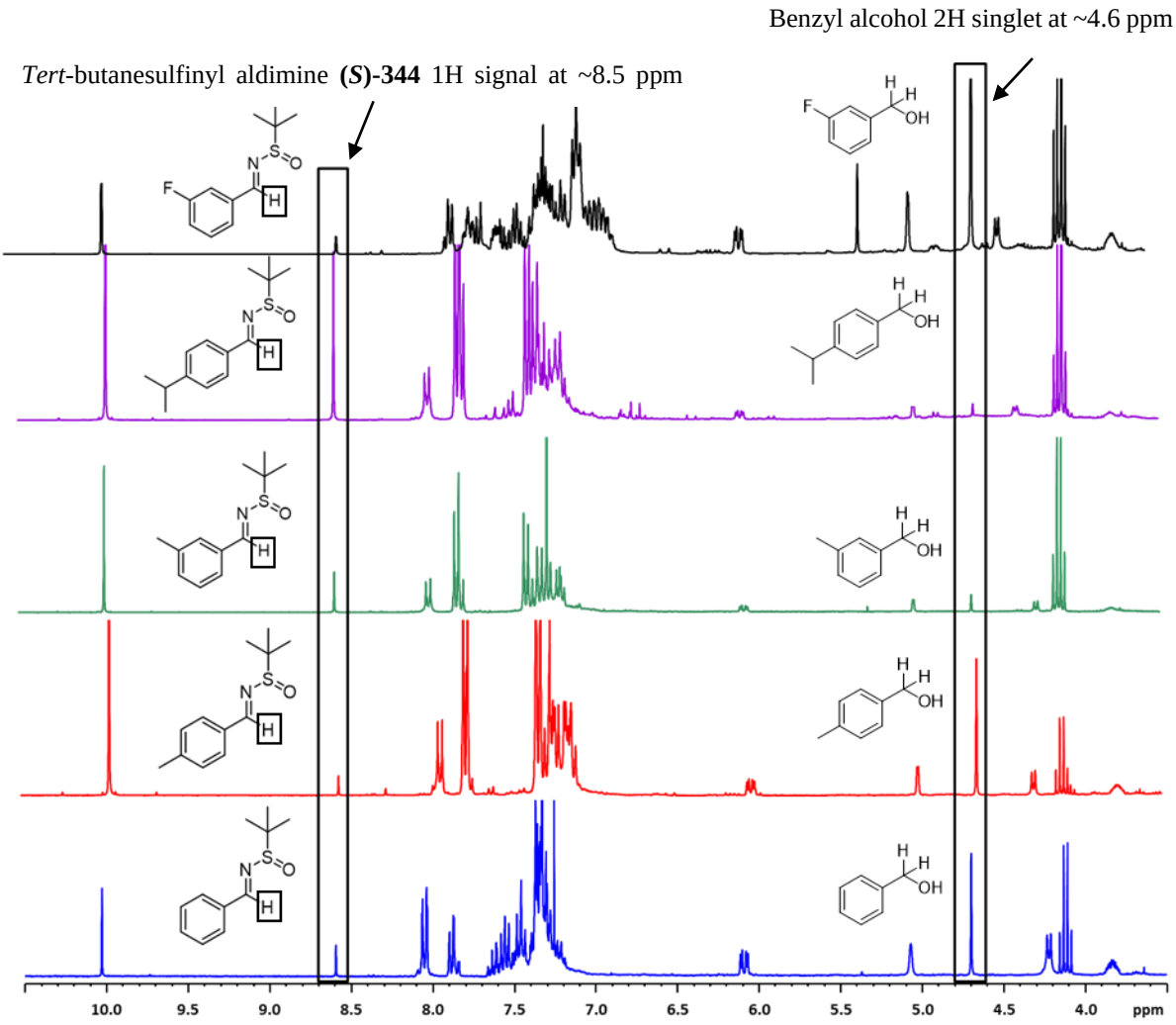
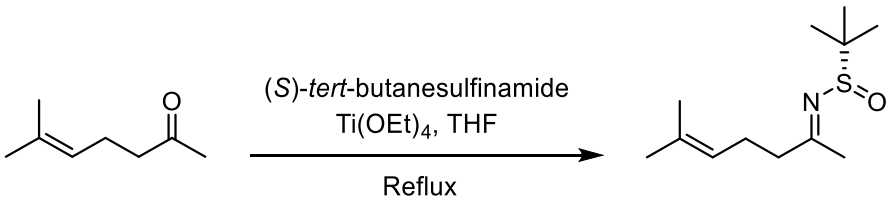


Figure 45. Overlay of ^{1}H NMR spectra of the crude reaction mixtures for the 2-butanone series indicating the possible formation of sulfinyl aldimine **(*S*)-344**

At present, there is no conclusive evidence for this hypothesis and thus, further investigation is warranted.

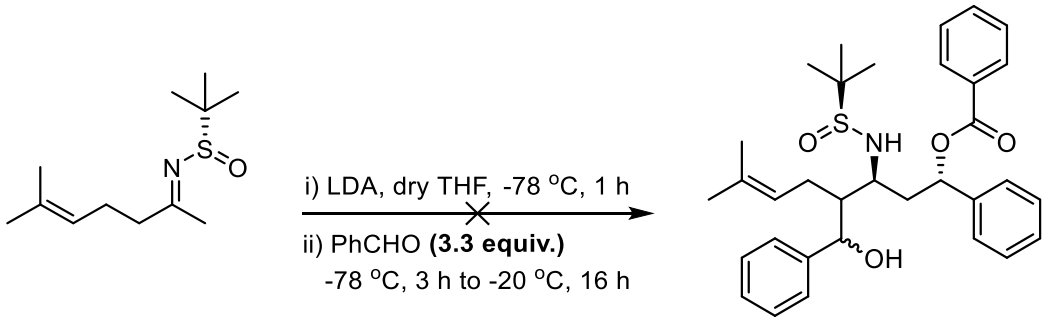
To further extend the scope, unsymmetrical methyl sulfinyl imine **(*S*)-346** was also tested. This compound possesses an alkenyl functionality which presents a useful site for further derivatisation. Firstly, **(*S*)-346** was prepared in a moderate yield of 34% under standard conditions **(Scheme 134)**.



345 **(*S*)-346**, 34%

Scheme 134. Preparation of **(*S*)-346**

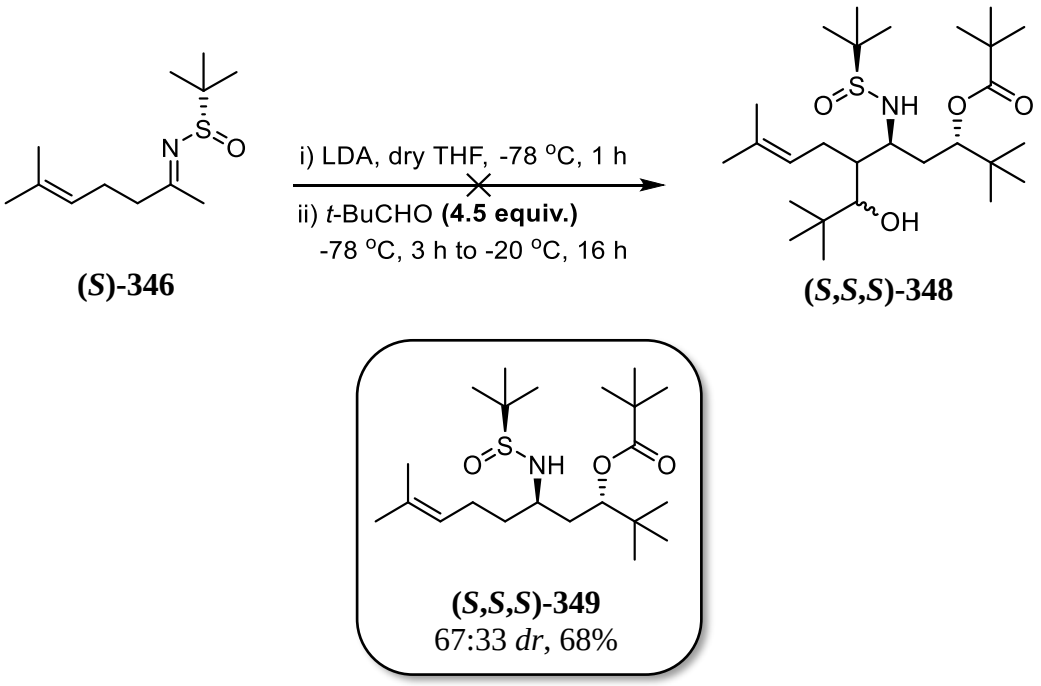
Unfortunately, reaction of **(*S*)-346** with benzaldehyde resulted in no desired product formation **(Scheme 135)**.



(*S*)-346 **(*S,S,S*)-347**

Scheme 135. Double aldol-Tishchenko reaction using alkenyl based sulfinyl imine **(*S*)-346**

Pivaldehyde was then substituted as the aldol acceptor. The major product isolated from this reaction was the aldol-Tishchenko product **(*S,S,S*)-349** and no double aldol-Tishchenko product **(*S,S,S*)-348** was detected **(Scheme 136)**. Moderate diastereoselectivity was achieved for this substrate (67:33 *dr*) and purification by column chromatography afforded **(*S,S,S*)-349** in a good yield of 68%.



Scheme 136. Examination of pivaldehyde as an aldol acceptor

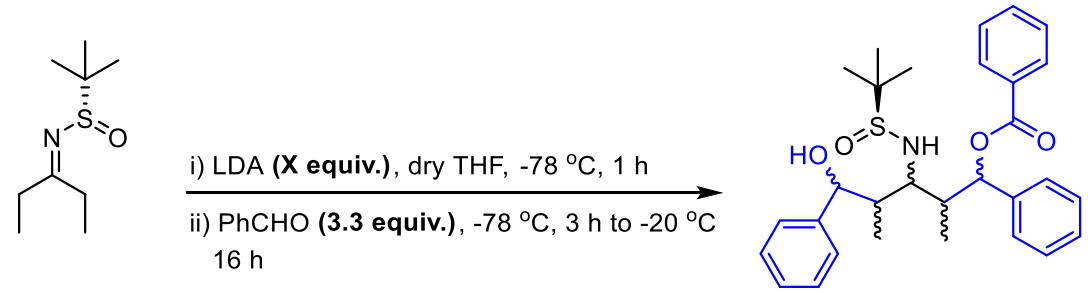
Following on from this work, we were then interested in testing if our methodology could be expanded to include other acyclic alkyl sulfinyl imines including symmetrical methylene sulfinyl imines. In contrast to methyl ketones, the methylene analogues provide a number of challenges including low reactivity towards aldol-addition due to their propensity towards a fast retro-aldol reaction of formed aldols.[53] Furthermore, the potential formation of *E*- and *Z*-azaenolates may present additional selectivity issues.

To begin, the reaction of 3-pentanone sulfinyl imine **(*S*)-335** and 4-heptanone sulfinyl imine **(*S*)-336** were chosen as our targets. Initial investigations involved reacting 3-pentanone sulfinyl imine **(*S*)-335** with benzaldehyde under the standard conditions using 1.1 equivalents of LDA **(Table 27, entry 1)**. Unfortunately, only poor conversion to the desired double aldol-Tishchenko product **350** was observed. Examination of the ^{1}H NMR spectrum showed a complex mixture consisting of **i)** double aldol-Tishchenko **ii)** double-aldol products in addition to a number of unidentified products.

Having previously determined that the yield could be improved by using 0.8 equivalents of LDA and warming to -15 °C overnight, we decided to test these conditions **(Table 27, entry 2)**. Disappointingly, this had no effect on product formation. A complex mixture was recovered upon work-up. Warming the reaction mixture to 0 °C and room temperature overnight **(Table**

27, entry 3 and 4) also proved unsuccessful. As observed with the 2-butanone series, substantial degradation of the sulfinyl imine occurred at higher temperatures.

Table 27. 3-pentanone sulfinyl imine **(*S*)-335** as an aldol donor



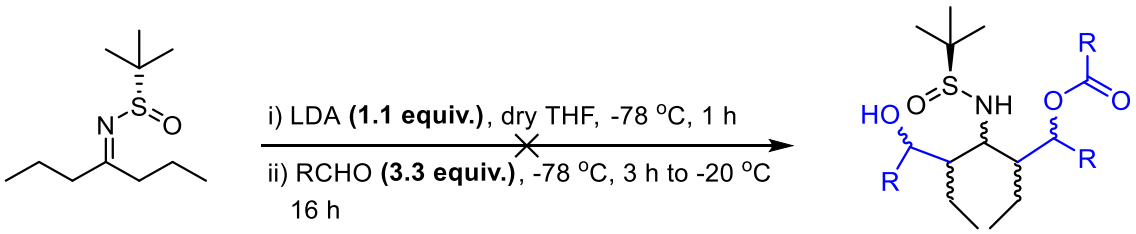
(*S*)-335 **350**

Entry	LDA (Equiv.)	Temperature (°C)	Time (h)	Result
1	1.1	-20	16	Complex mixture
2	0.8	-15	24	Complex mixture
3	0.8	0	16	Complex mixture
4	0.8	RT	16	Complex mixture

Substituting benzaldehyde with pivaldehdye as the aldol donor had no effect on product formation. Once again, ^{1}H NMR analysis showed a complex mixture of products.

Next, we felt that elongation of the alkyl chain and applying 4-heptanone sulfinyl imine **(*S*)-336** as the aldol donor might promote product formation. However, extending the carbon chain had no impact in the reaction of sulfinyl imine **(*S*)-336** with benzaldehyde **(Table 28, entry 1)**. ^{1}H NMR analysis of the crude material showed the presence of starting material, benzyl alcohol and unidentified side-products. We then examined pivaldehyde as an aldol acceptor **(Table 28, entry 2)**. In this case, only unreacted starting material was recovered.

Table 28. Attempted double aldol-Tishchenko using 4-heptanone sulfinyl imine **(*S*)-336**

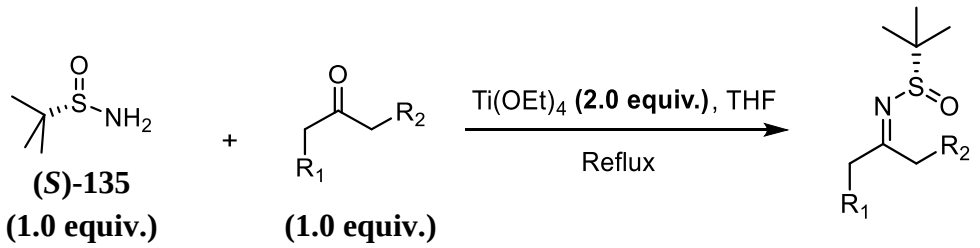


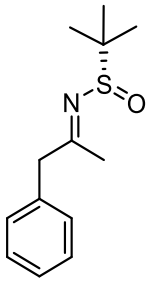
(*S*)-336 **351**

Entry	LDA (Equiv.)	R	Temperature (°C)	Time (h)	Result
1	1.1	Ph	-20	16	Complex mixture
2	1.1	*t*-Bu	-20	16	Unreacted starting material

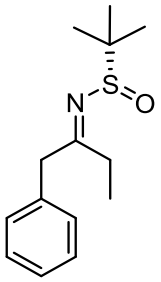
Acyclic symmetrical alkyl sulfinyl imines **(*S*)-335** and **(*S*)-336** proved unsuitable for our double aldol-Tishchenko methodology. This is most likely due to a number of competing reactions occurring at both α-sites. Investigations carried out by Nakajima and co-workers have demonstrated very low reactivity for any alkyl ketones other than methyl ketones in aldol reactions.[35]

A small study was then conducted to examine acyclic symmetrical and unsymmetrical benzylic sulfinyl imines. Firstly, the synthesis of (*S*)-*tert*-butanesulfinyl imines **(*S*)-352-354** was achieved in moderate yields **(Scheme 137)**. Analysis of the ^{1}H NMR spectra for both unsymmetrical sulfinyl imines **(*S*)-352** and **(*S*)-353** indicated the presence of *E*:*Z* isomers. Sulfinyl imine **(*S*)-352** was isolated as a 4:1 mixture of isomers presumably with a strong preference for the *E* isomer. In comparison, the ^{1}H NMR spectrum of sulfinyl imine **(*S*)-353** showed a 5:3 mixture of *E*:*Z* isomers. Overall, the yields obtained for these sulfinyl imines were lower in comparison to the previous substrates (33-61%). The low yield obtained for **(*S*)-352** is most likely due to the low purity of the ketone starting material (benzyl methyl ketone). However, **(*S*)-353** was isolated in an improved yield of 61%.

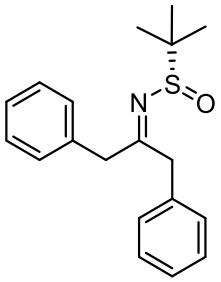




(*S*)-352, 33% (4:1 *E*:*Z*)



(*S*)-353, 61% (5:3 *E*:*Z*)

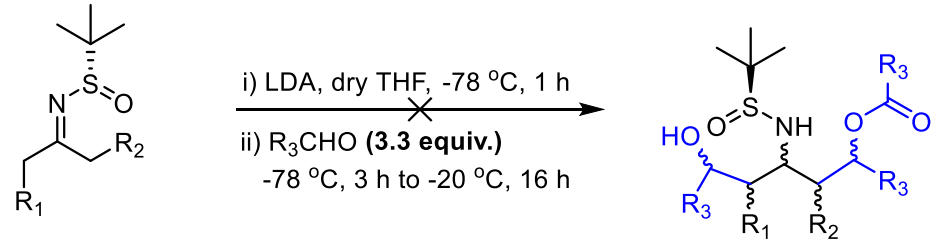


(*S*)-354, 42%

Scheme 137. Synthesis of benzylic sulfinyl imines

We then proceeded to apply sulfinyl imines **(*S*)-352-354** to our double aldol-Tishchenko methodology **(Table 29, entries 1-4)**. Disappointingly, we failed to observe any desired product formation using benzaldehyde as the aldol acceptor. In all three cases, a complex mixture was recovered which consisted of benzyl alcohol, degraded starting material and a number of unidentified products. Pivaldehyde was also investigated as an aldol acceptor using sulfinyl imine **(*S*)-352 (Table 29, entry 4)**. However, no formation of the corresponding product was detected.

Table 29. Attempted double aldol-Tishchenko reaction of **(*S*)-352-354**



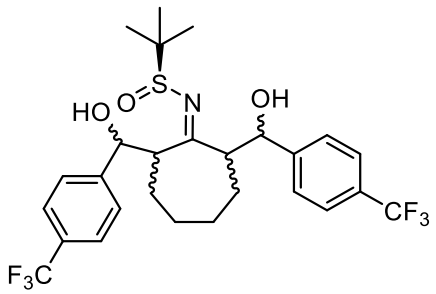
(*S*)-352-354

Entry	Starting material	LDA (Equiv.)	R_3	Temperature (°C)	Time (h)	Result
1	**(*S*)-352**	1.1	Ph	-20	16	Complex mixture
2	**(*S*)-353**	1.1	Ph	-20	16	Complex mixture
3	**(*S*)-354**	1.1	Ph	-20	16	Complex mixture
4	**(*S*)-352**	1.1	*t*-Bu	-20	16	Complex mixture

[a]Four chiral centres for sulfinyl imine **(*S*)-352**

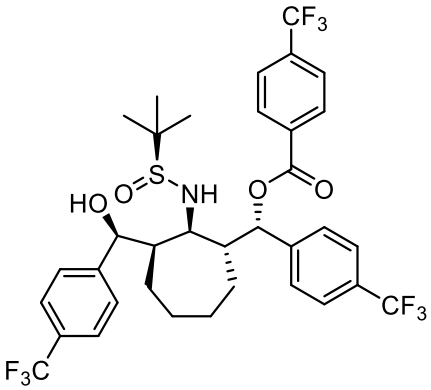
5.4.3.7 Mechanistic investigation

Previous mechanistic work carried out within the McGlacken group established that the mechanism of the aldol-Tishchenko reaction for the acetophenone series involves a reversible aldol step followed by an irreversible and stereodetermining hydride transfer.[3] Based on these experimental results, it is postulated that a similar mechanism is in operation for our double aldol-Tishchenko reaction. In order to gain an insight into the reaction mechanism, the reversibility of the aldol steps was examined. Firstly, the lithium alkoxide of double-aldol product **355** was treated with 0.8 equivalents of LDA and 1.0 equivalent of *m*-fluoro benzaldehyde at -78 ^{o}C, followed by warming the reaction mixture to -20 ^{o}C over 16 h **(Scheme 138)**. It should be noted that double aldol product **355** had been previously as a by-product during column chromatography from the reaction of cycloheptanone sulfinyl imine **(*S*)-291** with trifluoromethyl benzaldehyde. If both aldol reactions are reversible then a scrambled mixture of the Tishchenko products would be expected. Thus, an experiment was conducted to support this hypothesis.

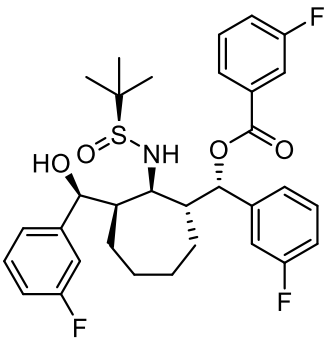


355, mixture of diastereomers

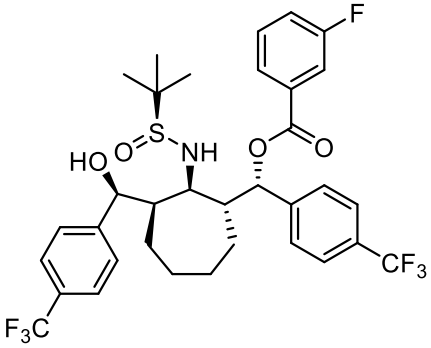
LDA (0.8 equiv.), -78 °C, 1 h
m-fluorobenzaldehyde (1.1 equiv.)
-78 °C to -20 °C, 16 h



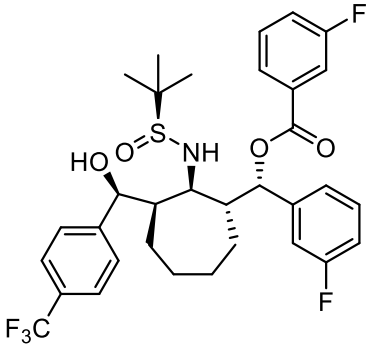
(*S*,*R*,*S*,*R*,*R*,*S*)-305
Predicted $[M + H]^+$: 738.2294
Found: 738.2302



(*S*,*R*,*S*,*R*,*R*,*S*)-300
Predicted $[M + H]^+$: 588.2390
Found: 588.2396



(*S*,*R*,*S*,*R*,*R*,*S*)-356
Predicted $[M + H]^+$: 688.2326
Found: 688.2323



(*S*,*R*,*S*,*R*,*R*,*S*)-357
Predicted $[M + H]^+$: 638.2358
Found: 638.2359

+ other crossover products

Scheme 138. Reversibility of aldol reaction crossover experiment. The above experiment was conducted by another member of the McGlacken group under my direct supervision.

Electron-spray ionization mass spectrometry (ESI-MS) analysis of the crude reaction mixture showed that a mixture of scrambled double aldol-Tishchenko products was present and thus confirmed reversible aldol steps **(Figure 46a-d)**. For example, as shown in **Figure 46b**, a peak corresponding to the double aldol-Tishchenko product with the incorporation of three *m*-fluoro benzaldehyde units **(*S*,*R*,*S*,*R*,*R*,*S*)-300** is observed in the high-resolution mass spectrum. This experimental result points to reversible aldol steps followed by an enantio- and diastereoselective non-reversible hydride transfer step.

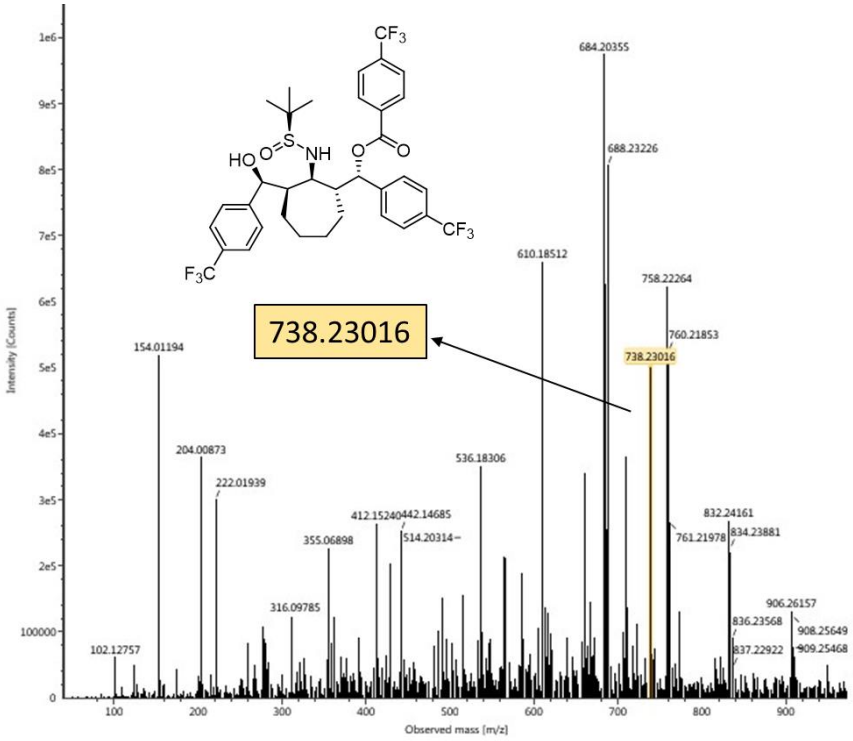


Figure 46a. High-resolution mass spectrum for lithium double-aldolate crossover experiment

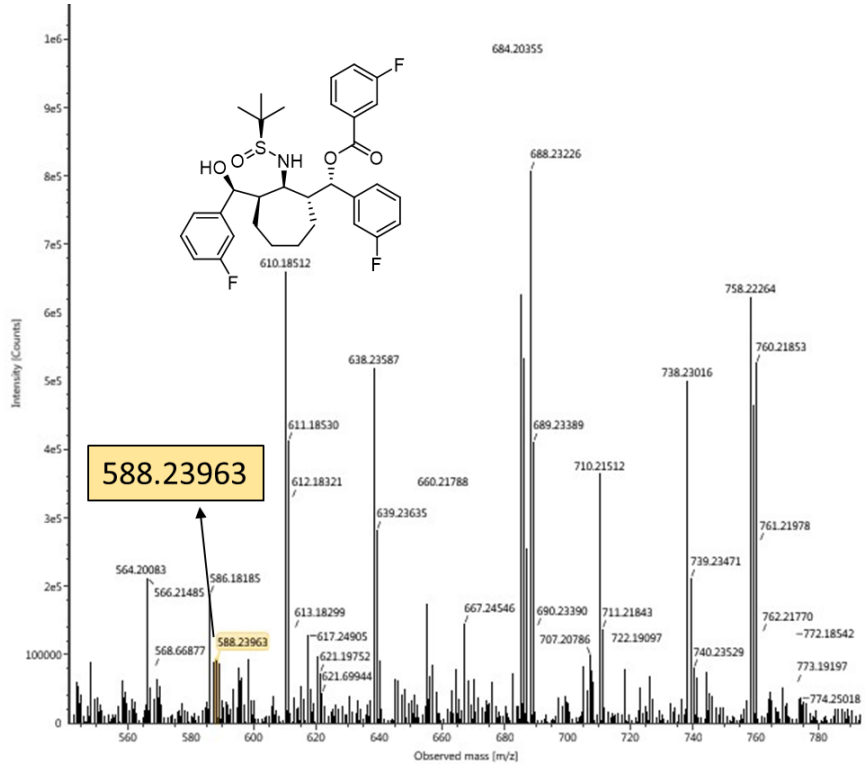


Figure 46b. High-resolution mass spectrum for lithium double-aldolate crossover experiment

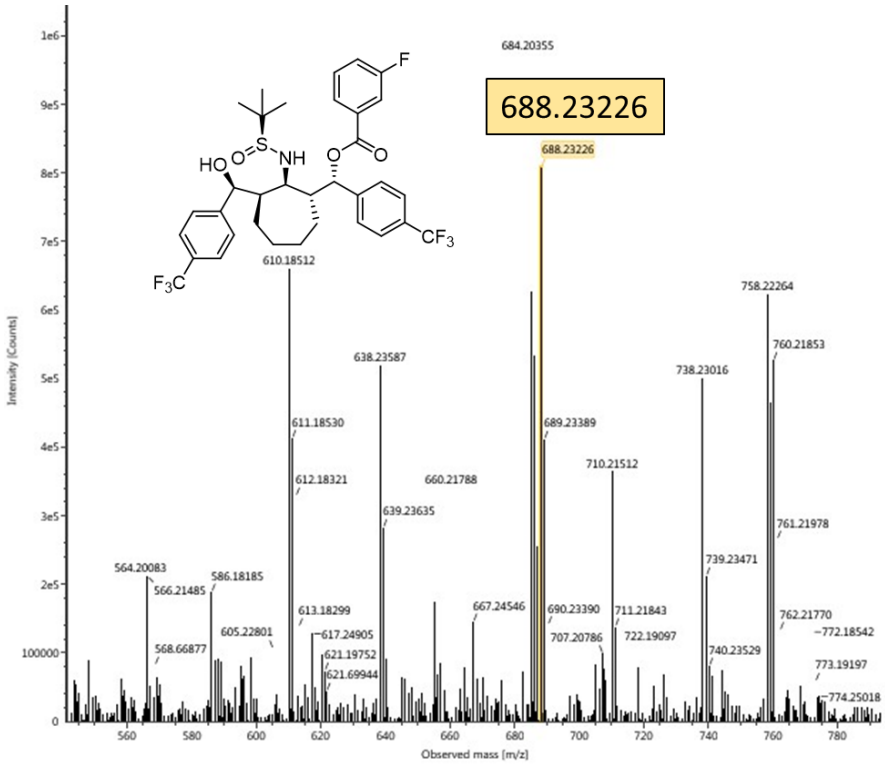


Figure 46c. High-resolution mass spectrum for lithium double-aldolate crossover experiment

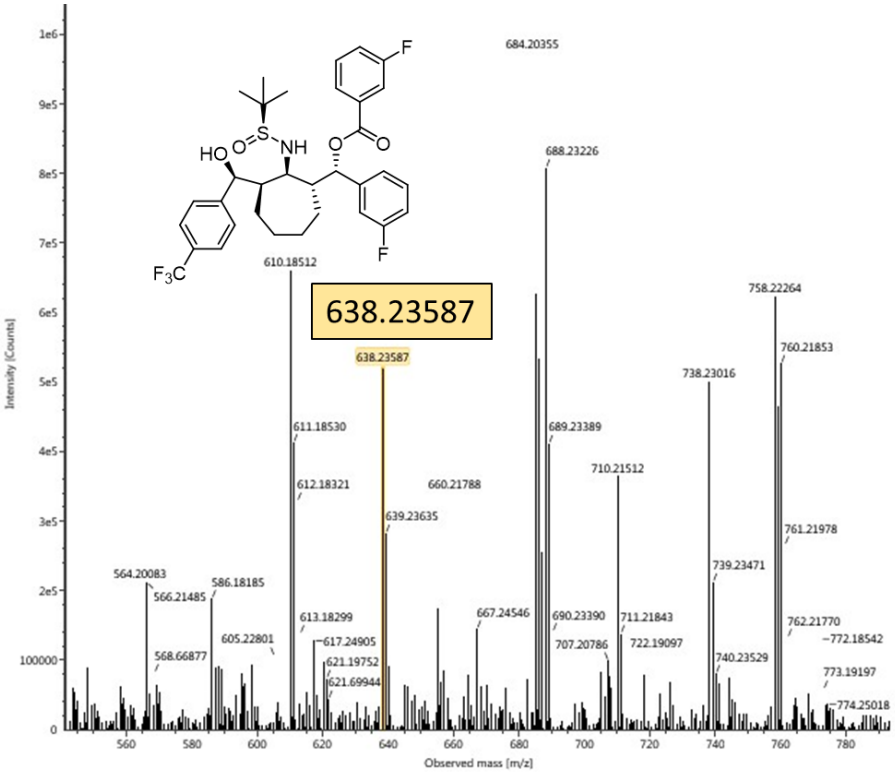


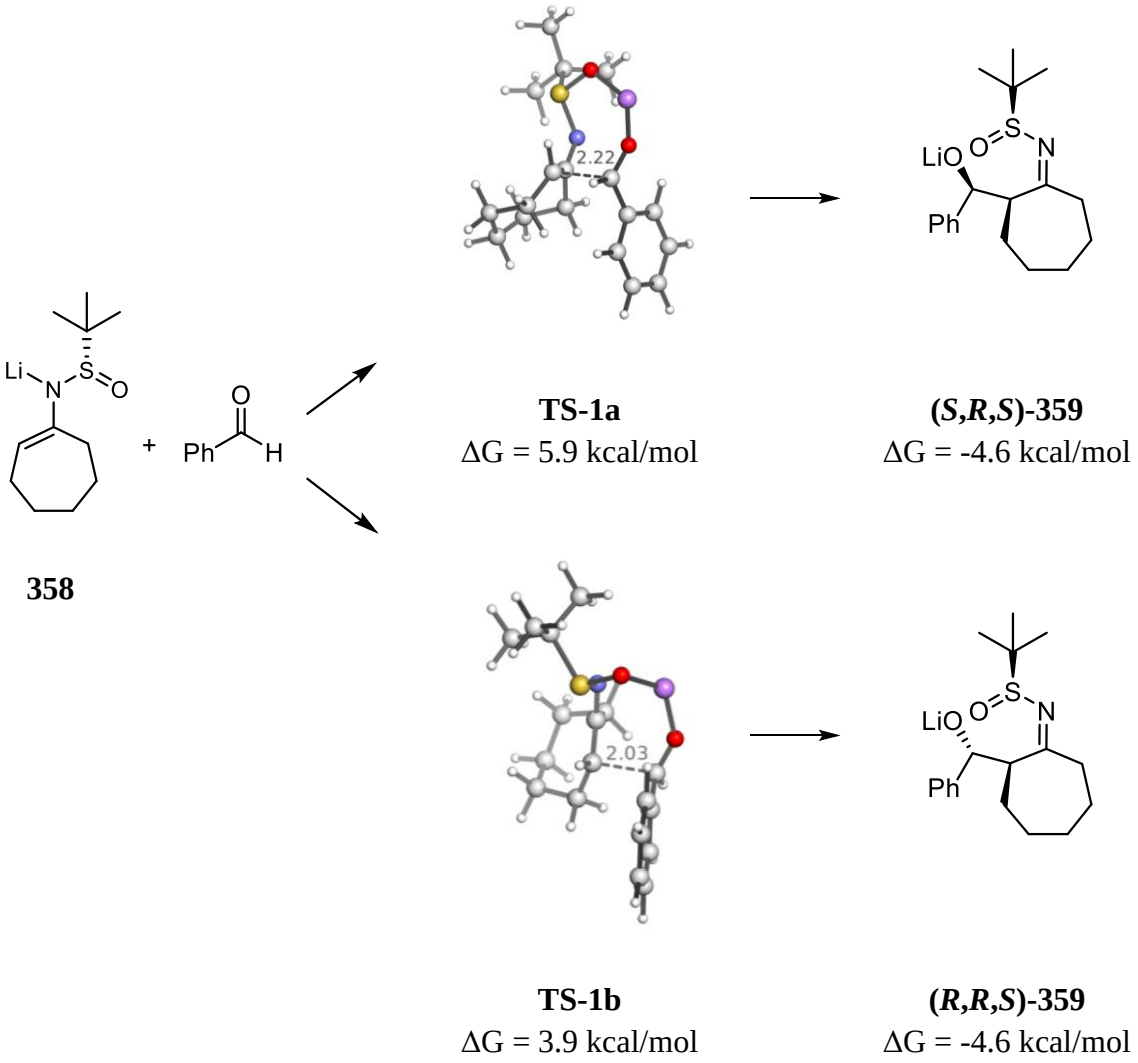
Figure 46d. High-resolution mass spectrum for lithium double-aldolate crossover experiment

5.5 Density functional theory (DFT) calculations

One of the most important and difficult tasks in the structure elucidation of chiral molecules is the assignment of absolute configuration.[54] For this project, X-ray crystallography was used to determine the absolute configuration of the cycloheptanone double aldol-Tishchenko series. DFT calculations were performed for the cycloheptanone and cyclopentanone double aldol-Tishchenko series. DFT is a computational method used to model the electronic structure of matter (atoms, molecules) in terms of the three dimensional electronic density of the system.[55] DFT calculations were performed by our collaborators, Prof. Ken Houk at the University of California, Los Angeles.

