Development of catalytic aza enolate reactions

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Submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

to

University College London

I, Osman Aslam confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Osman Aslam

Abstract

This thesis describes the development of catalytic aza enolate reactions and a study of their applications in a range of reactions. Detailed herein are advances in three main areas of aza enolate chemistry, namely; the development of a novel catalytic aza enolate aldol reaction; the investigation of aza enolate reactions with challenging electrophiles (such as epoxides); and the discovery of a multi-component reaction for the formation of oxazolidines.

The first chapter gives a brief overview of organocatalysis, summarising the main activation modes. This is followed by a detailed overview of aza enolate chemistry.

The second chapter describes the development of a catalytic aza enolate aldol reaction. This methodology was explored in more detail with different substrates and asymmetry was investigated, with varying degrees of success.

The third chapter describes the study of aza enolate reactions with a variety of challenging electrophiles. With epoxides and their derivatives, encouraging results were obtained. A new 3-component synthesis of oxazolidines from amines, ketones and epoxides was discovered during the course of this work and the synthesis of several novel oxozolidines was investigated.

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Abbreviations

AcOH	Acetic acid
MeCN	Acetonitrile
Ac	Acetyl
Å	Angstrom
Bn	Benzyl
bp	Boiling point
BBN	Borabicyclo[3.3.1]nonane
Bu	Butyl
Cat.	Catalytic
CAN	Ceric ammonium nitrate
CI	Chemical ionization
m-CPBA	*m*-Chloroperoxybenzoic acid
Cy	Cyclohexyl
Et_2O	Diethyl ether
DIPA	*N*,*N*-Diisopropylamine
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EI	Electron impact
EWG	Electron withdrawing group
E	Electrophile
ES	Electrospray ionisation
ee	Enantiomeric excess
EtOH	Ethanol
Et	Ethyl
EtOAc	Ethyl acetate
Eq. or equiv.	Equivalents
g	Grams
HMPT	Hexamethylphosphoramide
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry

h	Hour(s)
IR	Infrared spectroscopy
n	Integer number
i	Iso
LA	Lewis acid
LHMDS	Lithium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LUMO	Lowest unoccupied molecular orbital
LRMS	Low resolution mass spectrometry
mp	Melting point
Mes	Mesityl
m-	Meta
MeOH	Methanol
Me	Methyl
mg	Miligram
mL	Millilitre
mmol	Millimole
MMPP	Magnesium monoperoxyphthalate hexahydrate
nm	Nanometre
NMR	Nuclear magnetic resonance spectroscopy
Nu	Nucleophile
o-	Ortho
p-	Para
p-TsOH	*p*-Toluenesulfonic acid
ppm	Parts per million
Ph	Phenyl
Pr	Propyl
PCC	Pyridinium chlorochromate
PPTS	Pyridinium *p*-toluenesulfonate
Ref.	Reference
rt	Room temperature
SOMO	Singly occupied molecular orbital
Temp	Temperature

t or *tert*	Tertiary
TBS	*tert*-Butyl dimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBME	*tert*-Butyl methyl ether
THF	Tetrahydrofuran
TEMPO	(2,2,6,6-Tetramethyl-piperidin-1-yl)oxyl
TLC	Thin layer chromatography
Tol	Toluene
Et_3N	Triethylamine
UV	Ultraviolet
UCL	University College London
υ	Wavenumber cm^{-1}

Firstly, I would like to first thank my supervisor Dr. Tom Sheppard for his continual enthusiasm, patience, knowledge and support throughout my time at UCL and for his help in proofreading this thesis.

Since my time at UCL, I have made many great friends, all of whom have made my time more enjoyable and unforgettable. In particular, Fil, for his extremely humorous indecent conversations and for being my 'gym buddy'. My partner in 'crime' Matt 'The Penny' Pennell for his humour and general banter, Rachel 'Raquel' Lanigan, for her general relaxed attitude and for putting up with me and Matt teasing her. Favaad 'Fav', for his general banter and numerous coffee breaks. Chris 'Dr Ryan', for his ludicrous story telling, lunches and India. Eifion 'BFG', for his camaraderie and general sport talk. Ramiz 'Ram', for all the talks about politics and football. Vince 'Vincenzo', for being his fun and relaxed self, Rhian, for being my desk neighbour, Sam for introducing me into new music and Steve for his constant abuse. I would also like to thank Jarryl, Valentina, Ahmed, Joao, Italo, Gyuri, Jack, James, Persis and the numerous past and present people in labs 230 and 237 for making my day more enjoyable. A big thank you must go to Dr. Abil Aliev for his invaluable help and advice with NMR, Dr. Lisa Harris for her help with mass spec analyses.

I would also like to thank my second supervisor Dr. Jon Wilden and Dr. Richard Fitzmaurice, both of whom I am indebted to for their help and for proofreading my thesis.

Finally, and by no means least I would like to thank my friends and in particular my family for all their love and support throughout my studies.

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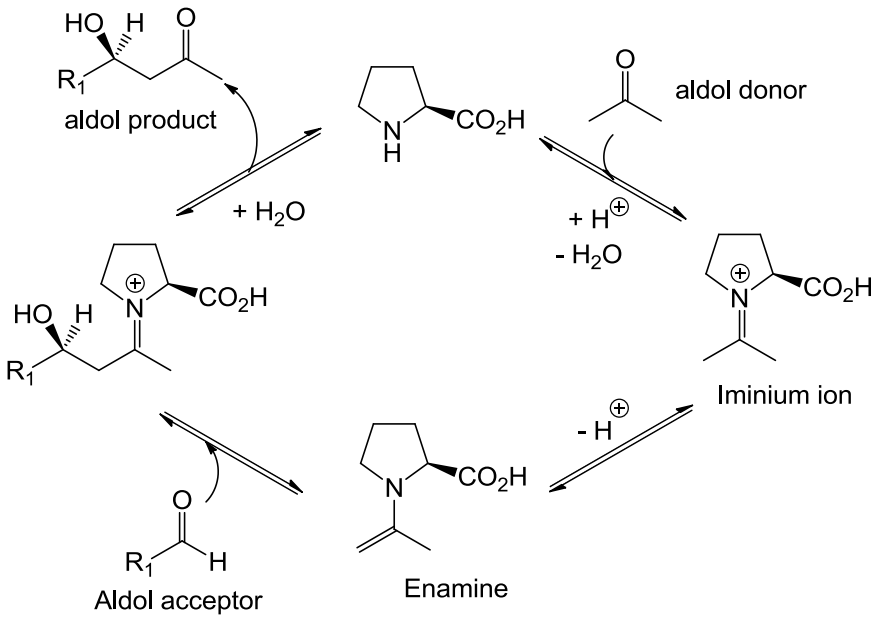
Any man can be a father. It takes someone special to be a dad.

For my dad

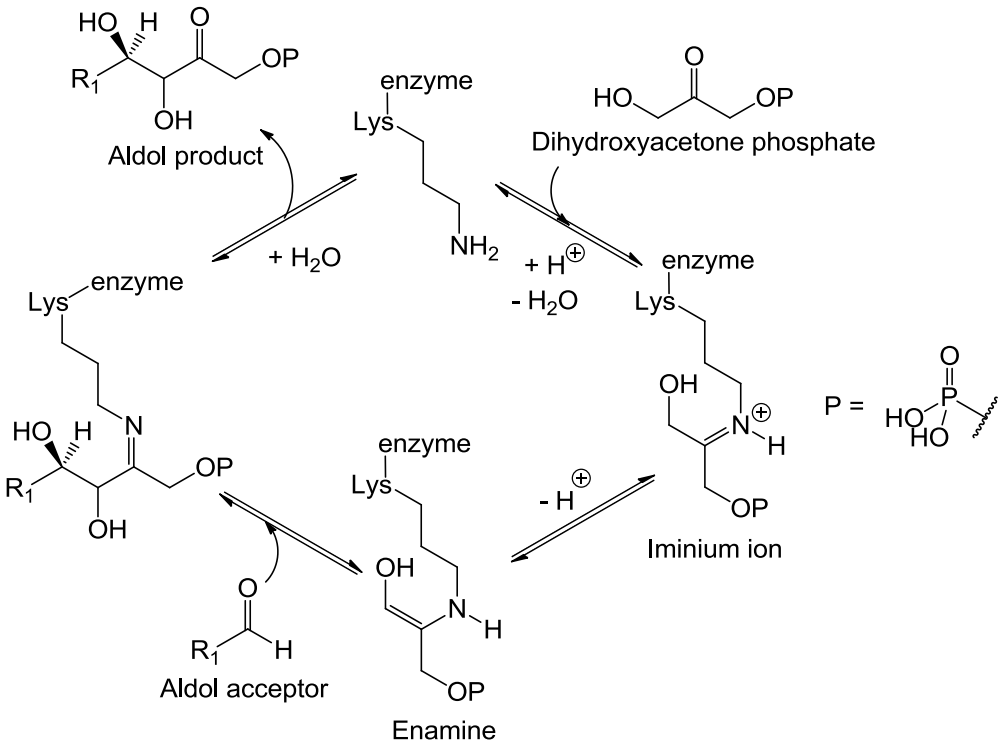
Chapter 1 - Introduction

1.1 Organocatalysis

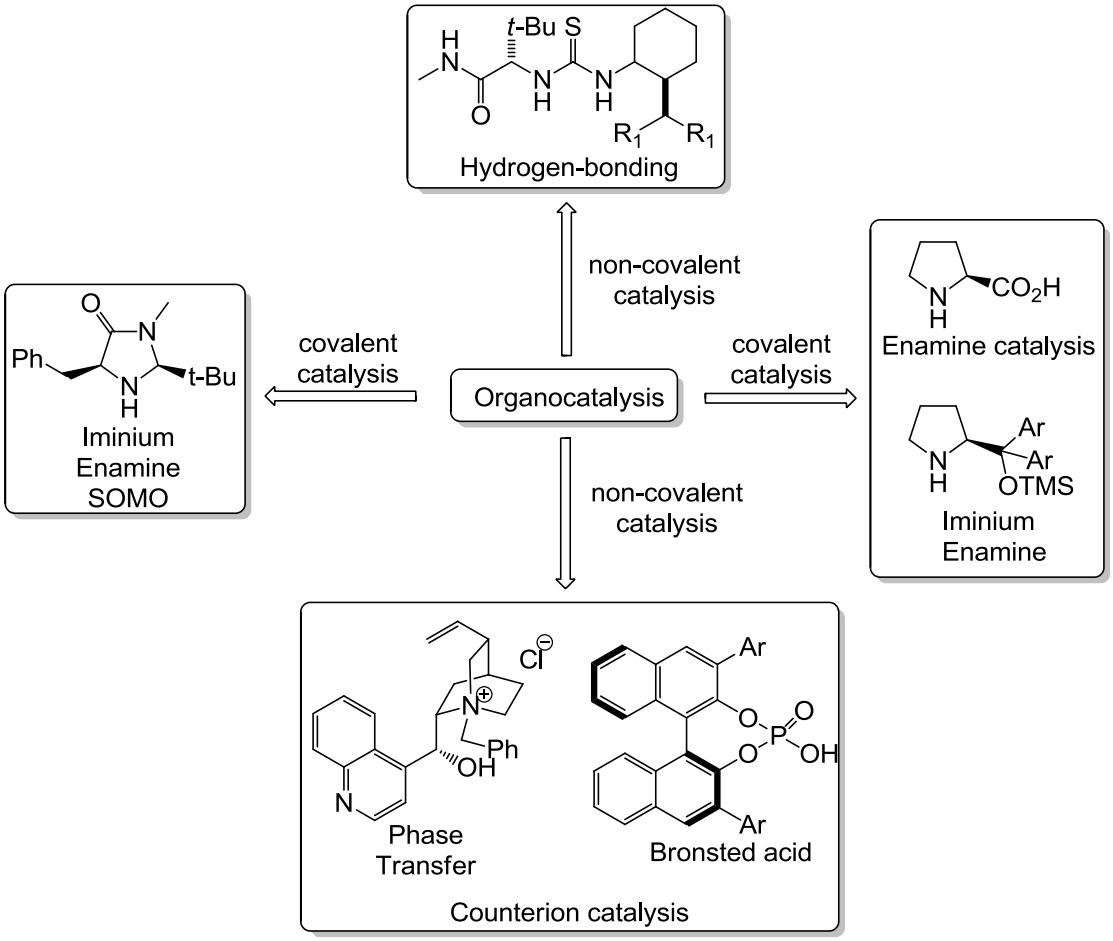
Chemical transformations that use organic catalysts, or organocatalysts (a term coined by David MacMillan to mean purely organic molecules that can act as catalysts), have been documented sporadically over the past century but until recently the field remained relatively dormant. It was not until the late 1990s that the field of organocatalysis was 'born' coalescing around a small number of articles that inspired an explosion of research.[1] From a mechanistic viewpoint, there are only a rather limited number of ''mechanistic categories'' to which all these reactions can be assigned.[1] The mechanisms by which metal-free enzymes (the majority of enzymes do not contain catalytically active metals) achieve rate accelerations have been a major field of research in bio-organic chemistry for decades.[2-7] However, the same mechanisms and categories of enzymatic catalysis also apply to organocatalytic reactions.[1] The catalysis of aldol reactions is a good example - in class I aldolases lysine provides the catalytically active amine group whereas typical organocatalysts for this purpose are secondary amines, the most simple being proline (Schemes 1 and 2). Organocatalytic reactions can be divided into two subgroups, those that proceed *via* ''covalent catalysis'' and those that involve ''non-covalent catalysis'' (Scheme 3). The former describes processes that involve the formation of covalent adducts between catalyst and substrate(s) within the catalytic cycle, the latter rely on non-covalent interactions such as hydrogen bonding or the formation of ion pairs (Scheme 3).[1]