5.5.1 Stereoselectivity of the aldol step

To gain an insight into the stereoselectivity of the aldol step, density functional theory (DFT) calculations were carried out for the initial reaction of cycloheptanone lithium azaenolate **358** with the first equivalent of benzaldehyde **(Scheme 139)**. In the present study, the aldol transition state structures leading to the *syn*- and *anti*-diastereomers were analysed, and the energies were calculated. For this system, an unsolvated model was used. Computational results indicated that the aldol reaction does not follow the Zimmerman-Traxler-type model. The transition states were found to proceed *via* an eight-membered lithium bound transition state. The activation energies of **TS-1a** and **TS-1b** leading to the *syn*-aldolate **(*S*,*R*,*S*)-359** and *anti*-aldolate **(*R*,*R*,*S*)-359** were calculated to be 5.9 and 3.9 kcal/mol, respectively. Both the *syn*-aldolate **(*S*,*R*,*S*)-359** and *anti*-aldolate **(*R*,*R*,*S*)-359** products were found to have the same energy and thus a non-selective aldol step is envisaged.



358

TS-1a
ΔG = 5.9 kcal/mol

(*S*,*R*,*S*)-359
ΔG = -4.6 kcal/mol

TS-1b
ΔG = 3.9 kcal/mol

(*R*,*R*,*S*)-359
ΔG = -4.6 kcal/mol

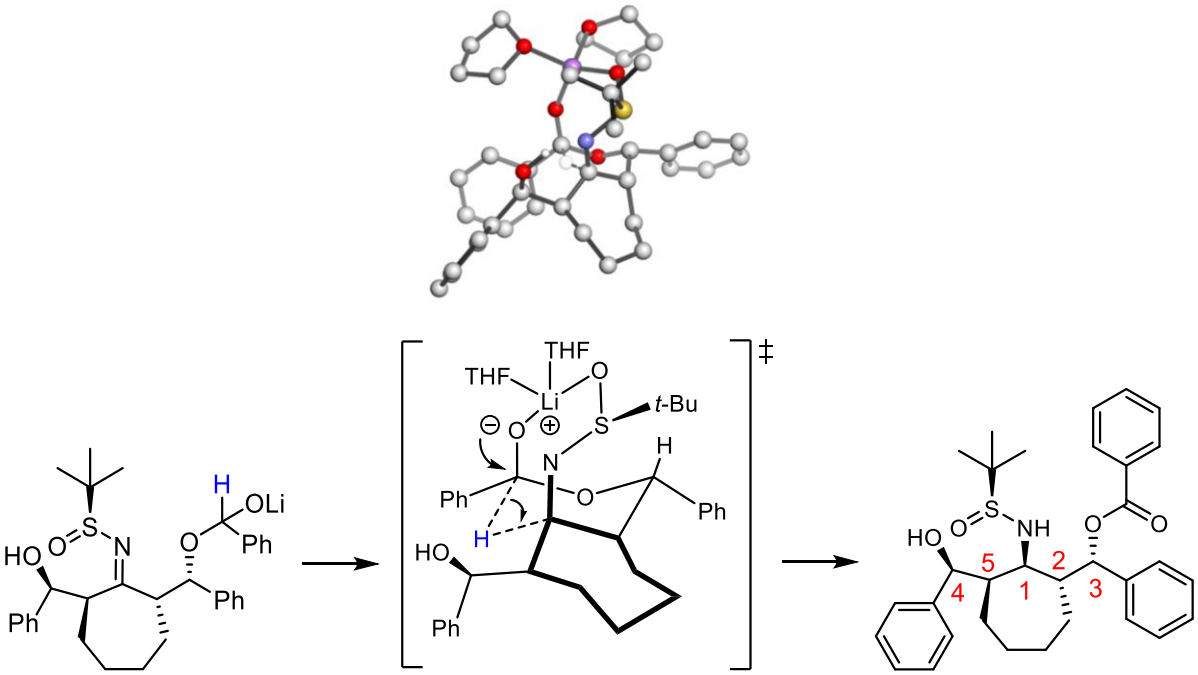
Scheme 139. Transition state structures for the aldol reaction of cycloheptanone lithium azaenolate and the first equivalent of benzaldehyde

These results confirmed the reversibility of the aldol reaction that was also observed experimentally. Thus, subsequent studies focused on the irreversible and stereo-determining intramolecular reduction step of the reaction sequence.

5.5.2 Stereoselectivity of the Tishchenko step

Cycloheptanone series

The reaction of cycloheptanone sulfinyl imine **(*S*)-291** and benzaldehyde was chosen as our model reaction. The corresponding double aldol-Tishchenko product **(*S*,*R*.*S*,*R*,*R*,*S*)-294** was formed in 73% yield and >90:4:2:2:2 *dr*. X-ray crystallographic analysis revealed that the stereochemistry of the major diastereomer matches that of the acetophenone major product. In this system, there is potential for the formation of 32 possible diastereomers, but only one diastereomer was observed almost exclusively under the reaction conditions. Thus, only three transition state structures were investigated using a disolvated transition state model. Various explicit solvation models were evaluated for computational modelling of the intramolecular hydride step of the reaction sequence. However, the disolvated lithium monomer was found to be the lowest energy complex. The first transition structure **TS-2a** was calculated based on the X-ray crystallographic data obtained for the major diastereomer **(Scheme 140)**. The formation of the major diastereomer (*S*,*R*,*S*,*R*,*R*,*S*) proceeds *via* a six-membered ring in a chair conformation **TS-2a** which places the two phenyl substituents in an equatorial position. The energy of activation (ΔG) of the hydride reduction step for this transition state was calculated to be 11.7 kcal/mol.

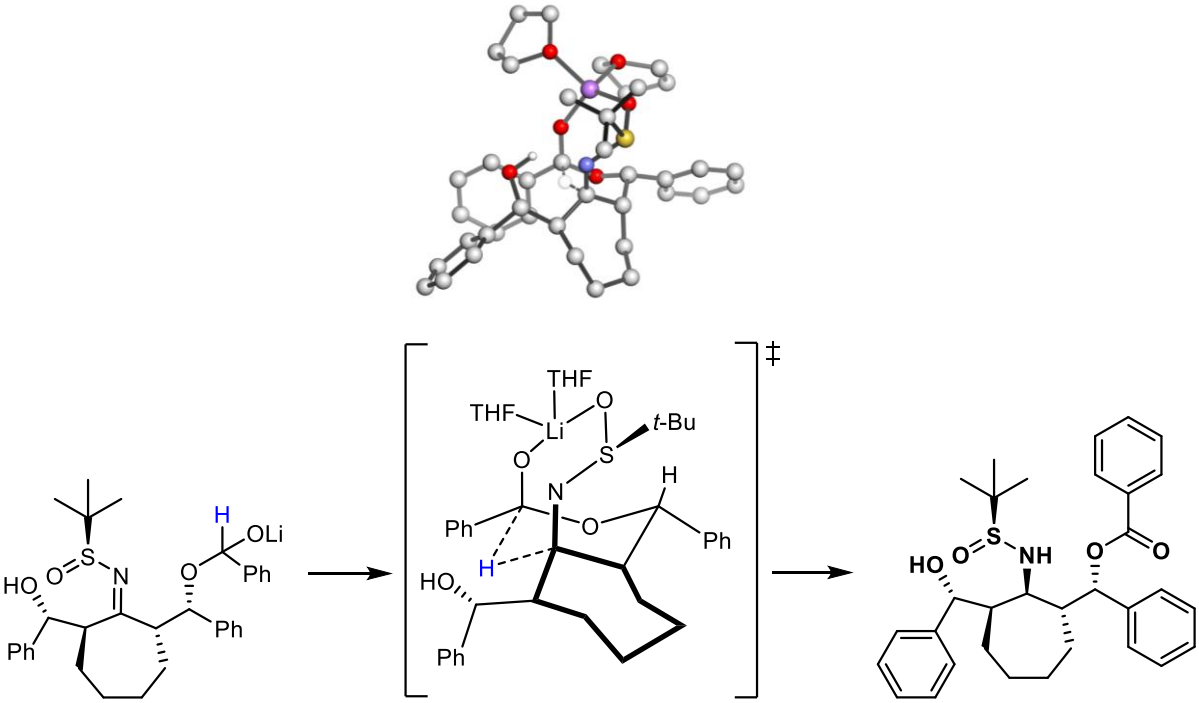


(*S*,*R*,*S*,*R*,*S*)-360 **TS-2a** **(*S*,*R*.*S*,*R*,*R*,*S*)-294**

ΔG = 11.7 kcal/mol

Scheme 140. Favoured TS: Calculated disolvated transition state leading to the formation of the major diastereomer

Transition states leading to two possible minor diastereomeric products were also calculated **(Scheme 141** and **Scheme 142)**. Firstly, the energy of the transition state leading to the *anti*-(4*R*,5*R*) product was examined **(TS-2b, Scheme 141)**. Computational results revealed that **TS-2b** is 1.7 kcal/mol higher in energy than **TS-2a**.

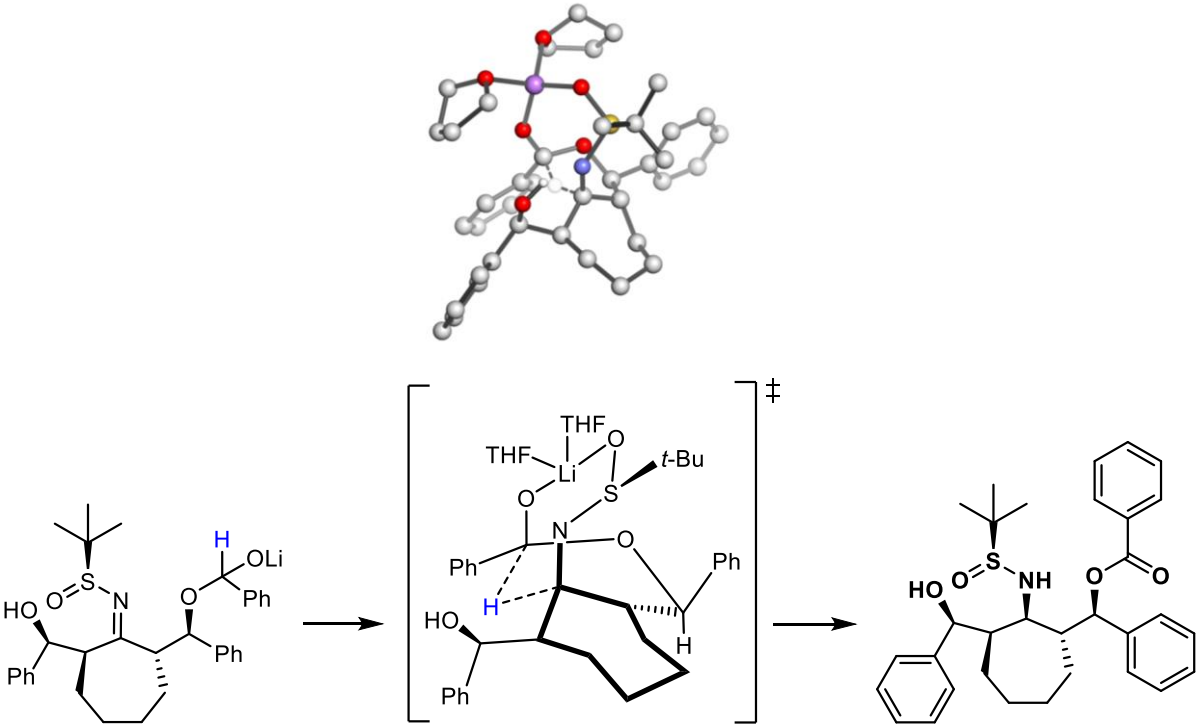


(*R*,*R*,*S*,*R*,*R*)-360 **TS-2b** **(*R*,*R*.*S*,*R*,*R*,*R*)-294**

$\Delta\Delta G^{\ddagger}$ = 1.7 kcal/mol

Scheme 141. Disolvated transition state leading towards the formation of a minor diastereomeric product

Next, the transition state barrier leading to product in which C1 and C3 are *cis* was calculated **(Scheme 142)**. In this case, the transition state **(TS-2c)** proceeds *via* a twist boat conformation. The phenyl group is in an equatorial position, thereby orientating the *t*-Bu group towards the six-membered ring of the twist-boat conformation to avoid an unfavourable steric interaction. A higher activation energy barrier was obtained for **TS-2c** ($\Delta\Delta G^{\ddagger}$ = 5.3 kcal/mol) in comparison to **TS-2a** and **TS-2b**. Thus, for the cycloheptanone-derived substrates, the transition state barrier leading towards product with C1 *R* and C3 *R* stereochemistry is higher in energy than products in which C1 and C3 are *trans*.



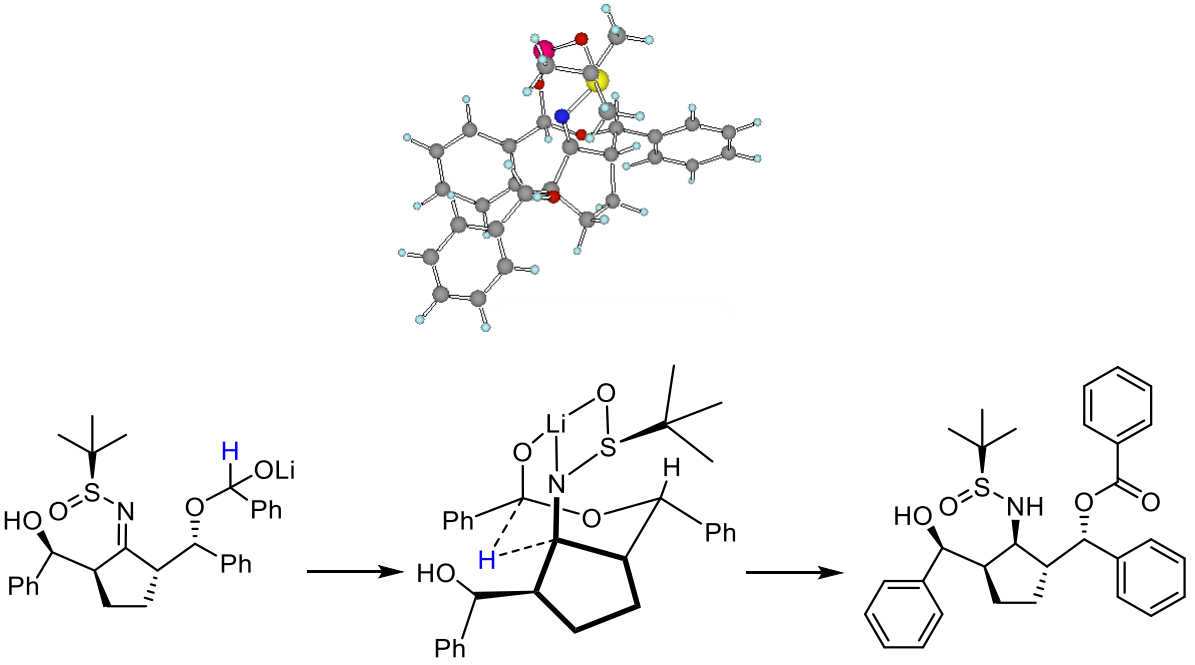
(*S*,*R*,*S*,*R*,*R*)-360 **TS-2c** **(*S*,*R*.*S*,*R*,*R*,*R*)-294**

$\Delta\Delta G^{‡}$ = 5.3 kcal/mol

Scheme 142. A disfavoured TS: Twist-boat conformation leading to the (*S*,*R*,*S*,*R*,*R*,*R*) diastereomer

Cyclopentanone series

For the cyclopentanone double aldol-Tishchenko product **(*S*,*R*,*S*,*R*,*R*,*S*)-318**, one unsolvated transition state structure was located **(Scheme 143)**. The formation of the (*S*,*R*,*S*,*R*,*R*,*S*) diastereomer proceeds *via* a six-membered chair-like transition state. The energy of activation (ΔG) for the reduction step for this transition state was calculated to be 14.0 kcal/mol.



(*S*,*R*,*S*,*R*,*S*)-361 **TS-3** **(*S*,*R*,*S*,*R*,*R*,*S*)-318**

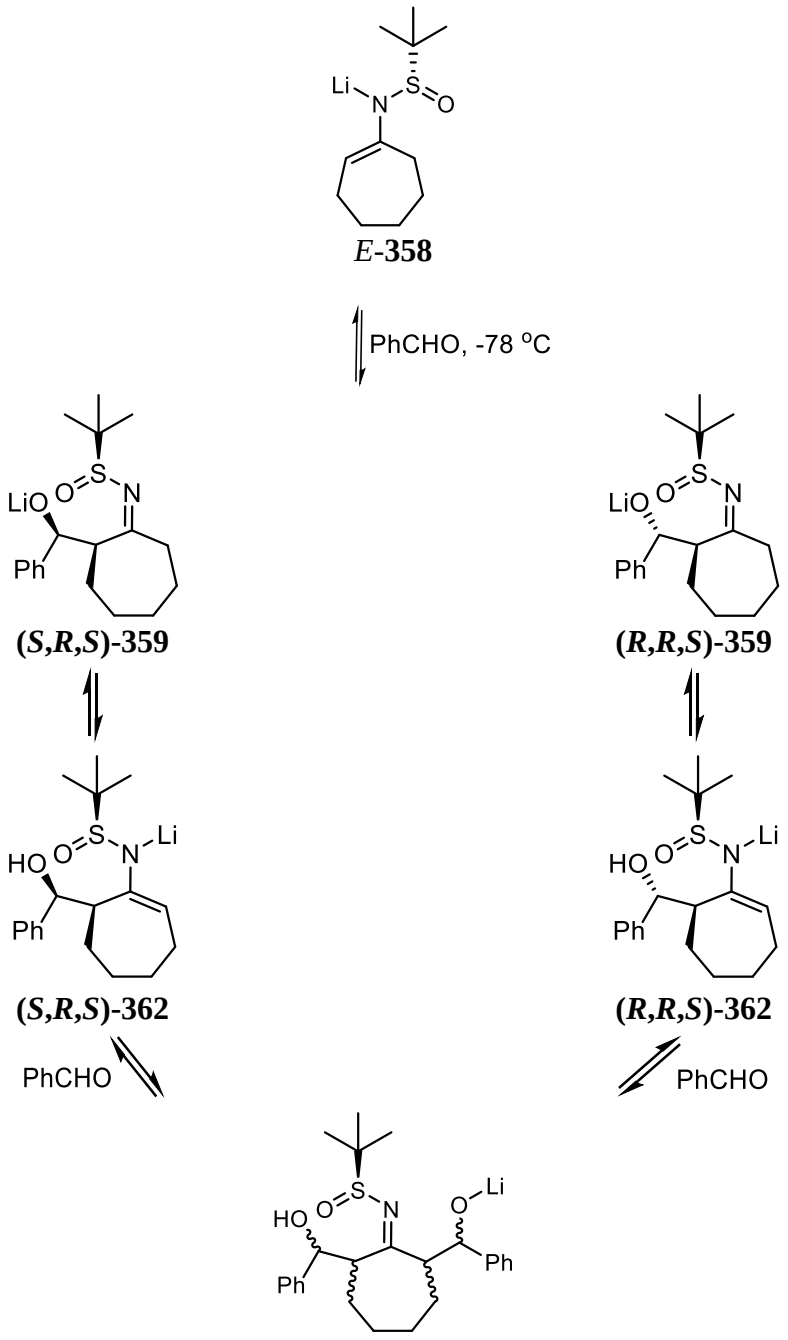
ΔG = 14.0 kcal/mol

Scheme 143. Chair conformation leading to the (*S*,*R*,*S*,*R*,*R*,*S*) diastereomer

Computational methods

DFT calculations were performed with Gaussian 16.[56] Spartan'16 was used for conformational searches.[57] Molecular geometry optimizations and frequency calculations were optimized at the B3LYP-D3/6-31G(d) level of theory. Frequency calculations were carried out to confirm the optimized structures as minima (zero imaginary frequencies) or transition state structures (one imaginary frequency) on the potential energy surface. Single point energies were calculated using M06-2X-D3/6-311+G(d,p), and a quasi-harmonic correction was applied using the GoodVibes program.[58] 3D renderings of optimized structures were generated using PyMol 2.3.2.[59] GaussView 6.0.16[60] was used to generate initial structures.

Following on from our mechanistic and computational studies, a plausible reaction mechanism for the double aldol-Tishchenko reaction can be proposed. Firstly, deprotonation of cycloheptanone sulfinyl imine **(*S*)-291** with LDA generates a planar lithium azaenolate ***E*-358 (Scheme 144)**. ***E*-358** then undergoes a non-selective aldol reaction with benzaldehyde to form lithium aldolate **359** as a mixture of isomers. The use of sub-stochiometric of LDA likely facilitates reversible aldolization steps. Equilibration of **359** to **362** generates a reactive azaenolate species which reacts with a second equivalent of benzaldehyde to afford the double-aldolate **363**.



E-**358**

(***S,R,S***)-**359** (***R,R,S***)-**359**

(***S,R,S***)-**362** (***R,R,S***)-**362**

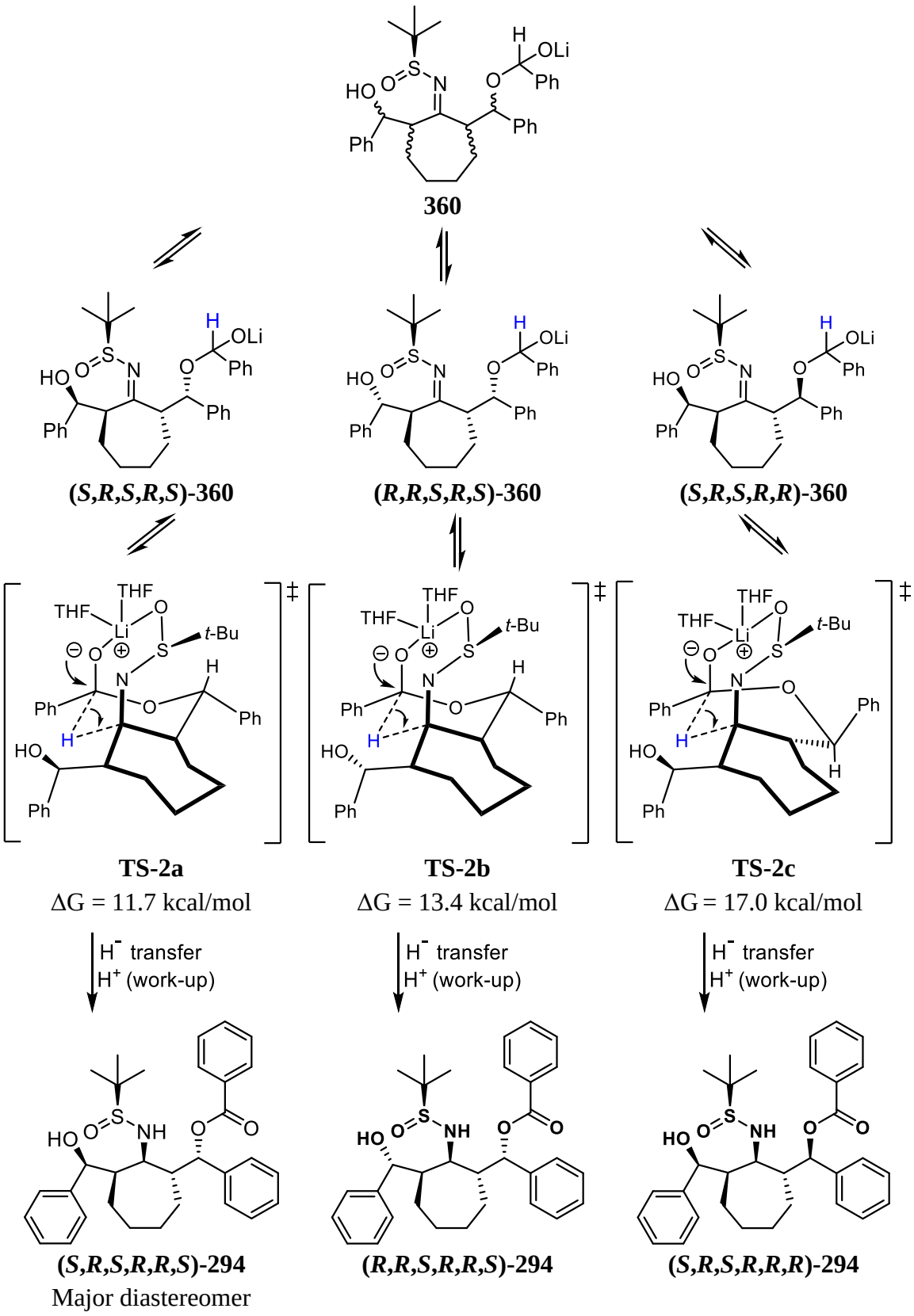
363, mixture of stereoisomers

Scheme 144. Non-selective aldol steps generating a mixture of stereoisomers

Subsequent reaction of double-aldolate **363** with the third equivalent of aldehyde would give lithium hemiacetal **360 (Scheme 145)**. It is postulated that the stereochemical outcome of this transformation is determined by the six-membered transition state involved in the irreversible hydride transfer. Therefore, the transition state which leads to faster hydride transfer dictates the stereochemistry of the final product. The observed stereochemistry for the double aldol-

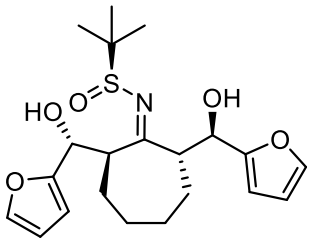
Tishchenko product **(*S*,*R*,*S*,*R*,*R*,*S*)-294** indicates that it is alkoxide **(*S*,*R*,*S*,*R*,*S*)-360** that leads to the lowest energy transition state for hydride transfer. This correlates with the computational data obtained for transition states **TS-2a-c**. A higher-energy transition state barrier was obtained for **TS-2b** (ΔG = 13.4 kcal/mol) and **TS-2c** (ΔG = 17.0 kcal/mol). Again, previous work carried out within our group has suggested that for the acetophenone derived aldol-Tishchenko series, an equilibrium effect funnels all aldolate intermediates through the lowest energy transition state for the hydride reduction step. It is likely that a similar phenomenon is in operation for the cycloheptanone series and that all aldolate intermediates are funnelled towards intermediate **(*S*,*R*,*S*,*R*,*S*)-360**. Thus, the stereodetermining hydride transfer proceeds *via* the sterically less encumbered and energetically more favourable **TS-2a** (ΔG = 11.7 kcal/mol) providing the major diastereomer **(*S*,*R*,*S*,*R*,*R*,*S*)-294**.

Overall, the reaction follows the Curtin-Hammett principle; all aldolates are in equilibrium and the stereochemical outcome depends on the relative energies of the transition states in the rate-determining hydride transfer step.



Scheme 145. Proposed reaction mechanism for the Tishchenko reduction step.

Interestingly, *o*-fluoro benzaldehyde and furfural failed to undergo a Tishchenko reaction and only double aldol products were isolated. The stereochemistry of the furfural derived double aldol product **(*R*,*R*,*S*,*R*,*R*)-317** is different (*anti*-) to that obtained for the benzaldehyde derived double aldol-Tishchenko products which was confirmed by crystallographic data **(Figure 47)**.

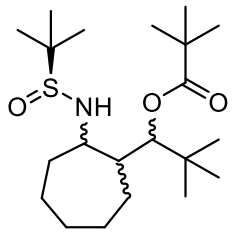


(*R*,*R*,*S*,*R*,*R*)-317

Figure 47. Furfural derived double-aldol product

In this case, the heteroaryl double-aldolate may not have equilibrated to the appropriate geometry for a Tishchenko reaction to occur. This may be due to either **i)** a slow retro-aldol process for this substrate or **ii)** slow rate of aldol addition for the *syn*-stereoisomer. Thus, for this reaction, the kinetic product **(*R*,*R*,*S*,*R*,*R*)-317** dominates, which may not be susceptible to a Tishchenko hydride transfer.

The reaction of cycloheptanone sulfinyl imine **(*S*)-291** and pivaldehyde generated only an aldol-Tishchenko product **328 (Figure 48)**. As previously discussed in **Section 5.4.3.4**, it is possible that the mono-aldolate of this reaction is more conducive to a Tishchenko reaction due to a favourable transition state for hydride transfer. Thus, in this case, it is likely that the double-aldolate failed to generate an appropriate transition state for a Tishchenko hydride transfer.

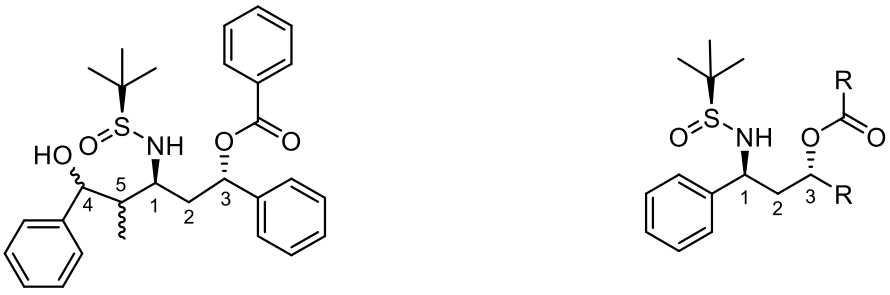


328

Figure 48. Aldol-Tishchenko product for the reaction of cycloheptanone sulfinyl imine **(*S*)-291** and pivaldehyde

5.6 Tentative assignment of relative stereochemistry by NMR spectroscopic analysis

Due to the difficulty in obtaining a suitable crystal for the 2-butanone derived double aldol-Tishchenko series, the absolute stereochemistry of the major diastereomer could not be confirmed. However, the relative stereochemistry was tentatively assigned based on previous experimental data and analysis of vicinal coupling constants. Firstly, we postulate that the stereochemistry between C-1 and C-3 of double aldol-Tishchenko product **337** to be analogous to the stereochemistry of the acetophenone derived aldol-Tishchenko product **364 (Figure 49)**. Thus, a 1,3-*anti* relative stereochemistry can be assigned for C-1 and C-3.

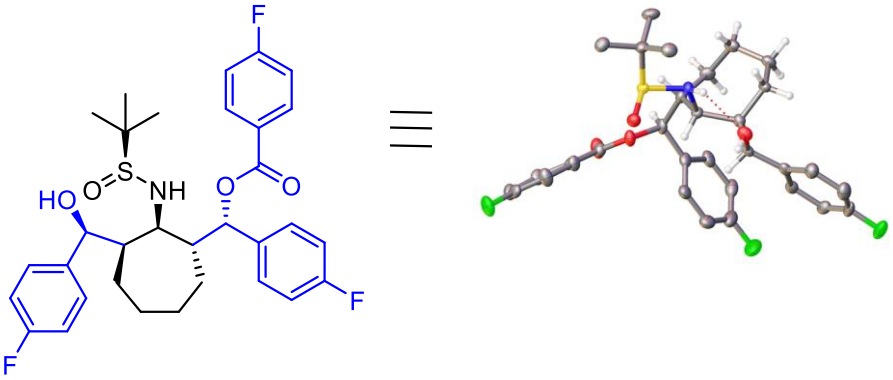


337 **364**

Figure 49. Tentative assignment of aldol-Tishchenko stereochemistry for 2-butanone derived 3-amino-1,5-diol derivative **337**

We hypothesize that the relative stereochemistry at C-4 and C-5 could be postulated based on analysis of the vicinal coupling constants (H-C-C-H, ^{3}J). Using the Karplus equation, it is possible to make an assumption about the relative stereochemistry which describes the relationship between vicinal coupling constants and the dihedral angle between the coupling constants.[61] The equation suggests that vicinal coupling constants will be maximal with protons at a dihedral angle of 180° and 0° (*anti* or eclipsed relationship) and will be minimal for protons at 90° (*syn*) to each other. The use of vicinal coupling constants (H-C-C-H, ^{3}J) for conformational analysis of acyclic systems is much more difficult in comparison to 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.[62] A prerequisite of this empirical rule is that an intramolecular hydrogen-bond exists between the carbonyl oxygen and the hydroxyl proton resulting in the formation of an intramolecularly hydrogen-bonded six-membered structure. This predictable conformation leads to a corresponding 'somewhat' predictable $^{3}J_{\text{H-H}}$ coupling constant.

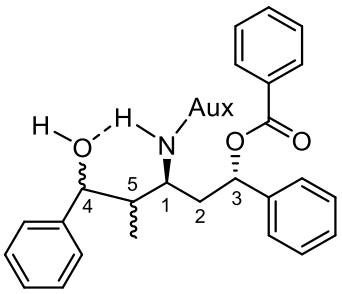
While this method is only applicable in limited cases and should be used with caution, there is evidence from the x-ray crystallographic structure of cycloheptanone derived double aldol-Tishchenko product **(*S*,*R*,*S*,*R*,*R*,*S*)-299** for the existence of an intramolecular hydrogen-bond between the hydroxyl group and the amine proton (N-H···O-H) **(Figure 50)**.



(*S*,*R*,*S*,*R*,*R*,*S*)-299

Figure 50. Crystal structure of **(*S*,*R*,*S*,*R*,*R*,*S*)-299** showing an intramolecular hydrogen-bond (N-H···O-H)

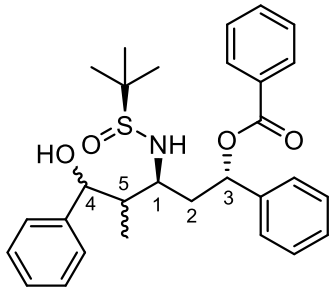
Therefore, for the 2-butanone derived double aldol-Tishchenko product **337** a predictable conformation can be presumed due to the hydrogen-bond between the hydroxyl group and the amine proton leading to **conformation A (Figure 51)**.



Conformation A

Figure 51. Hydrogen-bonding interaction leading to Conformation A for **337**

For product **337**, a small coupling constant is observed between H-4 and H-5 (J = 2.2 Hz) **(Figure 52)**.



337

^{1}H NMR splitting patterns **337**

1.99-2.12 (2H, m, H-5 and one of H-2)

2.13-2.27 (1H, ddd, J = 14.4, 10.2, 4.1 Hz, one of H-2)

3.75-3.86 (1H, m, H-1)

4.28 (1H, d, J = 5.1 Hz, O-H)

5.05 (1H, dd, J = 4.9, 2.2 Hz, H-4)

6.09 (1H, dd, J = 10.3, 3.6 Hz, H-3)

Compound	$^3J_{H4-H5}$ **(Hz)**
337	2.2

Figure 52. Vicinal coupling constant for **337**

Analysis of the Newman projections for both the *syn*- and *anti*-diastereomers enables us to make a prediction about the relative stereochemistry of the 2-butanone double aldol-Tishchenko product **337 (Figure 53)**. There are three possible staggered conformations for each diastereomer. For the *syn*-diastereomer, both hydrogen-bonded conformers have a gauche interaction between H-4 and H-5 which signifies a small J value. In comparison, the non-hydrogen bonded conformer has an *anti* relationship between H-4 and H-5 and thus a larger J value would be expected. Since the two hydrogen-bond conformers have similar predicted J values, a smaller J value is expected for the *syn*-diastereomer. This correlates with the experimental coupling constant obtained for **337** which shows a small J value between H-4 and H-5 (J = 2.2 Hz).

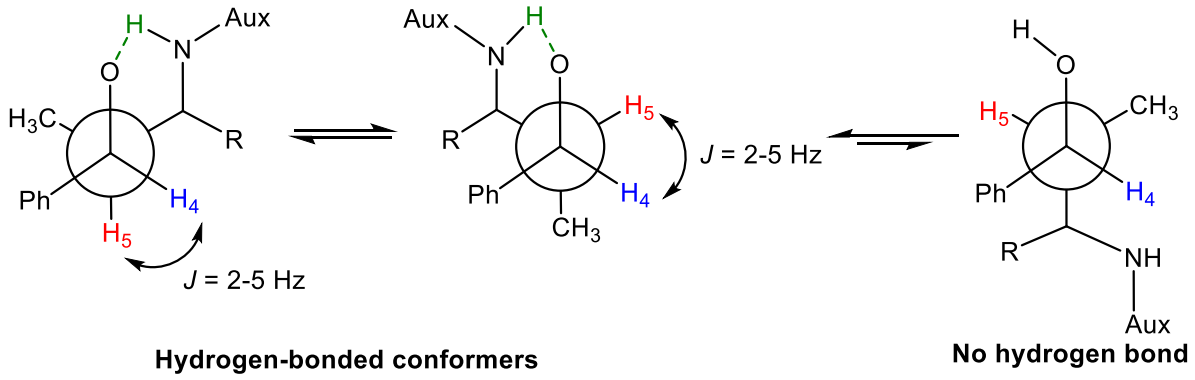


Figure 53. Staggered conformations for the *syn*-diastereomer

For the *anti*-diastereomer, one of the hydrogen-bonded conformers has an *anti* relationship while the other hydrogen-bonded conformer has a gauche interaction between H-4 and H-5. A gauche interaction is also present for the non-hydrogen conformer **(Figure 54)**.

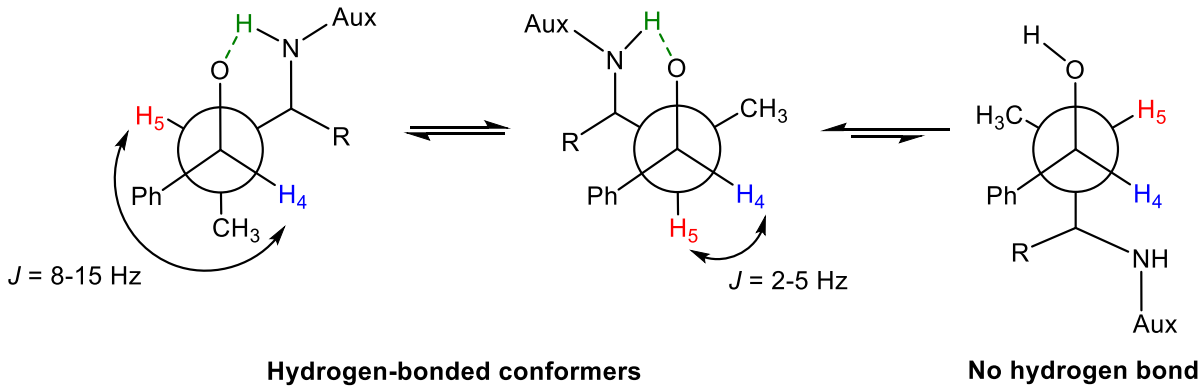
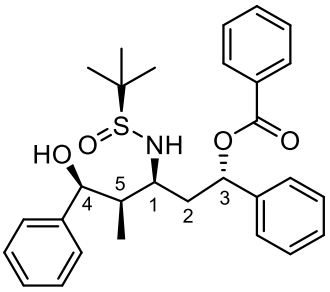
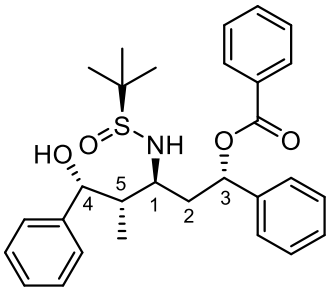


Figure 54. Staggered conformations for the *anti*-diastereomer

Using the above conformational analysis, it can be hypothesised that H-4 and H-5 are *syn* to each other. The stereochemical assignment of *syn*-configuration for the 2-butanone double aldol-Tishchenko products is consistent with the aldol stereochemical relationship observed for the cycloheptanone double aldol-Tishchenko products. Thus, the absolute stereochemistry of the major diastereomer for the 2-butanone derived double aldol-Tishchenko series could be either (*S*,*R*,*S*,*S*,*S*) or (*R*,*S*,*S*,*S*,*S*) **(Figure 55)**.



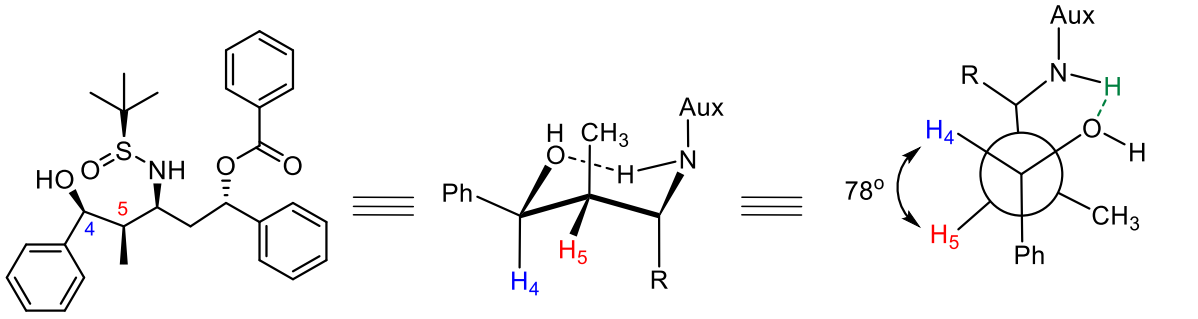
(*S*,*R*,*S*,*S*,*S*)-337



(*R*,*S*,*S*,*S*,*S*)-337

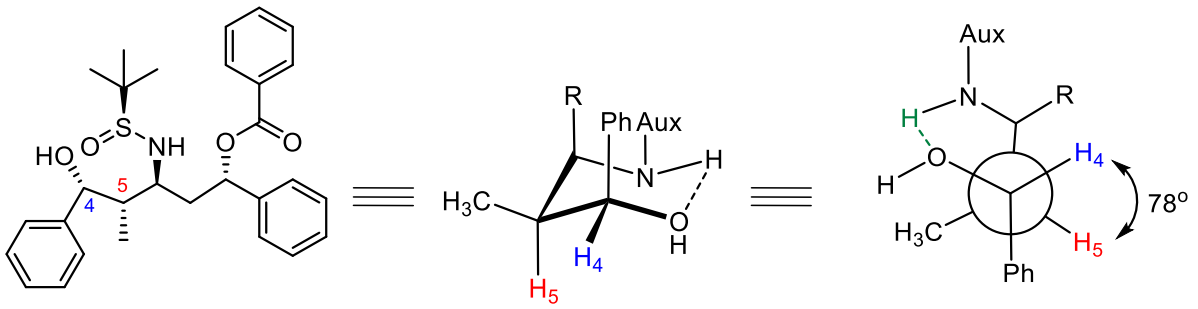
Figure 55. Assignment of relative stereochemistry for the 2-butanone double aldol-Tishchenko series

The intramolecular hydrogen-bonded six-membered ring conformations and the corresponding Newman projections are outlined below for each *syn*-diastereomer **(Figure 56)**. Using the Bothner-By equation, a dihedral angle of 78° is expected which is consistent with a *syn*-relationship between H-4 and H-5.



(*S*,*R*,*S*,*S*,*S*)-337

Newman projection along C_4 to C_5



(*R*,*S*,*S*,*S*,*S*)-337

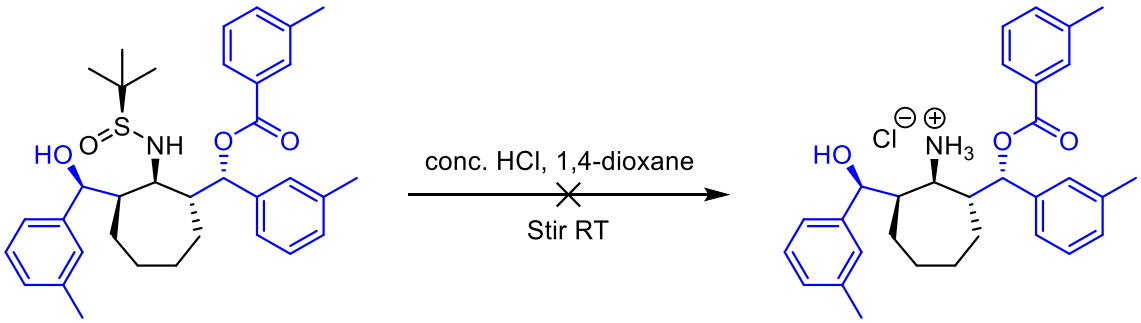
Newman projection along C_4 to C_5

Figure 56. Six-membered intramolecular hydrogen-bonded conformations and the corresponding Newman projections for both *syn* diastereomers

While analysis of coupling constants gives an indication of the relative stereochemistry, it is important to note that many other factors such as hybridisation, bond length, bond angle and electronegativity of substituents have an effect on the magnitude of coupling constants.[61b]

5.7 Cleavage of *tert*-butanesulfinyl auxiliary

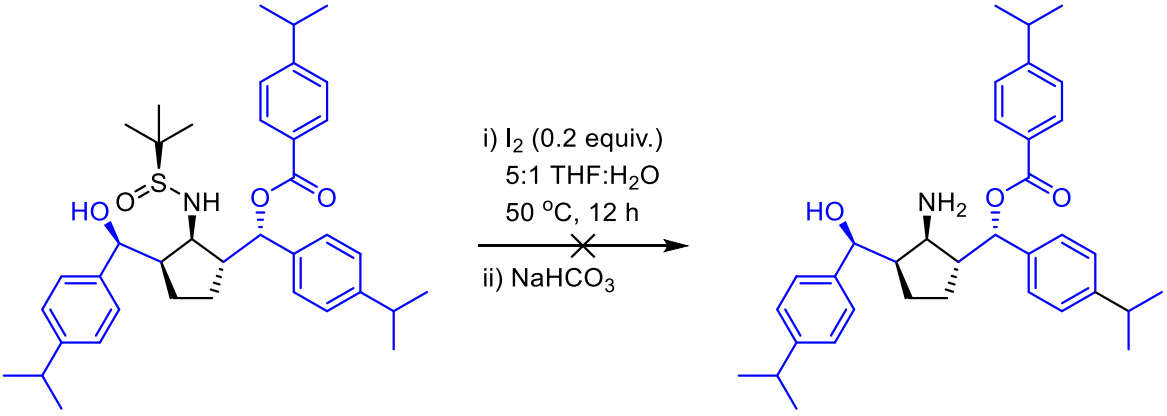
To further demonstrate the synthetic utility of our methodology, we investigated the deprotection of the (*S*)-*tert*-butanesulfinyl unit. The removal of the *tert*-butanesulfinyl group is typically carried out using conc. HCl.[63] Hence, compound **(*S*,*R*,*S*,*R*,*R*,*S*)-296** was stirred at room temperature in the presence of conc. HCl and 1,4-dioxane **(Scheme 146)**. However, this method proved incompatible with our amino diol substrates.



(*S*,*R*,*S*,*R*,*R*,*S*)-296 **(*S*,*R*,*S*,*R*,*R*,*S*)-365**

Scheme 146. Attempted cleavage using conc. HCl

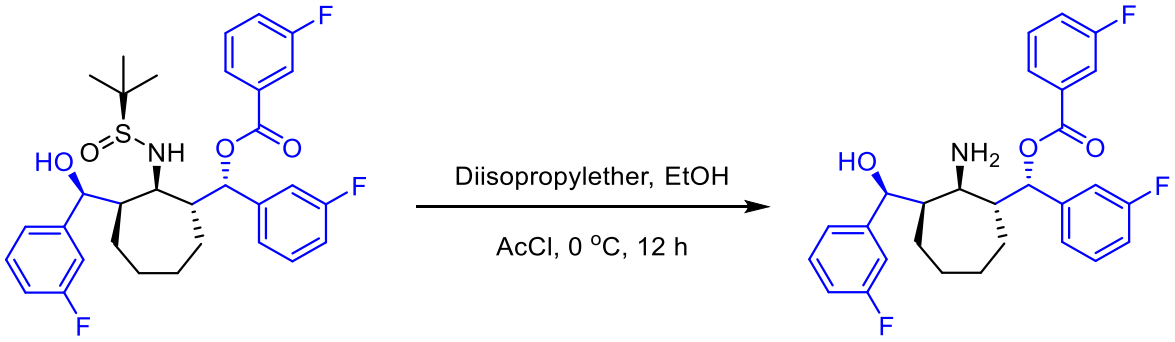
Thus, acid sensitive functional group compatible methods for the deprotection of *tert*-butanesulfinyl group were subsequently evaluated. Firstly, we examined an iodine mediated single electron transfer deprotection method developed by Zhang and co-workers.[64] The authors reported that this method was effective for the removal of both *tert*-butanesulfinyl and *p*-tolyl sulfinyl units in the presence of acid sensitive functional groups. Thus, we tested this method on substrate **(*S*,*R*,*S*,*R*,*R*,*S*)-321 (Scheme 147)**. Unfortunately, this reaction only resulted in decomposition of starting material with no observable cleavage of the *tert*-butanesulfinyl group.



(*S*,*R*,*S*,*R*,*R*,*S*)-321 **(*S*,*R*,*S*,*R*,*R*,*S*)-366**

Scheme 147. Iodine mediated deprotection of **(*S*,*R*,*S*,*R*,*R*,*S*)-321**

Eventually after considerable investigation, we identified a method that was compatible with our functional group sensitive substrates. Pleasingly, removal of the chiral auxiliary was achieved under mild acidic conditions to afford the free amine derivative **(*S*,*R*,*S*,*R*,*R*,*S*)-367** in high yield (80%) and without any loss of diastereomeric purity **(Scheme 148)**.[65]



(*S*,*R*,*S*,*R*,*R*,*S*)-300 **(*S*,*R*,*S*,*R*,*R*,*S*)-367**, 80%

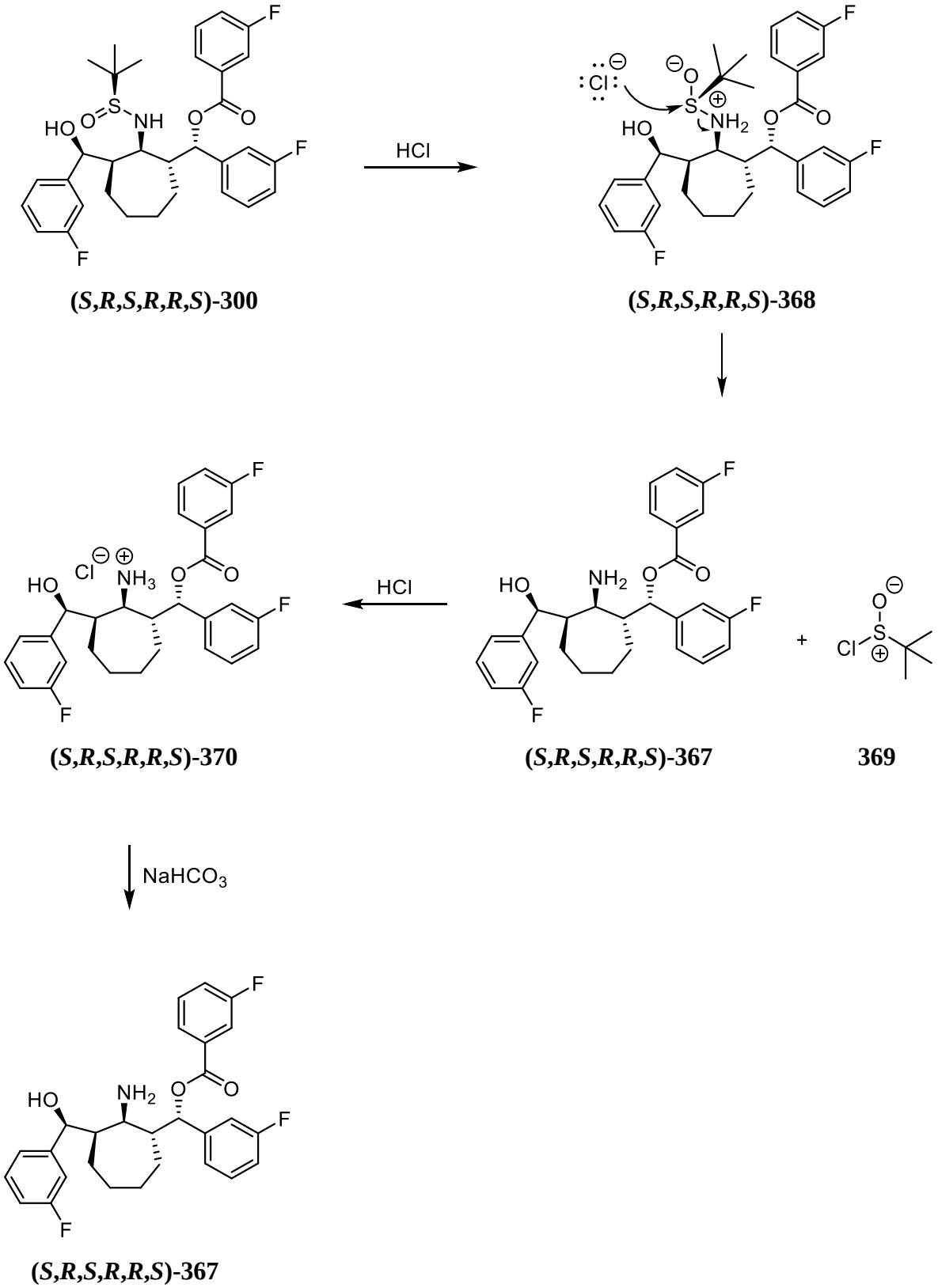
Scheme 148. Cleavage of *N*-*tert*-butanesulfinyl group under mild acidic conditions

Two possible mechanisms can be proposed for this transformation. In both cases, it is likely that reaction of acetyl chloride with ethanol would generate anhydrous HCl *in situ* **(Scheme 149)**.



Scheme 149. *In situ* formation of anhydrous HCl

The first pathway would involve simple deprotection of the *tert*-butanesulfinyl group in the presence of HCl affording the ammonium salt **(*S*,*R*,*S*,*R*,*R*,*S*)-370** and *tert*-butanesulfinyl chloride **369 (Scheme 150)**. Simple basic work-up would then afford the free amine **(*S*,*R*,*S*,*R*,*R*,*S*)-367**.



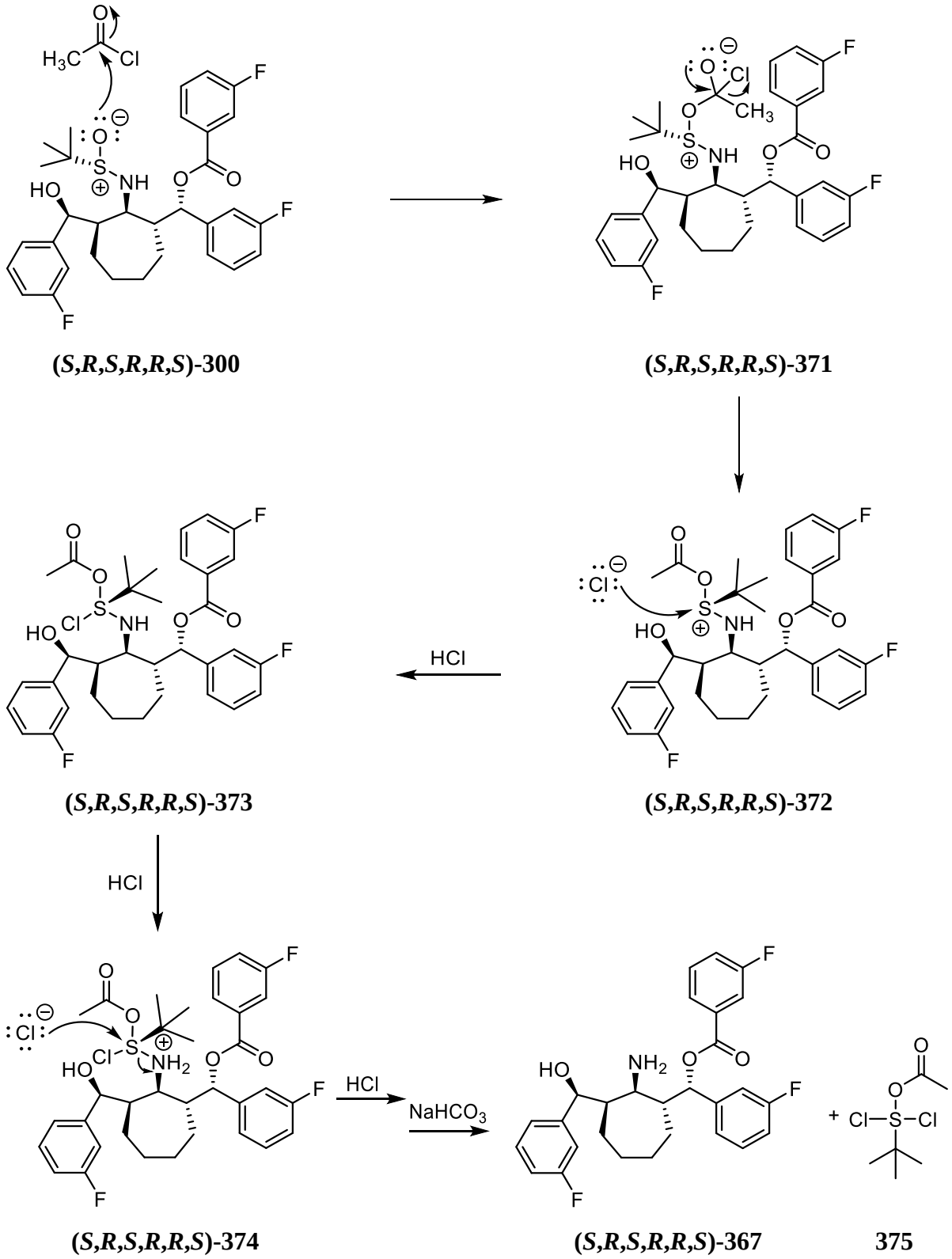
(*S*,*R*,*S*,*R*,*R*,*S*)-300 **(*S*,*R*,*S*,*R*,*R*,*S*)-368**

(*S*,*R*,*S*,*R*,*R*,*S*)-370 **(*S*,*R*,*S*,*R*,*R*,*S*)-367** **369**

(*S*,*R*,*S*,*R*,*R*,*S*)-367

Scheme 150. Possible reaction mechanism for the cleavage of the *tert*-butanesulfinyl auxiliary

The second possible mechanism would involve activation of the sulfoxide *via* reaction of **(*S*,*R*,*S*,*R*,*R*,*S*)-300** with acetyl chloride forming the sulfonium ion **(*S*,*R*,*S*,*R*,*R*,*S*)-372 (Scheme 151)**. This species could then be attacked by the chloride ion to generate tetrahedral intermediate **(*S*,*R*,*S*,*R*,*R*,*S*)-373**. Protonation of the amine in the presence of HCl followed by attack with the chloride ion would give the free amine **(*S*,*R*,*S*,*R*,*R*,*S*)-367** and *tert*-butanedichlorosulfanyl acetate **375**. Another equivalent of HCl could then form the amine hydrochloride salt. Basification with $NaHCO_3$ would afford the free amine **(*S*,*R*,*S*,*R*,*R*,*S*)-367**.



Scheme 151. Second possible mechanism for cleavage of the *tert*-butanesulfinyl auxiliary *via* activation of the sulfoxide

5.8 Derivatisation of double aldol-Tishchenko products

The success of our methodology prompted us to further explore the utility of these 3-amino-1,5-diol derivatives. We believe that these building blocks could provide an excellent opportunity to access a wide variety of important compounds. We were particularly interested in the cyclisation of these substrates to access *N*-heterocycles such as azetidines **(Figure 57)**. Azetidines represent an extraordinary class of strained aza-heterocyclic compounds which possess a wide range of biological properties.[66] For example, Carreira has shown that azetidine analogues are as potent as their parent *β*-lactams in a number of small-molecule cholesterol absorption inhibitor analogues of ezetimibe.[67]

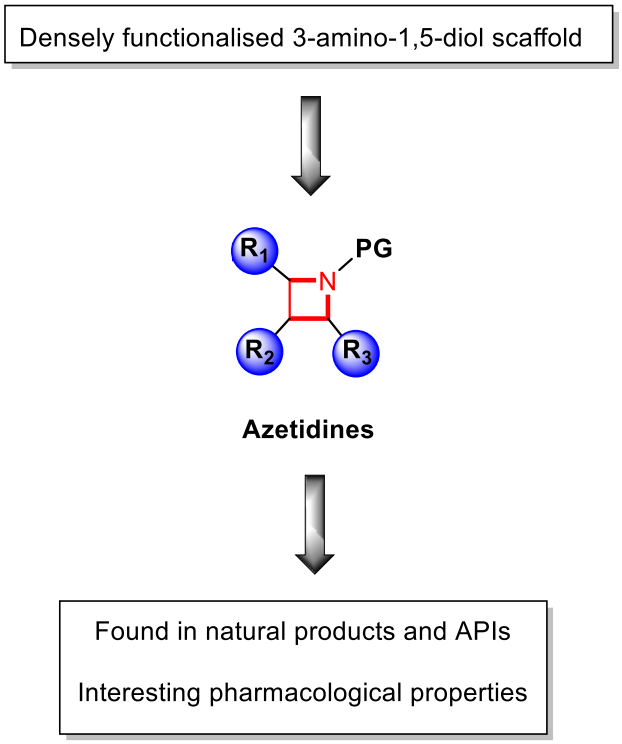
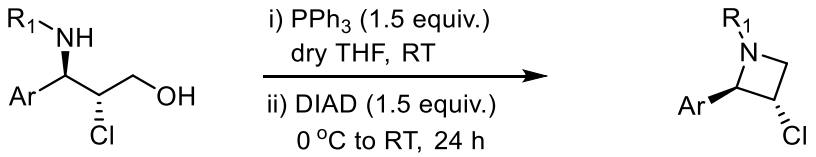


Figure 57. Synthetic utility of 3-amino-1,5-diol derivatives

The most commonly utilised method to induce cyclisation of amino alcohols involves activation of the hydroxyl group followed by ring closure. Thus, we decided to follow a procedure employed by Colpaert and co-workers which involved a Mitsunobu-type activation of *β*-chloro-*γ*-sulfonylamino alcohols **376** to form *trans*-2-aryl-3-chloroazetidines **377 (Scheme 152)**.[68]

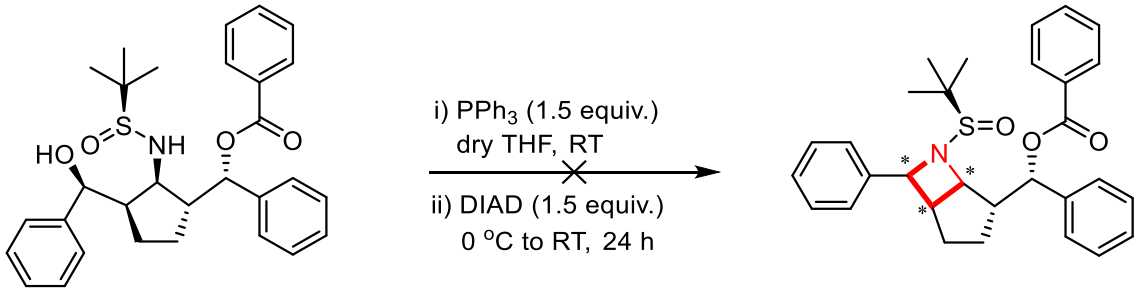


376 **377**

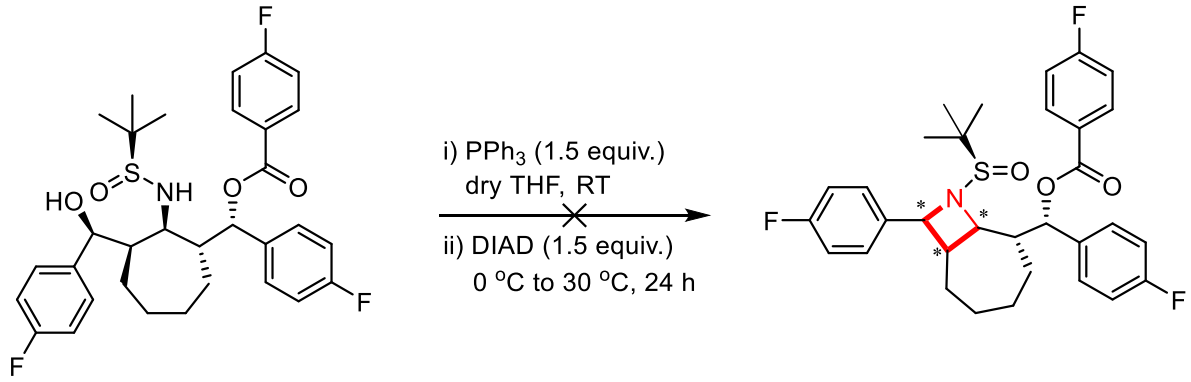
Ar = C_6H_5, R_1 = Tos (97%)
Ar = 4-$MeOC_6H_5$, R_1 = Tos (70%)
Ar = furan-2-yl, R_1 = $C_6H_5SO_2$ (72%)

Scheme 152. Colpaert's synthesis of *trans*-2-aryl-3-chloroazetidines

Firstly, we applied these conditions to both a five- and seven-membered 3-amino-1,5-diol derivative, **(*S*,*R*,*S*,*R*,*R*,*S*)-318** and **(*S*,*R*,*S*,*R*,*R*,*S*)-299 (Scheme 153)**. In this Mitsonobu-type reaction, we anticipated that the hydroxyl group would be activated by a PPh_3-DIAD complex proceeded by the intramolecular ring-closure with the amino group leading to a cyclic amine. For **(*S*,*R*,*S*,*R*,*R*,*S*)-299**, we decided to warm the reaction mixture to 30 °C to see if this would induce cyclisation. Unfortunately, there was no evidence of product formation in the ^{1}H NMR spectra of the crude reaction mixtures. In both cases, only starting materials were recovered following work-up.



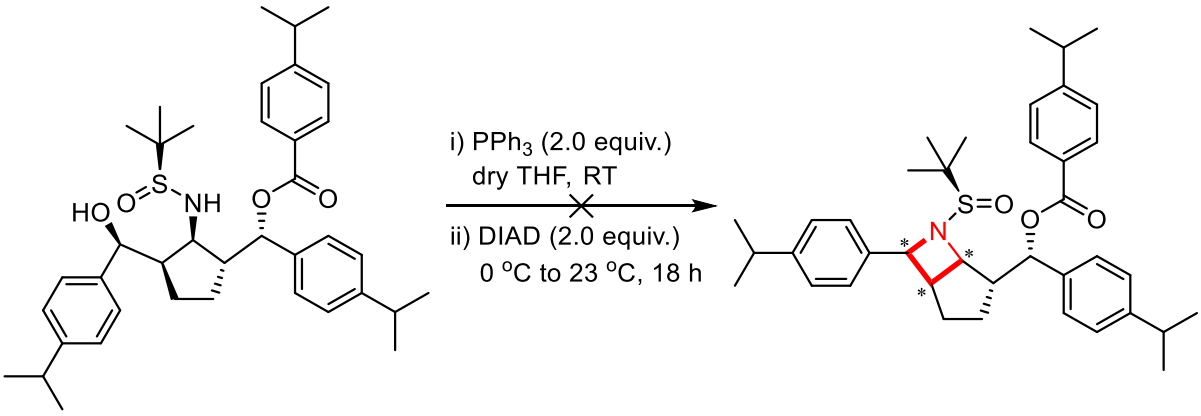
(*S*,*R*,*S*,*R*,*R*,*S*)-318 **378**



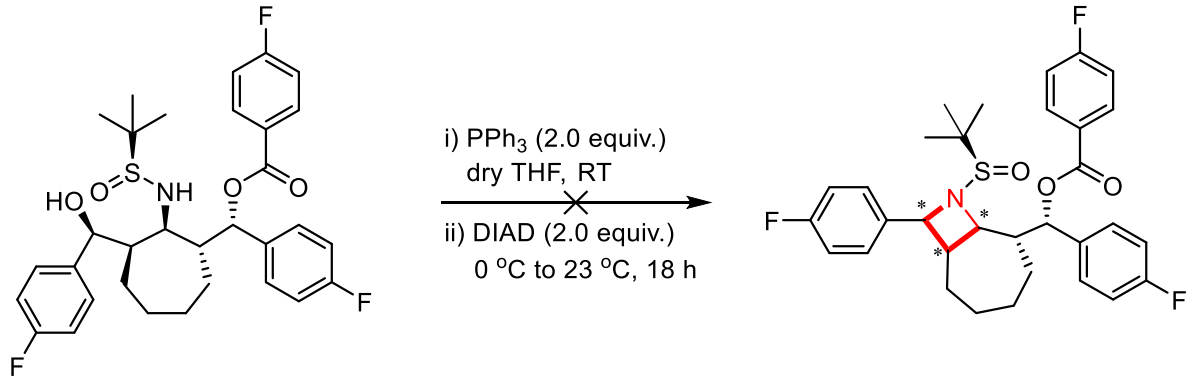
(*S*,*R*,*S*,*R*,*R*,*S*)-299 **379**

Scheme 153. Attempted cyclisation under Mitsonobu-type conditions

Next, we examined a similar procedure reported by Trost and co-workers in which a *Cbz*-amino alcohol was cyclised utilising slightly modified Mitsunobu conditions.[69] However, these conditions also failed to promote product formation with **(*S*,*R*,*S*,*R*,*R*,*S*)-321** and **(*S*,*R*,*S*,*R*,*R*,*S*)-299 (Scheme 154)**.



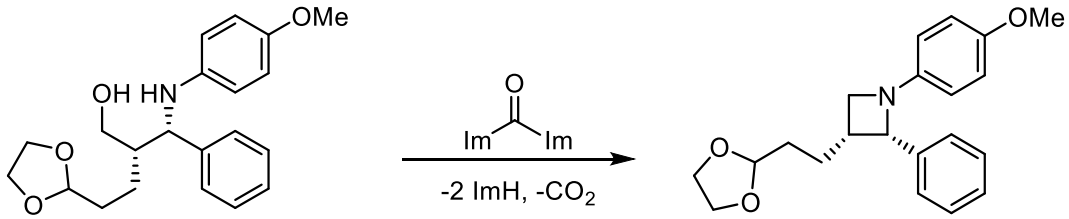
(*S*,*R*,*S*,*R*,*R*,*S*)-321 **380**



(*S*,*R*,*S*,*R*,*R*,*S*)-299 **381**

Scheme 154. Modified Mitsunobu conditions

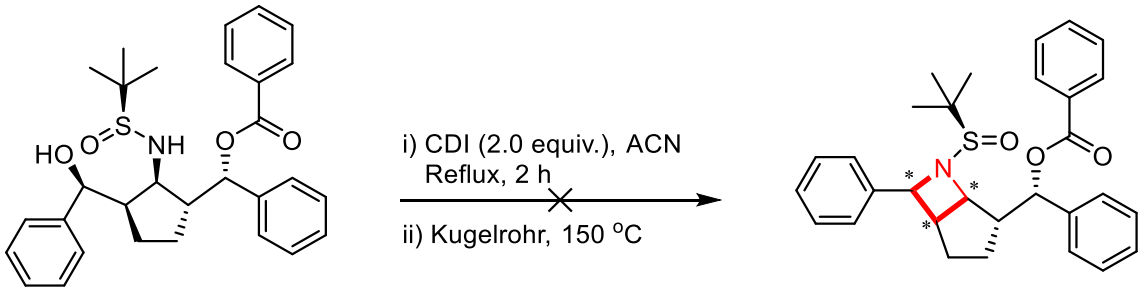
In a final attempt to cyclize our amino diol substrates we decided to employ a CDI-mediated ring closure described by Christmann and co-workers.[70] They achieved the cyclization of PMP-protected amino alcohols **(*S*,*S*)-382** to synthesize *N*-heterocylces including an azetidine analogue of ezetimibe **(*S*,*S*)-383 (Scheme 155)**.



(*S*,*S*)-382 **(*R*,*S*)-383**

Scheme 155. CDI-mediated ring closure of PMP-protected amino alcohols

This protocol avoids the use of toxic and expensive reagents employed in Mitsunobu-type reactions. The first step involved activation of the hydroxyl group to form a carbamate derivative of **(*S*,*R*,*S*,*R*,*R*,*S*)-318** under reflux conditions **(Scheme 156)**. This product was then heated in a Kugelrohr apparatus under high vacuum in an effort to cyclise the amino alcohol moiety to form **384**. Unfortunately, we observed no product formation.



(*S*,*R*,*S*,*R*,*R*,*S*)-318 **384**

Scheme 156. CDI-induced ring closure

In summary, the results of these transformation proved disappointing. It is likely that the steric hinderance about the sulfinyl nitrogen and the presence of the large sulfur atom would hinder the possibility of a successful nucleophilic attack following activation of the hydroxyl group. Due to time constraints, no further work was carried out in this area. Further studies are required to fully explore the synthetic potential of these compounds.

5.9 Conclusions and future work

Asymmetric aldol-Tishchenko reaction

Efforts to expand the substrate scope of the aldol-Tishchenko methodology proved moderately successful. A short substrate scope using propiophenone derived sulfinyl imines afforded the *anti*-1,3-amino alcohol derivatives in moderate to good yields and good diastereoselectivity. Attempts to utilise formaldehyde as an aldol acceptor and hydride donor failed. *N*-sulfinyl aldimine equivalents were investigated and shown not to facilitate an aldol-Tishchenko reaction. A strategy to furnish *anti*-1,3-diamines *via* use of aldimines as aldol acceptors and hydride donors was explored. Ultimately, the aldimines examined proved incompatible with our methodology. However, it may be worthwhile exploring aldimines possessing less sterically bulky *N*-substituents, for example, *N*-halogenated imines **(Figure 58)**.

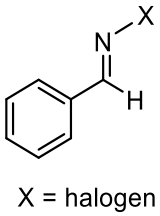
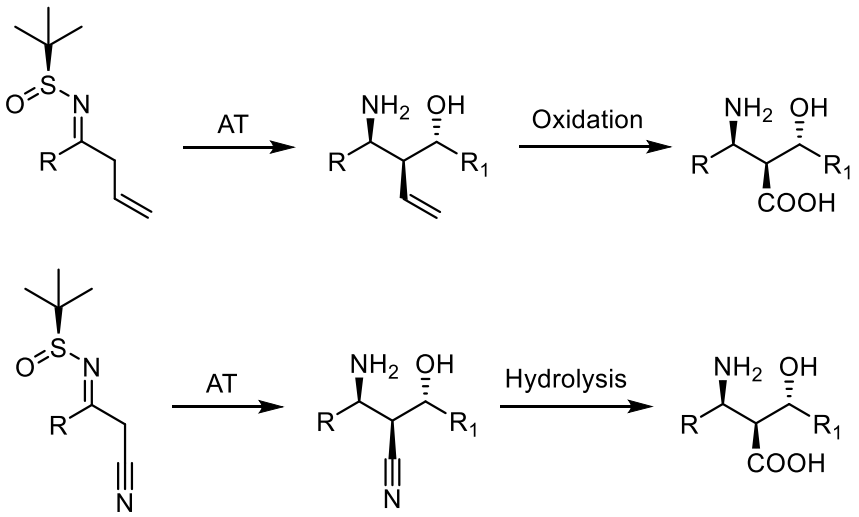


Figure 58. *N*-halogenated imines

Efforts to synthesise chiral secondary amines *via* an alternative quench protocol proved challenging. However, successful scale-up of the aldol-Tishchenko was achieved enabling the synthesis of three new bonds (C-N, C-C, C-O) and two new chiral centres (C-N and C-O) in one synthetic step.