Scheme 1 - Proline organocatalysis



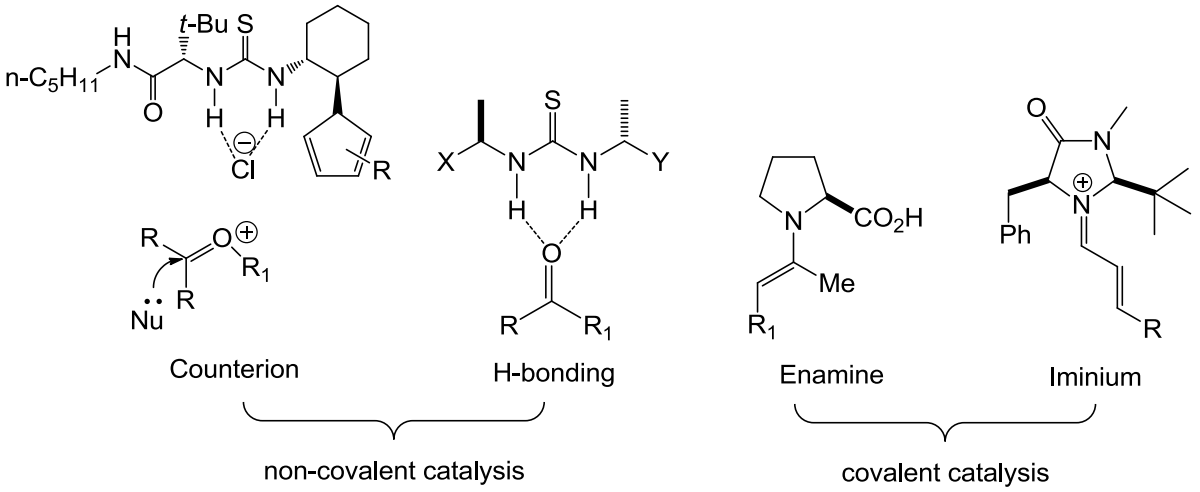
Scheme 2 – Class I aldolases



Scheme 3 – Organocatalysis split into subgroups, covalent and non-covalent catalysis

1.1.1 Brief overview of organocatalytic activation modes

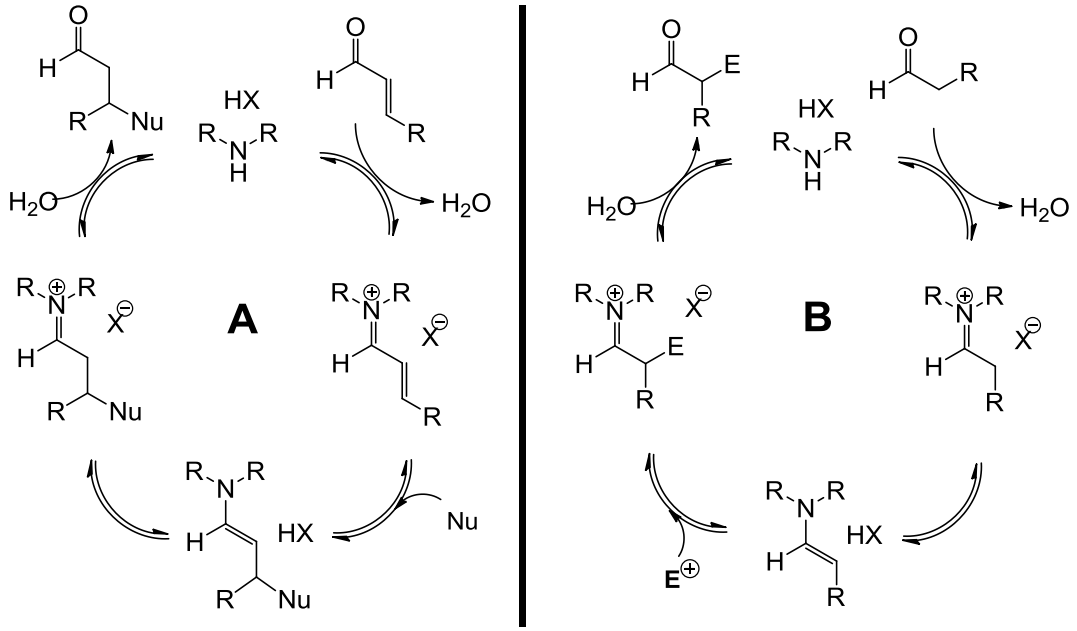
There are various activation modes used in organocatalytic reactions, below is a brief summary of the most commonly used activation modes that cover a large portion of the organocatalysis landscape (Scheme 4). As described earlier, organocatalysis can be split into two areas, covalent and non-covalent catalysis (Scheme 3). Covalent catalysis includes enamine, iminium and SOMO activation modes, whereas, non-covalent catalysis includes hydrogen bonding and counterion activation modes (phase transfer and Brønsted acid) (Scheme 3 and 4).



Scheme 4 – Most common organocatalytic activation modes

1.1.2 Brief history of organocatalysis

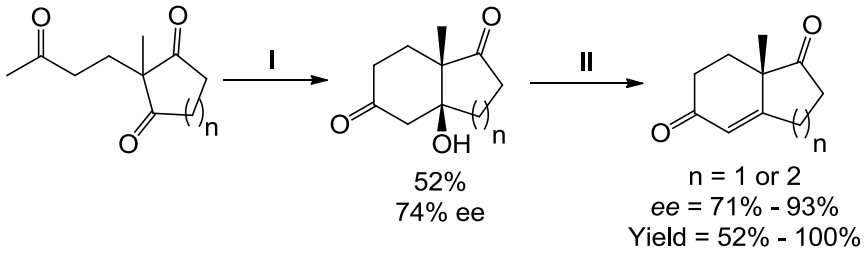
The development of enamine catalysis parallels that of iminium catalysis (Scheme 5). Like iminium catalysis, the concept took a long time to mature, and required a key discovery to stimulate interest, the discovery of intermolecular proline-catalysed aldol reactions by List *et al*. in 2000 set the field in motion.[8,9] Scheme 5 illustrates the catalytic cycles of iminium (**A**) and enamine catalysis (**B**).



Scheme 5 - Catalytic cycles of iminium (A) and enamine catalysis (B)

1.1.3 Enamine catalysis (HOMO activation)

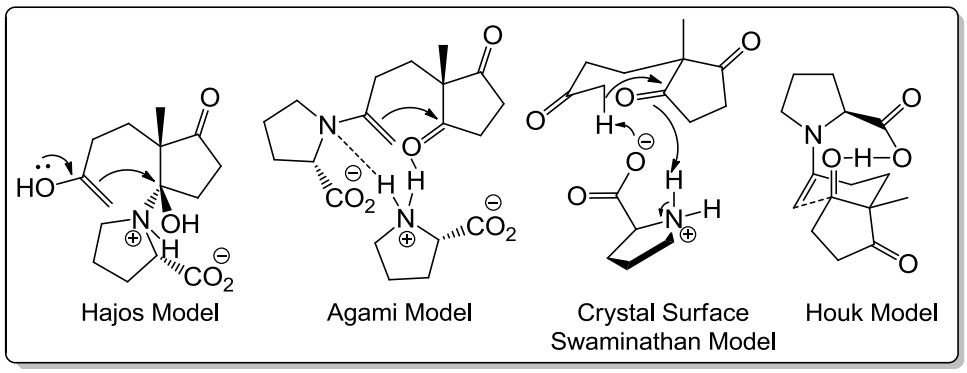
The first enantioselective enamine catalysed process, however, was the intramolecular aldol reaction known as the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) process (Scheme 6).[10,11] This involves using an achiral triketone as the starting material with a catalytic amount of proline to obtain the ketol in 52% yield and 74% *ee*, followed by dehydration to obtain the product in a yield ranging from 52-100% and an *ee* ranging from 71-63% (Scheme 6). This process was discovered in the early 1970s and although the significance of the HPESW reaction was recognized almost from the beginning, it was another 30 years until the first proline-catalysed intermolecular aldol reactions were described.[12]



[I] (S)-Proline (3 mol %), DMF, rt, 72 h. [II] p-TsOH, benzene, reflux.

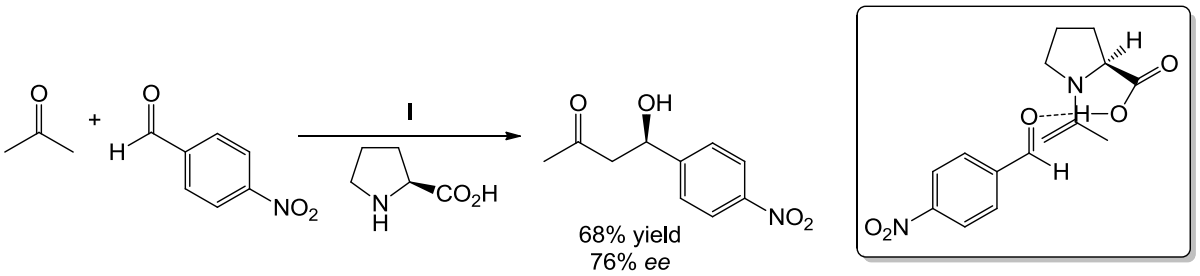
Scheme 6 – Intramolecular aldol reaction (HPESW process)

The reason for the long delay was partly due to the mechanism proposed in the initial studies by Agami,[13] who found a small non-linear effect which suggested the presence of more than one molecule of proline in the transition state (Scheme 7).[13-17]



Scheme 7 – Proline transition state(s)

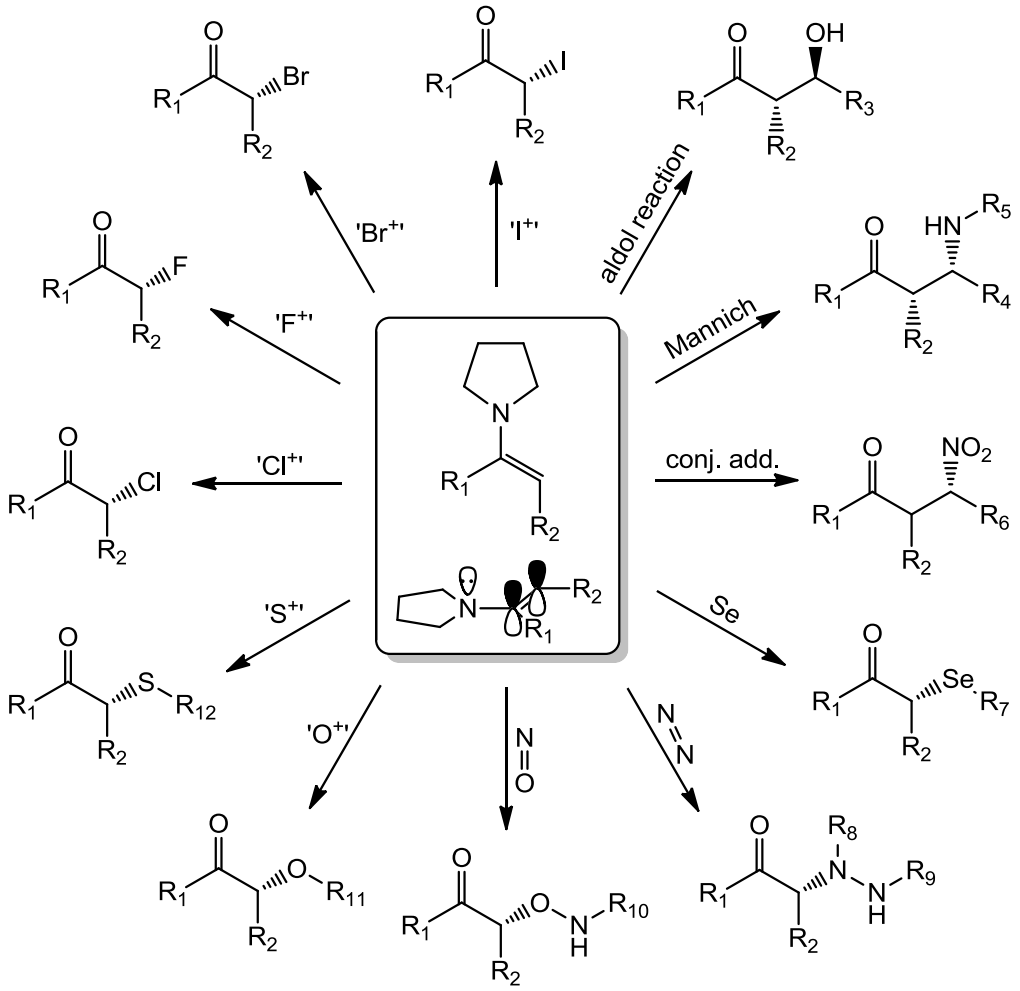
It was not until early 2000 with the discovery of the intermolecular proline-catalysed reaction (Scheme 8),[12] further studies by List *et al*. and several key modelling studies by the Houk group that enamine catalysis became widely accepted.[12,18,19]



[1] *Proline (30 mol %), DMSO, rt.*

Scheme 8 – Intermolecular proline-catalysed reaction

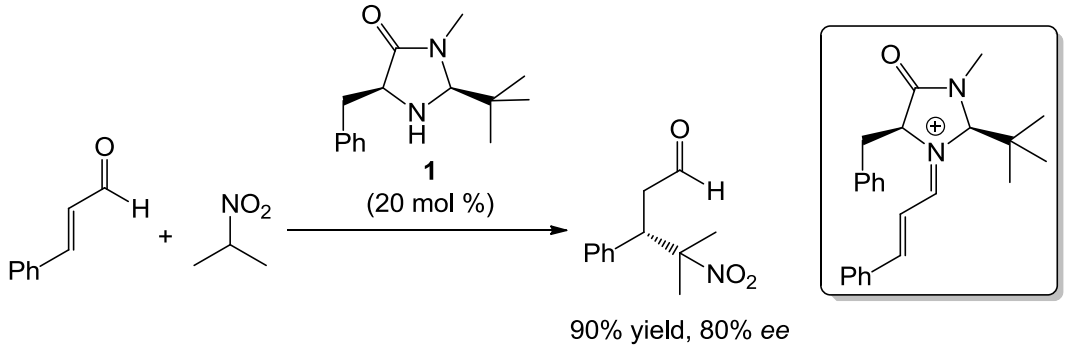
The most widely known example of enamine catalysis is the intermolecular proline catalysed reaction developed by List *et al.*[12] (Scheme 8). Other recent examples of enamine catalysis include aldehyde–aldehyde cross aldol coupling,[20,21] Mannich reaction,[8] Michael reaction,[22,23] α-amination,[24] α-oxygenation,[25] α-halogenation,[24,26-31] α-sulphenylation,[24] α-alkylation and so forth.[32,33] These reactions are often described as involving HOMO activation and in HOMO activation, the energy of the highest-occupied molecular orbital (HOMO) is increased due to the lone pair electrons of a nitrogen atom being higher in energy than those of an oxygen atom, further enhancing its reactivity compared to an enol. Enamines react readily with a wide variety of electrophiles, and the range of reactions are summarised in scheme 9.



Scheme 9 – Summary of enamine reactions with a wide variety of electrophiles

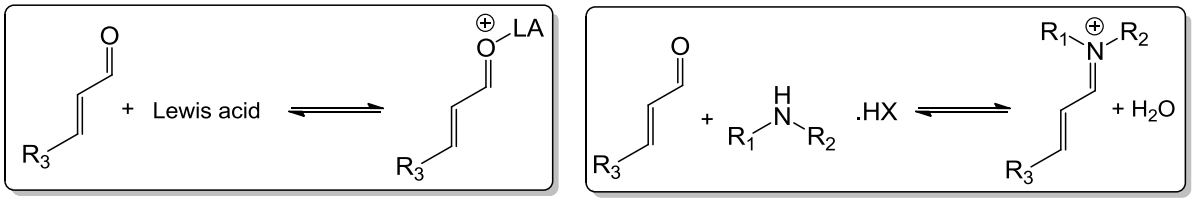
1.1.4 Iminium catalysis (LUMO activation)

MacMillan reported the first example of iminium catalysis with use of the imidazolidinonium salt **1**·HCl to generate iminium ion intermediates identifying a new catalytic strategy for the activation of α,β-unsaturated carbonyl compounds towards cycloaddition,[34] and more recently conjugate addition reactions have been reported using the same catalyst (Scheme 10).[9]



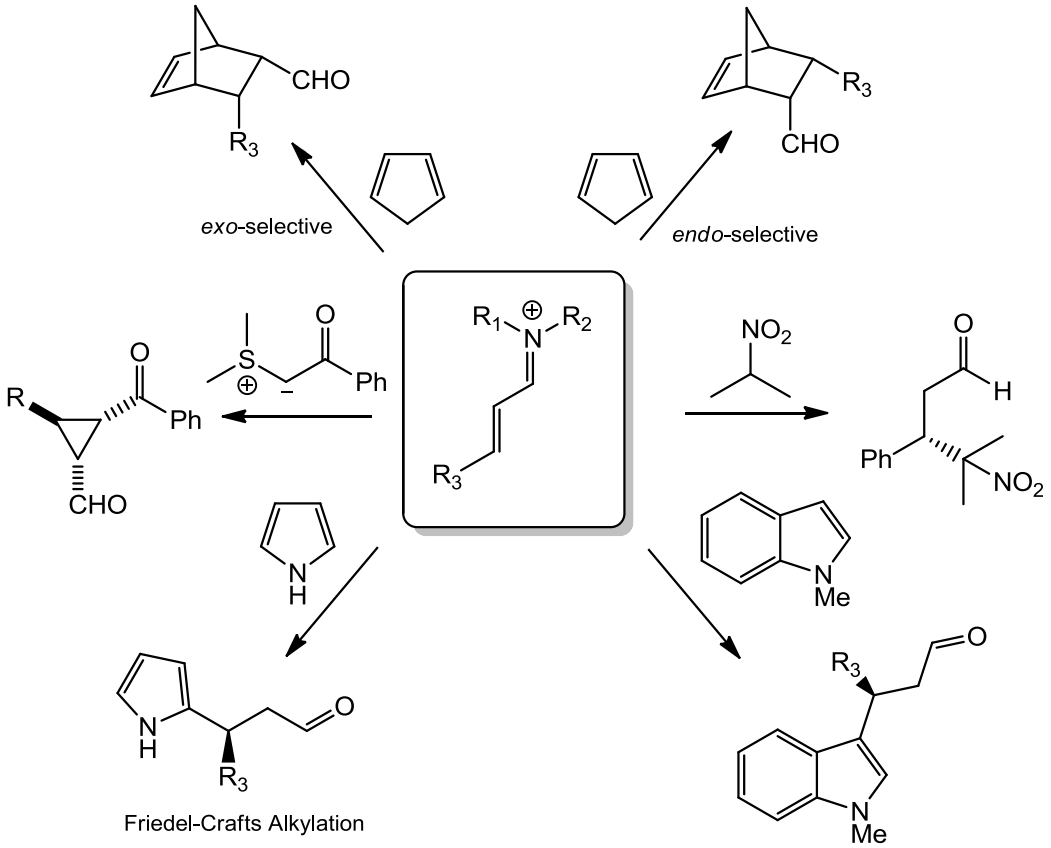
Scheme 10 – Iminium catalysis

In LUMO activation, the energy of the lowest-unoccupied molecular orbital (LUMO) is decreased. This is due to the reversible formation of the active iminium ion species, which mimics the π-electronics and equilibrium dynamics traditionally associated with Lewis acid activation of α,β-unsaturated carbonyl compounds, lowering the energy level of the LUMO associated with the π-system and activating a subsequent reaction (Scheme 11).



Scheme 11 – Concept of LUMO activation

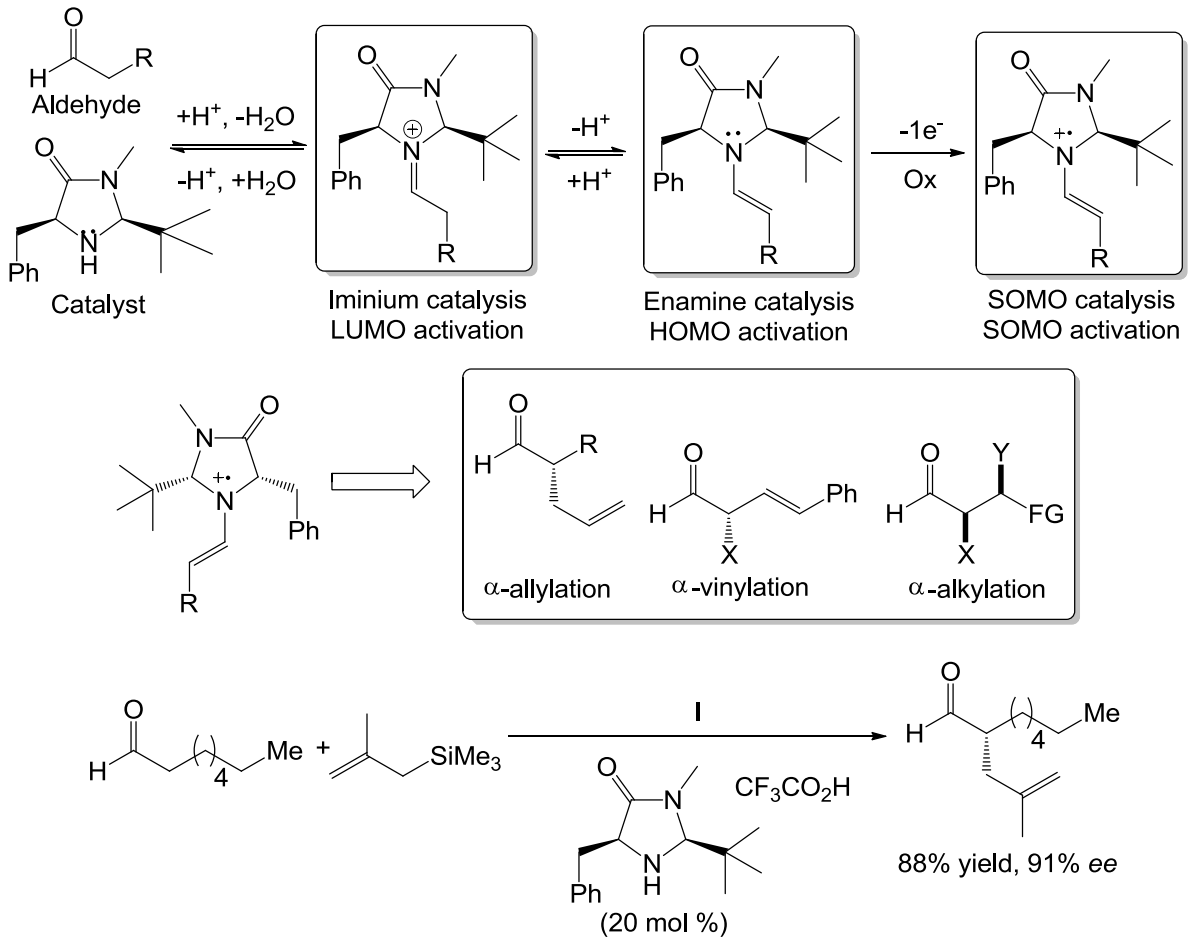
Other examples include; conjugate Friedel–Crafts reactions,[35] *exo*-selective Diels–Alder reactions,[36] cyclopropanations,[37] epoxidations[38] and many others (Scheme 12).[39-41]



Scheme 12 – Summary of iminium catalysis

1.1.5 SOMO catalysis (SOMO activation)

Given the capacity of enamines and iminium ions to rapidly interconvert (an enamine has four π electrons and iminium ion has two π electrons, Scheme 13),[42] MacMillan's group hypothesised that it may be possible to interrupt this equilibrium chemically and thereby to access a mode of catalytic activation that electronically bisects enamine and iminium formation (Scheme 13).[43] This would be *via* a one-electron oxidation of an enamine species and would generate a three-π-electron radical cation with a singly occupied molecular orbital (SOMO), that is activated for a range of transformations.[20] A variety of enantioselective transformations have been accomplished using this concept including α-allylation,[42] α-vinylation,[44,45] α-heteroarylation[42] and α-alkylation[46,47] (Scheme 13). Impressive as this is, there are still limitations. For example, each mole of aldehyde requires two equivalents of the oxidizing agent. It would be more efficient if the oxidant could be recycled during the reaction, possibly by air, so that a much smaller amount could be used.

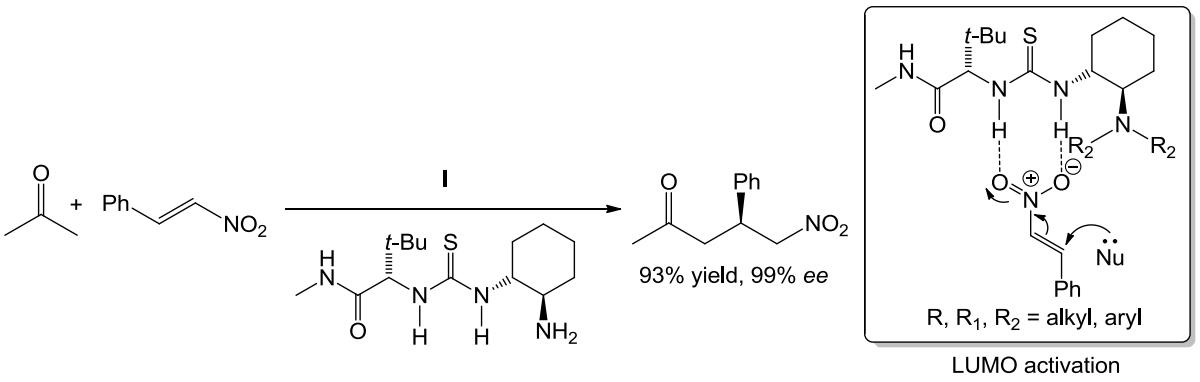


[I] CAN (2 eq.), $NaHCO_3$, DMF, −20 °C, 24 h.