Future work in this area will involve exploring other possible routes to access *β*-amino acids **(Scheme 157)**. This could be achieved *via* *α*,*γ*-unsaturated (*S*)-*tert*-butanesulfinyl imines. Oxidation of the alkenyl functionality would generate the acid. Alternatively, *β*-nitrile (*S*)-*tert*-butanesulfinyl imines could be utilised. Hydrolysis of the nitrile functionality would provide access to *β*-amino acids.



Scheme 157. Novel route to *β*-amino acids

Asymmetric double aldol-Tishchenko reaction

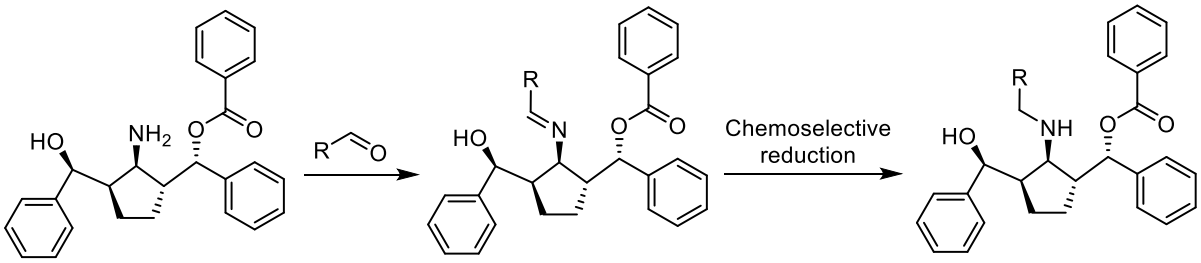
A novel approach to synthesize 3-amino-1,5-diol derivatives *via* a tandem double aldol-Tishchenko reaction was developed. Indeed, this method proved to be a highly diastereoselective method for the simultaneous introduction of four and five chiral centres in one-pot. A broad substrate scope was thoroughly examined. Excellent diastereoselectivities were obtained for the cycloheptanone and cyclopentanone series. *Meta*- and *para*-substituted benzaldehydes containing electron-withdrawing and electron-donating groups were well tolerated. The methodology was also applicable to a number of challenging aldol acceptors. However, aliphatic aldehydes were found not to promote a double aldol-Tishchenko reaction. Cyclohexanone and cyclooctanone sulfinyl imines did not work well under the reaction conditions utilising both benzaldehyde as well as an aliphatic and benzyl aldehyde.

A series of symmetrical and unsymmetrical acyclic alkyl sulfinyl imines were also examined. The 2-butanone derived sulfinyl imine furnished the desired products with very good diastereoselectivities albeit with slightly lower yields. Substituted benzaldehydes also worked best for this series. Symmetrical alkyl sulfinyl imines 3-pentanone and 4-heptanone proved ineffective as aldol donors.

Interestingly, we also were able to demonstrate improved yield when using sub-stoichiometric amounts of base. The likely reason for the improvement is the favourable conditions which allow for reversibility of the aldol steps.

A range of cleavage methods were investigated for the removal of the *tert*-butanesulfinyl group. Pleasingly, we managed to identify a suitable acid-sensitive functional group compatible method. To date, no success has been achieved in our attempts to further derivatise these highly functionalised scaffolds.

Future work will mainly focus on exploring a range of other transformations. Application of this strategy for the construction of chiral secondary amines will be investigated *via* reductive amination **(Scheme 158)**.



Scheme 158. Synthesis of chiral secondary amines

5.10 References

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Chapter 6

Experimental for Chapter 5

6.1 General procedures

Solvents employed were either distilled prior to use: tetrahydrofuran (THF), toluene and diethyl ether (Et_2O) were distilled from sodium/benzophenone dianion under nitrogen. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Alternatively, solvents were dried and stored over flame dried 4 Å molecular sieves (10-15% w/v) in Young's flask. The concentration of *n*-BuLi in hexanes was determined by titration with diphenylacetic acid. All aldehydes were freshly distilled prior to use and stored under an inert atmosphere. All other reagents were purchased from Sigma Aldrich, Fluorochem, Alfa Aesar and Acros unless otherwise noted. All non-aqueous reactions were carried out under oxygen-free nitrogen atmosphere using oven-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 and potassium permanganate staining.

Melting points were measured on a Thomas Hoover Capillary Melting Point apparatus.

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrophotometer. Liquid samples were examined as thin films interspersed on NaCl plates. Solid samples were either dispersed in KBr and recorded as pressed discs, or dissolved in dichloromethane, dispersed as thin films on NaCl plates and the dichloromethane allowed to evaporate before measurement of sample. NMR spectra were run in $CDCl_3$ using TMS as the internal standard at 25 °C. ^{1}H NMR (600 MHz) spectra, ^{1}H NMR (400 MHz) spectra and ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers respectively. ^{13}C (150.9 MHz) spectra, ^{13}C (100.6 MHz) spectra and ^{13}C (75.5 MHz) spectra were recorded on Bruker Avance 600, 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). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), *br* s (broad singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet), and m (multiplet). 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.

Low-resolution mass spectra were recorded on a Waters Quattro Micro triple quadropole instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water, containing 0.1% formic acid as the mobile phase. Samples were made up in acetonitrile at a concentration of *ca*. 1mg/mL. High-resolution mass spectra were recorded on a Waters LCT Premier TOF LC-MS instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water, containing 0.1% formic acid as the mobile phase. Samples were made up in acetonitrile at a concentration of *ca*. 1 mg/mL.

Optical rotations were recorded on a DigiPol 781 TDV Polarimeter at 589 nm or 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 and is expressed in units of 10^{-1} deg cm^2 g^{-1}. The specific rotations were recorded to indicate the direction of enantioselection and optically active samples are numbered with either (+)- or (-)- as prefix.

Single crystal X-ray data was collected at the University of Southampton using a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100(2) 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.

A Julabo FT902 cryocooler was used for low temperature reactions.

6.1.1 Analysis of known and novel compounds

^{1}H NMR spectra, ^{13}C NMR spectra, LRMS and IR analyses were recorded for all previously prepared compounds. For novel compounds, in addition to the previously mentioned analysis, HRMS was also obtained. For some compounds, only HRMS data is given due to the fact that the compound was not found using the LRMS instrument. Optical rotations were used to assign absolute stereochemistry for chiral compounds.

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.

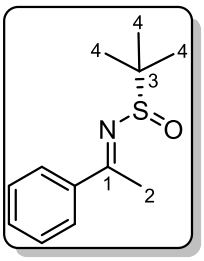
An arbitrary numbering system was employed to aid the assignment of ^{1}H NMR and ^{13}C NMR spectra.

6.2 Synthesis of (*S*)-*tert*-butanesulfinyl imines

General procedure for the synthesis of (*S*)-*tert*-butanesulfinyl imines

To a solution of **titanium ethoxide** (2.0 equiv.) in THF (4 mL per mmol of ketone) was added **ketone** (1.0 equiv.) and **(*S*)-*tert*-butanesulfinamide** (1.0 equiv.). The resulting mixture was heated at reflux and the reaction progress was monitored by TLC analysis. Once the reaction had gone to completion brine (4 mL per mmol of ketone) was added and allowed to stir vigorously for 30 min. The slurry was then filtered through a pad of Celite® and thoroughly washed with Et_2O. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude (*S*)-*tert*-butanesulfinyl imine which was purified by column chromatography on silica gel.

(*S*)-2-Methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide, (*S*)-199

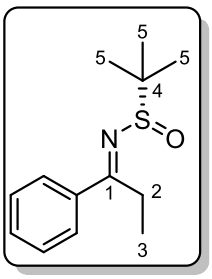


Compound **(*S*)-199** was prepared from the general procedure **6.2** outlined above using acetophenone (1.17 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*)-199** as a yellow solid (1.65 g, 74%).

Spectroscopic characteristics were consistent with previously reported data.[1]

M.p. 38-40 °C (lit.[1] m.p. 36-40 °C). $[\alpha]_D^{20}$ + 17.4 (c 1.03, CH_2Cl_2) (lit.[1] $[\alpha]_D^{20}$ + 13.0 (c 1.03, CH_2Cl_2) for *S*-enantiomer). IR ν_{max} (NaCl): 1603 (C=N stretch), 1073 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (9H, s, H-4), 2.77 (3H, s, H-2), 7.37-7.53 (3H, m, Ar-H), 7.89 (2H, d, *J* = 7.2 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.9 (C-2), 22.7 (C-4), 57.6 (C-3), 127.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 131.8 (Ar-CH), 138.9 (Ar-C), 176.5 (C-1) ppm. MS (ESI) *m*/*z*: 224 $(M + H)^+$.

(*S,E*)-2-Methyl-*N*-(1-phenylpropylidene)propane-2-sulfinamide, (*S*)-205

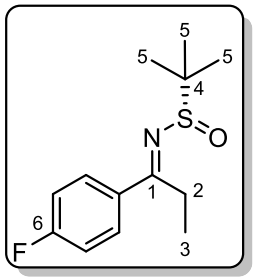


Compound **(*S*)-205** was prepared from the general procedure **6.2** outlined above using propiophenone (1.33 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (10:1, hexane:EtOAc) to give the title compound **(*S*)-205** as a bright yellow oil (1.79 g, 76%).

Spectroscopic characteristics were consistent with previously reported data.[1]

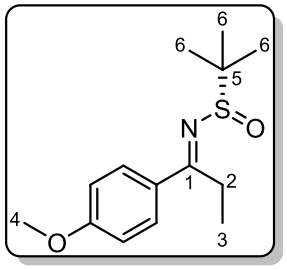
$[\alpha]_D^{20}$ + 1.9 (c 1.06, CH_2Cl_2) (lit.[1] $[\alpha]_D^{20}$ + 7.9 (c 1.06, CH_2Cl_2) for *S*-enantiomer). IR v_{max} (NaCl): 1603 (C=N stretch), 1073 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, t, *J* = 7.6 Hz, H-3), 1.33 (9H, s, H-5), 3.12-3.37 (2H, m, H-2), 7.39-7.54 (3H, m, Ar-H), 7.71-7.80 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.3 (C-3), 22.7 (C-5), 26.0 (C-2), 57.5 (C-4), 127.6 (Ar-CH), 128.7 (3 × Ar-CH), 131.7 (Ar-CH), 137.6 (Ar-C), 181.3 (C-1) ppm. MS (ESI) *m*/*z*: 238 $(M + H)^+$.

(*S*,*E*)-2-Methyl-*N*-(4-fluoro-1-phenylbutylidene)propane-2-sulfinamide, (*S*)-206



Compound **(*S*)-206** was prepared from the general procedure **6.2** outlined above using 4-fluoropropiophenone (1.39 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*)-206** as a bright yellow oil (2.22 g, 87%). $[\alpha]_D^{20}$ + 1.7 (c 1.06, CH_2Cl_2). IR v_{max} (NaCl): 1600 (C=N stretch), 1075 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.2 Hz, H-3), 1.31 (9H, s, H-5), 3.02-3.37 (2H, m, H-2), 7.03-7.15 (2H, m, Ar-H), 7.75-7.99 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.2 (C-3), 22.7 (C-5), 25.9 (C-2), 57.4 (C-4), 115.7 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, 2 × Ar-CH), 129.9 (d, $^3J_{C\text{-}F}$ = 9.0 Hz, 2 × Ar-CH), 133.8 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, Ar-C), 165.0 (d, $^1J_{C\text{-}F}$ = 253.9 Hz, C-6), 180.0 (C-1) ppm. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{19}FNOS$ $[M + H]^+$: 256.1171, found 256.1164.

(*S*,*E*)-2-Methyl-*N*-(4-methoxy-1-phenylbutylidene)propane-2-sulfinamide, (*S*)-207

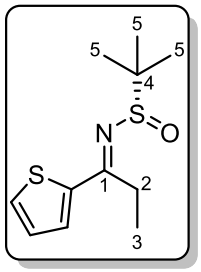


Compound **(*S*)-207** was prepared from the general procedure **6.2** outlined above using 4-methoxypropiophenone (1.75 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*)-207** as a bright yellow oil (2.11 g, 79%).

$[\alpha]_D^{23}$ - 19.5 (c 1.0, $CHCl_3$). IR v_{max} (NaCl): 1607 (C=N stretch), 1073 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (9H, s, H-6), 1.29 (2H, t, *J* = 7.6 Hz, H-3), 3.04-3.36 (2H, m, H-2), 3.86 (3H, s, H-4), 6.88-6.97 (2H, m, Ar-H), 7.72-8.03 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.4 (C-3), 22.7 (C-6), 25.9 (C-2), 55.5 (C-4), 57.1 (C-5), 114 (2 × Ar-

CH), 129.6 (2 × Ar-CH), 130.1 (Ar-C), 162.6 (Ar-C), 180.8 (C-1) ppm. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{22}NO_2S$ $[M + H]^+$: 268.1371, found 268.1363.

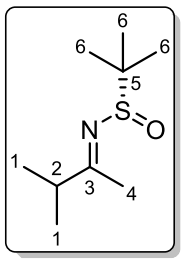
(*S*,*E*)-2-Methyl-*N*-(1-(2-thienyl)propylidene)propane-2-sulfinamide, (*S*)-208



Compound **(*S*)-208** was prepared from the general procedure **6.2** outlined above using 1-thiophen-2-yl-propan-1-one (1.25 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*)-208** as a yellow oil (0.943 g, 39%).

$[\alpha]_D^{20}$ - 106.8 (c 1.06, CH_2Cl_2). IR ν_{max} (NaCl): 1579 (C=N stretch), 1071 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (9H, s, H-5), 1.36 (3H, t, *J* = 7.6 Hz, H-3), 3.03-3.29 (2H, m, H-2), 7.08 (1H, dd, *J* = 5.1, 3.8 Hz, Ar-H), 7.48 (1H, dd, *J* = 5.1, 1.0 Hz, Ar-H), 7.51 7.08 (1H, dd, *J* = 3.8, 0.9 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9 (C-3), 22.6 (C-5), 26.8 (C-2), 57.7 (C-4), 128.0 (Ar-CH), 129.5 (Ar-CH), 132.1 (Ar-CH), 145.1 (Ar-C), 175.6 (C-1) ppm. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{18}NOS_2$ $[M + H]^+$: 244.0834, found 244.0835.

(*S*)-2-Methyl-*N*-(3-methylbutan-2-ylidene)propane-2-sulfinamide, (*S*)-209

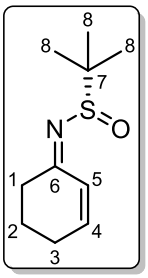


Compound **(*S*)-209** was prepared from the general procedure **6.2** outlined above using 3-methylbutan-2-one (5.35 mL, 50 mmol) and (*S*)-*tert*-butanesulfinamide (6.01 g, 50 mmol). The crude compound was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*)-209** as a pale yellow oil (5.52 g, 58%).

Spectroscopic characteristics were consistent with previously reported data.[1]

$[\alpha]_D^{20}$ + 197.4 (c 1.2, CH_2Cl_2) (lit.[2] $[\alpha]_D^{20}$ + 198.0 (c 1.2, CH_2Cl_2) for *S*-enantiomer). IR ν_{max} (NaCl): 1625 (C=N stretch), 1074 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.13, 1.14 (2 × 3H, d, *J* = 6.8 Hz, H-1), 1.24 (9H, s, H-6), 2.31 (3H, s, H-4), 2.56 (1H, sept, *J* = 6.8 Hz, H-2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.6, 19.9 (C-1), 21.1 (C-4), 22.8 (C-6), 41.4 (C-2), 56.5 (C-5), 189.3 (C-3) ppm. MS (ESI) *m*/*z*: 190 $(M + H)^+$.

(*S*,*E*)-2-Methyl-*N*-(2-cyclohexen-1-ylidene)propane-2-sulfinamide, (*S*)-210

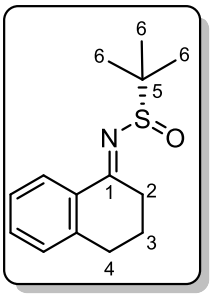


Compound **(*S*)-210** was prepared from the general procedure **6.2** outlined above using 2-cyclo-hexen-1-one (0.49 mL, 5 mmol) and (*S*)-*tert*-butanesulfinamide (0.606 g, 5 mmol). The crude compound was purified using column chromatography on silica gel (7:3, hexane:EtOAc) to give the title compound **(*S*)-210** as a yellow oil (0.552 g, 55%, 3:2 mixture of isomers).

Spectroscopic characteristics were consistent with previously reported data.[3] $[\alpha]_D^{20}$ + 325.5 (c 1.0, $CHCl_3$) (lit.[3] $[\alpha]_D^{20}$ - 331.9 (c 0.75, $CHCl_3$) for *R*-enantiomer). IR ν_{max} (NaCl): 1620 (C=N stretch), 1074 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (9H, s, H-8), 1.74-2.10 (2H, m, H-2), 2.17-2.37 (2H, m, H-3), 2.60 (0.8H, dd, *J* = 7.3, 5.6 Hz, H-1), 2.83 (0.6H, ddd, *J* = 17.0, 7.5, 4.8 Hz, H-1), 3.05 (0.6H, ddd, *J* = 17.0, 8.9, 5.2 Hz, H-1), 2.92-3.12 (0.6H, dt, *J* = 10.1, 1.8 Hz, H-5), 6.55-6.71 (1H, m, H-4), 7.12 (0.4H, dt, *J* = 10.2, 2.1 Hz, H-5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) **Major**; δ 22.1 (C-2), 22.3 (C-8), 25.3 (C-3), 31.0 (C-1), 56.7 (C-7), 130.6 (C-5), 144.9 (C-4), 178.0 (C-6) ppm. **Minor**; δ 22.4 (C-8), 22.6 (C-2), 26.1 (C-3), 36.2 (C-1), 57.0 (C-7), 123.2 (C-5), 146.1 (C-4), 175.7 (C-6) ppm. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{18}NOS$ $[M + H]^+$: 200.1107, found 200.1109.

COSY, HSQC and HMBC were used to aid in assignment.

(*S*)-*N*-(3,4-dihydronaphthalen-1(2H)-ylidene)-2-methylpropane-2-sulfinamide, (*S*)-211



Compound **(*S*)-211** was prepared from the general procedure **6.2** outlined above using α-tetralone (1.33 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*)-211** as a brown solid (0.831 g, 33%).

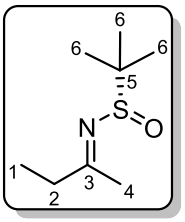
Spectroscopic characteristics were consistent with previously reported data.[4]

M.p. 60-63 °C (lit.[4] m.p. 65-66 °C). $[\alpha]_D^{27}$ - 6.3 (c 1.0, $CHCl_3$) (lit.[4] $[\alpha]_D^{27}$ + 10.5 (c 0.84, $CHCl_3$) for *R*-enantiomer). IR ν_{max} (NaCl): 1611 (C=N stretch), 1080 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (9H, s, H-6), 1.89-2.11 (2H, m, H-3), 2.83-2.91 (2H, m, H-4), 3.06 (1H, ddd, *J* = 17.5, 7.3, 4.7 Hz, one of H-2), 3.29 (1H, ddd , *J* = 17.5, 8.8, 5.2 Hz, one of H-2), 7.14-7.31 (2H, m, Ar-H), 7.33-7.43 (1H, td, *J* = 7.5, 1.4 Hz, Ar-H), 8.17 (1H, dd, *J* = 7.5, 1.0 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (C-6), 22.8 (C-3), 30.0 (C-4), 32.5 (C-2),

57.3 (C-5), 126.6 (Ar-CH), 127.2 (Ar-CH), 129.0 (Ar-CH), 132.1 (Ar-CH), 133.3 (Ar-C), 142.4 (Ar-C), 177.1 (C-1) ppm. MS (ESI) *m*/*z*: 250 $(M + H)^+$.

COSY and HSQC were used to aid in assignment.

(*S,E*)-*N*-(butan-2-ylidene)-2-methylpropane-2-sulfinamide, (*S*)-334

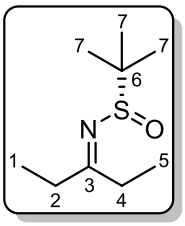


Compound **(*S*)-334** was prepared from the general procedure **6.2** outlined above using 2-butanone (0.90 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-334** as a pale yellow oil (0.725 g, 41%).

Spectroscopic characteristics were consistent with previously reported data.[1]

$[\alpha]_D^{20}$ + 139.42 (c 1.2, $CHCl_3$) (lit.[1] $[\alpha]_D^{20}$ + 98 (c 1.2, CH_2Cl_2) for *S*-enantiomer). IR ν_{max} (NaCl): 1624 (C=N stretch), 1073 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, t, *J* = 7.3 Hz, H-1), 1.23 (9H, s, H-6), 2.31 (3H, s, H-4), 2.42, 2.43 (2 × 1H, q, *J* = 7.3 Hz, H-2) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.0 (C-1), 22.3 (C-6), 22.9 (C-4), 36.8 (C-2), 56.4 (C-5), 186.2 (C-3) ppm. MS (ESI) *m*/*z*: 176 $(M + H)^+$.

(*S,E*)-2-Methyl-*N*-(pentan-3-ylidene)propane-2-sulfinamide, (*S*)-335



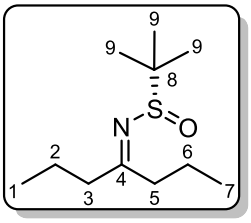
Compound **(*S*)-335** was prepared from the general procedure **6.2** outlined above using 3-pentanone (1.06 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*)-335** as a yellow oil (0.985 g, 52%).

Spectroscopic characteristics were consistent with previously reported data.[5]

$[\alpha]_D^{20}$ + 165.00 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 1628 (C=N stretch), 1075 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.08, 1.18 (2 × 3H, t, *J* = 7.6, 7.2 Hz, H-1 and H-5), 1.22 (9H, s, H-7), 2.32-2.56 (2H, m, one of each H-2 and H-4), 2.70 (2H, q, *J* = 7.6 Hz, one of each H-2 and H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.0, 12.0 (C-1 and C-5), 22.3 (C-7), 29.7, 33.6 (C-2 and C-4), 56.3 (C-6), 190.6 (C-3) ppm. MS (ESI) *m*/*z*: 190 $(M + H)^+$.

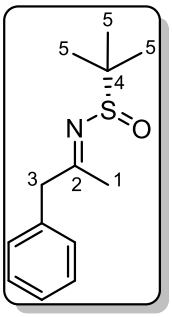
HSQC was used to aid in assignment.

(*S*)-*N*-(heptan-4-ylidene)-2-methylpropane-2-sulfinamide, (*S*)-336



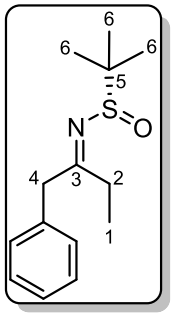
Compound **(*S*)-336** was prepared from the general procedure **6.2** outlined above using 4-heptanone (1.40 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*)-336** as a yellow oil (1.15 g, 53%). $[\alpha]_D^{20}$ + 157.20 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 1624 (C=N stretch), 1077 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87-1.04 (6H, m, H-1 and H-7), 1.21 (9H, s, H-9), 1.52-1.70 (4H, m, H-2 and H-6), 2.26-2.46 (2H, m, one of each H-3 and H-5), 2.49-2.77 (2H, m, one of each H-3 and H-5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 14.4 (C-1 and C-7), 19.1, 21.0 (C-2 and C-6), 22.2 (C-9), 38.5, 43.0 (C-3 and C-5), 56.3 (C-8), 188.8 (C-4) ppm. HRMS (ESI) *m*/*z* calcd for $C_{11}H_{24}NOS$ $[M + H]^+$: 218.1579, found 218.1573.

(*S*,*E*)-2-Methyl-*N*-(1-phenylpropan-2-ylidene)propane-2-sulfinamide, (*S*)-352



Compound **(*S*)-352** was prepared from the general procedure **6.2** outlined above using phenylacetone (1.61 mL, 12 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-352** as yellow oil (0.777 g, 33%, 4:1 mixture of *E*:*Z* isomers). $[\alpha]_D^{20}$ + 56.0 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 1624 (C=N stretch), 1074 (S=O stretch) cm^{-1}. ***E* isomer**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (9H, s, H-5), 2.29 (3H, s, H-1), 3.66, 3.70 (2H, ABq, J_{AB} = 14.3 Hz, H-3), 7.17-7.38 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3 (C-5), 29.4 (C-1), 50.3 (C-3), 56.8 (C-4), 127.2 (Ar-CH), 128.8 (Ar-CH), 128.9 (Ar-CH), 129.5 (Ar-CH), 129.5 (Ar-CH), 135.8 (Ar-C), 183.4 (C-2) ppm. ***Z* isomer**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (9H, s, H-5), 2.07 (3H, s, H-1), 4.06, 4.15 (2H, ABq, J_{AB} = 14.5 Hz, H-3), 7.17-7.38 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3 (C-5), 22.4 (C-1), 51.2 (C-3), 55.5 (C-4), 127.2 (Ar-CH), 128.4 (Ar-CH), 129.0 (Ar-CH), 129.6 (Ar-CH), 130.1 (Ar-CH), 130.1 (Ar-C), 206.5 (C-2) ppm. HRMS (ESI) *m*/*z* calcd for $C_{13}H_{20}NOS$ $[M + H]^+$: 238.1260, found 238.1261.

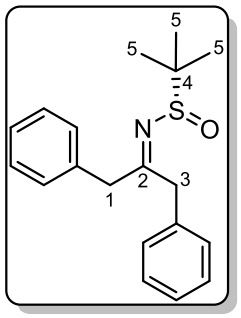
(*S*,*E*)-2-Methyl-*N*-(1-phenylbutan-2-ylidene)propane-2-sulfinamide, (*S*)-353



Compound **(*S*)-353** was prepared from the general procedure **6.2** outlined above using 1-phenylbutan-2-one (0.74 mL, 5 mmol) and (*S*)-*tert*-butanesulfinamide (0.606 g, 5 mmol). The crude compound was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*)-353** as a green oil (0.772 g, 61%, 5:3 mixture of *E*:*Z* isomers). $[\alpha]_D^{20}$ + 13.00 (c 0.1, $CHCl_3$). IR ν_{max} (NaCl): 1624 (C=N stretch), 1073 (S=O stretch) cm^{-1}. ***E* isomer**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, *J* = 7.2 Hz, H-1), 1.29 (9H, s, H-6), 2.37 (2H, q, *J* = 7.2 Hz, H-2), 4.12 (2H, s, H-4), 7.14-7.37 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.0 (C-1), 22.5 (C-6), 33.8 (C-2), 42.2 (C-4), 57.0 (C-5), 127.0 (2 × Ar-CH), 128.9 (2 × Ar-CH), 129.6 (Ar-CH), 136.1 (Ar-C), 185.9 (C-3) ppm. ***Z* isomer**; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (3H, t, *J* = 7.5 Hz, H-1), 1.16 (9H, s, H-6), 2.71 (2H, q, *J* = 7.5 Hz, H-2), 3.70 (2H, s, H-4), 7.14-7.37 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.0 (C-1), 22.3 (C-6), 28.8 (C-2), 47.3 (C-4), 56.7 (C-5), 127.0 (2 × Ar-CH), 128.6 (Ar-CH), 129.6 (2 × Ar-CH), 136.1 (Ar-C), 187.5 (C-3) ppm. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{22}NOS$ $[M + H]^+$: 252.1422, found 252.1414.

HSQC was used to aid in assignment.

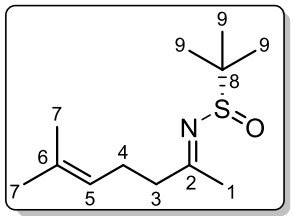
(*S*)-*N*-(1,3-diphenylpropan-2-ylidene)-2-methylpropane-2-sulfinamide, (*S*)-354



Compound **(*S*)-354** was prepared from the general procedure **6.2** outlined above using 1,3-diphenyl-2-propanone (1.97 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (6:1, hexane:EtOAc) to give the title compound **(*S*)-354** as a yellow oil (1.32 g, 42%).

$[\alpha]_D^{20}$ + 55.0 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 1627 (C=N stretch), 1074 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (9H, s, H-5), 3.59, 3.62 (2H, ABq, J_{AB} = 15.0 Hz, H-1/H-3), 4.08, 4.15 (2H, ABq, J_{AB} = 13.9 Hz, H-1/H-3), 7.02-7.14 (2H, m, Ar-H), 7.18-7.41 (8H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.5 (C-5), 41.0, 46.8 (C-1 and C-3), 57.4 (C-4), 127.0 (Ar-CH), 127.2 (Ar-CH), 128.6 (2 × Ar-CH), 129.0 (2 × Ar-CH), 129.6 (2 × Ar-CH), 129.7 (2 × Ar-CH), 135.6 (Ar-C), 136.1 (Ar-C), 183.1 (C-2) ppm. HRMS (ESI) *m*/*z* calcd for $C_{19}H_{24}NOS$ $[M + H]^+$: 314.1555, found 314.1564.

(*S*,*E*)-2-Methyl-*N*-(6-methylhept-5-en-2-ylidene)propane-2-sulfinamide, (*S*)-346

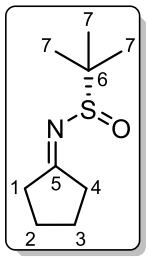


Compound **(*S*)-346** was prepared from the general procedure **6.2** outlined above using 6-methylhept-5-ene-2-one (1.62 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-346** as a yellow oil (0.784 g, 34%).

$[\alpha]_D^{20}$ + 79.40 (c 1.0, $CHCl_3$). IR ν_{max} (NaCl): 1624 (C=N stretch), 1076 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (9H, s, H-9), 1.59, 1.66 (2 × 3H, s, H-7), 2.21-2.35 (2H, m, one of each H-3 and H-4), 2.30 (3H, s, H-1), 2.37-2.47 (2H, m, one of each H-3 and H-4), 5.02-5.15 (1H, m, H-5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.9 (C-7), 22.3 (C-9), 23.2 (C-1), 24.4 (C-4), 25.9 (C-7), 43.7 (C-3), 56.5 (C-8), 123.2 (C-5), 132.8 (C-6), 185.2 (C-2) ppm. HRMS (ESI) *m*/*z* calcd for $C_{12}H_{24}NOS$ $[M + H]^+$: 230.1573, found 230.1575.

COSY and HSQC were used to aid in assignment.

(*S*,*E*)-2-Methyl-*N*-(cyclopentylidene)propane-2-sulfinamide, (*S*)-289



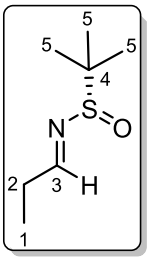
Compound **(*S*)-289** was prepared from the general procedure **6.2** outlined above using cyclopentanone (0.89 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-289** as a yellow oil (1.49 g, 80%).

Spectroscopic characteristics were consistent with previously reported data.[4]

$[\alpha]_D^{26}$ + 215.85 (c 1.0, CH_2Cl_2) (lit.[4] $[\alpha]_D^{26}$ - 241.3 (c 1.3, $CHCl_3$) for *R*-enantiomer). IR ν_{max} (NaCl): 1635 (C=N stretch), 1079 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s, H-7), 1.72-2.02 (4H, m, H-2 and H-3), 2.52 (2H, t, *J* = 7.5 Hz, one of each H-1 and H-4), 2.54-2.61 (1H, m, one of H-1/H-4), 2.81-2.99 (1H, dt, *J* = 19.2, 7.8 Hz, one of H-1/H-4) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (C-7), 23.6, 25.7 (C-2 and C-3), 33.9, 38.9 (C-1 and C-4), 56.3 (C-6), 195.0 (C-5) ppm. MS (ESI) *m*/*z*: 188 $(M + H)^+$.

HSQC was used to aid in assignment.

(*S*,*E*)-2-Methyl-*N*-(propylidene)propane-2-sulfinamide, (*S*)-227

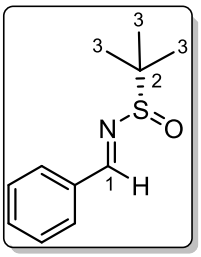


Compound **(*S*)-227** was prepared from the general procedure **6.2** outlined above using propionaldehyde (0.72 mL, 10 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-227** as a pale yellow oil (0.919 g, 57%).

Spectroscopic characteristics were consistent with previously reported data.[6]

$[\alpha]_D^{23}$ + 327.8 (c 1.0, $CHCl_3$) (lit.[6] $[\alpha]_D^{23}$ - 328.5 (c 1.0, $CHCl_3$) for *R*-enantiomer). IR ν_{max} (NaCl): 1625 (C=N stretch), 1084 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, t, *J* = 7.4 Hz, H-1), 1.19 (9H, s, H-5), 2.53 (2H, qd, *J* = 7.4, 4.3 Hz, H-2), 5.09 (1H, t, *J* = 4.3 Hz, H-3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.7 (C-1), 22.4 (C-5), 29.7 (C-2), 56.6 (C-4), 170.4 (C-3) ppm. HRMS (ESI) *m*/*z* calcd for $C_7H_{16}NOS$ $[M + H]^+$: 162.0953, found 162.0950.

(*S*,*E*)-*N*-benzylidene-2-methylpropane-2-sulfinamide, (*S*)-259



To a stirred solution of **titanium ethoxide** (2.20 mL, 10.5 mmol) in anhydrous THF at 0 °C was added freshly distilled **benzaldehyde** (0.51 mL, 5 mmol). **(*S*)-*tert*-butanesulfinamide** (0.509 g, 4.2 mmol) was added portion wise at 0 °C. The solution was stirred at 20 °C and monitored by TLC analysis. Once the sulfinamide was consumed brine (4 mL per mmol of ketone) was added to the reaction mixture. The solution was vigorously stirred for 30 min and the slurry was then filtered through a pad of Celite® with EtOAc. The phases were separated and the aqueous layer was washed with EtOAc (10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude (*S*)-*tert*-butanesulfinyl imine. The crude compound was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*)-259** as a pale yellow oil (0.796 g, 91%).

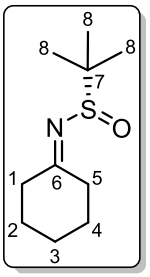
Spectroscopic characteristics were consistent with previously reported data.[7]

$[\alpha]_D^{20}$ + 115.75 (c 1.0, $CHCl_3$) (lit.[7] $[\alpha]_D^{20}$ + 124.4 (c 1.0, $CHCl_3$) for *S*-enantiomer). IR ν_{max} (NaCl): 1607 (C=N stretch), 1087 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (9H, s, H-3), 7.44-7.54 (3H, m, Ar-H), 7.83-7.88 (2H, m, Ar-H), 8.66 (1H, s, H-1) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (C-3), 57.8 (C-2), 128.9 (2 × Ar-CH), 129.4 (2 × Ar-CH), 132.4 (Ar-CH), 134.1 (Ar-C), 162.8 (C-1) ppm. MS (ESI) *m*/*z*: 210 $(M + H)^+$.

6.2.1 Synthesis of cyclic (*S*)-*tert*-butanesulfinyl imines (*S*)-290-292

6.2.1.1 Synthesis of cyclic (*S*)-*tert*-butanesulfinyl imine (*S*)-290

(*S*)-*N*-Cyclohexylidene-2-methylpropane-2-sulfinamide, (*S*)-290



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). The resulting mixture was allowed to stir for 15 min followed by the slow addition of **(*S*)-*tert*-butanesulfinamide** (0.727 g, 6 mmol). The mixture was heated at 60 °C and the reaction progress was monitored by TLC analysis. Once the reaction had gone to completion brine (4 mL per mmol of ketone) was added and the solution was allowed to stir vigorously for 30 min. The slurry was then filtered through a pad of Celite® and thoroughly washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude (*S*)-*tert*-butanesulfinyl imine. The crude compound was purified using column chromatography on silica gel (6:1, Et_2O:EtOAc) to give the title compound **(*S*)-290** as a colourless oil (0.562 g, 56%).

Spectroscopic characteristics are consistent with previously reported data.[6]

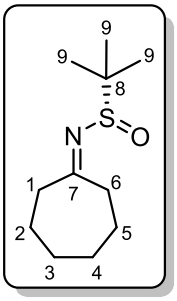
$[\alpha]_D^{23}$ + 74.13 (c 0.325, $CHCl_3$) (lit.[6] $[\alpha]_D^{23}$ - 184.0 (c 1.0, $CHCl_3$) for *R*-enantiomer). IR ν_{max} (NaCl): 1614 (C=N stretch), 1072 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (9H, s, H-8), 1.61-1.88 (6H, m, H-2, H-3 and H-4), 2.43 (2H, t, *J* = 6.3 Hz, one of each H-1 and H-5), 2.65-2.80 (1H, m, one of H-1/H-5), 2.81-2.98 (1H, m, one of H-1/H-5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (C-8), 27.5, 28.0, 34.5 (C-2, C-3 and C-4), 40.7 (C-1 and C-5), 56.0 (C-7), 188.7 (C-6) ppm. MS (ESI) *m*/*z*: 202 $(M + H)^+$.