Scheme 13 – SOMO catalysis

1.1.6 Hydrogen bonding-catalysis (LUMO activation)

The first real use of hydrogen-bonding catalysis in organocatalysis was the work conducted independently by Corey *et al.*[48] and Jacobsen *et al.*[49] in reporting an asymmetric variant of the Strecker reaction. Since then a variety of examples have been reported,[50] which include the Mannich reaction,[51] the Biginelli reaction,[52] the Pictet–Spengler reaction,[53] and the Aza-Henry reaction.[54] A recent example is the enantioselective Michael addition to nitroalkenes catalysed *via* thioureas (Scheme 14).[55]

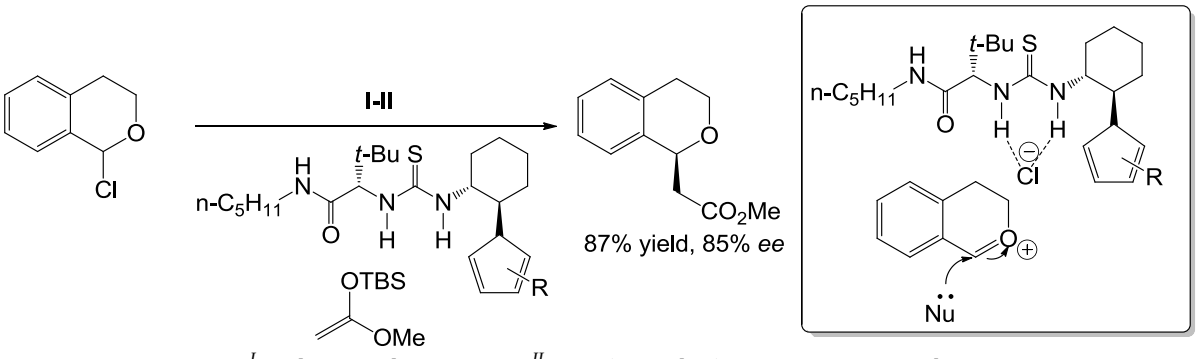


[I] Benzoic acid, Tol, rt.

Scheme 14 – Hydrogen bonding catalysis

1.1.7 Counter-ion catalysis

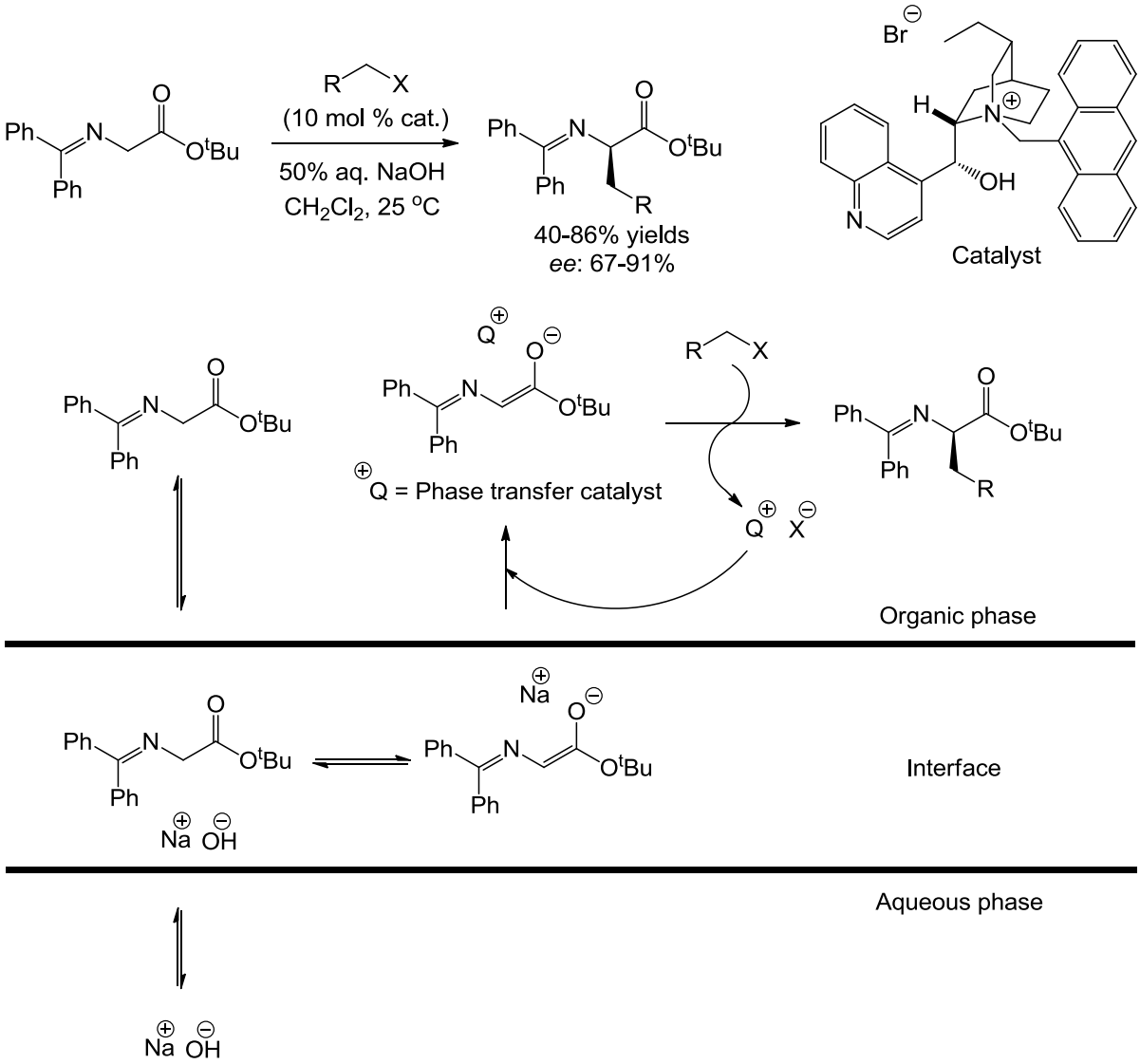
Jacobsen expanded on the work with hydrogen bonding catalysis to develop a novel form of organocatalytic activation that directs highly enantioselective additions to *in-situ* generated *N*-acyl-iminium ions[56] and oxocarbenium ions (Scheme 15).[57,58] In this system, chiral thiourea catalysts, electrostatically bind to and ionise the weak carbon-chlorine bonds of chloroamides and chloroacetals to generate an ion pair. The resulting anionic catalyst-chloride complex behaves as a chiral counter-ion; this directs the approach of nucleophiles to a single face of the transient α-heteroatom stabilised cationic species.[58]



[I] BCl_3, CH_2Cl_2, 0 °C to rt. [II] Cat. (10 mol %), TBME, −78 °C, 6 h.

Scheme 15 – Counter-ion catalysis

Another example of counter-ion catalysis is phase transfer catalysis (PTC). This involves the use of PTCs to facilitate the transfer of a molecule or ion from one reaction phase to another and by doing so it can greatly accelerate the rate of heterogeneous (polyphasic) reaction processes (Scheme 16).[59] An example is the work from Lygo *et al*. with the use of *Chinchona* alkaloid derivatives as enantioselective PTCs in the asymmetric alkylation of glycine imines to generate a range of α-amino acid derivatives in good enantioselectivity (Scheme 16).[60]



Scheme 16 - Phase transfer catalysis

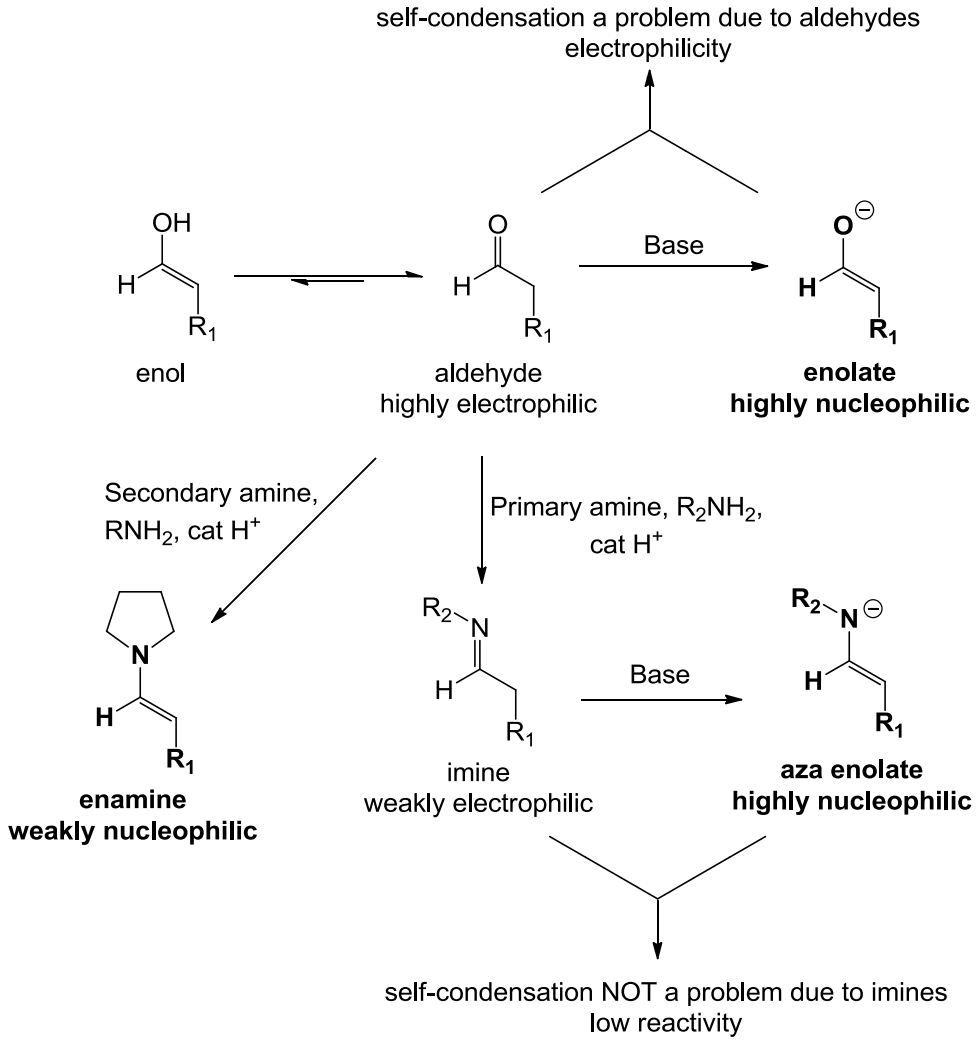
1.1.8 Limitations of organocatalysis

Recently organocatalysis has grown immensely; however, there are still limitations with each of the generic activation modes involved. In enamine catalysis, the relatively narrow substrate scope is a limiting factor as particularly reactive electrophiles have to be used.[61] Even though iminium catalysis is a maturing field, some obstacles would need to be addressed before it

becomes a method of choice for large scale synthesis.[62] This includes catalyst activity, for example, and the lowering of the high catalyst loading required for asymmetric induction. A better understanding of the subtleties involved in the amount of water present in the reaction and the role of co-acid additives would also be beneficial.[62] To date, only a handful of activation modes are used to accomplish many new asymmetric transformations. SOMO catalysis[47] was recently developed as an alternative activation mode to enable multiple new transformations. With SOMO catalysis, there are still limitations, for example, each mole of aldehyde requires two equivalents of the oxidising agent.[62] Therefore, in order to further expand the scope of organocatalysis and to overcome some of the limitations, new activation modes will need to be developed. The aim of this project is to develop a new method for the catalytic formation of aza enolates, providing a new organocatalytic activation mode. It is hoped that this will enable the use of relatively unreactive electrophiles in organocatalytic reactions and thus expand the scope of organocatalysis.

1.2 Introduction to aza enolate chemistry

Aza enolates are generated from imines, which are prepared by reaction of a primary amine with an aldehyde or ketone. Treatment of an imine with a base leads to an aza enolate which is highly nucleophilic. Aza enolates have been shown to undergo reactions with a variety of unreactive electrophiles such as epoxides (Chapter 3). A major advantage of the use of aza enolates compared to normal enolates (derived from aldehydes or ketones), is that they do not normally undergo self-condensation reactions (Scheme 17).



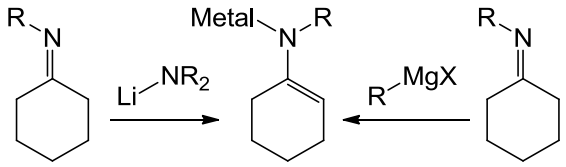
Scheme 17 – Generation of aza enolates

1.2.1 A note on aza enolate nomenclature

Over the past forty-fifty years various names have been used to describe anions derived from imines including metalloenamines (and metallated enamines)[63], metallated Schiff bases[64], imine anions[65,66], enamides[67-69], hydrazones[70-72] and more recently aza-enolates.[73] The latter is preferred for the purpose of this thesis as it emphasises both the source of these species and their high reactivity, whereas, metallated enamines suggests that the anions are derived from enamines and not imines.[74]

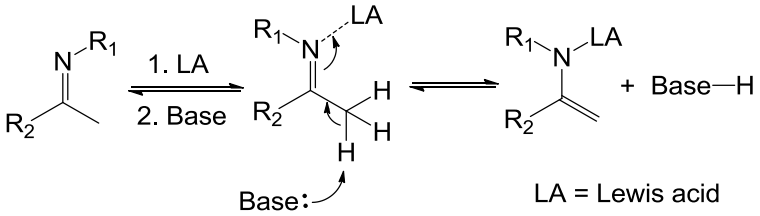
1.2.2 Hard and soft enolisation of imines

Hard enolisation (deprotonation) is normally irreversibly achieved using a strong base. A good example is where imines may be transformed into their conjugate bases (aza enolates) with a base such as LDA or a Grignard reagent (Scheme 18).



Scheme 18 – Hard enolisation of imines

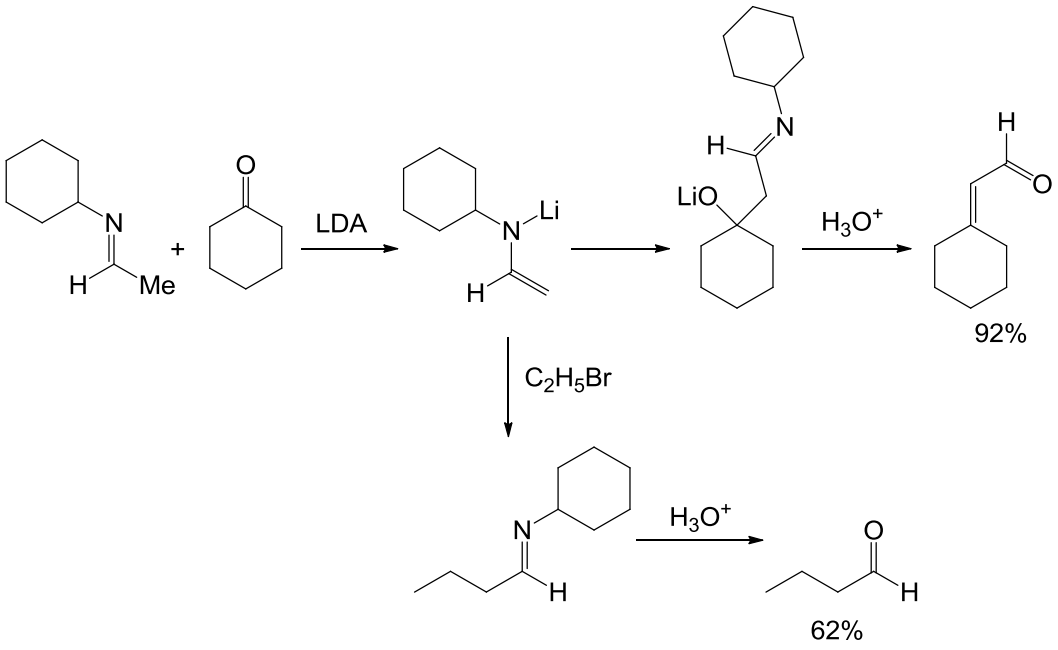
Soft enolisation provides a milder approach to the deprotonation of imine compounds and occurs when a relatively weak amine base and an imine activating component (such as a Lewis acid) act in concert to effect reversible deprotonation (Scheme 19).[75]



Scheme 19 – Soft enolisation of imines

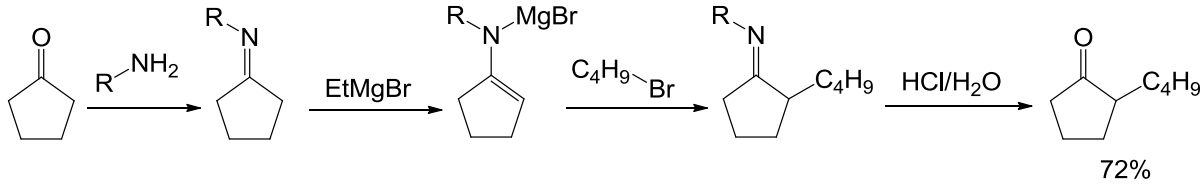
1.2.3 Generation and reaction of aza enolates *via* hard enolisation

In 1963 both Stork *et al.*[76] and Wittig *et al.*[64] reported on the reactions of aza enolates by α-deprotonation of imines with strong bases. Wittig[64] demonstrated the use of lithiated aza enolates derived from aldehydes as nucleophiles for achieving a direct aldol reaction, and for a reaction with alkyl halides (Scheme 20).[64]



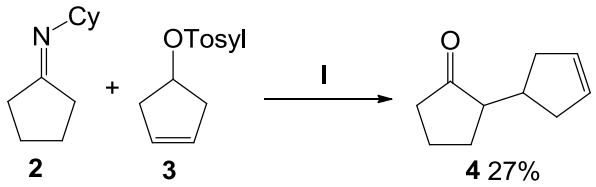
Scheme 20 – Lithiated aza enolates derived from aldehydes as nucleophiles

Simultaneously, Stork and Dowd demonstrated that monoalkylation of a ketone could be accomplished in high yield *via* reaction of a magnesium aza enolate with alkyl halides and sulfonates (Scheme 21).[76]



Scheme 21 – Monoalkylation of a ketone *via* reaction of a magnesium aza enolate

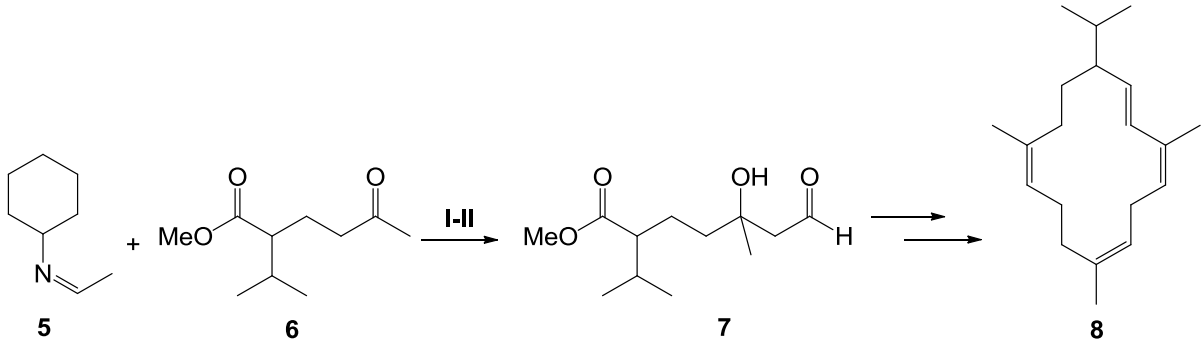
From this innovative work, Gates *et al*, demonstrated the alkylation of an aza enolate derived from an imine **2** with 3-cyclopentyl tosylate **3** in 1974 (Scheme 22).[77] The imine was prepared using a procedure developed by Stork (*vide infra*),[76] subsequent reaction with a Grignard led to the formation of the aza enolate then the product **4** in a 27% yield.



*[I] EtMgBr, THF, **2**, reflux, 1 h, then 0 °C, **3**, then reflux 18 h.*

Scheme 22 – Alkylation of aza enolates with 3-cyclopentyl tosylate (3)

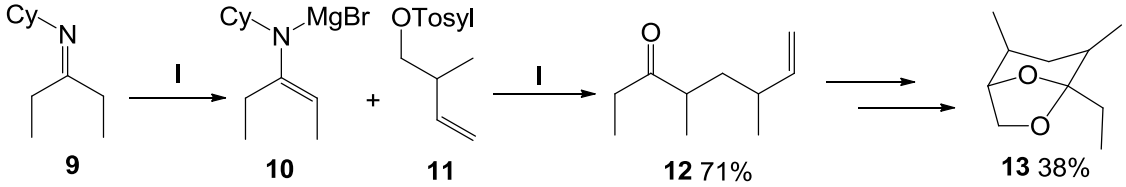
Leading on from this, Dauben *et al*., demonstrated the use of aza enolates from imine **5** for the synthesis of a fourteen-membered diterpene (±)-Cembrene **8**. The key step was the formation of the aza enolate with LDA followed by reaction with **6**,[78,79] then to afford hydroxyaldehyde **7** in 77% yield (Scheme 23).[80]



*[I] Dry Et_2O, DIPA, CH_3-Li, 1 h, 0 °C. [II] Imine **5**, −78 °C, **6**, 25 min, then 25 h at −78 °C.*

Scheme 23 – (±)-Cembrene synthesis

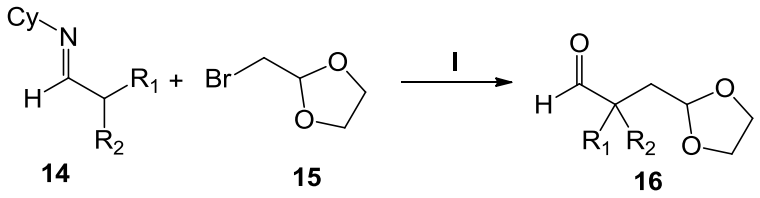
In 1976, Silverstein demonstrated the use of aza enolates in the synthesis of optically active Multistriatin **13**. Initial attempts to form Multistriatin (**13**) yielded only small amounts of the product (5%) *via* a non aza enolate approach; therefore, an alternative method was attempted using aza enolates derived from imine **9** and a Grignard reagent. The key intermediate **12** was synthesised in a 71% yield by reaction of aza enolate **10** with the tosylate **11** in THF (Scheme 24).[81] Following this, epoxidation of **12** with *m*-CPBA and then cyclisation using $SnCl_4$ formed the product Multistriatin **13**.



*[I] EtMgBr, THF, rt, then at reflux for 8 h, then 5 °C then tosylate **11**, 45 min, then at reflux 1 h.*[81]

Scheme 24 – Multistriatin synthesis

In the same year, Normant *et al*.[82] and Schlessinger *et al*.[83] independently demonstrated the reaction of aza enolates with a variety of alkyl halides. Firstly, Normant *et al*. demonstrated the reaction of aza enolates derived from imine **14** with alkyl halide **15** in the synthesis of aldehyde **16** in good yields ranging from 61-85% (Table 1).[82]

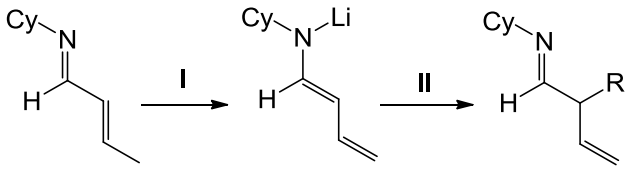


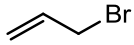
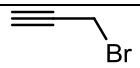
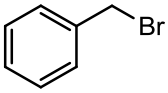
Entry	R_1	R_2	Yield (%)
1	Me	H	79
2	Et	H	83
3	$^{n}C_4H_9$	H	85
4	Et	Et	68

*[I] LDA, HMPT, THF −60 °C, **14**, then −10 °C, 2 h, then **15**, −60 °C, 5 h.*[82]

Table 1 – Reaction of aza enolates derived from imines with alkyl halides

Schlessinger *et al*. demonstrated the use of aza enolates derived from α,β-unsaturated ketones[83] and aldehydes[83] to undergo clean alkylation with alkyl halides at the α- instead of γ-position in excellent yields (Table 2).

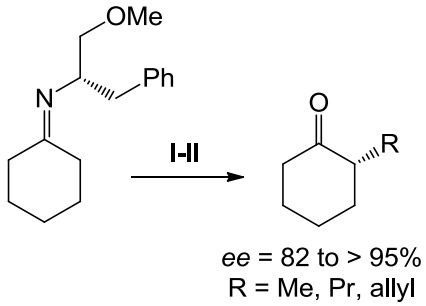


Alkyl halide	Reaction time (h)	Yield (%)
Me-I	4.5	98
	4.5	100
	3.5	95
	4.0	100
	20.0	95

[I] LDA, 0 °C, HMPT, 10 min, then −78 °C, 30 min. [II] Alkyl halide, reaction time, −78 °C.[83]

Table 2 - Aza enolates derived from α,β-unsaturated ketones and aldehydes

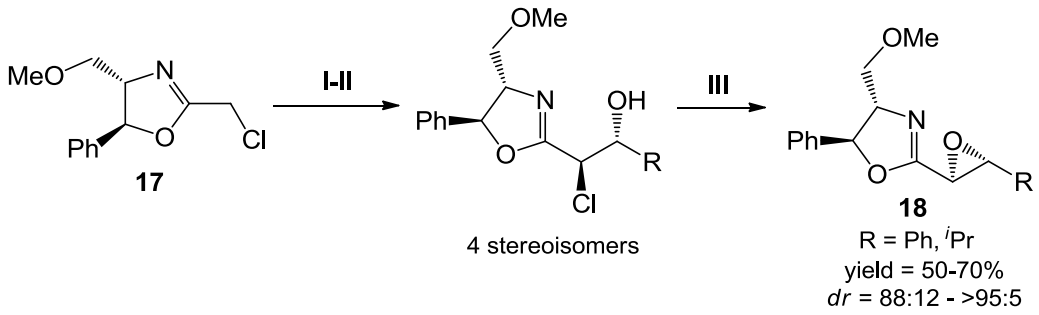
In 1976 Meyers reported the alkylation of aza enolates containing an acyclic amino acid-based auxiliary and accomplished good yields and high enantioselectivities with an imine derived from cyclohexanone (Scheme 25).[70,71]



[I] LDA, THF. [II] RX.[70]