HSQC was used to aid in assignment.

6.2.1.2 Synthesis of cyclic (*S*)-*tert*-butanesulfinyl imines (*S*)-291 and (*S*)-292

To a solution of **titanium ethoxide** (3.0 equiv.) in anhydrous THF (4 mL per mmol of ketone) was added **ketone** (1.1 equiv.). The resulting mixture was allowed to stir for 15 min followed by the slow addition of **(*S*)-*tert*-butanesulfinamide** (1.0 equiv.). The mixture was heated at 65 °C and the reaction progress was monitored by TLC analysis. Once the reaction had gone to completion brine (4 mL per mmol of ketone) was added and allowed to stir vigorously for 30 min. The slurry was then filtered through a pad of Celite® and thoroughly washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude (*S*)-*tert*-butanesulfinyl imine.

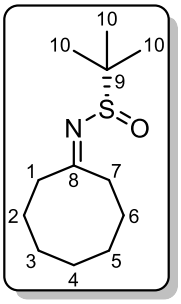
(*S*,*E*)-2-Methyl-*N*-(cycloheptylidene)propane-2-sulfinamide, (*S*)-291



Compound **(*S*)-291** was prepared from the general procedure **6.2.1.2** outlined above using cycloheptanone (1.30 mL, 11 mmol) and (*S*)-*tert*-butanesulfinamide (1.21 g, 10 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-291** as a yellow oil (1.79 g, 83%).

Spectroscopic characteristics were consistent with previously reported data.[8] $[\alpha]_D^{22}$ + 158.30 (c 1.0, $CHCl_3$) (lit.[8] $[\alpha]_D^{22}$ + 173.3 (c 0.1, $CHCl_3$) for *S*-enantiomer.) IR ν_{max} (NaCl): 1606 (C=N stretch), 1074 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (9H, s, H-9), 1.47-1.82 (8H, m, H-2, H-3, H-4 and H-5), 2.53-2.69 (2H, m, one of each H-1 and H-6), 2.71-2.89 (1H, m, one of H-1/H-6), 2.94-3.12 (1H, m, one of H-1/H-6) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (C-9), 25.4, 26.4, 29.8, 29.9 (C-2, C-3, C-4 and C-5), 36.5, 42.3 (C-1 and C-6), 56.1 (C-8), 192.0 (C-7) ppm. MS (ESI) *m*/*z*: 216 $(M + H)^+$.

(*S*,*E*)-2-Methyl-*N*-(cyclooctylidene)propane-2-sulfinamide, (*S*)-292

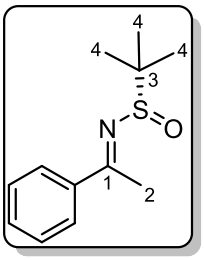


Compound **(*S*)-292** was prepared from the general procedure **6.2.1.2** outlined above using cyclooctanone (0.72 mL, 5.5 mmol) and (*S*)-*tert*-butanesulfinamide (0.606 g, 5 mmol). The crude compound was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*)-292** as a yellow oil (0.875 g, 76%).

Spectroscopic characteristics were consistent with previously reported data.[8] $[\alpha]_D^{22}$ + 186.0 (c 1.0, $CHCl_3$) (lit.[8] $[\alpha]_D^{22}$ + 173.3 (c 0.1, $CHCl_3$) for *S*-enantiomer.) IR ν_{max} (NaCl): 1608 (C=N stretch), 1075 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (9H, s, H-10), 1.26-1.62 (10H, m, H-2, H-3, H-4, H-5 and H-6), 2.34-2.62 (2H, m, one of each H-1 and H-7), 2.63-3.00 (2H, m, one of each H-1 and H-7) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.3 (C-10), 25.1, 26.0, 26.4, 27.1, 27.2 (C-2, C-3, C-4, C-5 and C-6), 34.6, 40.7 (C-1 and C-7), 56.1 (C-9), 193.9 (C-8) ppm. MS (ESI) *m*/*z*: 230 $(M + H)^+$.

6.2.2 Scale-up procedure

(*S*)-2-Methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide, (*S*)-199



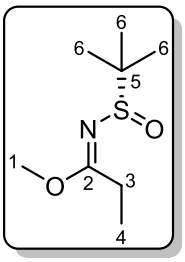
In a 500 mL two-necked round-bottomed flask equipped with a reflux condenser connected to a Schlenk line, a rubber septum and a Teflon®-coated octagonal magnetic stir bar (4.5 × 1.0 cm) and under nitrogen atmosphere were added **(*S*)-(-)-2-methylpropane-2-sulfinamide** (63 mmol, 7.623 g, 1.0 equiv.), **acetophenone** *via* plastic syringe (63 mmol, 7.34 mL, 1.0 equiv.) and anhydrous tetrahydrofuran *via* glass syringe (250 mL (4 mL per mmol of ketone)). To the stirred mixture was added **titanium ethoxide** *via* plastic syringe (126 mmol, 26.5 mL, 2.0 equiv.). The resulting pale yellow mixture was heated at reflux in an oil bath and the reaction progress was monitored by TLC analysis. Once complete (26 h), the dark yellow reaction mixture was allowed to cool to room temperature and brine (200 mL) was added to the reaction mixture with rapid stirring before filtration through a pad of Celite® (50 g) using a perforated filter funnel (10 cm diameter) supported with filter paper (90 mm diameter) that was packed with Et_2O. The pad of Celite® was flushed three times with Et_2O (40 mL). The liquid was transferred to a 2 L separatory funnel and the phases were separated. The aqueous phase was extracted two more times with Et_2O (60 mL). The filtrate was dried over anhydrous $MgSO_4$ (*ca.* 40 g), filtered through cotton wool into a 1 L round-bottomed flask and concentrated under reduced pressure (45-50 mmHg, 30 °C) to afford the crude product which was then purified *via* column chromatography on silica gel (5:1, hexane:EtOAc). (*S*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide **(*S*)-199** was dried under high vacuum overnight and isolated as a yellow solid (9.443 g, 67%).

Spectroscopic characteristics were consistent with previously reported data.[1]

M.p. 38-40 °C (lit.[1] m.p. 36-40 °C). $[\alpha]_D^{20}$ + 17.4 (c 1.03, CH_2Cl_2) (lit.[1] $[\alpha]_D^{20}$ + 13.0 (c 1.03, CH_2Cl_2) for *S*-enantiomer). IR ν_{max} (NaCl): 1603 (C=N stretch), 1073 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (9H, s, H-4), 2.77 (3H, s, H-2), 7.40-7.52 (3H, m, Ar-H), 7.89 (2H, d, *J* = 7.2 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.7 (C-2), 22.5 (C-4), 57.4 (C-3), 127.2 (2 × Ar-CH), 128.4 (2 × Ar-CH), 131.6 (Ar-CH), 138.7 (Ar-C), 176.3 (C-1) ppm. MS (ESI) *m*/*z*: 224 $(M + H)^+$.

6.3 Synthesis of (*S*)-*tert*-butanesulfinyl imidate

(*S,E*)-Methyl-*N*-(*tert*-butylsulfinyl)propionimidate, (*S*)-242



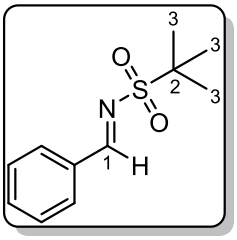
To a round-bottomed flask charged with **(*S*)-*tert*-butanesulfinamide** (0.500 g, 4.13 mmol) was added **trimethyl orthopropionate** (1.76 mL, 12.4 mmol) and ***p*-toluenesulfonic acid monohydrate** (0.003 mL, 0.02 mmol). The resulting solution was stirred for 3 h at 100 °C. The reaction mixture was allowed cool to room temperature and the volatile materials were removed *in vacuo*. The crude compound was purified using column chromatography on silica gel (10:1, Et_2O:EtOAc) to give the title compound **(*S*)-242** as a colourless oil (0.691 g, 87%).

Spectroscopic characteristics were consistent with previous reported data.[9]

$[\alpha]_D^{25}$ + 92.30 (c 1.0, MeOH) (lit.[9] $[\alpha]_D^{25}$ - 116.00 (c 0.1, MeOH) for *R*-enantiomer). IR ν_{max} (NaCl): 1611 (C=N stretch), 1080 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, *J* = 7.6 Hz, H-4), 1.22 (9H, s, H-6), 2.68 (1H, dq, *J* = 14.5, 7.6 Hz, one of H-3), 2.71 (1H, dq, *J* = 14.5, 7.6 Hz, one of H-3), 3.77 (3H, s, H-1) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 10.8 (C-4), 22.0 (C-6), 26.3 (C-3), 54.2 (C-1), 55.8 (C-5), 178.0 (C-2) ppm. MS (ESI) *m*/*z*: 192 $(M + H)^+$.

6.4 Synthesis of imines

(*E*)-*N*-benzylidene-2-methylpropane-2-sulfonamide, 257



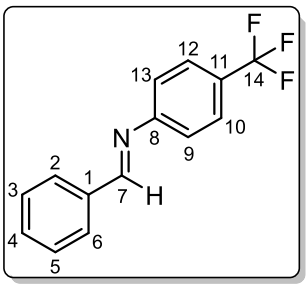
To a stirred mixture of **benzaldehyde** (0.95 mL, 9.3 mmol) and ***tert*-butylsulfonamide** (1.40 g, 10.2 mmol) in CH_2Cl_2 (50 mL) was added **trifluoroacetic anhydride** (1.42 mL, 10.2 mmol). The solution was heated at reflux temperature for 12 h. The reaction mixture was allowed cool to ambient temperature and then poured into cold H_2O (30 mL). The organic layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **257** as a white crystalline solid (0.879 g, 42%).

Spectroscopic characteristics were consistent with previously reported data.[10]

M.p. 161-165 °C (lit.[2] m.p. 162-168 °C). IR ν_{max} (NaCl): 1604 (C=N stretch), 1075 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (9H, s, H-3), 7.49-7.58 (2H, m, Ar-H), 7.61-7.69 (1H, m, Ar-H), 7.93-8.01 (2H, m, Ar-H), 9.05 (1H, s, H-1) ppm. ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 24.2 (C-3), 58.4 (C-2), 129.2 (2 × Ar-CH), 131.4 (2 × Ar-CH), 132.6 (Ar-CH), 134.9 (Ar-C), 172.8 (C-1) ppm. MS (ESI) *m*/*z*: 226 $(M + H)^+$.

(*E*)-1-Phenyl-*N*-(4-(trifluoromethyl)phenyl)methanimine, 258



To a stirred solution of **benzaldehyde** (1.02 mL, 10 mmol) in CH_2Cl_2 was added **4-trifluoromethylaniline** (1.26 mL, 10 mmol) and three spatula tips of **anhydrous $MgSO_4$**. The solution was stirred vigorously at room temperature for three days. The reaction mixture was then filtered through filter paper with CH_2Cl_2. The crude compound was purified *via* recrystallisation from hexane to give the title compound **258** as a yellow solid (1.98 g, 80%). Spectroscopic characteristics were consistent with previously reported data.[11]

M.p. 65-67 °C (lit.[12] m.p. 69-71 °C). IR ν_{max} (NaCl): 1603 (C=N stretch), 1108 (C-F stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.30 (2H, m, H-9 and H-13), 7.43-7.57 (3H, m, H-3, H-4 and H-5), 7.58-7.70 (2H, m, H-10 and H-12), 7.85-7.96 (2H, m, H-2 and H-6), 8.42 (1H, s, H-7) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 121.1 (C-9 and C-13), 124.4 (q, $^1J_{C\text{-}F}$ = 272.3 Hz, C-14), 126.4 (q, $^3J_{C\text{-}F}$ = 3.6 Hz, C-10 and C-12), 127.8 (q, $^2J_{C\text{-}F}$ = 32.6 Hz, C-11), 129.0 (C-3 and C-5), 129.2 (C-2 and C-6), 132.1 (C-4), 135.9 (C-1), 155.4 (C-8), 162.1 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{14}H_{11}F_3N$ $[M + H]^+$: 250.0838, found 250.0832.

HSQC and HMBC were used to aid in assignment.

6.5 Aldol-Tishchenko reaction of (*S*)-*tert*-butanesulfinyl imines

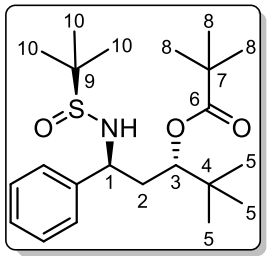
6.5.1 General procedure for the synthesis of *anti*-1,3-amino esters

To a Schlenk tube under N_2 atmosphere, containing diisopropylamine (1.2 equiv.) in anhydrous THF (5 mL per mmol of sulfinyl imine) was added *n*-BuLi (1.1 equiv.) at 0 °C. The solution was allowed to stir for 20 min to generate a solution of LDA. The reaction mixture was cooled to -78 °C and ***tert*-butanesulfinyl imine** (1.0 equiv.) was added in one portion (solid) or slowly (neat), dropwise (oil). After the reaction mixture was allowed to stir for 1 h at -78 °C, freshly distilled **aldehyde** (3.0 equiv.) was added slowly (neat), dropwise. The reaction mixture was kept at -78 °C for 3 h and was allowed warm to -20 °C over 16 h.

Work-up conditions as per 1 mmol of sulfinyl imine

The reaction mixture was quenched with sat. aq. NH_4Cl solution (1.5 mL) and allowed warm to room temperature. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was purified using column chromatography on silica gel.

(1*S*,3*S*)-1-(((*S*)-*Tert*-butylsulfinyl)amino)-4,4-dimethyl-1-phenylpentan-3-yl pivalate, (*S*,*S*,*S*)-202

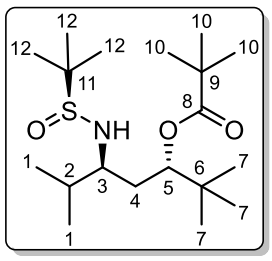


Compound **(*S*,*S*,*S*)-202** was prepared from the general procedure **6.5.1** outlined above using sulfinyl imine **(*S*)-199** (0.233 g, 1 mmol) and pivaldehdye (0.33 mL, 3 mmol). The crude compound (93:7 *dr*) was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*,*S*,*S*)-202** as a pale yellow solid (0.219 g, 55% mixture of diastereomers).

Spectroscopic characteristics were consistent with previously reported data.[2]

Major diastereomer: m.p. 161-166 ºC (lit.[2] m.p. 162-168 ºC). $[\alpha]_D^{23}$ + 47.5 (c 1.0, $CHCl_3$) (lit.[2] $[\alpha]_D^{23}$ + 42.4 (c 1.0, $CHCl_3$) for *S*,*S*,*S*-diastereomer). IR ν_{max} (NaCl): 3244 (N-H stretch), 2917 (C-H stretch), 1726 (C=O stretch), 1164 (C-O stretch), 1040 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (9H, s, H-5), 1.12 (9H, s, H-10), 1.16 (9H, s, H-8), 1.85 (1H, ddd, *J* = 14.1, 10.7, 3.1 Hz, one of H-2), 2.27 (1H, ddd, *J* = 14.4, 10.9, 1.4 Hz, one of H-2), 3.97-4.07 (1H, m, H-1), 4.12 (1H, d, *J* = 6.3 Hz, N-H), 5.00 (1H, dd, *J* = 10.7, 1.4 Hz, H-3), 7.16-7.41 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.8 (C-10), 26.2 (C-5), 27.5 (C-8), 34.9 (C-4), 37.3 (C-2), 39.3 (C-7), 56.3 (C-9), 57.4 (C-1), 77.4 (C-3), 127.6 (2 × Ar-CH), 127.8 (Ar-CH), 128.7 (2 × Ar-CH), 142.2 (Ar-C), 178.7 (C-6) ppm. MS (ESI) *m*/*z*: 396 $(M + H)^+$.

(3*S*,5*S*)-5-(((*S*)-*Tert*-butylsulfinyl)amino)-2,2,6-trimethylheptan-3-yl pivalate, (*S*,*S*,*S*)-225



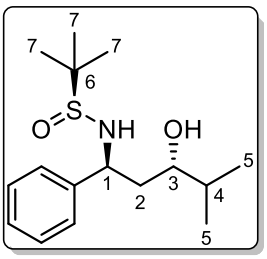
To a Schlenk tube under N_2 atmosphere, containing diisopropylamine (5.07 mL, 36 mmol) in anhydrous THF (150 mL) was added *n*-BuLi (12.3 mL, 2.5 M, 33 mmol) at 0 °C. The mixture was allowed to stir at 0 °C for 20 min to generate a solution of LDA. The reaction mixture was cooled to -78 °C and ***tert*-butanesulfinyl imine (*S*)-209** (5.670 g, 30 mmol) was added slowly, dropwise. After the reaction mixture was allowed to stir for 1 h

at -78 °C, freshly distilled **aldehyde** (9.76 mL, 90 mmol) was added slowly (neat), dropwise. The reaction mixture was kept at -78 °C for 3 h and was allowed warm to -20 °C over 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (45 mL) and allowed warm to room temperature. Sat. aq. NH_4Cl (30 mL) was added and the mixture was extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude compound (>97:3 *dr*) was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*,*S*,*S*)-225** as a pale yellow solid (2.04 g, 19%).

Spectroscopic characteristics were consistent with previously reported data.[2]

Major diastereomer: m.p. 89-91 °C (lit.[2] m.p. 88-93 °C). $[\alpha]_D^{23}$ + 24.0 (c 1.0, $CHCl_3$) (lit.[2] $[\alpha]_D^{23}$ + 24.5 (c 1.0, $CHCl_3$) for *S*,*S*,*S*-diastereomer). IR ν_{max} (NaCl): 3273 (N-H stretch), 2960 (C-H stretch), 1729 (C=O stretch), 1160 (C-O stretch), 1050 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (9H, s, H-7), 0.92, 0.93 (2 × 3H, d, *J* = 6.8 Hz, H-1), 1.23 (9H, s, H-12), 1.27 (9H, s, H-10), 1.54-1.64 (2H, m, H-4), 2.02-2.20 (1H, m, H-2), 2.61-2.74 (1H, m, H-3), 3.76 (1H, d, *J* = 7.9 Hz, N-H), 4.86-5.03 (1H, m, H-5) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.0, 20.2 (C-1), 23.0 (C-12), 26.2 (C-7), 27.5 (C-10), 32.6 (C-2), 32.8 (C-4), 34.8 (C-6), 39.2 (C-9), 56.4 (C-11), 60.1 (C-3), 77.4 (C-5), 178.5 (C-8) ppm. MS (ESI) *m*/*z*: 362 $(M + H)^+$.

(*S*)-*N*-((1*S*,3*S*)-3-Hydroxy-4-methyl-1-phenylpentyl)-2-methylpropane-2-sulfinamide, (*S*,*S*,*S*)-271



To a 500 mL, two-necked round-bottomed flask under nitrogen atmosphere equipped with a Teflon®-coated octagonal rare earth magnetic stir bar (3.5 × 0.8 cm), a vacuum adaptor connected to a Schlenk line and a rubber septum, containing diisopropylamine (50.6 mmol, 7.1 mL, 1.2 equiv.) in anhydrous THF (125 mL) was added *n*-BuLi *via* glass syringe over 4 minutes (46.4 mmol, 2.3 M, 20.2 mL, 1.1 equiv.) at 0 °C (cooled using an ice bath). The mixture was allowed to stir at 0 °C for 1 h. The solution was cooled to -78 °C with a cryocooler and **(*S*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfinamide (*S*)-199** (42.2 mmol, 9.4 g, 1.0 equiv.) dissolved in 75 mL anhydrous THF was added *via* glass syringe over 30-35 mins. After the reaction mixture was allowed to stir for 3 h at -78 °C, freshly distilled **isobutyraldehyde** (92.8 mmol, 8.46 mL, 2.2 equiv.) was added *via* glass syringe slowly (neat) (over 20-25 mins). The reaction mixture was kept at -78 °C for 1 h and allowed

warm to -30 °C using a cryocooler which took approx. 2 h. Once it was at -30 °C, the reaction mixture was left at this temperature for 24 h. The reaction was then checked by TLC analysis and ^{1}H NMR spectroscopy. The reaction was not complete so it was warmed to -20 °C and kept at this temperature for 24 h. The reaction was then judged to be complete by TLC analysis and ^{1}H NMR spectroscopy. The reaction mixture was quenched with sat. aq. NH_4Cl solution (63 mL) and allowed warm to room temperature with stirring. The reaction mixture was transferred to a 2 L separatory funnel. Sat. aq. NH_4Cl (400 mL) was added and the mixture was extracted with EtOAc (5 × 500 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ (*ca*. 60 g), filtered through cotton wool into a 1 L round-bottomed flask, and concentrated under reduced pressure (45-50 mmHg, 30 °C) to give the crude product **(*S*,*S*,*S*)-270** (>98:2 *dr*) as an orange oil (16.274 g) which was used in the next step without further purification.

Ester cleavage step

In a 1 L round-bottomed flask, to a stirring solution of crude material (16.274 g, 44.3 mmol, 1.0 equiv.) in MeOH (420 mL) was added KOH (9.45 g, 168.8 mmol, 3.8 equiv.) at room temperature. The mixture was heated to reflux overnight (16 h) using an oil bath under nitrogen atmosphere. The solution was then cooled to room temperature and concentrated under reduced pressure (45-50 mmHg, 40 ºC). CH_2Cl_2 (1 L) was added and the organic layer was washed with water (3 × 800 mL). The aqueous layer was neutralised with conc. HCl which was added dropwise *via* a pipette and checked after each drop with litmus paper. The aqueous layer was then back extracted with CH_2Cl_2 (5 × 500 mL). The organic layers were combined, dried over anhydrous $MgSO_4$ (*ca*. 60 g), filtered through a glass funnel (15 cm diameter) and cotton wool into a 1 L round-bottomed flask. The filtrate was concentrated under reduced pressure (45-50 mmHg, 30 ºC). Hexane:CH_2Cl_2 (1:1, 200 mL) were added and a white solid appeared which was then filtered through a pad of Celite® (50 g) using a perforated filter funnel (10 cm diameter) supported with filter paper (90 mm diameter) that was packed with Et_2O into a 1 L round-bottomed flask. The Celite® was washed with hexane:CH_2Cl_2 (1:1, 50 mL). The solvent was evaporated under reduced pressure (45-50 mmHg, 30 ºC) and a brown gum was obtained. Warm hexane (50 mL, 30 ºC) was added and the solution was cooled to 0 ºC in the fridge overnight. The material after this recrystallisation was not crystalline (flaky off-white solid). A second recrystallisation was carried out repeating the process from the addition of 200 mL hexane:CH_2Cl_2 and by use of a minimum amount of warm hexane. The solution was cooled to

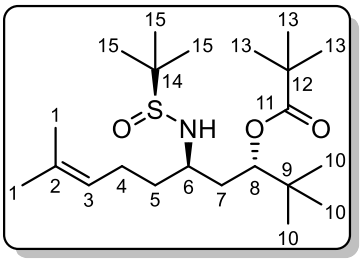
0 ºC in the fridge overnight. The final product which crashed out was vacuum filtered using a Büchner funnel (2 cm inner diameter) and dried under high vacuum overnight to afford the title compound **(*S*,*S*,*S*)-271** as a pale yellow solid (3.31 g, 26%).

Spectroscopic characteristics were consistent with previously reported data.[2]

Major diastereomer: m.p. 134-136 ºC (lit.[2] m.p. 134-136 ºC). $[\alpha]_D^{23}$ - 57.0 (c 1.0, $CHCl_3$) (lit.[2] $[\alpha]_D^{23}$ - 57.7 (c 1.0, $CHCl_3$) for *S*,*S*,*S*-diastereomer). IR ν_{max} (KBr): 3307 (N-H stretch), 3249 (O-H stretch), 2960 (C-H stretch), 1034 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89, 0.93 (2 × 3H, d, *J* = 6.8 Hz, H-5), 1.16 (9H, s, H-7), 1.58-1.75 (1H, m, H-4), 1.80-1.88 (2H, m, H-2), 2.80 (1H, *br* s, O-H), 3.48-3.58 (1H, m, H-3), 3.97 (1H, d, *J* = 6.9 Hz, N-H), 4.70 (1H, q, *J* = 6.8 Hz, H-1), 7.21-7.38 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.8, 18.9 (C-5), 23.0 (C-7), 33.8 (C-4), 43.2 (C-2), 54.2 (C-1), 56.8 (C-6), 72.6 (C-3), 126.9 (2 × Ar-CH), 127.5 (Ar-C), 128.8 (2 × Ar CH), 143.5 (Ar-CH) ppm. HRMS (ESI) *m*/*z* calcd for $C_{16}H_{28}NO_2S$ $[M + H]^+$: 298.1841, found 298.1837.

Absolute stereochemistry was assigned by crystallographic data **(Appendix II)**.

(3*S*,5*R*)-5-(((S)-*Tert*-butylsulfinyl)amino)-2,2,9-trimethyldec-8-en-3-yl pivalate, (*S*,*S*,*S*)-349

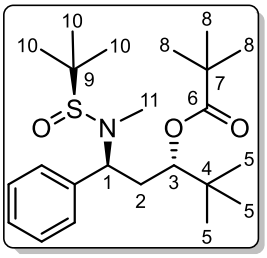


Compound **(*S*,*S*,*S*)-349** was prepared from the general procedure **6.5.1** outlined above using sulfinyl imine **(*S*)-346** (0.100 g, 0.44 mmol) and pivaldehyde (0.22 mL, 1.98 mmol, 4.5 equiv.). The crude compound (67:33 *dr*) was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*,*S*,*S*)-349** as a sticky colourless oil (0.120 g, 68% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 49.20 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3281 (N-H stretch), 2965 (C-H stretch), 1730 (C=O stretch), 1284 (C-O stretch), 1074 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (9H, s, H-10), 1.22 (9H, s, H-15), 1.26 (9H, s, H-13), 1.39-1.57 (2H, m, one of each H-5 and H-7), 1.59, 1.66 (2 × 3H, s, H-1), 1.83-1.98 (2H, m, one of each H-5 and H-7), 1.99-2.10 (2H, m, H-4), 2.76-2.89 (1H, m, H-6), 4.36 (1H, d, *J* = 5.3 Hz, N-H), 4.98 (1H, dd, *J* = 11.2, 1.5 Hz, H-8), 5.01-5.12 (1H, m, H-3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 17.9 (C-1), 23.0 (C-15), 24.8 (C-4), 25.9 (C-1), 26.2 (C-10), 27.5 (C-13), 34.6 (C-5), 35.2 (C-9),

37.2 (C-7), 39.3 (C-12), 52.9 (C-6), 56.0 (C-14), 77.7 (C-8), 123.9 (C-3), 132.4 (C-2), 178.1 (C-11) ppm. HRMS (ESI) *m*/*z* calcd for $C_{22}H_{42}NO_3S$ [M - H]$^-$: 400.2885, found 400.2886. COSY and HSQC were used to aid in assignment.

(1*S*,3*S*)-1-(((*S*)-*Tert*-butylsulfinyl)(methyl)amino)-4,4-dimethyl-1-phenylpentan-3-yl pivalate, (*S*,*S*,*S*)-249



Compound **(*S*,*S*,*S*)-249** was prepared from the general procedure **6.5.1** outlined above using sulfinyl imine **(*S*)-199** (0.223 g, 1 mmol) and pivaldehyde (0.33 mL, 3 mmol). The reaction mixture was quenched with **methyl iodide** (0.19 mL, 3 mmol) at -20 ^oC, allowed warm to room temperature and subsequently stirred at this temperature for 7 h. The reaction mixture was cooled to -20 ^oC, quenched with sat. aq. NH_4Cl solution (1.5 mL) and allowed warm to room temperature. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude compound was purified using column chromatography on silica gel (5:1, hexane:EtOAc) to give the title compound **(*S*,*S*,*S*)-249** as a white solid (0.151 g, 37%).

Major diastereomer: m.p. 93-95 ^oC. $[\alpha]_D^{20}$ - 22.6 (c 1.0, CH_2Cl_2). IR ν_{max} (NaCl): 3336 (O-H stretch), 2967 (C-H stretch), 1725 (C=O stretch), 1157 (C-O stretch), 1072 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (9H, s, H-5), 1.13 (9H, s, H-10), 1.25 (9H, s, H-8), 2.00 (1H, ddd, *J* = 14.1, 10.1, 3.4 Hz, one of H-2), 2.29-2.45 (1H, m, one of H-2), 2.41 (3H, s, H-11), 4.36 (1H, dd, *J* = 9.5, 3.7 Hz, H-1), 5.04 (1H, dd, *J* = 10.2, 1.1 Hz, H-3), 7.21-7.39 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.5 (C-10), 26.1 (C-5), 26.5 (C-11), 27.4 (C-8), 33.0 (C-4), 35.2 (C-2), 39.1 (C-7), 59.4 (C-9), 66.1 (C-1), 77.9 (C-3), 127.9 (2 × Ar-CH), 128.3 (Ar-CH), 128.5 (2 × Ar-CH), 140.0 (Ar-C), 178.0 (C-6) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{40}NO_3S$ [M + H]$^+$: 410.2729, found 410.2727.

Note: Diastereoselectivity could not be determined from the ^1H NMR spectrum of the crude reaction mixture due to overlapping signals.

6.5.2 General procedure for the synthesis of *anti*-1,3-amino alcohols

To a Schlenk tube under N_2 atmosphere, containing diisopropylamine (1.2 equiv.) in anhydrous THF (5 mL per mmol of sulfinyl imine) was added *n*-BuLi (1.1 equiv.) at 0 °C. The solution was allowed to stir for 20 min to generate a solution of LDA. ***Tert*-butanesulfinyl imine** (1.0 equiv.) was added slowly (neat), dropwise. The reaction mixture was cooled to -78 °C, freshly distilled **aldehyde** (2.2 equiv.) was added slowly (neat), dropwise. The reaction mixture was kept at -78 °C for 3 h and was allowed warm to -20 °C over 16 h.

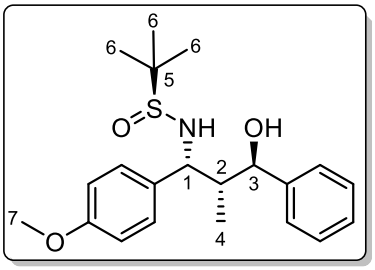
Work-up conditions as per 1 mmol of sulfinyl imine

The reaction mixture was quenched with sat. aq. NH_4Cl solution (1.5 mL) and allowed warm to room temperature. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product which was purified using column chromatography on silica gel.

Cleavage of ester functionality

To a vigorously stirred solution of the crude reaction mixture (approx. 1 mmol) in 10 mL MeOH was added KOH (0.224 g). The mixture was stirred at room temperature for 3 h. The solution was concentrated under reduced pressure. CH_2Cl_2 (25 mL) was added and washed with H_2O (20 mL). The aqueous layer was neutralised and back extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude compound.

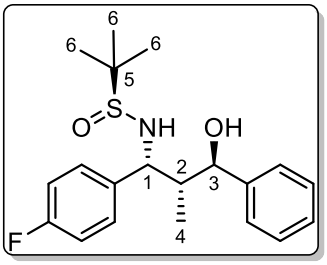
(*S*)-*N*-((1*R*,2*R*,3*R*)-1-(4-Methoxyphenyl)-3-hydroxy-2-methyl-3-phenylpropyl)-2-methylpropane-2-sulfinamide, (*S*,*R*,*R*,*R*)-220



Compound **(*S*,*R*,*R*,*R*)-220** was prepared from the general procedure **6.5.2** outlined above using sulfinyl imine **(*S*)-207** (0.240 g, 0.90 mmol) and benzaldehyde (0.20 mL, 1.98 mmol). The crude compound (80:10:10 *dr*) was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*R*,*R*)-220** as a pale yellow solid (0.161 g, 48% mixture of diastereomers). **Major diastereomer**: m.p. 156-159 °C. $[\alpha]_D^{23}$ + 88.2 (c 0.3, $CHCl_3$). IR ν_{max} (NaCl): 3236 (N-H stretch), 2961 (C-H stretch), 1175 (C-O stretch), 1036 (S=O stretch) cm^{-1}. ^1H NMR (300

MHz, $CDCl_3$) δ 0.67 (3H, d, *J* = 7.1 Hz, H-4), 1.28 (9H, s, H-6), 2.25-2.37 (1H, m, H-2), 3.43 (1H, *br* s, O-H), 3.80 (3H, s, H-7), 4.54 (1H, d, *J* = 8.0 Hz, H-3), 4.61 (1H, d, *J* = 5.8 Hz, N-H), 4.80 (1H, dd, *J* = 5.8, 2.8 Hz, H-1), 6.83-6.90 (2H, m, Ar-H), 7.15-7.42 (7H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.3 (C-4), 22.9 (C-6), 46.8 (C-2), 55.4 (C-7), 55.9 (C-5), 60.0 (C-1), 77.5 (C-3), 113.4 (2 × Ar-CH), 126.9 (2 × Ar-CH), 127.9 (Ar-CH), 128.6 (2 × Ar-CH), 128.7 (2 × Ar-CH), 133.3 (Ar-C), 143.2 (Ar-C), 150.0 (Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{30}NO_3S$ $[M + H]^+$: 376.1946, found 376.1935.

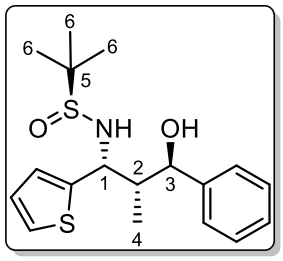
(*S*)-*N*-((1*R*,2*R*,3*R*)-1-(4-Fluorophenyl)-3-hydroxy-2-methyl-3-phenylpropyl)-2-methylpropane-2-sulfinamide, (*S*,*R*,*R*,*R*)-221



Compound **(*S*,*R*,*R*,*R*)-221** was prepared from the general procedure **6.5.2** outlined above using sulfinyl imine **(*S*)-206** (0.238 g, 0.93 mmol) and benzaldehyde (0.21 mL, 2.05 mmol). The crude compound (82:13:5 *dr*) was purified using column chromatography on silica gel (3:2, hexane:Et_2O) to give the title compound **(*S*,*R*,*R*,*R*)-221** as a white solid (0.180 g, 53% mixture of diastereomers).

Major diastereomer: m.p. 176-179 ºC. $[\alpha]_D^{23}$ + 113.33 (c 0.03, $CHCl_3$). IR ν_{max} (NaCl): 3167 (N-H stretch), 2853 (C-H stretch), 1155 (C-O stretch), 1070 (S=O stretch) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.69 (3H, d, *J* = 7.2 Hz, H-4), 1.29 (9H, s, H-6), 2.26-2.32 (1H, m, H-2), 3.34 (1H, *br* s, O-H), 4.55 (1H, d, *J* = 7.9 Hz, H-3), 4.70 (1H, d, *J* = 5.5 Hz, N-H), 4.84 (1H, dd, *J* = 5.5, 2.8 Hz, H-1), 6.99-7.04 (2H, m, Ar-H), 7.21-7.25 (2H, m, Ar-H), 7.27-7.31 (1H, m, Ar-H), 7.34-7.41 (4H, m, Ar-H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 12.1 (C-4), 22.9 (C-6), 46.8 (C-2), 55.6 (C-5), 60.0 (C-1), 77.5 (C-3), 115.1 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, 2 × Ar-CH), 126.8 (2 × Ar-CH), 128.0 (Ar-CH), 128.9 (2 × Ar-CH), 129.1 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 2 × Ar-CH), 137.2 (d, $^4J_{C\text{-}F}$ = 2.3 Hz, Ar-C), 142.9 (Ar-C), 162.0 (d, $^1J_{C\text{-}F}$ = 245.3 Hz, Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{20}H_{27}FNO_2S$ $[M + H]^+$: 364.1741, found 364.1739.

(*S*)-*N*-((1*R*,2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenyl-1-(thiophen-2-yl)propyl)-2-methylpropane-2-sulfinamide, (*S*,*R*,*R*,*R*)-222



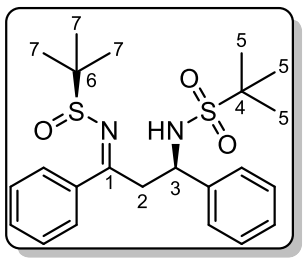
Compound **(*S*,*R*,*R*,*R*)-222** was prepared from the general procedure **6.5.2** outlined above using sulfinyl imine **(*S*)-208** (0.224 g, 0.92 mmol) and benzaldehyde (0.21 mL, 2.02 mmol). The crude compound (62:38 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*R*,*R*)-222** as a pale yellow solid (0.131 g, 41% mixture of diastereomers).

Major diastereomer: m.p. 129-134 °C. $[\alpha]_D^{25}$ + 153.6 (c 0.6, $CHCl_3$). IR ν_{max} (NaCl): 3583 (N-H stretch), 2924 (C-H stretch), 1040 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (3H, d, *J* = 7.1 Hz, H-4), 1.32 (9H, s, H-6), 2.39-2.53 (1H, m, H-2), 3.45 (1H, *br* s, O-H), 4.61 (1H, s, N-H), 4.62 (1H, d, *J* = 8.6 Hz, H-1), 5.19 (1H, dd, *J* = 6.5, 2.3 Hz, H-3), 6.87-6.93 (1H, m, Ar-H), 6.94-7.02 (1H, m, Ar-H), 7.20 (1H, dd, *J* = 5.1, 1.1 Hz, Ar-H), 7.24-7.45 (5H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.4 (C-4), 23.0 (C-6), 46.9 (C-2), 56.4 (C-5), 57.6 (C-1), 76.9 (C-3), 124.1 (2 × Ar-CH), 127.0 (2 × Ar-CH), 127.1 (Ar-CH), 127.9 (Ar-CH), 128.6 (2 × Ar-CH), 143.0 (Ar-C), 146.8 (Ar-C) ppm. HRMS (ESI) *m*/*z* calcd for $C_{18}H_{25}NO_2S_2Na$ $[M + Na]^+$: 374.1219, found 374.1211.