Scheme 25 – Aza enolates containing an acyclic amino acid based auxilary

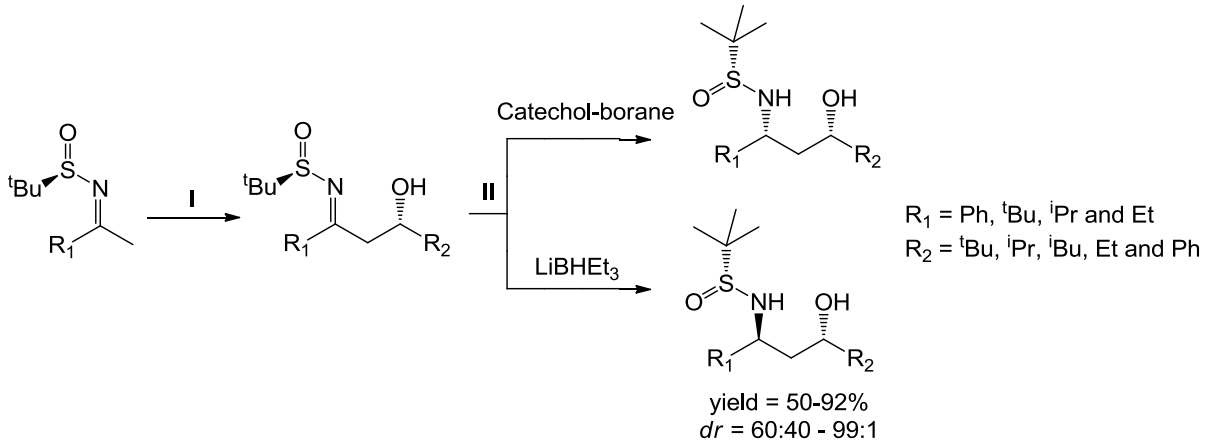
In 2001, Florio *et al*. reported the coupling of oxazoline-derived aza enolates **17** with aldehydes using a variety of different metal aza enolates such as titanium, boron, aluminium, and tin. Titanium aza enolates produced the best yields with good diasteromeric ratios of the product **18** (Scheme 26).[84]



[I] LDA, THF, 1 min, 100 °C, then, Bu_2BOTf or $Ti(iPrO)_4$ or Et_2AlCl or SnOTf, 30 min, 100 °C. [II] PhCHO, THF, then rt. [III] NaOH, [i]PrOH

Scheme 26 - Oxazoline-derived aza enolates with aldehydes

In 2003, Ellman *et al*. demonstrated the use of magnesium and zinc aza enolates in a diastereoselective aldol reaction. This involved using an *N*-sulfinyl imines derived from a ketone, treating the imine with LDA at −78 °C in the presence of a Lewis acid ($ZnBr_2$ or $MgBr_2$) to generate the aza enolate, then reacting this with the corresponding aldehyde to give a β-hydroxyimine. These were then selectively reduced by either catecholborane or $LiBHEt_3$ to produce *syn*- and *anti*-1,3-amino alcohols in good diasteroselectivities and yields (Scheme 27).[85] Ellman *et al*. have also carried out reactions of similar aza enolates with Michael acceptors.[86]

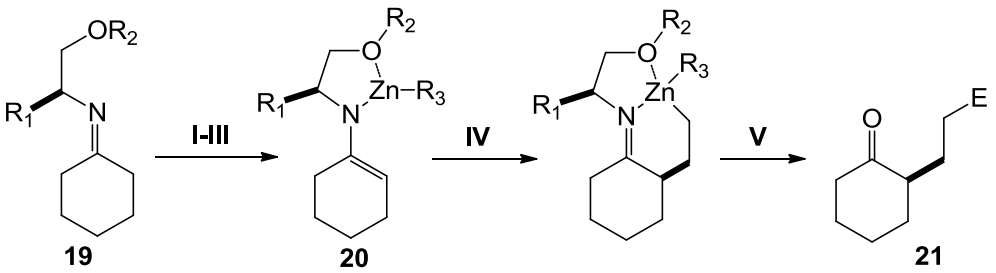


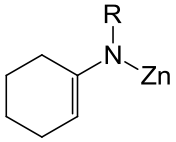
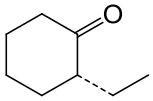
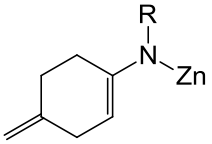
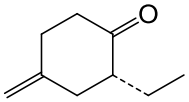
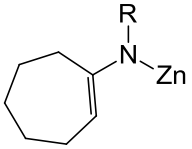
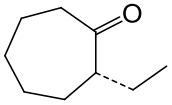
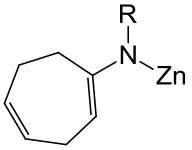
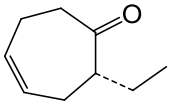
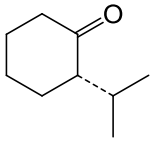
[I] LDA, −78 °C, THF, 45 min, then, $MgBr_2$ or $ZnBr_2$, −78 °C, 45 min, then R_2CHO, −78 °C, 3h. [II] Reduction.

Scheme 27 - Diastereoselective aldol reaction using magnesium and zinc aza enolates

In that same year, Nakamura *et al*. reported an enantioselective synthesis of α-substituted ketones through three-component coupling of an optically active zinc aza enolate, alkene, and an electrophile (E^+) (Table 3, selected examples).[67,68] The significant step involves the addition of a zinc aza enolate such as **20** derived from imine **19** (prepared from (*S*)-valinol or

(*S*)-*t*-leucinol) to an unactivated alkene to give the corresponding product **21**. Nakamura reported that the alkoxy substituent on the nitrogen enamide plays a significant role for tuning the reactivity and thermal stability of the nucleophile. The reactions generally proceed in high yield and give products with high enantiomeric excess.

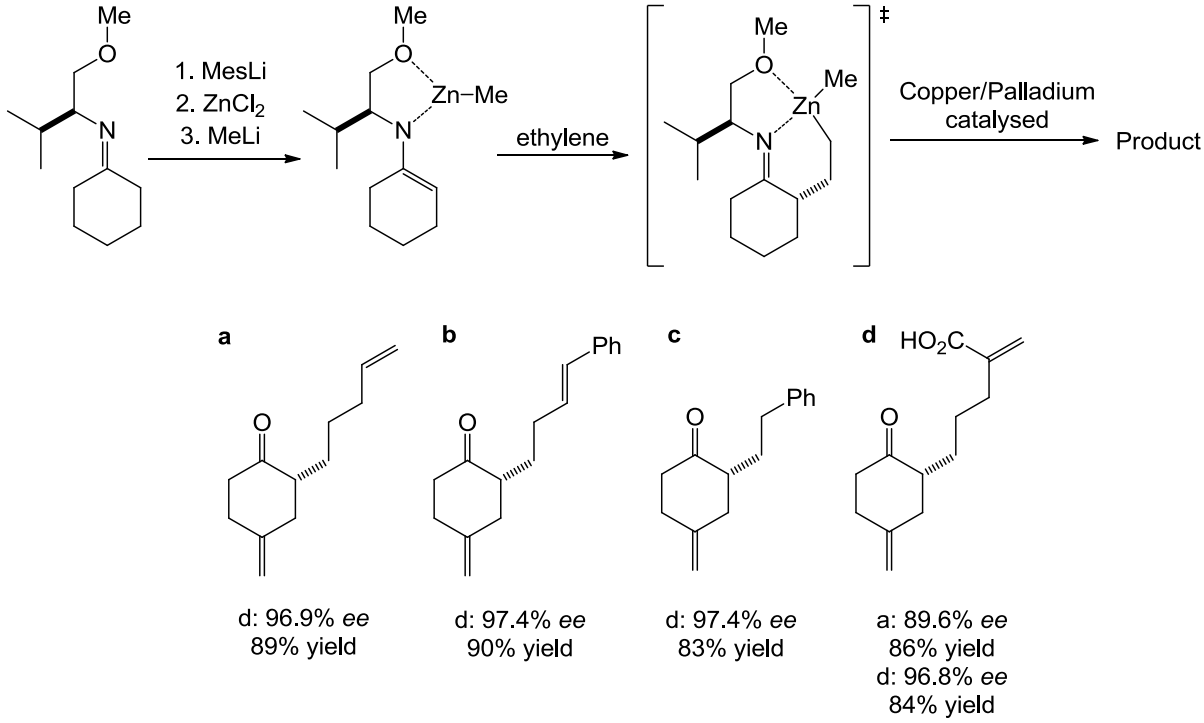


Entry	Zinc enamide	Product	*ee* (%), yield (%)
1	 $R_1 = {}^t$Bu, $R_2 = Me_3Si$, $R_3 = Me$		95, 91 (99, 29)[a]
2	 $R_1 = {}^i$Pr, $R_2 = Me$, $R_3 = Me$		91, 93 (94, 38)[a]
3	 $R_1 = {}^t$Bu, $R_2 = Me_3Si$, $R_3 = Me$		96, 82 (99, 34)[a]
4	 $R_1 = {}^t$Bu, $R_2 = Me_3Si$, $R_3 = Me$		96, 93
5*	 $R_1 = {}^t$Bu, $R_2 = Me_3Si$, $R_3 = Me$		93, 47 (98, 15)[a]

[I] MesLi, 0 °C, Et_2O. [II] $ZnCl_2$. [III] R_3Li, hexane. [IV] Ethylene (20 atm), 40 °C, 24 h. [V] E^+, H_3O^+. [a] The data in parentheses refer to the yield and selectivity determined for the ketone product obtained. [*] Propene atmosphere (8 atm), 60 °C for 48 h.

Table 3 - Three-component coupling of an optically active zinc aza enolate, alkene, and an electrophile (E^+)

Following on from this, Nakamura *et al*. reported the reaction of the initial addition products (Entry 2, table 3) *via* palladium- and copper-catalysed reactions (Scheme 28).[68]

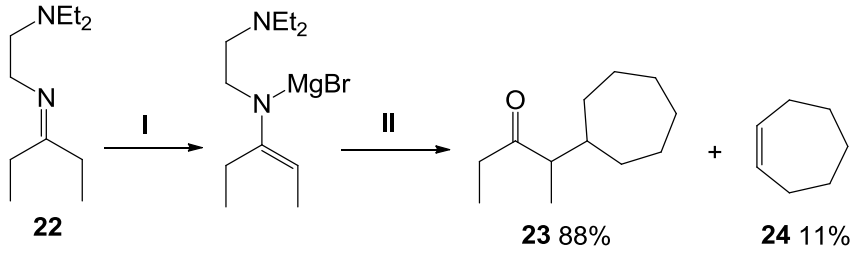


(a) Allyl bromide (2 eq.)/CuBr•SMe_2 (20 mol %). (b) β-bromostyrene (2 eq., >99.9%E)/$Pd(PPh_3)_4$ (5 mol %). (c) Iodobenzene (2 eq.)/ $Pd(PPh_3)_4$ (5 mol %). (d) Ethyl-2-(bromomethyl)acrylate (2 eq.)/CuBr•SMe_2 (1 eq.).

Scheme 28 – Nakamura work continued[68]

1.2.4 Alkylation reactions with alkyl chlorides and fluorides

Building upon this work the Nakamura group reported that the use of magnesium enamides bearing an internal nitrogen coordination site expands the scope of aza enolate alkylation reactions to unreactive alkyl halides, particularly alkyl chlorides and fluorides. Initial screening was carried out to discover the best reaction conditions and under the optimised conditions chlorocycloheptane and imine **22** reacted to give the alkylated product **23** in an 88% yield (Scheme 29). In addition, cycloheptene **24** was also produced in 11% yield, suggesting competitive elimination reactions were taking place (Scheme 29).[69]



[I] MesMgBr, THF, rt, then, 80 °C, 1 h. [II] Chlorocycloheptane, THF, 45 °C, 24 h, then, 60 °C, 12 h, then H_3O^+.

Scheme 29 - Aza enolate alkylation reactions with chlorocycloheptane

The optimised conditions were applied to a range of different aza enolates and alkyl halides (Table 4 – selected examples).

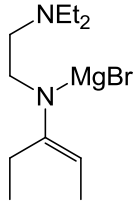
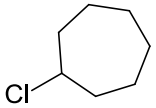
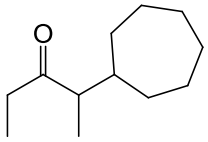
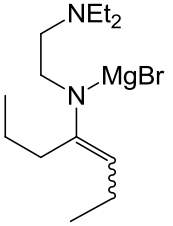
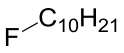
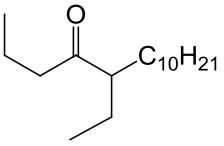
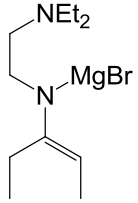
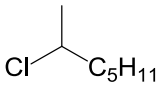
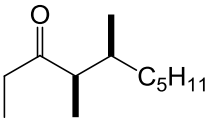
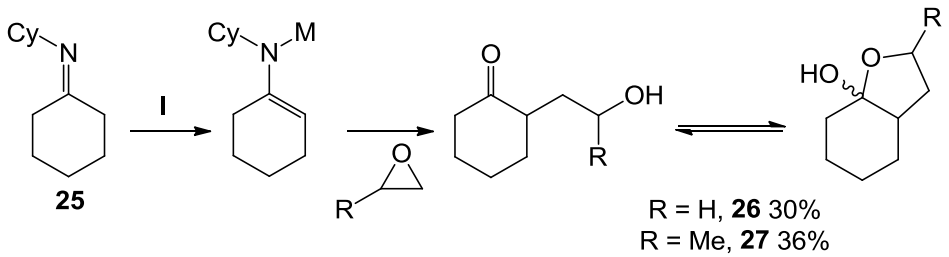
Entry	Enamide	Alkyl halide	Temp, time	Product (% yield)
1			60 °C, 12 h	 (**86**)
2			60 °C, 36 h	 (**97**)
3			60 °C, 12 h	 *syn*:*anti* (2:1) (**85**)

Table 4 – Optimised alkylation reactions

1.2.5 Reactions with epoxides and their derivatives *via* hard enolisation

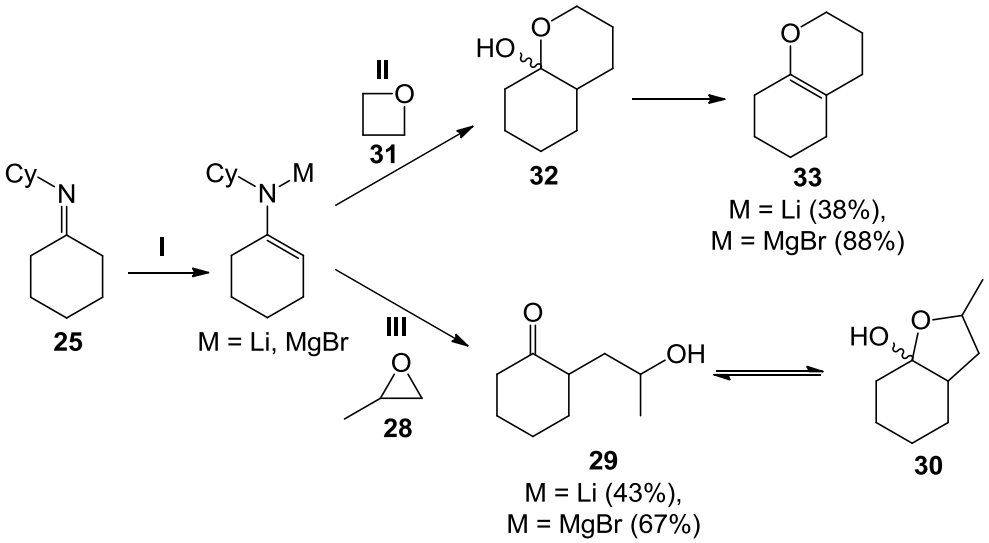
The first use of aza enolates to ring open epoxide and oxetane was reported by Tarbell *et al.*[87] and Hudrlik *et al.*[88]. Firstly, Tarbell and Harvey[87] reported the use of cyclohexanone imine **25**, which was treated with EtMgBr and then reacted with two different epoxides to produce the corresponding products **26** and **27** (Scheme 30).



[I] EtMgBr, THF, reflux, 2 h, then 0 °C then epoxide, then rt, 25 h, HCl.[87]

Scheme 30 – Aza enolates derived from imines ring opening epoxides

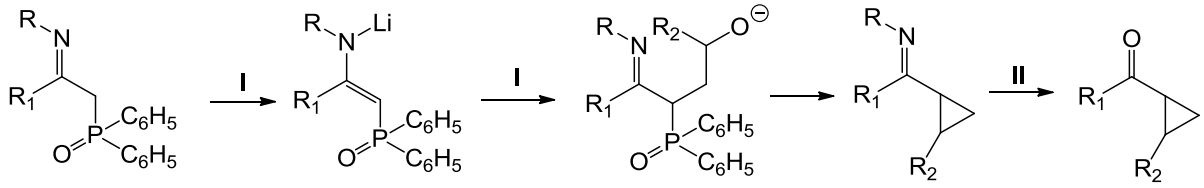
Hudrlik *et al*. expanded on the work by Tarbell and Harvey by improving the yield of the reaction with epoxide **28**, by using milder acid hydrolysis to give products **29** and **30** (Scheme 31).[88] In addition, Hudrlik *et al*. reported the first use of aza enolates as nucleophiles for the ring opening of oxetane **31** in good yield to give the cyclic enol ether **33** (Scheme 31).



*[I] EtMgBr or [n]BuLi, THF, reflux, 2 h, then 0 °C then either [II] Oxetane **23** or [III] Propylene oxide **22**, then rt, 25 h, AcOH.*[88]

Scheme 31 – Aza enolates derived from imines ring opening epoxides and oxetane

In 1971, Aguiar *et al*. demonstrated the reaction of lithium aza enolates derived from phosphono imines with a variety of epoxides in moderate yields (Table 5).[89] Aguiar *et al*. also extended this methodology to the use of thiophosphonates.[90]

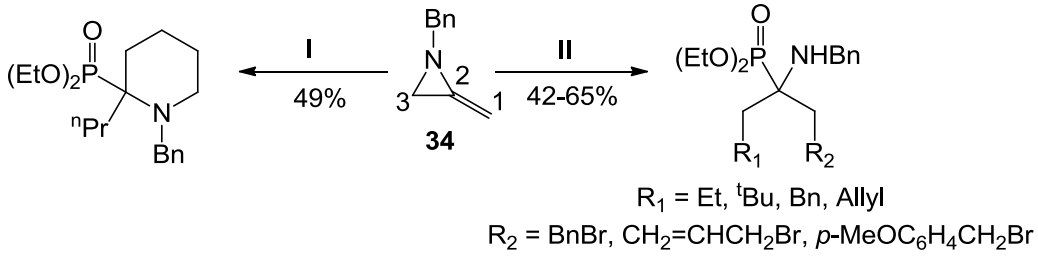


R	R_1	R_2	Yield (%)
$^{n}C_4H_9$	C_6H_5	C_6H_5	58
$^{n}C_4H_9$	$^{n}C_3H_7$	C_6H_5	58
$^{n}C_4H_9$	$^{n}C_3H_7$	Me	40
$^{n}C_4H_9$	$^{t}C_4H_9$	C_6H_5	65

[I] ^{n}BuLi, THF, -78 °C, then epoxide, 12 h. [II] H_3O^+.[89]

Table 5 - Lithium aza enolates derived from phosphono imines ring opening epoxides

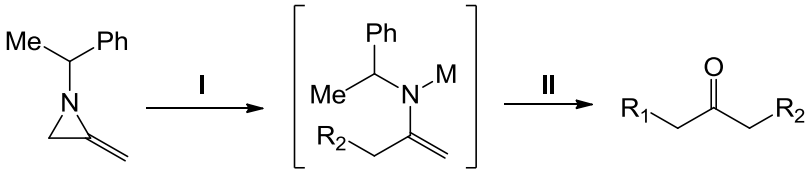
Recently, Shipman *et al*. reported the use of methyleneaziridines in a four-component reaction for the formation of α-amino phosphonates (Scheme 32).[91,92] The reaction involves opening of the aziridine **34** at C-3 by using a Grignard reagent under Cu(I) catalysis, resulting in the generation of a magnesium aza enolate which reacts with the corresponding carbon electrophile (R_2-X) to form a variety of products in a 42-65% yield (Scheme 32).



[I] EtMgCl, cat. CuI, THF, then $I(CH_2)_3I$, then $LiP(O)(OEt)_2$. [II] R_1MgCl, cat. CuI, THF, then R_2-X, then PhP(O)H(OEt), then H_3O^+.

Scheme 32 – Ring opening of aziridines for the formation of α-amino phosphonates

Shipman *et al*. expanded this work to include other electrophiles (Table 6). However, a major limitation to this chemistry was the use of excess Grignard reagent (3 eq.) to drive this reaction to completion.[92]



Entry	R_1	R_2	X	Yield (%)
1	Bu	Bu	Cl	78
2	Octyl	$H_2C=CHCH_2$	Br	80
3	Octyl	$H_2C=CHCH_2$ CH_2	OTs	67
4	Bu	4-$MeC_6H_4CH_2$	Cl	75
5	Bu	4-$MeC_6H_4CH_2$	Cl	80

[I] R^1MgCl, CuI (20 mol %), THF, −30 °C, then rt, 24 h. [II] R^2X then H_3O^+

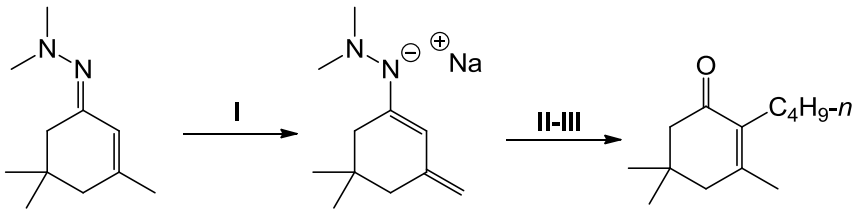
Table 6 – Summary of ring opening of aziridines with different electrophiles

1.2.6 Aza enolates derived from hydrazones *via* hard enolisation

Since excellent reviews[93-96] have already been published on the subject, so the formation and reactions of hydrazone-derived aza enolates will only be briefly presented.

1.2.6.1 Short history of synthetic applications of hydrazones

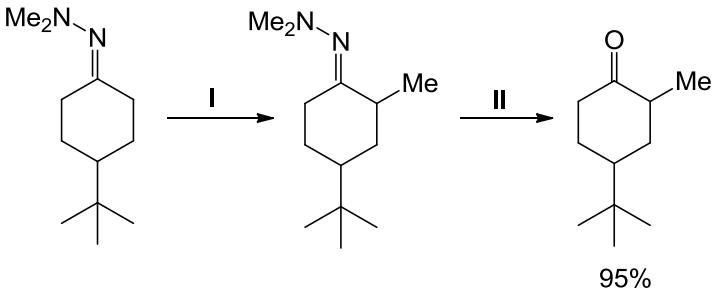
In 1971, Stork and Benaim reported the concept of using the anions derived by deprotonation of disubstituted hydrazones for achieving α-alkylation of α,β-unsaturated ketones (Scheme 33).[63]



[I] NaH, HMPT, THF. [II] $^nC_4H_9Br$, THF. [III] HCl.

Scheme 33 – Stork hydrazone chemistry

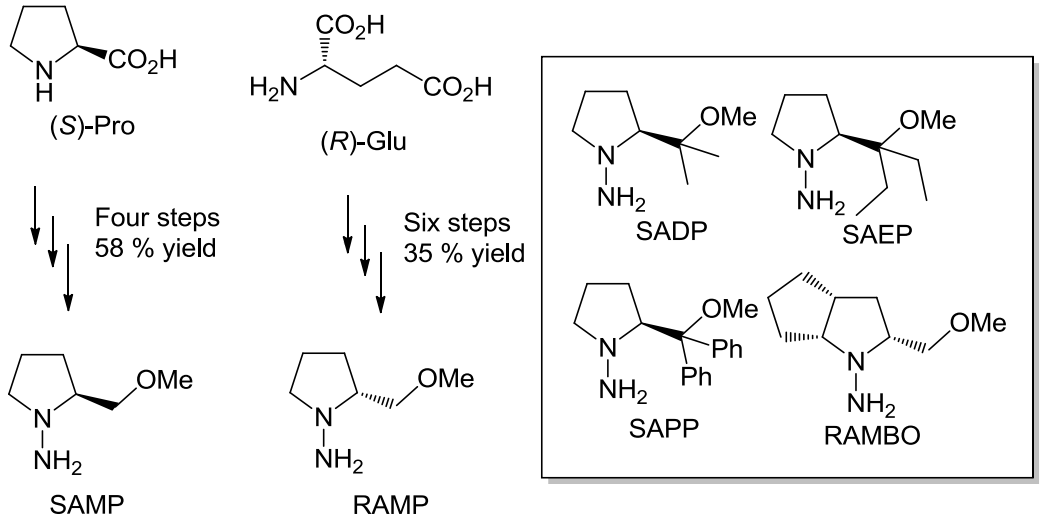
From this pioneering work, it took another five years before the use of *N*,*N*-dialkylhydrazones gained widespread application, particularly, until the landmark papers published by Corey and Enders (Scheme 34)[72,97-101] and independently by Normand *et al*.[102]



[I] LDA, 0 °C, 20 h, then CH_3I, 0 °C, 10 h. [II] Sodium periodate, THF, rt.[72,103]

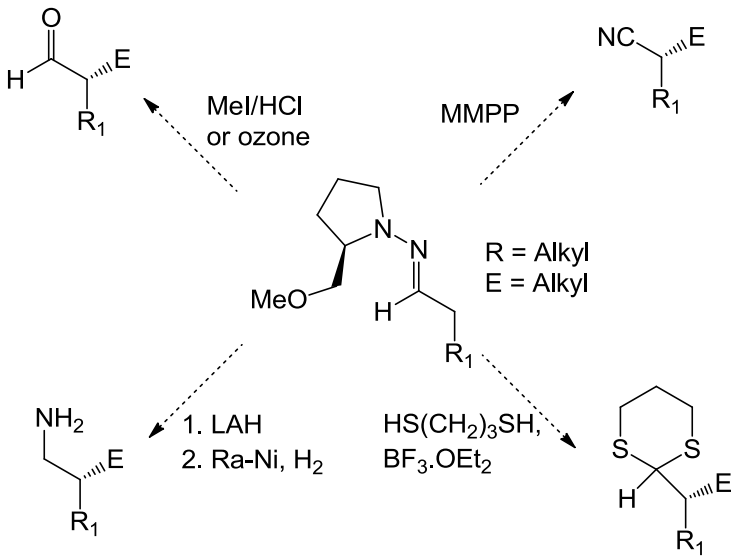
Scheme 34 – Corey and Enders dialkylhydrazone chemistry

For the asymmetric alkylation of ketones and aldehydes, a highly practical method was developed by the Enders group using hydrazones.[93,97,104-108] These now widely used auxiliaries are known as SAMP and RAMP (acronyms for **S**-or **R**-1-**a**mino-2-**m**ethoxymethyll**p**yrrolidine). This constitutes an asymmetric version of the dimethyl hydrazone methodology originally developed by Corey and Enders in 1976 (*vide supra*). These auxiliaries are available from either proline or pyroglutamic acid (Scheme 35).[107,109]



Scheme 35 – SAMP/RAMP chiral auxiliaries and their derivatives

After work-up, the crude α-substituted hydrazones can be purified by distillation or column chromatography. Subsequent cleavage of the hydrazone restores the original carbonyl function to provide substituted ketones or aldehydes (Scheme 36).[110] After alkylation, cleavage may be affected with a number of reagents. Among these are oxidative cleavage (ozonolysis, sodium perborate,[111] or magnesium peroxyphthalate),[112] and acidic hydrolysis (methyl iodide and dilute HCl,[106,113] or BF_3 and water[101,102]).