Note: It was not possible to isolate pure minor diastereomer for full characterisation.

6.6 Aza-Mannich reaction using *N*-*tert*-butanesulfinyl imine (*S*)-199 and *N*-*tert*-butanesulfonyl imine 257

(*R*,*Z*)-3-(((*S*)-*Tert*-butylsulfinyl)imino)-1,3-dipehnylpropyl)-2-methylpropane-2-sulfonamide, (*S*,*R*)-260



To a Schlenk tube under N_2 atmosphere, containing LiHMDS (1.1 mmol) in anhydrous THF (5 mL), was added **(*S*)-*tert*-butanesulfinyl imine (*S*)-199** (0.223 g, 1 mmol) in one portion at -78 °C. After the reaction mixture was allowed to stir for 1 h at -78 °C, **sulfonyl imine 257** (0.293 g, 1.3 mmol) was added in one portion. The reaction mixture was stirred at -78 °C for 3 h and allowed warm to -50 °C overnight. The reaction mixture was quenched cold at -78 °C by the dropwise addition of AcOH (0.12 mL) in THF (1.3 mL). EtOAc (30 mL) was added and the mixture was extracted with 1M $NaHCO_3$ (3 × 10 mL). The organic layer was washed with brine (2 × 10 mL). The combined organic layers were dried

over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude compound (>98:2 *dr*) was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound **(*S*,*R*)-260** as a bright yellow solid (0.425 g, 95%). Spectroscopic characteristics were consistent with previously reported data.[13]

Major diastereomer: m.p. 149-154 °C. $[\alpha]_D^{20}$ - 43.43 (c 0.35, $CHCl_3$). IR ν_{max} (NaCl): 3583 (N-H stretch), 2982 (C-H stretch), 1590 (C=N stretch), 1312 (S=O sulfone stretch), 1129 (C-N stretch), 1070 (S=O sulfoxide stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (9H, s, H-7), 1.44 (9H, s, H-5), 3.42 (1H, dd, *J* = 13.5, 4.7 Hz, one of H-2), 3.75 (1H, dd, *J* = 13.4, 11.9 Hz, one of H-2), 4.75-4.87 (1H, m, H-3), 7.03 (1H, d, *J* = 7.5 Hz, N-H), 7.22-7.62 (8H, m, Ar-H), 7.88-7.98 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.8 (C-5), 24.1 (C-7), 43.2 (C-2), 55.9 (C-3), 58.4 (C-6), 59.2 (C-4), 126.5 (2 × Ar-CH), 127.9 (Ar-CH), 128.0 (2 × Ar-CH), 129.0 (2 × Ar-CH), 129.1 (2 × Ar-CH), 132.5 (Ar-CH), 136.9 (Ar-C), 143.7 (Ar-C), 177.7 (C-1) ppm. HRMS (ESI) *m*/*z* calcd for $C_{23}H_{33}N_2O_3S_2$ $[M + H]^+$: 449.1927, found 449.1931.

6.7 Double aldol-Tishchenko reaction of cyclic (*S*)-*tert*-butanesulfinyl imines

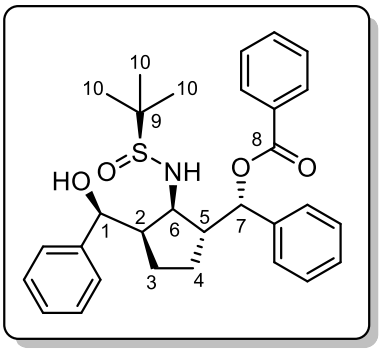
6.7.1 Synthesis of cyclopentanone derived 3-amino-1,5-diol precursors

To a Schlenk tube under N_2 atmosphere, containing diisopropylamine (1.2 equiv.) in anhydrous THF (5 mL), was added *n*-BuLi (1.1 equiv.) at 0 °C. The mixture was allowed to stir at 0 °C for 20 min to generate a solution of LDA. ***Tert*-butanesulfinyl imine** (1.0 equiv.) was carefully weighed out and the amount added was accurately recorded. The **sulfinyl imine** was then added slowly (neat), dropwise at 0 °C. After the reaction mixture was allowed to stir for 1 h at 0 °C, the solution was cooled to -78 °C and freshly distilled **aldehyde** (3.3 equiv.) was added slowly (neat), dropwise. The reaction mixture was kept at -78 °C for 3 h and allowed warm to -20 °C over 16 h.

Work-up conditions as per 1 mmol of sulfinyl imine

The reaction mixture was quenched with sat. aq. NH_4Cl solution (1.5 mL) at -20 °C. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was purified using column chromatography on silica gel.

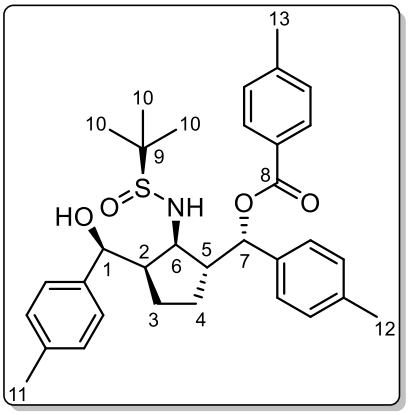
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(phenyl)methyl)cyclopentyl)(phenyl)methyl benzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-318



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-318** was prepared from the general procedure **6.7.1** outlined above using sulfinyl imine **(*S*)-289** (0.187 g, 1 mmol) and benzaldehyde (0.34 mL, 3.3 mmol). The crude compound (90:6:4 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-318** as a sticky pale yellow oil (0.245 g, 48% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 52.00 (c 0.05, $CHCl_3$). IR ν_{max} (NaCl): 3583 (N-H stretch), 1722 (C=O stretch), 1110 (C-N stretch), 1026 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.20-1.36 (2H, m, H-3), 1.29 (9H, s, H-10), 1.40-1.60 (1H, m, one of H-4), 1.69-1.90 (1H, m, one of H-4), 2.30 (1H, quint, *J* = 9.1 Hz, H-2), 2.44 (1H, dq, *J* = 9.2, 3.2 Hz, H-5), 3.51 (1H, dt, *J* = 9.5, 6.6 Hz, H-6), 4.14 (1H, d, *J* = 6.5 Hz, N-H), 4.55-4.67 (2H, m, O-H and H-1), 6.26 (1H, d, *J* = 3.2 Hz, H-7), 7.18-7.37 (10H, m, Ar-H), 7.44-7.55 (2H, m, Ar-H), 7.57-7.66 (1H, m, Ar-H), 8.06-8.15 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.4 (C-4), 22.9 (C-10), 25.8 (C-3), 52.5 (C-2), 52.9 (C-5), 56.2 (C-9), 64.2 (C-6), 74.1 (C-7), 78.6 (C-1), 125.9 (2 × Ar-CH), 126.7 (2 × Ar-CH), 127.7 (2 × Ar-CH), 128.4 (2 × Ar-CH), 128.6 (2 × Ar-CH), 128.7 (2 × Ar-CH), 129.8 (2 × Ar-CH), 130.3 (Ar-C), 133.4 (Ar-CH), 140.2 (Ar-C), 143.3 (Ar-C), 165.8 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{30}H_{36}NO_4S$ $[M + H]^+$: 506.2360, found 506.2364.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(*p*-tolyl)methyl)cyclopentyl)(*p*-tolyl)methyl 4-methylbenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-319

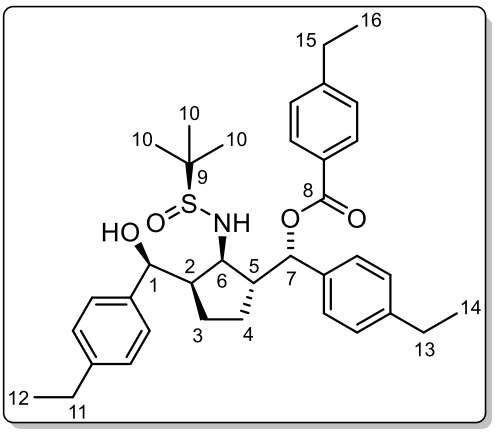


Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-319** was prepared from the general procedure **6.7.1** outlined above using sulfinyl imine **(*S*)-289** (0.178 g, 0.95 mmol) and *p*-tolualdehyde (0.37 mL, 3.1 mmol). The crude compound was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-319** as sticky colourless oil (0.253 g, 49% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 63.60 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3412 (N-H stretch), 2959 (C-H stretch), 1720 (C=O stretch), 1177 (C-O stretch), 1105 (C-N stretch), 1043 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.39 (2H, m, H-3), 1.28 (9H, s, H-10), 1.40-1.60 (1H, m, one of H-4), 1.64-1.85 (1H, m, one of H-4), 2.20-2.49 (2H, m, H-2 and H-5), 2.30, 2.40 (3 × 3H, s (overlapping 2 × 3H, s and 1 × 3H, s) H-11, H-12 and H-13), 3.48 (1H, dt, *J* = 9.4, 6.6 Hz, H-6), 4.14 (1H, d, *J* = 6.5 Hz, N-H), 4.52 (1H, *br* s, O-H), 4.57 (1H, d, *J* = 9.0 Hz, H-1), 6.20 (1H, d, *J* = 3.2 Hz, H-7), 7.04-7.32 (10H, m, Ar-H), 7.89-8.05 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2, 21.8 (overlapping C-11, C-12 and C-13), 21.6 (C-4), 22.9 (C-10), 25.8 (C-3), 52.5 (C-2), 53.9 (C-5), 56.1 (C-9), 64.2 (C-6), 74.0 (C-7), 78.4 (C-1), 125.9 (2 × Ar-CH), 126.6 (2 × Ar-CH), 127.6 (Ar-C), 129.1 (2 × Ar-CH), 129.2 (2 × Ar-CH), 129.3 (2 × Ar-CH), 129.8 (2 × Ar-CH), 137.2 (Ar-C), 137.3 (2 × Ar-C), 140.4 (Ar-C), 144.0 (Ar-C), 165.9 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{33}H_{41}NO_4SNa$ $[M + Na]^+$: 570.2649, found 570.2648.

Note: Diastereoselectivity could not be determined from the ^1H NMR spectrum of the crude reaction mixture due to overlapping signals.

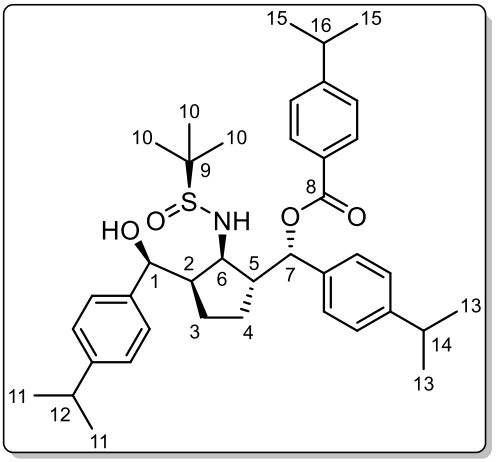
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-(4-ethylphenyl)(hydroxy)methyl)cyclopentyl)(4-ethylphenyl)methyl 4-ethylbenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-320



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-320** was prepared from the general procedure **6.7.1** outlined above using sulfinyl imine **(*S*)-289** (0.122 g, 0.65 mmol) and *p*-ethylbenzaldehyde (0.29 mL, 2.15 mmol). The crude compound (94:6 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-320** as a sticky yellow oil (0.173 g, 45% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 73.00 (c 0.1, $CHCl_3$). IR ν_{max} (NaCl): 3583 (N-H stretch), 2964 (C-H stretch), 1722 (C=O stretch), 1177 (C-O stretch), 1103 (C-N stretch), 1049 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.15-1.33 (2H, m, H-3), 1.19, 1.20, 1.28 (3 × 3H, t, *J* = 7.6 Hz, H-12, H-14 and H-16), 1.28 (9H, s, H-10), 1.45-1.62 (1H, m, one of H-4), 1.69-1.88 (1H, m, one of H-4), 2.30 (1H, quint, *J* = 9.0 Hz, H-2), 2.44 (1H, dq, *J* = 9.1, 3.5 Hz, H-5), 2.60, 2.73 (3 × 2H, q, *J* = 7.6 Hz (overlapping 2 × 2H, q and 1 × 2H, q) H-11, H-13 and H-15), 3.50 (1H, dt, *J* = 9.4, 6.6 Hz, H-6), 4.17 (1H, d, *J* = 6.5 Hz, N-H), 4.58 (overlapping 1H, *br* s, O-H and 1H, d, *J* = 9.0 Hz, H-1), 6.20 (1H, d, *J* = 3.3 Hz, H-7), 7.07-7.17 (4H, m, Ar-H), 7.17-7.35 (6H, m, Ar-H), 8.00-8.06 (2H, m Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.4, 15.6 (overlapping C-12, C-14 and C-16), 21.7 (C-4), 22.9 (C-10), 26.0 (C-3), 28.6, 29.1 (overlapping C-11, C-13 and C-15), 52.5 (C-2), 53.9 (C-5), 56.1 (C-9), 64.3 (C-6), 74.1 (C-7), 78.5 (C-1), 126.0 (2 × Ar-CH), 126.7 (2 × Ar-CH), 127.9 (overlapping 2 × Ar-CH and Ar-C), 128.0 (2 × Ar-CH), 128.2 (2 × Ar-CH), 130.0 (2 × Ar-CH), 137.5 (Ar-C), 140.6 (Ar-C), 143.6 (2 × Ar-C), 150.2 (Ar-C), 165.9 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{47}NO_4SNa$ $[M + Na]^+$: 612.3118, found 612.3120.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-isopropylphenyl)methyl)cyclopentyl)(4-isopropylphenyl)methyl 4-isopropylbenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-321



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-321** was prepared from the general procedure **6.7.1** outlined above using sulfinyl imine **(*S*)-289** (0.176 g, 0.94 mmol) and *p-iso*-propyl benzaldehyde (0.47 mL, 3.1 mmol). The crude compound (93:7 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-321** as a sticky yellow oil (0.285 g, 48% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 38.40 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3583 (N-H stretch), 2960 (C-H stretch), 1721 (C=O stretch), 1107 (C-N stretch), 1053 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.16-1.32 (2H, m, H-3), 1.20, 1.22, 1.29 (3 × 6H, d, *J* = 6.9 Hz, H-11, H-13 and H-15), 1.27 (9H, s, H-10), 1.46-1.64 (1H, m, one of H-4), 1.69-1.89 (1H, m, one of H-4), 2.31 (1H, quint, *J* = 8.7 Hz, H-2), 2.45 (1H, dq, *J* = 9.0, 3.4 Hz, H-5), 2.86, 2.99 (3 × 1H, sept, *J* = 6.9 Hz (overlapping 2 × 1H, sept and 1 × 1H, sept) H-12, H-14 and H-16), 3.36-3.70 (1H, m, H-6), 4.10 (1H, d, *J* = 5.9 Hz, N-H), 4.54 (1H, *br* s, O-H), 4.58 (1H, d, *J* = 9.2 Hz, H-1), 6.20 (1H, d, *J* = 3.2 Hz, H-7), 7.09-7.39 (10H, m, Ar-H), 7.98-8.07 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (C-4), 22.9 (C-10), 23.9, 24.1 (overlapping C-11, C-13 and C-15), 26.1 (C-3), 33.9, 34.5 (overlapping C-12, C-14 and C-16), 52.5 (C-2), 53.9 (C-5), 56.0 (C-9), 64.3 (C-6), 74.2 (C-7), 78.6 (C-1), 126.1 (2 × Ar-CH), 126.5 (2 × Ar-CH), 126.6 (2 × Ar-CH), 126.7 (2 × Ar-CH), 126.8 (2 × Ar-CH), 128.0 (Ar-C), 130.0 (2 × Ar-CH), 137.6 (Ar-C), 140.8 (Ar-C), 148.2 (Ar-C), 148.3 (Ar-C), 154.8 (Ar-C), 165.9 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{39}H_{53}NO_4SNa$ $[M + Na]^+$: 654.3588, found 654.3584.

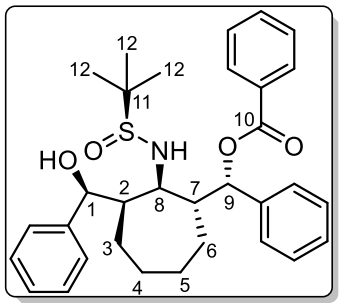
6.7.2 Synthesis of cycloheptanone derived 3-amino-1,5-diol precursors

To a Schlenk tube under N_2 atmosphere, containing diisopropylamine (1.2 equiv.) in anhydrous THF (5 mL per mmol of sulfinyl imine), was added *n*-BuLi (1.1 equiv.) at 0 °C. The mixture was allowed to stir at 0 °C for 20 min to generate a solution of LDA. ***Tert*-butanesulfinyl imine** (1.0 equiv.) was carefully weighed out and pre-dissolved in 1.0 mL of dry THF. The solution of **sulfinyl imine** was then slowly added to the LDA solution at 0 °C. After the reaction mixture was allowed to stir for 1 h at 0 °C, the solution was cooled to -78 °C and freshly distilled **aldehyde** (3.3 equiv.) was added slowly (neat), dropwise. Solid aldehydes were pre-dissolved in 1.0 mL of dry THF. The reaction mixture was kept at -78 °C for 3 h and allowed warm to -20 °C over 16 h.

Work-up conditions as per 1 mmol of sulfinyl imine

The reaction mixture was quenched with sat. aq. NH_4Cl solution (1.5 mL) at -20 °C. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was purified using column chromatography on silica gel.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(phenyl)methyl)cycloheptyl)(phenyl)methyl benzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-294



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-294** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and benzaldehyde (0.34 mL, 3.3 mmol). The crude compound (>90:4:2:2:2 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-294** as a sticky colourless oil (0.390 g, 73% mixture of diastereomers).

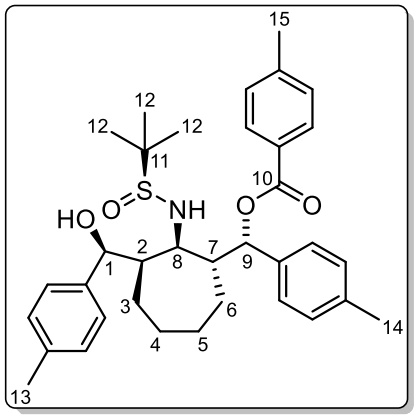
Major diastereomer: $[\alpha]_D^{20}$ + 81.60 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 2928 (C-H stretch), 1721 (C=O stretch), 1268 (C-O stretch), 1107 (C-N stretch), 1042 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96-1.51 (3H, m, one of each H-3, H-4 and H-5), 1.33 (9H, s, H-12), 1.52-1.77 (4H, m, one of each H-3, H-4, H-5 and H-6), 1.78-1.93 (1H, m, one of H-6), 2.00-2.09 (1H, m, H-2), 2.19-2.33 (1H, m, H-7), 3.75-3.88 (1H, m, H-8), 4.23 (1H, d, *J* = 5.4 Hz, O-H), 4.58 (1H, d, *J* = 5.7 Hz, N-H), 4.94 (1H, d, *J* = 5.2 Hz, H-1), 6.26 (1H, d, *J* = 4.3 Hz, H-9),

7.15-7.41 (10H, m, Ar-H), 7.46-7.55 (2H, m, Ar-H), 7.57-7.66 (1H, m, Ar-H), 8.12-8.20 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.6 (C-3), 23.1 (C-12), 25.1 (C-6), 27.6, 29.6 (C-4 and C-5), 47.5 (C-2), 52.9 (C-7), 56.4 (C-11), 62.2 (C-8), 76.3 (C-1), 76.8 (C-9), 125.8 (2 × Ar-CH), 126.1 (2 × Ar-CH), 126.7 (Ar-CH), 127.9 (Ar-CH), 128.1 (2 × Ar-CH), 128.7 (2 × Ar-CH), 128.7 (2 × Ar-CH), 129.9 (2 × Ar-CH), 130.3 (Ar-C), 133.4 (Ar-CH), 139.6 (Ar-C), 144.3 (Ar-C), 165.7 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{39}NO_4SNa$ $[M + Na]^+$: 556.2492, found 556.2494.

Note: Utilising 0.8 equivalents of LDA and warming the reaction mixture to -15 °C over a period of 24 h afforded **(*S*,*R*,*S*,*R*,*R*,*S*)-294** in an improved yield of 80%.

COSY, HSQC and HMBC were used to aid in assignment.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(*p*-tolyl)methyl)cycloheptyl)(*p*-tolyl)methyl 4-methylbenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-295

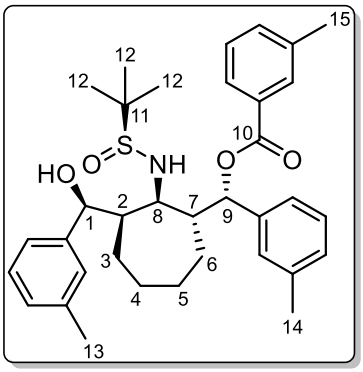


Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-295** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-tolualdehyde (0.39 mL, 3.3 mmol). The crude compound (95:3:2 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-295** as a sticky yellow oil (0.355 g, 62% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 93.2 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3138 (O-H stretch), 2925 (C-H stretch), 1719 (C=O stretch), 1270 (C-O stretch), 1178 (C-O stretch), 1102 (C-N stretch), 1043 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98-1.13 (2H, m, one of each H-4 and H-5), 1.31 (9H, s, H-12), 1.38-1.76 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.78-1.91 (1H, m, one of H-6), 1.92-2.02 (1H, m, H-2), 2.23-2.38 (1H, m, H-7), 2.31, 2.33, 2.43 (3 × 3H, s, H-13, H-14 and H-15), 3.74-3.85 (1H, m, H-8), 4.16 (1H, *br* s, O-H), 4.61 (1H, d, *J* = 5.1 Hz, N-H), 4.87 (1H, s, H-1), 6.16 (1H, d, *J* = 4.7 Hz, H-9), 7.01-8.08 (10H, m, Ar-H), 7.99-8.08 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (C-3), 21.1, 21.2, 21.8 (C-13, C-14 and C-15), 23.0 (C-12), 25.4 (C-6), 27.1, 29.4 (C-4 and C-5), 47.3 (C-2), 52.3 (C-7), 56.2 (C-11), 61.8 (C-8), 76.5 (C-1), 76.6 (C-9), 125.6 (2 × Ar-CH), 126.1 (2 × Ar-CH), 127.7 (Ar-C), 128.8 (2 × Ar-CH), 129.3 (2 × Ar-CH), 129.4 (2 × Ar-CH), 130.0 (2 × Ar-CH), 136.1 (Ar-C), 136.6 (Ar-C), 137.5 (Ar-C), 141.3 (Ar-C), 143.9

(Ar-C), 165.6 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{44}NO_4S$ [M - H]$^-$: 574.2991, found 574.2988.

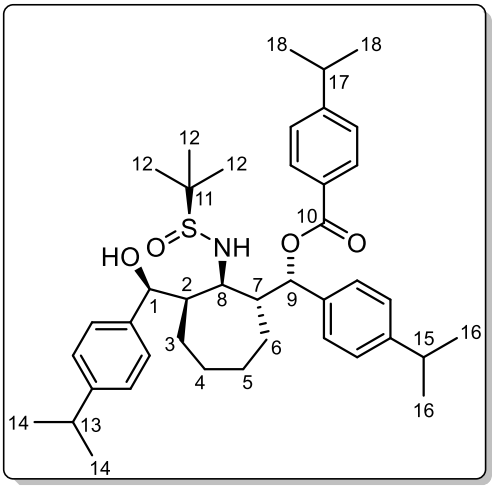
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(m-tolyl)methyl)cycloheptyl)(m-tolyl)methyl 3-methylbenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-296



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-296** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *m*-tolualdehyde (0.39 mL, 3.3 mmol). The crude compound (94:3:3 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-296** as a white foamy solid (0.435 g, 76% mixture of diastereomers).

Major diastereomer: m.p. 81-86 ºC. $[\alpha]_D^{20}$ + 85.20 (c 0.25, $CHCl_3$). IR v_{max} (NaCl): 3327 (O-H stretch), 2926 (C-H stretch), 1718 (C=O stretch), 1275 (C-O stretch), 1105 (C-N stretch), 1042 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01-1.35 (2H, m, one of each H-4 and H-5), 1.32 (9H, s, H-12), 1.39-1.77 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.79-1.93 (1H, m, one of H-6), 1.94-2.03 (1H, m, H-2), 2.32, 2.36, 2.44 (3 × 3H, s, H-13, H-14 and H-15), 2.24-2.41 (1H, m, H-7), 3.77-3.85 (1H, m, H-8), 4.17 (1H, d, *J* = 5.5 Hz, O-H), 4.59 (1H, d, *J* = 5.3 Hz, N-H), 4.87 (1H, d, *J* = 5.3 Hz, H-1), 6.18 (1H, d, *J* = 4.7 Hz, H-9), 6.96-7.06 (3H, m, Ar-H), 7.07-7.20 (4H, m, Ar-H), 7.22-7.30 (1H, m, Ar-H), 7.33-7.45 (2H, m, Ar-H), 7.92-7.99 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (C-3), 21.5, 21.6, 21.7 (C-13, C-14 and C-15), 23.1 (C-12), 25.4 (C-6), 27.1, 29.4 (C-4 and C-5), 47.2 (C-2), 52.3 (C-7), 56.3 (C-11), 61.8 (C-8), 76.7 (C-1), 76.9 (C-9), 122.7 (Ar-CH), 123.3 (Ar-CH), 126.4 (Ar-CH), 127.0 (Ar-CH), 127.0 (Ar-CH), 127.4 (Ar-CH), 128.0 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 130.3 (Ar-C), 130.5 (Ar-CH), 134.1 (Ar-CH), 137.6 (Ar-C), 138.3 (Ar-C), 138.4 (Ar-C), 139.5 (Ar-C), 144.2 (Ar-C), 165.9 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{46}NO_4S$ [M + H]$^+$: 576.3148, found 576.3147.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-isopropylphenyl)methyl)cycloheptyl)(4-isopropylphenyl)methyl 4-isopropylbenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-297



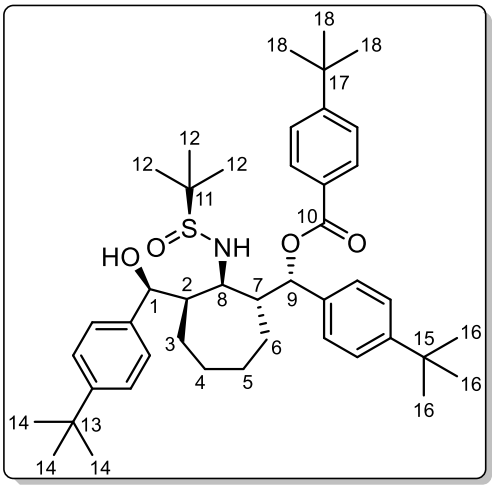
Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-297** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p-iso*-propyl benzaldehyde (0.50 mL, 3.3 mmol). The crude compound (<91:4:3:2 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-297** as a pale yellow foamy solid (0.463 g, 70% mixture of diastereomers).

Major diastereomer: m.p. 83-87 °C. $[\alpha]_D^{20}$ + 82.40 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3226 (O-H stretch), 2960 (C-H stretch), 1719 (C=O stretch), 1270 (C-O stretch), 1104 (C-N stretch), 1052 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.00-1.36 (2H, m, one of each H-4 and H-5), 1.23, 1.30 (3 × 6H, d, *J* = 6.9 Hz (overlapping 2 × 6H, d and 1 × 6H, d) H-14, H-16 and H-18), 1.31 (9H, s, H-12), 1.41-1.79 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.80-1.93 (1H, m, one of H-6), 1.94-2.05 (1H, m, H-2), 2.24-2.39 (1H, m, H-7), 2.88, 3.00 (3 × 1H, sept, *J* = 6.9 Hz (overlapping 2 × 1H, sept and 1H, sept) H-13, H-15 and H-17), 3.79-3.89 (1H, m, H-8), 4.10 (1H, *br* s, O-H), 4.61 (1H, d, *J* = 5.3 Hz, N-H), 4.88 (1H, d, *J* = 1.0 Hz, H-1), 6.19 (1H, d, *J* = 4.5 Hz, H-9), 7.08-7.15 (4H, m, Ar-H), 7.16-7.30 (4H, m, Ar-H), 7.31-7.39 (2H, m, Ar-H), 8.04-8.13 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.5 (C-3), 23.1 (C-12), 23.9, 24.0, 24.1 (C-14, C-16 and C-18), 25.6 (C-6), 27.2, 29.5 (C-4 and C-5), 33.8, 33.9, 34.5 (C-13, C-15 and C-17), 47.1 (C-2), 52.2 (C-7), 56.3 (C-11), 61.8 (C-8), 76.6 (C-1), 76.7 (C-9), 125.7 (2 × Ar-CH), 126.1 (2 × Ar-CH), 126.2 (2 × Ar-CH), 126.7 (4 × Ar-CH), 128.1 (Ar-C), 130.2 (2 × Ar-CH), 136.8 (Ar-C), 141.6 (Ar-C), 147.1 (Ar-C), 148.4 (Ar-C), 154.7 (Ar-C), 165.7 (C-10) ppm.HRMS (ESI) *m*/*z* calcd for $C_{41}H_{57}NO_4SNa$ $[M + Na]^+$: 682.3901, found 682.3885.

Note: Only partial separation of diastereomers could be achieved.

(*R*)-(4-(*Tert*-butyl)phenyl)((1*R*,2*R*,3*R*)-3-((*S*)-(4-(*tert*-butyl)phenyl)(hydroxy)methyl)-2-(((*S*)-*tert*-butylsulfinyl)amino)cycloheptyl)methyl 4-(*tert*-butyl)benzoate,

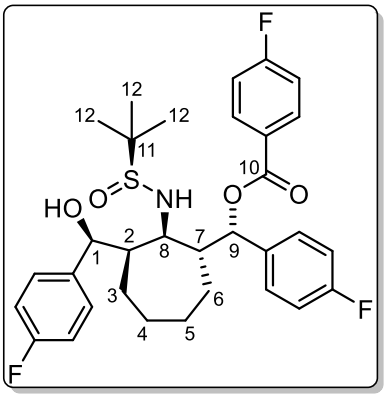
(*S*,*R*,*S*,*R*,*R*,*S*)-298



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-298** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p-tert*-butylbenzaldehyde (0.55 mL, 3.3 mmol). The crude compound (97:2:1 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-298** as a pale yellow solid (0.414 g, 59% mixture of diastereomers).

Major diastereomer: m.p. 109-113 °C. $[\alpha]_D^{20}$ + 62.55 (c 0.275, $CHCl_3$). IR ν_{max} (NaCl): 3223 (O-H stretch), 2962 (C-H stretch), 1721 (C=O stretch), 1270 (C-O stretch), 1114 (C-N stretch), 1043 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.02-1.41 (2H, m, one of each H-4 and H-5), 1.30, 1.37 (overlapping 4 × 9H, s, H-12, H-14, H-16 and H-18), 1.47-1.77 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.79-1.94 (1H, m, one of H-6), 1.97-2.06 (1H, m, H-2), 2.26-2.40 (1H, m, H-7), 3.82-3.89 (1H, m, H-8), 4.12 (1H, d, *J* = 5.3 Hz, O-H), 4.59 (1H, d, *J* = 5.2 Hz, N-H), 4.88 (1H, d, *J* = 4.8 Hz, H-1), 6.20 (1H, d, *J* = 4.4 Hz, H-9), 7.06-7.18 (2H, m, Ar-H), 7.19-7.42 (6H, m, Ar-H), 7.47-7.57 (2H, m, Ar-H), 8.07-8.13 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C-3), 23.0 (C-12), 25.6 (C-6), 27.1, 29.5 (C-4 and C-5), 31.3, 31.4, 31.5 (C-14, C-16 and C-18), 34.5, 34.6, 35.2 (C-13, C-15 and C-17), 47.0 (C-2), 52.0 (C-7), 56.2 (C-11), 61.8 (C-8), 76.6 (C-1), 76.8 (C-9), 124.9 (2 × Ar-CH), 125.4 (2 × Ar-CH), 125.5 (2 × Ar-CH), 125.6 (2 × Ar-CH), 125.9 (2 × Ar-CH), 127.6 (Ar-C), 129.8 (2 × Ar-CH), 136.5 (Ar-C), 141.2 (Ar-C), 149.3 (Ar-C), 150.6 (Ar-C), 156.9 (Ar-C), 165.7 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{44}H_{63}NO_4SNa$ $[M + Na]^+$: 724.4370, found 724.4367.

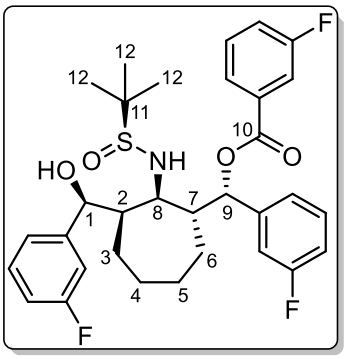
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-(4-fluorophenyl)(hydroxy)methyl)cycloheptyl)(4-fluorophenyl)methyl 4-fluorobenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-299



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-299** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-fluorobenzaldehyde (0.35 mL, 3.3 mmol). The crude compound (>98:2 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-299** as a white foamy solid (0.386 g, 66% mixture of diastereomers).

Major diastereomer: m.p. 71-76 °C. $[\alpha]_D^{20}$ + 90.00 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3222 (O-H stretch), 2931 (C-H stretch), 1723 (C=O stretch), 1268 (C-O stretch), 1090 (C-N stretch), 1040 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.87-1.28 (2H, m, one of each H-4 and H-5), 1.25 (9H, s, H-12), 1.30-1.69 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.71-1.94 (2H, m, H-2 and one of H-6), 2.11-2.22 (1H, m, H-7), 3.64-3.71 (1H, m, H-8), 4.27 (1H, d, *J* = 5.5 Hz, O-H), 4.57 (1H, d, *J* = 5.4 Hz, H-1), 4.83 (1H, d, *J* = 5.2 Hz, N-H), 6.12 (1H, d, *J* = 4.3 Hz, H-9), 6.81-7.04 (4H, m, Ar-H), 7.04-7.16 (4H, m, Ar-H), 7.16-7.28 (2H, m, Ar-H), 8.01-8.13 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.8 (C-3), 23.1 (C-12), 25.1 (C-6), 27.4, 29.6 (C-4 and C-5), 47.5 (C-2), 52.5 (C-7), 56.5 (C-11), 61.6 (C-8), 75.8 (C-1), 76.4 (C-9), 114.9 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, 2 × Ar-CH), 115.8 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, 2 × Ar-CH), 115.9 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, 2 × Ar-CH), 126.3 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, Ar-C), 127.3 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 × Ar-CH), 127.8 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, 2 × Ar-CH), 132.5 (d, $^3J_{C\text{-}F}$ = 9.4 Hz, 2 × Ar-CH), 135.2 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, Ar-C), 139.9 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, Ar-C), 161.8 (d, $^1J_{C\text{-}F}$ = 244.9 Hz, Ar-C), 162.4 ($^1J_{C\text{-}F}$ = 246.6 Hz, Ar-C), 166.2 (d, $^1J_{C\text{-}F}$ = 254.9 Hz, Ar-C), 164.6 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{35}F_3NO_4S$ $[M - H]^-$: 586.2239, found 586.2244. Absolute stereochemistry was assigned by crystallographic data **(Appendix II)**.

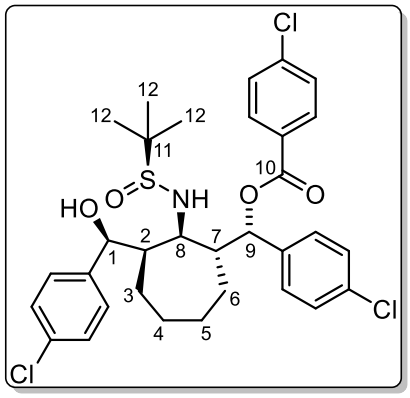
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-(3-fluorophenyl)(hydroxy)methyl)cycloheptyl)(3-fluorophenyl)methyl 3-fluorobenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-300



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-300** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *m*-fluorobenzaldehyde (0.35 mL, 3.3 mmol). The crude compound (>97:3 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-300** as a white foamy solid (0.431 g, 73% mixture of diastereomers).

Major diastereomer: m.p. 77-82 °C. $[\alpha]_D^{20}$ + 76.92 (c 0.26, $CHCl_3$). IR v_{max} (NaCl): 3139 (O-H stretch), 2931 (C-H stretch), 1727 (C=O stretch), 1270 (C-O stretch), 1042 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.93-1.25 (2H, m, one of each H-4 and H-5), 1.34 (9H, s, H-12), 1.39-1.87 (6H, m, H-3 and H-6 and one of each H-4 and H-5), 1.96-2.06 (1H, m, H-2), 2.12-2.23 (1H, m, H-7), 3.70-3.81 (1H, m, H-8), 4.56 (1H, d, *J* = 5.7 Hz, O-H), 4.63 (1H, d, *J* = 6.0 Hz, N-H), 4.96 (1H, d, *J* = 5.6 Hz, H-1), 6.25 (1H, d, *J* = 3.4 Hz, H-9), 6.82-6.92 (1H, m, Ar-H), 6.93-7.05 (4H, m, Ar-H), 7.06-7.11 (1H, m, Ar-H), 7.18-7.25 (1H, m, Ar-H), 7.29-7.37 (2H, m, Ar-H), 7.49 (1H, dt, *J* = 8.1, 5.6 Hz, Ar-H), 7.82 (1H, ddd, *J* = 9.2, 2.6, 1.5 Hz, Ar-H), 7.95 (1H, dt, *J* = 7.7, 1.2 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C-3), 23.1 (C-12), 24.8 (C-6), 28.2, 29.7 (C-4 and C-5), 47.8 (C-2), 53.4 (C-7), 56.6 (C-11), 62.3 (C-8), 75.4 (C-1), 76.4 (C-9), 112.9 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, Ar-CH), 113.2 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, Ar-CH), 113.5 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, Ar-CH), 114.9 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, Ar-CH), 116.8 (d, $^2J_{C\text{-}F}$ = 23.0 Hz, Ar-CH), 120.7 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, Ar-CH), 121.3 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, Ar-CH), 121.5 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, Ar-CH), 125.7 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, Ar-CH), 129.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, Ar-CH), 130.4 (d, $^3J_{C\text{-}F}$ = 8.1 Hz, Ar-CH), 130.5 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, Ar-CH), 132.0 (d, $^3J_{C\text{-}F}$ = 7.4 Hz, Ar-C), 142.2 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, Ar-C), 147.2 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, Ar-C), 162.8 (d, $^1J_{C\text{-}F}$ = 250 Hz, Ar-C), 163.0 (d, $^1J_{C\text{-}F}$ = 245 Hz, Ar-C), 163.1 (d, $^1J_{C\text{-}F}$ = 246.7 Hz, Ar-C), 164.5 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{36}F_3NO_4SNa$ $[M + Na]^+$: 610.2209, found 610.2213.

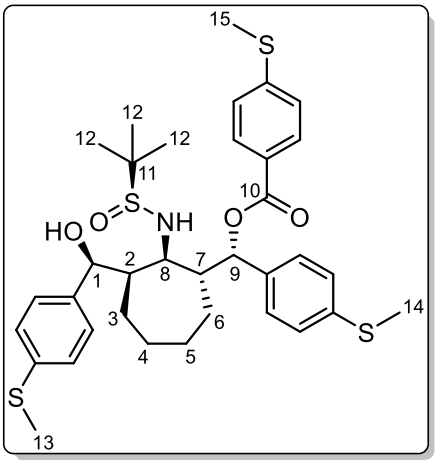
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-(4-chlorophenyl)(hydroxy)methyl)cycloheptyl)(4-chlorophenyl)methyl 4-chlorobenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-301



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-301** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-chlorobenzaldehyde (0.464 g, 3.3 mmol). The crude compound (98:2 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-301** as a sticky colourless oil (0.391 g, 61% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 124.00 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3228 (O-H stretch), 2928 (C-H stretch), 1722 (C=O stretch), 1268 (C-O stretch), 1092 (C-N stretch), 1041 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82-1.23 (2H, m, one of each H-4 and H-5), 1.32 (9H, s, H-12), 1.36-1.76 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.77-1.92 (2H, m, one of H-6 and H-2), 2.14-2.26 (1H, m, H-7), 3.70-3.81 (1H, m, H-8), 4.43 (1H, d, *J* = 5.6 Hz, O-H), 4.62 (1H, d, *J* = 5.6 Hz, N-H), 4.89 (1H, d, *J* = 5.4 Hz, H-1), 6.18 (1H, d, *J* = 3.6 Hz, H-9), 7.09-7.17 (2H, m, Ar-H), 7.19-7.38 (6H, m, Ar-H), 7.43-7.52 (2H, m, Ar-H), 8.02-8.13 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (C-3), 23.1 (C-12), 25.3 (C-6), 27.7, 29.7 (C-4 and C-5), 47.5 (C-2), 52.7 (C-7), 56.5 (C-11), 61.7 (C-8), 75.7 (C-1), 76.4 (C-9), 127.2 (2 × Ar-CH), 127.4 (2 × Ar-CH), 128.3 (2 × Ar-CH), 128.4 (Ar-C), 129.0 (2 × Ar-CH), 129.1 (2 × Ar-CH), 131.3 (2 × Ar-CH), 132.4 (Ar-C), 133.9 (Ar-C), 137.9 (Ar-C), 140.1 (Ar-C), 142.7 (Ar-C), 164.8 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{36}Cl_3NO_4SNa$ $[M + Na]^+$: 658.1322, found 658.1311.

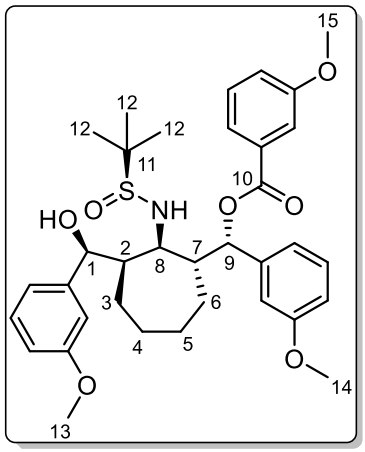
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-(methylthio)phenyl)methyl)cycloheptyl)(4-(methylthio)phenyl)methyl 4-(methylthio)benzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-302



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-302** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.140 g, 0.65 mmol) and *p*-thiomethoxybenzaldehyde (0.29 mL, 2.15 mmol). The crude compound (96:4 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-302** as a sticky colourless oil (0.203 g, 46% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 166.00 (c 0.1, $CHCl_3$). IR ν_{max} (NaCl): 3234 (O-H stretch), 2922 (C-H stretch), 1715 (C=O stretch), 1268 (C-O stretch), 1105 (C-N stretch), 1040 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.97-1.27 (2H, m, one of each H-4 and H-5), 1.31 (9H, s, H-12), 1.38-1.77 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.78-1.98 (2H, m, one of H-6 and H-2), 2.20-2.36 (1H, m, H-7), 2.48, 2.55 (3 × 3H, s (overlapping 2 × 3H, s and 1 × 3H, s) H-13, H-14 and H-15), 3.76-3.85 (1H, m, H-8), 4.30 (1H, d, *J* = 5.3 Hz, O-H), 4.63 (1H, d, *J* = 5.2 Hz, N-H), 4.90 (1H, d, *J* = 4.4 Hz, H-1), 6.12 (1H, d, *J* = 4.1 Hz, H-9), 7.07-7.41 (10H, m, Ar-H), 8.01-8.11 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 15.0, 15.8, 16.1 (C-13, C-14 and C-15), 20.9 (C-3), 23.0 (C-12), 25.5 (C-6), 27.3, 29.6 (C-4 and C-5), 47.3 (C-2), 52.3 (C-7), 56.3 (C-11), 62.0 (C-8), 76.2 (C-1), 76.5 (C-9), 125.2 (2 × Ar-CH), 126.2 (Ar-C), 126.3 (2 × Ar-CH), 126.5 (2 × Ar-CH), 126.6 (2 × Ar-CH), 126.7 (2 × Ar-CH), 130.2 (2 × Ar-CH), 136.3 (2 × Ar-C), 138.2 (Ar-C), 141.3 (Ar-C), 146.1 (Ar-C), 165.4 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{45}NO_4S_4Na$ $[M + Na]^+$: 694.2124, found 694.2121.

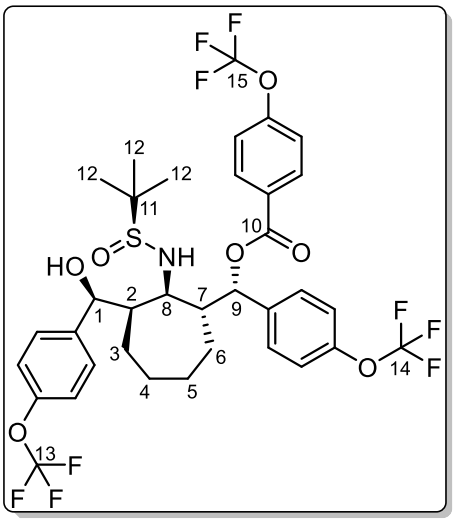
(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-methoxyphenyl)methyl)cycloheptyl)(4-methoxyphenyl)methyl 4-methoxybenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-303



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-303** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.140 g, 0.65 mmol) and *m*-methoxybenzaldehyde (0.26 mL, 2.15 mmol). The crude compound (98:2 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-303** as a sticky colourless oil (0.146 g, 36% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 74.32 (c 0.41, $CHCl_3$). IR ν_{max} (NaCl): 3391 (O-H stretch), 2932 (C-H stretch), 1719 (C=O stretch), 1275 (C-O stretch), 1103 (C-N stretch), 1042 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.03-1.24 (2H, m, one of each H-4 and H-5), 1.33 (9H, s, H-12), 1.45-1.78 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.79-1.92 (1H, m, one of H-6), 2.00-2.09 (1H, m, H-2), 2.15-2.29 (1H, m, H-7), 3.74-3.83 (1H, m, H-8), 3.77, 3.78, 3.87 (3 × 3H, s, H-13, H-14 and H-15), 4.33 (1H, d, *J* = 5.5 Hz, O-H), 4.60 (1H, d, *J* = 5.8 Hz, N-H), 4.93 (1H, d, *J* = 4.7 Hz, H-1), 6.21 (1H, d, *J* = 4.0 Hz, H-9), 6.70-6.75 (1H, m, Ar-H), 6.76-6.85 (2H, m, Ar-H), 6.86-6.95 (3H, m, Ar-H), 7.12-7.21 (2H, m, Ar-H), 7.24-7.32 (1H, m, Ar-H), 7.36-7.45 (1H, m, Ar-H), 7.65 (1H, dd, *J* = 2.5, 1.5 Hz, Ar-H), 7.76 (1H, td, *J* = 7.8, 1.3 Hz, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (C-3), 23.1 (C-12), 25.0 (C-6), 27.8, 29.6 (C-4 and C-5), 47.6 (C-2), 53.0 (C-7), 55.3, 55.6 (overlapping C-13, C-14 and C-15), 56.4 (C-11), 62.2 (C-8), 76.1 (C-1), 76.7 (C-9), 111.5 (Ar-CH), 112.2 (Ar-CH), 112.5 (2 × Ar-CH), 114.6 (Ar-CH), 118.1 (Ar-CH), 118.4 (Ar-CH), 119.6 (Ar-CH), 122.2 (Ar-CH), 129.0 (Ar-CH), 129.7 (Ar-CH), 129.8 (Ar-CH), 131.5 (Ar-C), 141.3 (Ar-C), 146.1 (Ar-C), 159.6 (Ar-C), 159.8 (2 × Ar-C), 165.6 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{46}NO_7S$ $[M + H]^+$: 624.2990, found 624.2990.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-(trifluoromethoxy)phenyl)methyl)cycloheptyl)(4-(trifluoromethoxy)phenyl)methyl 4-(trifluoromethoxy)benzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-304

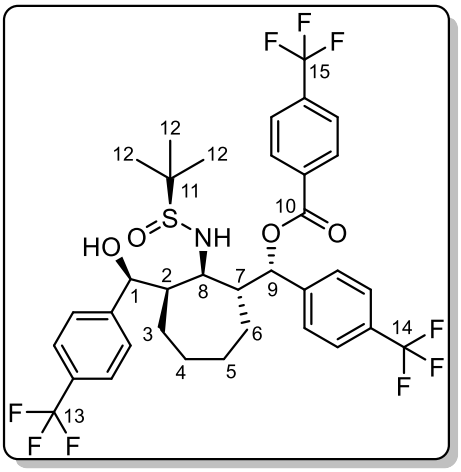


Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-304** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-trifluoromethoxybenzaldehyde (0.47 mL, 3.3 mmol). The crude compound (97:3 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-304** as a white foamy solid (0.552 g, 70% mixture of diastereomers).

Major diastereomer: m.p. 59-64 ^{o}C. $[\alpha]_D^{20}$ + 71.60 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3326 (O-H stretch), 2932 (C-H stretch), 1726 (C=O stretch), 1261 (C-O stretch), 1040 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92-1.25 (2H, m, one of each H-4 and H-5), 1.33 (9H, s, H-12), 1.41-1.79 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.79-1.97 (2H, m, one of H-6 and H-2), 2.14-2.30 (1H, m, H-7), 3.74-3.85 (1H, m, H-8), 4.48 (1H, d, *J* = 5.6 Hz, O-H), 4.64 (1H, d, *J* = 5.6 Hz, N-H), 4.96 (1H, d, *J* = 5.2 Hz, H-1), 6.25 (1H, d, *J* = 3.6 Hz, H-9), 7.07-7.15 (2H, m, Ar-H), 7.16-7.28 (4H, m, Ar-H), 7.29-7.39 (4H, m, Ar-H), 8.17-8.24 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.0 (C-3), 23.1 (C-12), 25.2 (C-6), 28.0, 29.8 (C-4 and C-5), 47.7 (C-2), 53.1 (C-7), 56.6 (C-11), 62.0 (C-8), 75.6 (C-1), 76.4 (C-9), 120.5, 120.6 (q, $^1J_{C\text{-}F}$ = 258.8 Hz and overlapping 2 × q, $^1J_{C\text{-}F}$ = 257.2, 257.6 Hz, C-13, C-14 and C-15), 120.6 (2 × Ar-CH), 120.7 (2 × Ar-CH), 121.2 (2 × Ar-CH), 127.1 (2 × Ar-CH), 127.4 (2 × Ar-CH), 128.3 (Ar-C), 132.0 (2 × Ar-CH), 138.1 (Ar-C), 142.9 (Ar-C), 148.1 (d, $^3J_{C\text{-}F}$ = 2.1 Hz, Ar-C), 148.9 (d, $^3J_{C\text{-}F}$ = 2.1 Hz, Ar-C), 153.2 (d, $^3J_{C\text{-}F}$ = 1.7 Hz, Ar-C), 164.5 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{36}F_9NO_7SNa$ $[M + Na]^+$: 808.1961, found 808.1962.

Absolute stereochemistry was assigned by crystallographic data **(Appendix II)**.

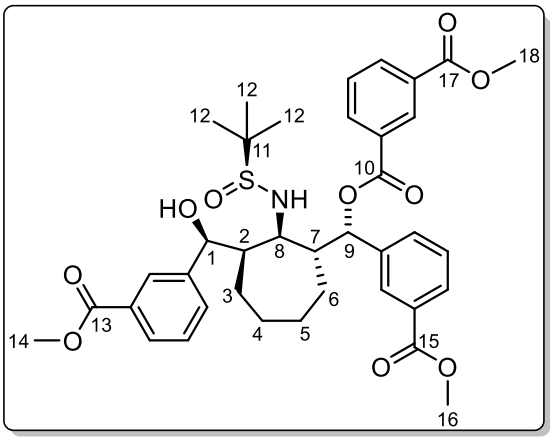
(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-(trifluoromethyl)phenyl)methyl)cycloheptyl)(4-(trifluoromethyl)phenyl)methyl 4-(trifluoromethyl)benzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-305



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-305** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-trifluoromethylbenzaldehyde (0.45 mL, 3.3 mmol). The crude compound (93:4:3 *dr*) was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-305** as a sticky colourless oil (0.322 g, 44% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 76.95 (c 0.18, $CHCl_3$). IR ν_{max} (NaCl): 3366 (O-H stretch), 2951 (C-H stretch), 1723 (C=O stretch), 1280 (C-O stretch), 1107 (C-N stretch), 1038 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.22 (2H, m, one of each H-4 and H-5), 1.36 (9H, s, H-12), 1.48-1.91 (6H, m, H-3 and H-6 and one of each H-4 and H-5), 1.92-1.99 (1H, m, H-2), 2.15-2.29 (1H, m, H-7), 3.79-3.89 (1H, m, H-8), 4.54 (1H, d, *J* = 5.8 Hz, O-H), 4.67 (1H, d, *J* = 6.0 Hz, N-H), 5.02 (1H, d, *J* = 5.7 Hz, H-1), 6.33 (1H, d, *J* = 2.7 Hz, H-9), 7.29-7.37 (2H, m, Ar-H), 7.39-7.47 (2H, m, Ar-H), 7.48-7.56 (2H, m, Ar-H), 7.61-7.69 (2H, m, Ar-H), 7.76-7.85 (2H, m, Ar-H), 8.25-8.33 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (C-3), 23.1 (C-12), 25.1 (C-6), 28.4, 29.9 (C-4 and C-5), 47.8 (C-2), 53.5 (C-7), 56.8 (C-11), 62.2 (C-8), 75.5 (C-1), 76.7 (C-9), 123.7, 124.0, 124.3 (q, $^1J_{C\text{-}F}$ = 273.1, 272.2, 272.6 Hz, C-13, C-14 and C-15), 125.1 (q, $^3J_{C\text{-}F}$ = 3.8 Hz, 2 × Ar-CH), 125.9 (q, $^3J_{C\text{-}F}$ = 3.5 Hz, 4 × Ar-CH), 126.1 (2 × Ar-CH), 126.2 (2 × Ar-CH), 129.1 (q, $^2J_{C\text{-}F}$ = 32.9 Hz, Ar-C), 130.3 (q, $^2J_{C\text{-}F}$ = 32.2 Hz, Ar-C), 130.4 (2 × Ar-CH), 133.2 (Ar-C), 135.3 (q, $^2J_{C\text{-}F}$ = 32.7 Hz, Ar-C), 144.6 (Ar-C), 149.6 (Ar-C), 164.4 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{37}F_9NO_4S$ $[M + H]^+$: 738.2294, found 738.2305.

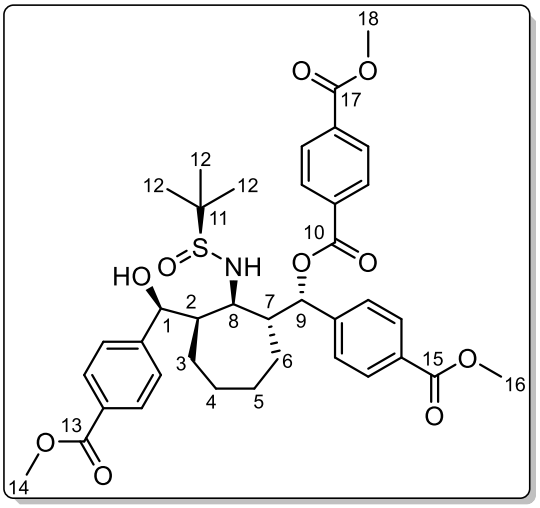
(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(3-(methoxycarbonyl)phenyl)methyl)cycloheptyl)(3-(methoxycarbonyl)phenyl)methyl methyl isophthalate, (*S*,*R*,*S*,*R*,*R*,*S*)-306



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-306** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and methyl 3-formylbenzoate (0.542 g, 3.3 mmol). The crude compound (97:3 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-306** as a sticky colourless oil (0.377 g, 53% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 97.20 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3308 (O-H stretch), 2951 (C-H stretch), 1725 (C=O stretch), 1287 (C-O stretch), 1094 (C-N stretch), 1039 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90-1.22 (2H, m, one of each H-4 and H-5), 1.38 (9H, s, H-12), 1.41-1.77 (5H, m, H-3 and one of each H-4, H-5 and H-6), 1.78-1.91 (1H, m, one of H-6), 2.02-2.13 (1H, m, H-2), 2.16-2.28 (1H, m, H-7), 3.74-3.83 (1H, m, H-8), 3.91, 3.98 (3 × 3H, s (overlapping 2 × 3H, s and 1 × 3H, s) H-14, H-16 and H-18), 4.51 (1H, d, *J* = 5.8 Hz, O-H), 4.62 (1H, d, *J* = 6.3 Hz, N-H), 5.03 (1H, d, *J* = 5.9 Hz, H-1), 6.35 (1H, d, *J* = 3.8 Hz, H-9), 7.33-7.40 (1H, m, Ar-H), 7.43-7.51 (2H, m, Ar-H), 7.52-7.57 (1H, m, Ar-H), 7.59-7.66 (1H, m, Ar-H), 7.89 (1H, dt, *J* = 7.7, 1.4 Hz, Ar-H), 7.93-8.06 (3H, m, Ar-H), 8.30 (1H, dt, *J* = 7.8, 1.6 Hz, Ar-H), 8.35 (1H, dt, *J* = 7.8, 1.6 Hz, Ar-H), 8.77-8.80 (1H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.9 (C-3), 23.1 (C-12), 24.4 (C-6), 28.2, 29.6 (C-4 and C-5), 47.7 (C-2), 52.2, 52.4, 52.6 (C-14, C-16 and C-18), 53.6 (C-7), 56.7 (C-11), 62.5 (C-8), 75.5 (C-1), 76.4 (C-9), 126.9 (Ar-CH), 127.2 (Ar-CH), 128.1 (Ar-CH), 128.3 (Ar-CH), 129.0 (Ar-CH), 129.1 (Ar-CH), 129.2 (Ar-CH), 130.1 (Ar-C), 130.4 (Ar-CH), 130.4 (Ar-C), 130.6 (Ar-CH), 130.8 (Ar-C), 131.0 (Ar-C), 131.1 (Ar-CH), 134.1 (Ar-CH), 134.4 (Ar-CH), 140.1 (Ar-C), 144.7 (Ar-C), 164.9 (C-10), 166.2, 166.8, 167.4 (C-13, C-15 and C-17) ppm. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{46}NO_{10}S$ $[M + H]^+$: 708.2837, found 708.2841.

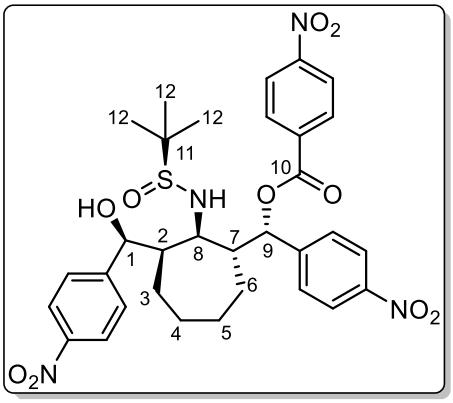
(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-(methoxycarbonyl)phenyl)methyl)cycloheptyl)(4-(methoxycarbonyl)phenyl)methyl methyl terephthalate, (*S*,*R*,*S*,*R*,*R*,*S*)-307



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-307** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and methyl 4-formylbenzoate (0.542 g, 3.3 mmol). The crude compound (98:2 *dr*) was purified using column chromatography on silica gel (1:1, hexane: EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-307** as a sticky colourless oil (0.359 g, 51% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 129.40 (c 0.28, $CHCl_3$). IR ν_{max} (NaCl): 3366 (O-H stretch), 2951 (C-H stretch), 1723 (C=O stretch), 1280 (C-O stretch), 1107 (C-N stretch), 1018 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.20 (2H, m, one of each H-4 and H-5), 1.36 (9H, s, H-12), 1.40-1.89 (6H, m, H-3 and H-6 and one of each H-4 and H-5), 1.97-2.08 (1H, m, H-2), 2.15-2.27 (1H, m, H-7), 3.77-3.95 (1H, m, H-8), 3.90, 3.91, 3.97 (3 × 3H, s, H-14, H-16 and H-18), 4.57 (1H, d, *J* = 5.8 Hz, O-H), 4.68 (1H, d, *J* = 6.1 Hz, N-H), 5.03 (1H, d, *J* = 5.6 Hz, H-1), 6.33 (1H, d, *J* = 3.2 Hz, H-9), 7.29-7.34 (2H, m, Ar-H), 7.35-7.42 (2H, m, Ar-H), 7.91-7.98 (2H, m, Ar-H), 8.01-8.08 (2H, m, Ar-H), 8.14-8.27 (4H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (C-3), 23.1 (C-12), 24.7 (C-6), 28.3, 29.8 (C-4 and C-5), 47.8 (C-2), 52.1, 52.3, 52.7 (C-14, C-16 and C-18), 53.6 (C-7), 56.7 (C-11), 62.4 (C-8), 75.7 (C-1), 76.7 (C-9), 125.8 (4 × Ar-CH), 128.7 (Ar-C), 129.5 (2 × Ar-CH), 129.9 (2 × Ar-CH and Ar-C), 130.0 (2 × Ar-CH), 130.1 (2 × Ar-CH), 133.6 (Ar-C), 134.6 (Ar-C), 144.6 (Ar-C), 149.6 (Ar-C), 164.8 (C-10), 166.3, 166.7, 167.1 (C-13, C-15 and C-17) ppm. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{45}NO_{10}S$ $[M + Na]^+$: 730.2656, found 730.2656.

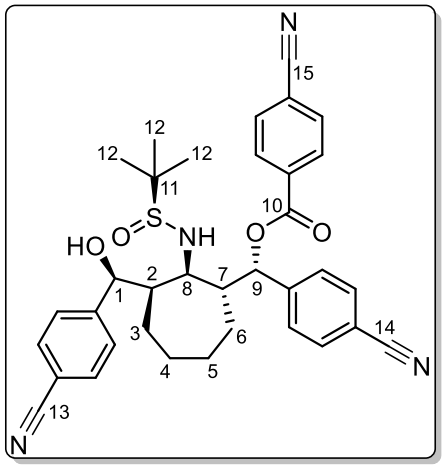
(*S*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(4-nitrophenyl)methyl)cycloheptyl)(4-nitrophenyl)methyl 4-nitrobenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-308



Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-308** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-nitrobenzaldehyde (0.499 g, 3.3 mmol). The crude compound (>95:5 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-308** as a sticky yellow oil (0.244 g, 36% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 127.20 (c 0.28, $CHCl_3$). IR ν_{max} (NaCl): 3325 (O-H stretch), 2931 (C-H stretch), 1731 (C=O stretch), 1347 (N-O stretch), 1268 (C-O stretch), 1100 (C-N stretch), 1034 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-1.17 (2H, m, one of each H-4 and H-5), 1.40 (9H, s, H-12), 1.44-1.85 (6H, m, H-3 and H-6 and one of each H-4 and H-5), 2.03-2.23 (2H, m, H-2 and H-7), 3.75-3.87 (1H, m, H-8), 4.75 (1H, d, *J* = 6.6 Hz, O-H), 4.81 (1H, d, *J* = 6.1 Hz, N-H), 5.12 (1H, d, *J* = 6.0 Hz, H-1), 6.42 (1H, d, *J* = 2.6 Hz, H-9), 7.40-7.51 (4H, m, Ar-H), 8.08-8.28 (4H, m, Ar-H), 8.31-8.42 (4H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (C-3), 23.1 (C-12), 24.1 (C-6), 29.2, 29.9 (C-4 and C-5), 48.1 (C-2), 54.4 (C-7), 57.1 (C-11), 62.7 (C-8), 74.8 (C-1), 76.3 (C-9), 123.5 (2 × Ar-CH), 123.8 (2 × Ar-CH), 124.2 (2 × Ar-CH), 126.5 (2 × Ar-CH), 126.7 (2 × Ar-CH), 131.1 (2 × Ar-CH), 134.7 (Ar-C), 146.6 (Ar-C), 147.0 (Ar-C), 147.8 (Ar-C), 151.2 (Ar-C), 151.6 (Ar-C), 164.8 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{37}N_4O_{10}S$ $[M + H]^+$: 669.2225, found 669.2227.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-(4-cyanophenyl)(hydroxy)methyl)cycloheptyl)(4-cyanophenyl)methyl 4-cyanobenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-309

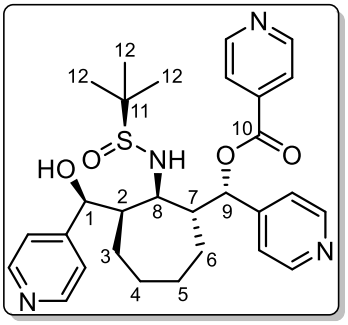


Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-309** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *p*-cyanobenzaldehyde (0.433 g, 3.3 mmol). The crude compound (98:2 *dr*) was purified using column chromatography on silica gel (2 : 1, hexane:EtOAc) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-309** as a white solid (0.217 g, 36% mixture of diastereomers).

Major diastereomer: m.p. 142-146 ºC. $[\alpha]_D^{20}$ + 133.60 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3308 (O-H stretch), 2928 (C-H stretch), 2229 (C≡N stretch), 1729 (C=O stretch), 1269 (C-O stretch), 1102 (C-N stretch), 1026 (S=O stretch) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77-1.17 (2H, m, one of each H-4 and H-5), 1.37 (9H, s, H-12), 1.45-1.82 (6H, m, H-3 and H-6 and one of each H-4 and H-5), 1.97-2.05 (1H, m, H-2), 2.07-2.17 (1H, m, H-7), 3.67-3.80 (1H, m, H-8), 4.66 (1H, d, *J* = 6.1 Hz, O-H/N-H), 4.67 (1H, d, *J* = 6.5 Hz, O-H/N-H), 5.04 (1H, d, *J* = 6.1 Hz, H-1), 6.33 (1H, d, *J* = 2.8 Hz, H-9), 7.35-7.45 (4H, m, Ar-H), 7.56-7.62 (2H, m, Ar-H), 7.63-7.70 (2H, m, Ar-H), 7.80-7.89 (2H, m, Ar-H), 8.20-8.28 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.1 (C-3), 23.1 (C-12), 24.3 (C-6), 28.9, 29.8 (C-4 and C-5), 47.9 (C-2), 54.0 (C-7), 57.0 (C-11), 62.4 (C-8), 75.0 (C-1), 76.4 (C-9), 110.7 (Ar-C), 112.2 (Ar-C), 117.4 (Ar-C), 117.8, 118.4, 119.0 (C-13, C-14 and C-15), 126.4 (2 × Ar-CH), 126.6 (2 × Ar-CH), 130.4 (2 × Ar-CH), 132.1 (2 × Ar-CH), 132.7 (4 × Ar-CH), 133.2 (Ar-C), 144.6 (Ar-C), 149.6 (Ar-C), 164.0 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{35}H_{37}N_4O_4S$ $[M + H]^+$: 609.2536, found 609.2531.

COSY and HSQC were used to aid in assignment.

(*R*)-((1*R*,2*R*,3*R*)-2-(((*S*)-*Tert*-butylsulfinyl)amino)-3-((*S*)-hydroxy(pyridin-4-yl)methyl)cycloheptyl)(pyridin-4-yl)methyl isonicotinate, (*S*,*R*,*S*,*R*,*R*,*S*)-310

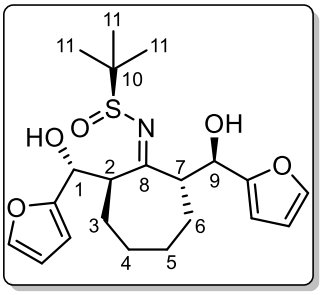


Compound **(*S*,*R*,*S*,*R*,*R*,*S*)-310** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.100 g, 0.46 mmol) and 4-pyridine carboxaldehyde (0.14 mL, 1.52 mmol). The crude compound (90:6:4 *dr*) was purified using column chromatography on silica gel (CH_2Cl_2, 5% MeOH) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-310** as a sticky colourless oil (0.110 g, 45% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 70.53 (c 0.57, $CHCl_3$). IR ν_{max} (NaCl): 3234 (O-H stretch), 2930 (C-H stretch), 1733 (C=O stretch), 1276 (C-O stretch), 1117 (C-N stretch), 1039 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.76-1.18 (2H, m, one of each H-4 and H-5), 1.37 (9H, s, H-12), 1.41-1.84 (6H, m, H-3 and H-6 and one of each H-4 and H-5), 1.94-2.06 (1H, m, H-2), 2.10-2.21 (1H, m, H-7), 3.73-3.84 (1H, m, H-8), 4.84 (1H, d, *J* = 6.1 Hz, N-H), 5.00 (1H, s, H-1), 5.18 (1H, *br* s, O-H), 6.31 (1H, d, *J* = 2.2 Hz, H-9), 7.11-7.25 (4H, m, Ar-H), 7.93-8.01 (2H, m, Ar-H), 8.33-8.72 (4H, m, Ar-H), 8.76-8.05 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.2 (C-3), 23.1 (C-12), 24.5 (C-6), 28.9, 30.0 (C-4 and C-5), 47.6 (C-2), 53.5 (C-7), 56.9 (C-8), 62.3 (C-11), 74.4 (C-1), 76.0 (C-9), 120.6 (2 × Ar-CH), 121.1 (2 × Ar-CH), 123.0 (2 × Ar-CH), 136.7 (Ar-C), 148.3 (Ar-C), 149.6 (2 × Ar-CH), 150.3 (2 × Ar-CH), 151.1 (2 × Ar-CH), 153.4 (Ar-C), 164.2 (C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{36}N_4O_4SNa$ $[M + Na]^+$: 559.2349, found 559.2344.

Double-aldol products

(*S*)-*N*-((2*R*,7*R*)-2,7-Bis((*S*)-furan-2-yl(hydroxy)methyl)cycloheptyl)-2-methylpropane-2-sulfinamide, (*R*,*R*,*S*,*R*,*R*)-317



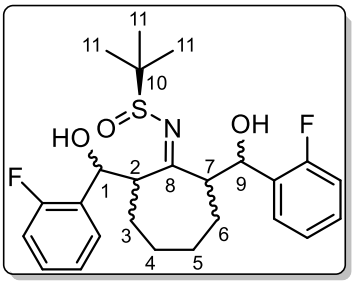
Compound **(*R*,*R*,*S*,*R*,*R*)-317** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and furfural (0.27 mL, 3.3 mmol). The crude compound (80:20 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **(*R*,*R*,*S*,*R*,*R*)-317** as a sticky brown oil (0.242 g, 59% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 82.20 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3351 (O-H stretch), 2928 (C-H stretch), 1614 (C=N stretch), 1151 (C-O stretch), 1051 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.94-1.40 (4H, m, one of each H-3, H-4, H-5 and H-6), 1.35 (9H, s, H-11), 1.52-1.89 (4H, m, one of each H-3, H-4, H-5 and H-6), 3.24-3.36 (1H, m, H-2), 3.53 (1H, d, *J* = 2.3 Hz, O-H), 4.14 (1H, dt, *J* = 10.4, 6.6 Hz, H-7), 4.57 (1H, t, *J* = 10.5 Hz, H-9), 5.08 (1H, dd, *J* = 9.1, 2.1 Hz, H-1), 5.15 (1H, d, *J* = 10.8 Hz, O-H), 6.24-6.43 (4H, m, Ar-H), 7.32-7.47 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (C-11), 25.8, 28.2, 29.7, 32.2 (C-3, C-4, C-5 and C-6), 51.9 (C-2), 53.6 (C-7), 58.1 (C-10), 67.7 (C-9), 70.0 (C-1), 107.8 (Ar-CH), 108.5 (Ar-CH), 110.3 (2 × Ar-CH), 142.5 (Ar-CH), 142.7 (Ar-CH), 154.4 (2 × Ar-C), 192.7 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{29}NO_5SNa$ $[M + Na]^+$: 430.1659, found 430.1658. Absolute stereochemistry was assigned by crystallographic data **(Appendix II)**.

COSY, HSQC and HMBC were used to aid in assignment.

Note: Assignment of H-1 and H-9 was based on an intramolecular hydrogen-bond between the hydroxyl proton (C_1H-OH) and the sulfoxide moiety which would presumably lead to a more downfield shift for H-1. This hydrogen-bonding interaction was evident in the crystal structure.

(*S*)-*N*-((2*R*,7*R*)-2,7-Bis((*S*)-(2-fluorophenyl)(hydroxy)methyl)cycloheptyl)-2-methylpropane-2-sulfinamide, 311

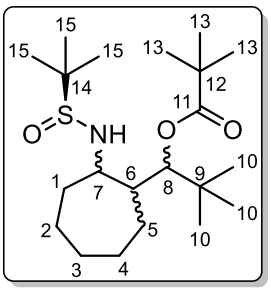


Compound **311** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.215 g, 1 mmol) and *o*-fluorobenzaldehyde (0.27 mL, 3.3 mmol). The crude compound (91:9 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **311** as a sticky colourless oil (0.256 g, 55% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 66.93 (c 0.325, $CHCl_3$). IR ν_{max} (NaCl): 3370 (O-H stretch), 2929 (C-H stretch), 1616 (C=N stretch), 1124 (C-O stretch), 1034 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.67-1.77 (8H, m, one of each H-3, H-4, H-5 and H-6), 1.34 (9H, s, H-11), 3.00-3.16 (1H, m, H-2), 3.48 (1H, *br* s, O-H), 3.81 (1H, dt, *J* = 10.3, 6.9 Hz, H-7), 4.91 (1H, t, *J* = 10.3 Hz, H-9), 5.34 (1H, d, *J* = 10.8 Hz, H-1), 5.44 (1H, d, *J* = 9.3 Hz, O-H), 6.84-7.29 (6H, m, Ar-H), 7.58-7.76 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.6 (C-11), 25.6, 27.4, 29.7, 31.8 (C-3, C-4, C-5 and C-6), 54.6 (C-2), 56.7 (C-7), 58.2 (C-10), 67.0 (d, $^3J_{C\text{-}F}$ = 3.5 Hz, C-9), 69.6 (d, $^3J_{C\text{-}F}$ = 3.4 Hz, C-1), 115.0 (d, $^4J_{C\text{-}F}$ = 2.8 Hz, Ar-H), 115.3 (d, $^4J_{C\text{-}F}$ = 2.5 Hz, Ar-H), 124.8 (d, $^2J_{C\text{-}F}$ = 28.8 Hz, Ar-H), 124.9 (d, $^2J_{C\text{-}F}$ = 29.0 Hz, Ar-H), 128.2 (d, $^3J_{C\text{-}F}$ = 4.0 Hz, Ar-H), 128.6 (d, $^3J_{C\text{-}F}$ = 4.1 Hz, Ar-H), 129.2 (d, $^2J_{C\text{-}F}$ = 30.7 Hz, Ar-C), 129.4 (d, $^2J_{C\text{-}F}$ = 32.5 Hz, Ar-C), 129.4 (d, $^3J_{C\text{-}F}$ = 3.2 Hz, Ar-H), 129.5 (d, $^3J_{C\text{-}F}$ = 3.2 Hz, Ar-H), 160.1 (d, $^1J_{C\text{-}F}$ = 245.5 Hz, Ar-C), 161.1 (d, $^1J_{C\text{-}F}$ = 245.5 Hz, Ar-C), 193.8 (C-8) ppm. HRMS (ESI) *m*/*z* calcd for $C_{25}H_{31}F_2NO_3SNa$ $[M + Na]^+$: 486.1885, found 486.1878.

Absolute stereochemistry was not determined.

1-(2-(((*S*)-*Tert*-butylsulfinyl)amino)cycloheptyl)-2,2-dimethylpropyl pivalate, 328



Compound **328** was prepared from the general procedure **6.7.2** outlined above using sulfinyl imine **(*S*)-291** (0.100 g, 0.46 mmol) and pivaldehyde (0.22 mL, 2.07 mmol) with the following modifications: Deprotonation of sulfinyl imine **(*S*)-291** was carried out using 0.8 equivalents of LDA. The reaction mixture was warmed to 0 °C over 16 h following the addition of 4.5 equivalents of pivaldehyde. The crude

compound (41:40:17:2 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **328** (0.144 g, 81% mixture of diastereomers).

Major diastereomer: Sticky yellow oil. $[\alpha]_D^{20}$ + 59.00 (c 0.15, $CHCl_3$). IR v_{max} (NaCl): 3402 (N-H stretch), 2957 (C-H stretch), 1723 (C=O stretch), 1280 (C-O stretch), 1163 (C-N stretch), 1051 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (9H, s, H-10), 1.21 (9H, s, H-15), 1.23 (9H, s, H-13), 1.10-1.38 (3H, m, one of each H-3, H-4 and H-5), 1.46-1.59 (2H, m, H-2), 1.65-2.04 (6H, m, H-1 and H-6 and one of each H-3, H-4 and H-5), 3.31 (1H, d, *J* = 4.8 Hz, N-H), 3.48 (1H, quint, *J* = 4.7 Hz, H-7), 4.96 (1H, d, *J* = 0.5 Hz, H-8) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.2 (C-2), 23.0 (C-15), 25.5 (C-5), 27.1 (C-10), 27.6 (C-13), 29.0, 29.8 (C-3 and C-4), 34.5 (C-1), 35.9 (C-9), 39.4 (C-12), 46.7 (C-6), 55.6 (C-14), 59.2 (C-7), 80.4 (C-8), 178.1 (C-11) ppm. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{42}NO_3S$ $[M + H]^+$: 388.2880, found 388.2885.

Major diastereomer: Sticky red oil. $[\alpha]_D^{20}$ + 65.33 (c 0.15, $CHCl_3$). IR v_{max} (NaCl): 3284 (O-H stretch), 2957 (C-H stretch), 1711 (C=O stretch), 1282 (C-O stretch), 1159 (C-N stretch), 1073 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (9H, s, H-10), 1.24 (9H, s, H-15), 1.29 (9H, s, H-13), 1.35-1.78 (8H, m, H-2, H-3, H-4 and one of each H-1 and H-5), 1.79-1.97 (1H, m, one of H-5), 2.08-2.19 (1H, m, H-6), 2.24-2.38 (1H, m, one of H-1), 3.62 (1H, *br* s, N-H), 3.75-3.84 (1H, m, H-7), 4.55 (1H, d, *J* = 6.2 Hz, H-8) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.9 (C-2), 23.2 (C-15), 25.6 (C-5), 26.8 (C-10), 27.0, 27.5 (C-3 and C-4), 27.5 (C-13), 33.2 (C-1), 36.5 (C-9), 38.6 (C-12), 43.1 (C-6), 51.5 (C-7), 55.4 (C-14), 82.6 (C-8), 179.6 (C-11) ppm. HRMS (ESI) *m*/*z* calcd for $C_{21}H_{42}NO_3S$ $[M + H]^+$: 388.2880, found 388.2873.

COSY, HSQC and HMBC were used to aid in assignment.

Note: Absolute stereochemistry was not determined.

6.7.3 Synthesis of 2-butanone derived 3-amino-1,5-diol precursors

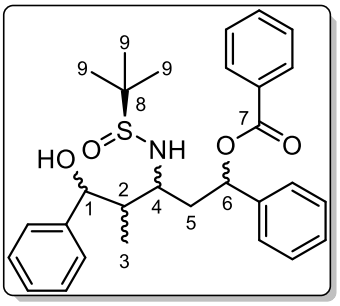
To a Schlenk tube under N_2 atmosphere, containing diisopropylamine (1.2 equiv.) in anhydrous THF (5 mL per mmol of sulfinyl imine), was added *n*-BuLi (1.1 equiv.) at 0 °C. The mixture was allowed to stir at 0 °C for 20 min to generate a solution of LDA. ***Tert*-butanesulfinyl imine** (1.0 equiv.) was carefully weighed out and the amount added was accurately recorded. The **sulfinyl imine** was then added slowly (neat), dropwise at -78 °C. After the reaction mixture was allowed to stir for 1 h at -78 °C, freshly distilled **aldehyde** (3.3 equiv.) was added slowly (neat), dropwise. The reaction mixture was kept at -78 °C for 3 h and allowed warm to -20 °C over 16 h.

Work-up conditions as per 1 mmol of sulfinyl imine

The reaction mixture was quenched with sat. aq. NH_4Cl solution (1.5 mL) at -20 °C. Sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was purified using column chromatography on silica gel.

Note: Absolute stereochemistry was not determined for the 2-butanone series.

3-(((*S*)-*Tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-diphenylpentyl benzoate, 337



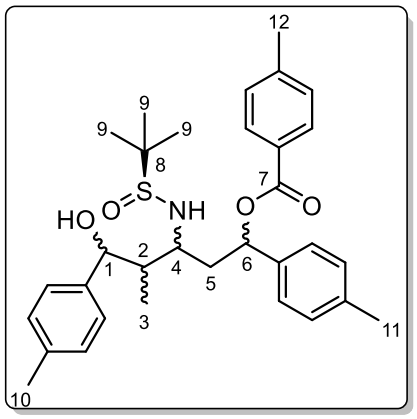
Compound **337** was prepared from the general procedure **6.7.3** outlined above using sulfinyl imine **(*S*)-334** (0.084 g, 0.48 mmol) and benzaldehyde (0.16 mL, 1.58 mmol). The crude compound (>98:2 *dr*) was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **337** as a sticky yellow oil (0.076 g, 32% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 60.40 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3307 (O-H stretch), 2927 (C-H stretch), 1720 (C=O stretch), 1270 (C-O stretch), 1108 (C-N stretch), 1027 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 7.1 Hz, H-3), 1.31 (9H, s, H-9), 1.99-2.12 (2H, m, H-2 and one of H-5), 2.13-2.27 (1H, ddd, *J* = 14.4, 10.2, 4.1 Hz, one of H-5), 3.75-3.86 (1H, m, H-4), 4.28 (1H, d, *J* = 5.1 Hz, O-H), 4.30 (1H, d, *J* = 6.8 Hz, N-H), 5.05 (1H, dd, *J* = 4.9, 2.2 Hz, H-1), 6.09 (1H, dd, *J* = 10.3, 3.6 Hz, H-6), 7.16-7.51 (12H, m, Ar-H), 7.52-7.63 (1H, m, Ar-H), 8.00-8.08 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.1 (C-3), 23.0 (C-9), 43.4 (C-5), 44.4 (C-2), 56.6 (C-8), 58.1 (C-4), 73.5 (C-6), 75.9 (C-1), 125.9 (2 × Ar-CH), 126.3 (2 × Ar-CH), 126.9 (Ar-CH), 128.2 (2 × Ar-CH), 128.3 (Ar-CH), 128.6 (2 × Ar-CH), 128.8 (2 × Ar-CH), 129.7 (2 × Ar-CH), 130.3 (Ar-C), 133.2 (Ar-CH), 140.8 (Ar-C), 144.1 (Ar-C), 165.8 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{35}NO_4SNa$ $[M + Na]^+$: 516.2179, found 516.2175.

Note: Utilising 0.8 equivalents of LDA and warming the reaction mixture to -20 °C over a period of 16 h afforded **337** in an improved yield of 45%.

COSY and HSQC were used to aid in assignment.

3-(((*S*)-*Tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-di-*p*-tolylpentyl 4-methylbenzoate, 338



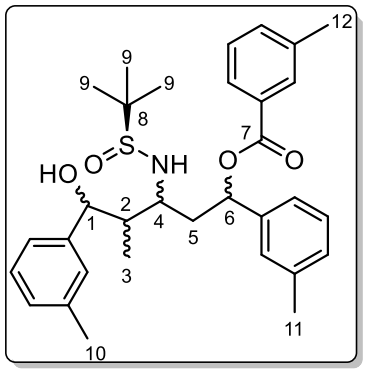
Compound **338** was prepared from the general procedure **6.7.3** outlined above using sulfinyl imine **(*S*)-334** (0.166 g, 0.95 mmol) and *p*-tolualdehyde (0.51 mL, 4.3 mmol). The crude compound (<97:3 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **338** as a sticky colourless oil (0.224 g, 44% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 78.00 (c 0.1, $CHCl_3$). IR ν_{max} (NaCl): 3339 (O-H stretch), 2922 (C-H stretch), 1718 (C=O stretch), 1271 (C-O stretch), 1102 (C-N stretch), 1041 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.9 Hz, H-3), 1.29 (9H, s, H-9), 1.95-2.09 (2H, m, H-2 and one of H-5), 2.12-2.25 (1H, ddd, *J* = 14.3, 9.9, 3.3 Hz, one of H-5), 2.32, 2.41 (3 × 3H, s (overlapping 2 × 3H, s and 1 × 3H, s) H-10, H-11 and H-12), 3.67-3.85 (1H, *br* m, H-4), 4.18 (1H, *br* s, O-H), 4.29 (1H, d, *J* = 4.6 Hz, N-H), 5.00 (1H, *br* s, H-1), 6.02 (1H, dd, *J* = 10.0, 3.5 Hz, H-6), 7.02-7.37 (10H, m, Ar-H), 7.86-8.00 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.2 (C-3), 21.2, 21.3, 21.8 (C-10, C-11 and C-12), 23.0 (C-9), 43.2 (C-5), 44.3 (C-2), 56.5 (C-8), 58.0 (C-4), 73.3 (C-6), 75.9 (C-1), 125.8 (2 × Ar-CH), 126.3 (2 × Ar-CH), 127.7 (Ar-C), 128.9 (2 × Ar-CH), 129.3 (2 × Ar-CH), 129.5 (2 × Ar-CH), 129.8 (2 × Ar-CH), 136.4 (Ar-C), 137.9 (Ar-C), 138.0 (Ar-C), 141.2 (Ar-C), 143.8 (Ar-C), 165.9 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{41}NO_4S$ $[M + Na]^+$: 558.2630, found 558.2627.

Note: 4.5 equivalents of *p*-tolualdehyde was utilised in an effort to improve the yield.

COSY and HSQC were used to aid in assignment.

3-(((*S*)-*Tert*-butylsulfinyl)amino)-5-hydroxy-4-methyl-1,5-di-*m*-tolylpentyl 3-methylbenzoate, 339



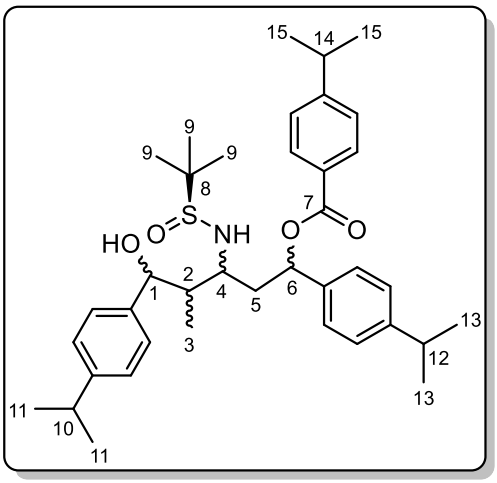
Compound **339** was prepared from the general procedure **6.7.3** outlined above using sulfinyl imine **(*S*)-334** (0.114 g, 0.65 mmol) and *m*-tolualdehyde (0.25 mL, 2.15 mmol). The crude compound (<90:10 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **339** as a sticky pale yellow oil (0.131 g, 38% mixture of diastereomers).

Major diastereomer: $[\alpha]_D^{20}$ + 59.20 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 3305 (O-H stretch), 2961 (C-H stretch), 1719 (C=O stretch), 1275 (C-O stretch), 1105 (C-N stretch), 1041 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 7.1 Hz, H-3), 1.32 (9H, s, H-9), 1.97-2.11 (2H, m, H-2 and one of H-5), 2.13-2.25 (1H, ddd, *J* = 14.5, 10.3, 4.2 Hz, one of H-5), 2.33, 2.42 (3 × 3H, s (overlapping 2 × 3H, s and 1 × 3H, s) H-10, H-11 and H-12), 3.74-3.92 (1H, m, H-4), 4.28 (overlapping 1H, d, *J* = 6.5 Hz, N-H and 1H, *br* s, O-H), 5.03 (1H, *br* s, H-1), 6.04 (1H, dd, *J* = 10.2, 3.5 Hz, H-6), 6.96-7.45 (10H, m, Ar-H), 7.82-7.92 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.0 (C-3), 21.4, 21.6, 21.6 (C-10, C-11 and C-12), 23.0 (C-9), 43.4 (C-5), 44.2 (C-2), 56.6 (C-8), 58.2 (C-4), 73.5 (C-6), 76.1 (C-1), 122.9 (Ar-CH), 123.3 (Ar-CH), 126.5 (Ar-CH), 126.9 (Ar-CH), 127.0 (Ar-CH), 127.6 (Ar-CH), 128.1 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 129.0 (Ar-CH), 130.3 (Ar-CH), 130.3 (Ar-C), 134.0 (Ar-CH), 137.8 (Ar-C), 138.4 (Ar-C), 138.4 (Ar-C), 140.8 (Ar-C), 144.1 (Ar-C), 166.0 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{32}H_{42}NO_4S$ $[M + H]^+$: 536.2829, found 536.2831.

Note: Separation of diastereomers could not be achieved on this occasion.

COSY and HSQC were used to aid in assignment.

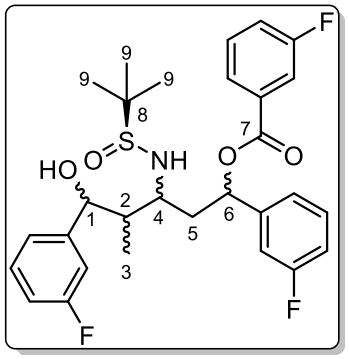
3-(((S)-*Tert*-butylsulfinyl)amino)-5-hydroxy-1,5-bis(4-isopropylphenyl)-4-methylpentyl 4-isopropylbenzoate, 340



Compound **340** was prepared from the general procedure **6.7.3** outlined above using sulfinyl imine **(*S*)-334** (0.120 g, 0.68 mmol) and *p-iso*-propylbenzaldehyde (0.34 mL, 2.24 mmol). The crude compound (>98:2 *dr*) was purified using column chromatography on silica gel (2:1, hexane:EtOAc) to give the title compound **340** as a sticky pale yellow oil (0.106 g, 25% of pure diastereomer).

Major diastereomer: $[\alpha]_D^{20}$ + 48.00 (c 0.25, $CHCl_3$). IR ν_{max} (NaCl): 2961 (C-H stretch), 1717 (C=O stretch), 1270 (C-O stretch), 1103 (C-N stretch), 1053 (S=O stretch) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 7.1 Hz, H-3), 1.22, 1.24, 1.27 (3 × 6H, d, *J* = 6.9 Hz, H-11, H-13 and H-15), 1.30 (9H, s, H-9), 1.97-2.13 (2H, m, H-2 and one of H-5), 2.14-2.26 (1H, ddd, *J* = 14.4, 10.2, 4.4 Hz, one of H-5), 2.88, 3.00 (3 × 1H, sept, *J* = 6.9 Hz (overlapping 2 × 1H, sept and 1 × 1H, sept) H-10, H-12 and H-14), 3.74-3.86 (1H, m, H-4), 4.31 (1H, d, *J* = 6.4 Hz, N-H), 5.02 (1H, d, *J* = 1.8 Hz, H-1), 6.05 (1H, dd, *J* = 10.1, 3.7 Hz, H-6), 7.10-7.36 (10H, m, Ar-H), 7.94-8.04 (2H, m, Ar-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 6.29 (C-3), 23.0 (C-9), 23.9, 24.1, 24.2 (C-11, C-13 and C-15), 33.9, 34.0, 34.4 (C-10, C-12 and C-14), 43.1 (C-5), 44.3 (C-2), 56.6 (C-8), 58.2 (C-4), 73.2 (C-6), 76.0 (C-1), 125.9 (2 × Ar-CH), 126.3 (2 × Ar-CH), 126.4 (2 × Ar-CH), 126.7 (2 × Ar-CH), 126.8 (2 × Ar-CH), 128.1 (Ar-C), 130.0 (2 × Ar-CH), 138.2 (Ar-C), 141.6 (Ar-C), 147.5 (Ar-C), 148.8 (Ar-C), 154.6 (Ar-C), 165.9 (C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{38}H_{54}NO_4S$ $[M + H]^+$: 620.3750, found 620.3754.

3-(((*S*)-*Tert*-butylsulfinyl)amino)-1,5-bis(3-fluorophenyl)-5-hydroxy-4-methylpentyl 3-fluorobenzoate, 341



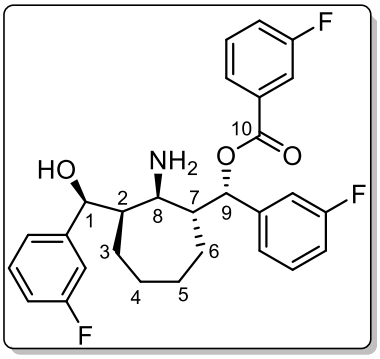
Compound **341** was prepared from the general procedure **6.7.3** outlined above using sulfinyl imine **(*S*)-334** (0.092 g, 0.52 mmol) and *m*-fluorobenzaldehyde (0.18 mL, 1.72 mmol). The crude compound was purified using column chromatography on silica gel (1:1, hexane:EtOAc) to give the title compound **341** as a sticky colourless oil (0.135 g, 47% of pure diastereomer).

Major diastereomer: $[\alpha]_D^{20}$ + 68.44 (c 0.225, $CHCl_3$). IR ν_{max} (NaCl): 3338 (O-H stretch), 2965 (C-H stretch), 1725 (C=O stretch), 1269 (C-O stretch), 1093 (C-N stretch), 1039 (S=O stretch) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, d, *J* = 7.1 Hz, H-3), 1.33 (9H, s, H-9), 1.96-2.08 (2H, m, H-2 and one of H-5), 2.09-2.33 (1H, ddd, *J* = 14.5, 10.6, 4.5 Hz, one of H-5), 3.75-3.89 (1H, m, H-4), 4.26 (1H, d, *J* = 6.7 Hz, O-H), 4.54 (1H, d, *J* = 5.3 Hz, N-H), 5.08 (1H, dd, *J* = 5.2, 1.4 Hz, H-1), 6.07 (1H, dd, *J* = 10.5, 3.2 Hz, H-6), 6.90 (1H, dddd, *J* = 9.1, 3.7, 2.6, 0.9 Hz, Ar-H), 6.99 (1H, dddd, *J* = 9.3, 5.4, 2.6, 0.9 Hz, Ar-H), 7.07-7.18 (4H, m, Ar-H), 7.20-7.38 (3H, m, Ar-H), 7.46 (1H, dt, *J* = 8.1, 5.5 Hz, Ar-H), 7.73 (1H, ddd, *J* = 9.2, 2.6, 1.5 Hz, Ar-H), 7.86 (1H, dt, *J* = 7.8, 1.1 Hz, Ar-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 5.8 (C-3), 23.0 (C-9), 43.6 (C-5), 44.4 (C-2), 56.8 (C-8), 58.0, (C-4), 73.2 (C-6), 75.3 (C-1), 113.0 (d, $^2J_{C\text{-}F}$ = 22.3 Hz, Ar-CH), 113.2 (d, $^2J_{C\text{-}F}$ = 22.1 Hz, Ar-CH), 113.7 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, Ar-CH), 115.4 (d, $^2J_{C\text{-}F}$ = 21.0 Hz, Ar-CH), 116.7 (d, $^2J_{C\text{-}F}$ = 22.9 Hz, Ar-CH), 120.6 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, Ar-CH), 121.3 (d, $^4J_{C\text{-}F}$ = 2.6 Hz, Ar-CH), 121.9 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, Ar-CH), 125.5 (d, $^4J_{C\text{-}F}$ = 3.0 Hz, Ar-CH), 129.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, Ar-CH), 130.4 (d, $^3J_{C\text{-}F}$ = 8.0 Hz, Ar-CH), 130.6 (d, $^3J_{C\text{-}F}$ = 8.2 Hz, Ar-CH), 132.1 (d, $^3J_{C\text{-}F}$ = 7.4 Hz, Ar-C), 143.0 (d, $^3J_{C\text{-}F}$ = 6.9 Hz, Ar-C), 146.9 (d, $^3J_{C\text{-}F}$ = 6.7 Hz, Ar-C), 162.7 (d, $^1J_{C\text{-}F}$ = 247.0 Hz, Ar-C), 163.0 (d, $^1J_{C\text{-}F}$ = 245.1 Hz, Ar-C), 163.1 (d, $^1J_{C\text{-}F}$ = 246.4 Hz, Ar-C), 164.6 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C-7) ppm. HRMS (ESI) *m*/*z* calcd for $C_{29}H_{32}F_3NO_4SNa$ $[M + Na]^+$: 570.1896, found 570.1889.

Note: Diastereoselectivity could not be determined from the ^1H NMR spectrum of the crude reaction mixture due to overlapping signals.

6.8 Cleavage of *tert*-butanesulfinyl auxiliary

(*R*)-((1*R*,2*R*,3*R*)-2-Amino-3-((*S*)-(3-fluorophenyl)(hydroxy)methyl)cycloheptyl)(3-fluorophenyl)methyl 3-fluorobenzoate, (*S*,*R*,*S*,*R*,*R*,*S*)-367



To a solution of 3-amino-1,5-diol derivative **(*S*,*R*,*S*,*R*,*R*,*S*)-300** (0.048 g, 0.082 mmol) in ethanol (0.33 mL) was added diisopropyl ether (0.34 mL). The resulting solution was cooled to 0 ^{o}C and acetyl chloride (0.019 g, 0.018 mL, 0.25 mmol) was added dropwise. The mixture was stirred at 0 ^{o}C overnight. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 0.3 mL of H_2O and subsequently washed with CH_2Cl_2. $NaHCO_3$ (3 mL) was added to the aqueous layer and extracted twice with CH_2Cl_2 (0.5 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product which was purified using column chromatography on silica gel (CH_2Cl_2, 5% MeOH) to give the title compound **(*S*,*R*,*S*,*R*,*R*,*S*)-367** as a sticky colourless oil (0.032 g, 80% of pure diastereomer).

Major diastereomer: $[\alpha]_D^{20}$ + 113.00 (c 0.1, $CHCl_3$). IR ν_{max} (NaCl): 3370 (O-H stretch), 3076 (N-H stretch), 2929 (C-H stretch), 1729 (C=O stretch), 1446 (C-F stretch), 1180 (C-O stretch), 1108 (C-N stretch), 1034 (S=O stretch) cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.91-1.04 (1H, m, one of H-4/H-5), 1.12-1.23 (1H, m, one of H-4/H-5), 1.30-1.40 (1H, m, one of H-3), 1.42-1.59 (2H, m, one of each H-3 and H-6), 1.60-1.72 (1H, m, one of H-4/H-5), 1.74-1.88 (3H, m, H-2 and one of each H-4/H-5 and H-6), 1.90-2.03 (1H, m, H-7), 2.34-3.77 (4H, m, overlapping 2H, *br* s, NH_2, 1H, *br* s, O-H and 1H, m, H-8), 4.87 (1H, s, H-1), 6.23 (1H, d, *J* = 4.2 Hz, H-9), 6.89 (1H, td, *J* = 8.1, 2.3 Hz, Ar-H), 6.98-7.06 (3H, m, Ar-H), 7.07-7.13 (1H, m, Ar-H), 7.14-7.20 (1H, m, Ar-H), 7.21-7.20 (2H, m, Ar-H), 7.31-7.41 (1H, m, Ar-H), 7.50 (1H, dt, *J* = 8.3, 5.5 Hz, Ar-H), 7.75-7.81 (1H, m, Ar-H), 7.89-7.93 (1H, m, Ar-H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$) δ 20.0 (C-3), 25.7 (C-6), 28.7, 29.6 (C-4 and C-5), 47.4 (C-2), 57.3 (overlapping C-7 and C-8), 77.2 (C-9), 77.7 (C-1), 113.0 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz, Ar-CH), 113.4 (d, $^{2}J_{C\text{-}F}$ = 22.1 Hz, 2 × Ar-CH), 115.0 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz, Ar-CH), 116.7 (d, $^{2}J_{C\text{-}F}$ = 23.1 Hz, Ar-CH), 120.8 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz, Ar-CH), 121.3 (d, $^{4}J_{C\text{-}F}$ = 2.9 Hz, Ar-CH), 122.0 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, Ar-CH), 125.6 (d, $^{4}J_{C\text{-}F}$ = 3.2 Hz, Ar-CH), 129.5 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz, Ar-CH), 130.5 (d, $^{3}J_{C\text{-}F}$ = 8.3 Hz, Ar-CH), 130.6 (d, $^{3}J_{C\text{-}F}$ = 7.5 Hz, Ar-CH), 131.9 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz, Ar-C), 141.9 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz, Ar-C), 146.6 (d, $^{3}J_{C\text{-}F}$ = 7.2 Hz, Ar-C), 162.8 (d, $^{1}J_{C\text{-}F}$ = 247.8 Hz, Ar-C), 163.0 (d, $^{1}J_{C\text{-}F}$ =

244.9 Hz, Ar-C), 163.1 (d, $^{1}J_{C\text{-}F}$ = 247.2 Hz, Ar-C), 164.8 (d, $^{4}J_{C\text{-}F}$ = 2.8 Hz, C-10) ppm. HRMS (ESI) *m*/*z* calcd for $C_{28}H_{28}F_3NO_3$ $[M + H]^+$: 484.2094, found 484.2099.

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“The greatest victory is victory over ourselves, remember it’s always too soon to quit!”

Appendix I

Publications

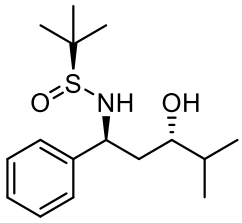
"Preparation of *anti*-1,3-Amino Alcohol Derivatives Through an Asymmetric Aldol-Tishchenko Reaction of Chiral Sulfinimines" Mackey, P.; Cano, R.; Foley, V. M.; McGlacken, G. P., *Org*. *Synth.* **2017**, *94*, 259-279.

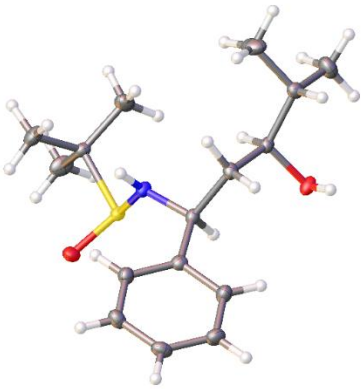
Manuscript in preparation: "Tandem Double-aldol Tishchenko Reaction Forming Five Contiguous Chiral Centres: Scope and Computational Explorations of Mechanisms and Selectivities" **2020**, Mackey, P.; Turlik, A.; Ando, K.; Light, M. E.; Houk, K. N.; McGlacken, G. P.

Appendix II

I

X-ray crystallographic data for (*S*,*S*,*S*)-271



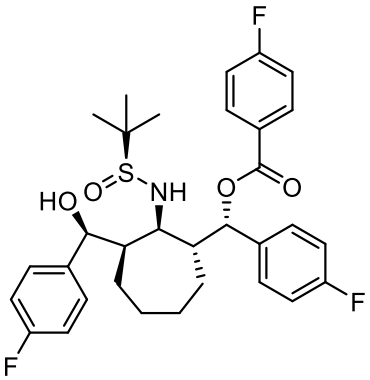


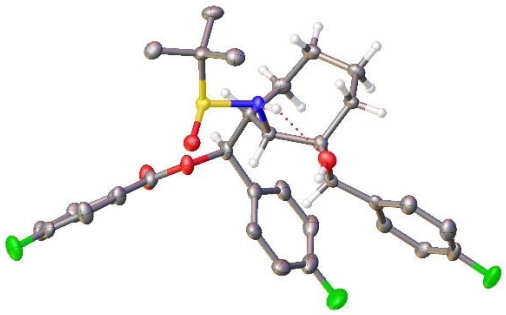
Empirical formula	$C_{16}H_{27}NO_2S$	
***D*$_{calc.}$**	1.178 g cm^{-3}	
μ	0.195 mm^{-1}	
Formula Weight	297.44	
Colour	clear colourless	
Shape	prism	
Size	0.28×0.02×0.01 mm^3	
T	100 K	
Crystal system	monoclinic	
Space group	$P2_1$	
Flack parameter	0.01	
Hooft parameter	0.03	
Unit cell dimensions	*a* = 6.0632 Å	α = 90°
	b = 13.0944 Å	β = 104.859°
	c = 10.9302 Å	γ = 90°
V	838.77 Å^3	
Z	2	
Z'	1	
Wavelength	0.71073 Å	
Radiation type	MoK$_\alpha$	

Θ_{min}	3.661°
Θ_{max}	28.693°
Measured Refl.	9358
Independent Refl.	4285
Reflections Used	4090
R_{int}	0.0397
Parameters	194
Restraints	1
Largest Peak	0.272
Deepest Hole	-0.193
Goodness-of-fit on F^2	1.034
wR_2 **(all data)**	0.0824
wR_2	0.0808
R_1 **(all data)**	0.0368
R_1	0.0350

II

X-ray crystallographic data for (*S*,*R*,*S*,*R*,*R*,*S*)-299



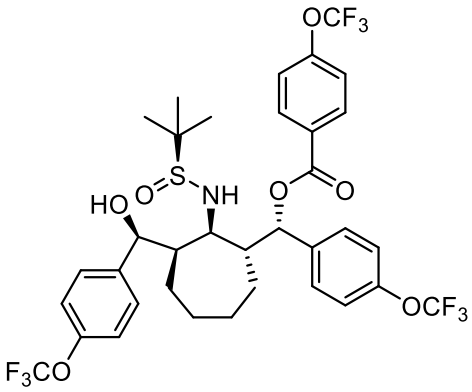


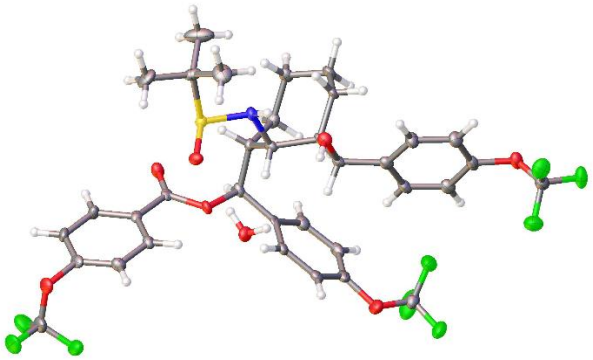
Empirical Formula	$C_{32}H_{36.5}F_3NO_{4.25}S$	
	$C_{32}H_{36}F_3NO_4S$, $0.25(H_2O)$	
$D_{calc.}$	1.186 g cm^{-3}	
μ	0.149 mm^{-1}	
Formula Weight	592.18	
Colour	clear colourless	
Shape	irregular	
Size	0.24×0.15×0.02 mm^3	
T	100 K	
Crystal System	orthorhombic	
Space Group	$P2_12_12$	
Flack Parameter	-0.02	
Hooft Parameter	-0.00	
Unit cell dimensions	a = 41.6676 Å	$\alpha = 90^\circ$
	b = 22.1967 Å	$\beta = 90^\circ$
	c = 14.3476 Å	$\gamma = 90^\circ$
V	13269.9 Å^3	
Z	16	
Z'	4	

Wavelength	0.71073 Å
Radiation type	MoK_{α}
Θ_{min}	1.759°
Θ_{max}	28.500°
Measured Refl.	104314
Independent Refl.	33638
R_{int}	0.0794
Parameters	1479
Restraints	6
Largest Peak	0.583
Deepest Hole	-0.300
Goodness-of-fit on F^2	1.025
wR_2 **(all data)**	0.1310
wR_2	0.1166
R_1 **(all data)**	0.1102
R_1	0.0630

III

X-ray crystallographic data for (*S*,*R*,*S*,*R*,*R*,*S*)-304



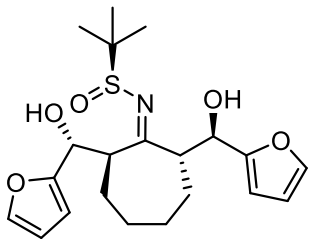


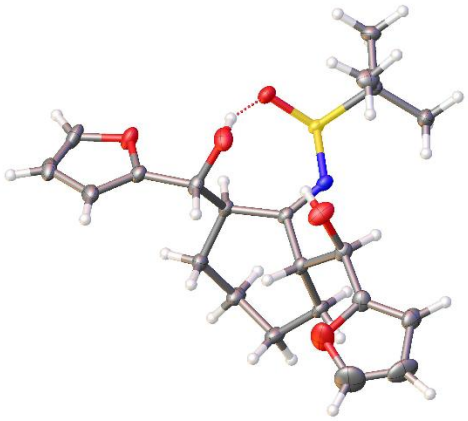
Empirical formula	$C_{35}H_{37}F_9NO_{7.5}S$	
***D*$_{calc.}$**	1.450 g cm^{-3}	
μ	0.185 mm^{-1}	
Formula Weight	794.71	
Colour	clear yellow	
Shape	block	
Space Group	$P2_12_12_1$	
Size	0.23×0.09×0.07 mm^3	
T	100 K	
Crystal System	orthorhombic	
Flack Parameter	0.05	
Hooft Parameter	0.06	
Unit cell dimensions	a = 17.5557 Å	$\alpha = 90^\circ$
	b = 19.9884 Å	$\beta = 90^\circ$
	c = 20.7472 Å	$\gamma = 90^\circ$
V	7280.4 Å^3	
Z	8	
Z'	2	
Wavelength	0.71073 Å	
Radiation type	MoK$_\alpha$	

Θ_{min}	3.040°
Θ_{max}	28.498°
Measured Refl.	86253
Independent Refl.	18143
R_{int}	0.1231
Parameters	981
Restraints	840
Largest Peak	0.469
Deepest Hole	-0.418
Goodness-of-fit on F^2	1.111
wR_2 **(all data)**	0.1288
wR_2	0.1170
R_1 **(all data)**	0.1296
R_1	0.0880

IV

X-ray crystallographic data for (*R*,*R*,*S*,*R*,*R*)-317





Formula	$C_{21}H_{29}NO_5S$	
***D*$_{calc.}$**	1.287 g cm^{-3}	
μ	0.185 mm^{-1}	
Formula Weight	407.51	
Colour	clear colourless	
Shape	prism	
Space Group	*C*2	
Size	0.39×0.29×0.10 mm^3	
T	100 K	
Crystal System	monoclinic	
Flack Parameter	0.07	
Hooft Parameter	0.05	
Unit cell dimensions	*a* = 20.0761 Å	*α* = 90˚
	b = 8.9229 Å	*β* = 105.531˚
	c = 12.1819 Å	*γ* = 90˚
V	2102.55 Å^3	
Z	4	
Z'	1	
Wavelength	0.71073 Å	

Radiation type	MoK_{α}
Θ_{min}	2.890°
Θ_{max}	29.743°
Measured Refl.	24997
Independent Refl.	5564
R_{int}	0.0526
Parameters	264
Restraints	1
Largest Peak	0.323
Deepest Hole	-0.192
Goodness-of-fit on F^2	1.033
wR_2 **(all data)**	0.0882
wR_2	0.0867
R_1 **(all data)**	0.0391
R_1	0.0370