Scheme 36 – Examples of possible cleavage products

Prior to 2000, the vast majority of reactions were α-alkylations (Table 7, selected examples). This involved α-branched acyclic and cyclic ketones,[94] dioxanones,[114] and β-keto esters.[94] The alkylating agents used include alkyl, allyl, and benzyl halides (Br, I), tosyl-aziridines and methyl sulfate.[93,94]

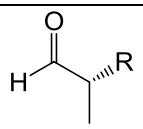
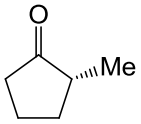
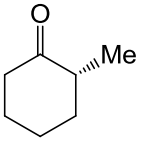
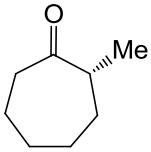
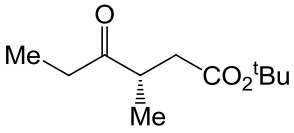
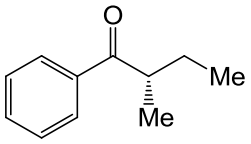
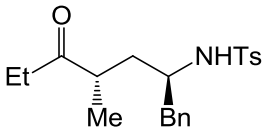
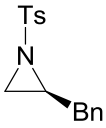
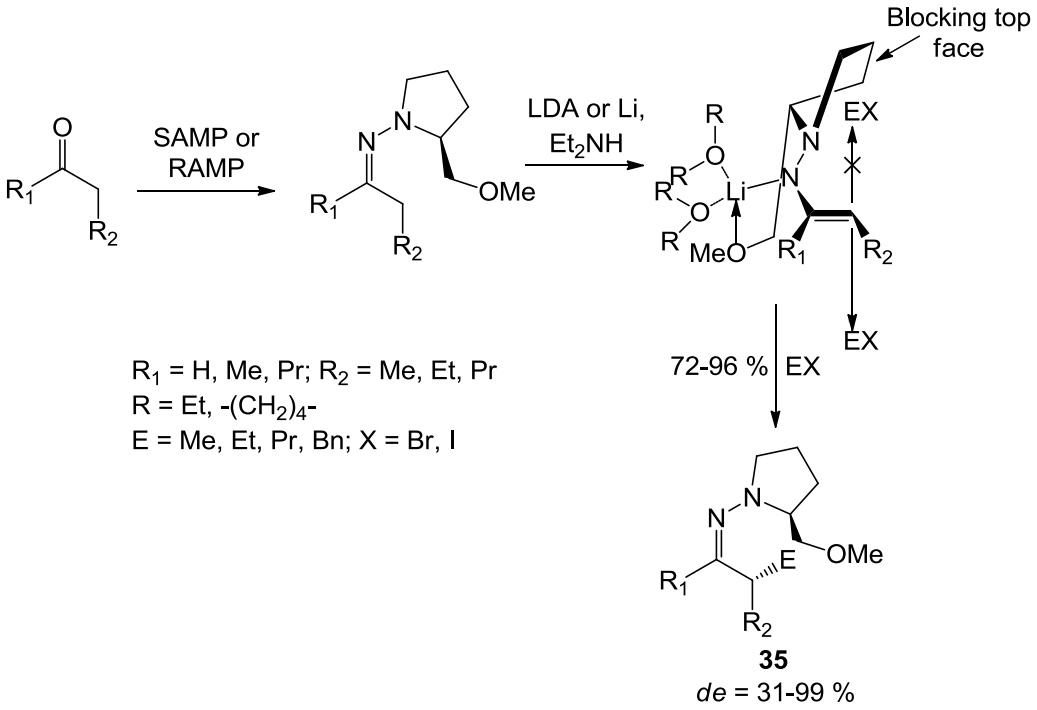
Product	Electrophile	% Yield	% *ee*	Ref
	EtI, $C_6H_{13}I$	71 52	95 >95	113
	Me_2SO_4	66	86	113
	Me_2SO_4	70	>99	113
	MeI	59	94	113
	$BrCH_2CO_2{}^tBu$	53	>95	113
	EtI	44	>97	106
		80	>98	93

Table 7 – Examples of products using hydrazone chemistry

1.2.6.2 Stereochemistry of SAMP/RAMP reactions

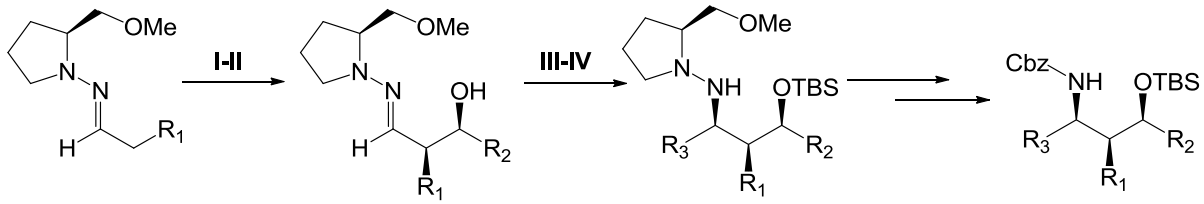
Deprotonation of SAMP hydrazones by LDA (or other Li bases) results in the formation of aza-enolates, which can be trapped by electrophiles to obtain diaseteromerically enriched compounds (**35**) (Scheme 37).[100,104,105,115] The absolute configuration of the products results from the diastereotopic face selective attack of the electrophilic reagent on one of the sides of the SAMP or RAMP hydrazone aza enolate (Scheme 37).[96] The stereochemical outcome of the reaction can be explained by a so-called S_E2' front mechanism[116] meaning front side attack leading to retention of configuration. Because of the reaction pathway, it is possible to predict the resulting diastereomer. The synthesis of the desired product can therefore be controlled by the use of either SAMP or RAMP as the chiral auxiliary.[93]



Scheme 37 – Stereochemistry of SAMP/RAMP reactions

1.2.6.3 Recent synthetic applications of hydrazones *via* soft enolisation

The Enders group were able to demonstrate a $TiCl_4$ mediated aza enolate aldol reaction, combined with subsequent 1,2-addition of organocerium to an aldehyde hydrazone. This led to the effective synthesis of *syn*-configured *N*,*O*-protected 1,3-amino alcohols in good yields (18-58%) and with good diastereoselectivities (83-96%) (Scheme 38).[117]

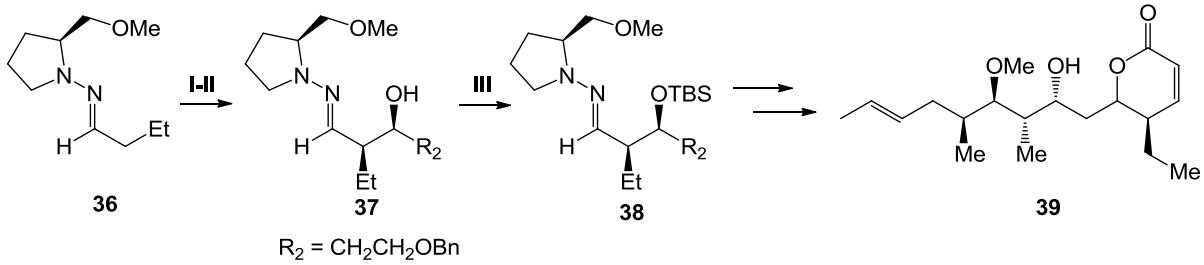


[I] $TiCl_4$, DIPEA, −78 °C. [II] R_2CHO. [III] TBSCl, DIPEA. [IV] $R_3Li/CeCl_3$.

Scheme 38 – Soft enolisation using hydrazones

A more recent example was the use of titanium aza enolates of SAMP/RAMP hydrazones **36** with benzylprotected 3-hydroxypropanal in an asymmetric total synthesis of Pironetin **39**, a polyketide with immunosuppressive, antitumor, and plant-growth-regulating activities.[110] The TBS-protected product **38** (Scheme 39) was obtained in good yield (80% over two steps), with moderate diastereoselectivity (55%). The synthesis of the natural product required in

addition to the aza enolate aldol reaction to form **37**, a Mukaiyama aldol reaction, asymmetric alkylation and a ring-closing metathesis as other key steps.

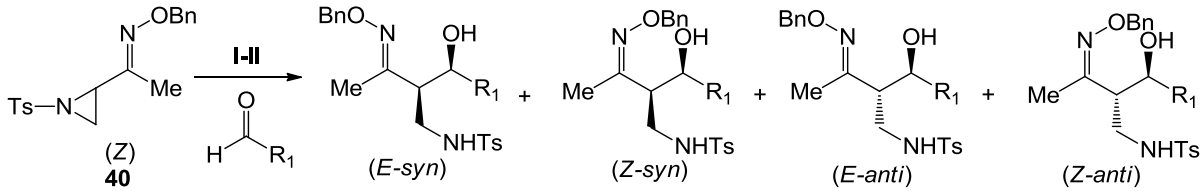


[I] $TiCl_4$ DIPEA, −78 °C. [II] $BnO(CH_2)_2CHO$. [III] TBSOTf, lutidine.

Scheme 39 - Asymmetric total synthesis of Pironetin (39)

1.2.7 Generation of aza enolates by aziridine ring opening *via* soft enolisation

Shimizu *et al*. reported the ring opening of aziridines **40** with TiI_4 to form titanium oxime aza enolates, which in turn was subjected to an aldol reaction with aldehydes to give aldol products in good yields and good diastereoselectivities (Table 8). This is very similar to the work reported by Shipman *et al.* with the use of methyleneaziridines in a four-component reaction for the formation of α-amino phosphonates *via* hard enolisation (Scheme 32, *vide supra*).



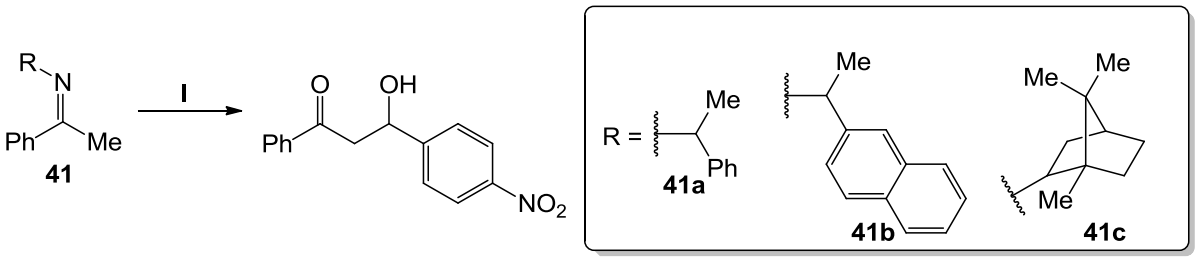
Entry	R_1	% Yield	(*E*)-*syn*:(*Z*)-*syn*[a]	(*E*)-*anti*:(*Z*)-*anti*[a]
1	4-$MeOC_6H_4$	100	7:14	2:77
2	4-ClC_6H_4	93	6:21	4:69
3	*cyclo*-C_6H_{11}	54	0:23	0:77
4	$PhCH_2CH_2$	25	0:30	7:63

[I] TiI_4 (3 eq.), R_1CHO (1.5 eq.), BF_3•OEt_2, EtCN, −78 °C to rt, 15 h. [a] based on isolated isomers.[118]

Table 8 – Aza enolate generation *via* aziridine ring opening

1.2.8 Generation of aza enolates *via* soft enolisation

In 1979, Sugasawa and Toyoda demonstrated the use of boron aza enolates in an enantioselective aldol reaction using aza enolates derived from chiral imines **41** to obtain moderate *ee*'s between 3-42% (Table 9).[119] Importantly, this was the first example of generating aza enolates from imines *via* soft enolisation using a mild base and a Lewis acid.

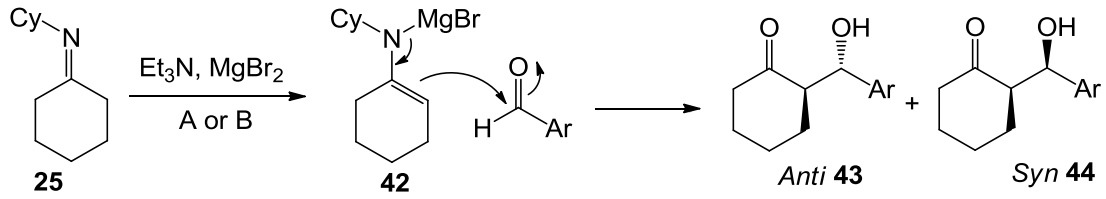


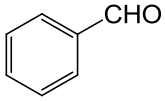
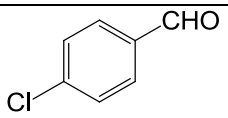
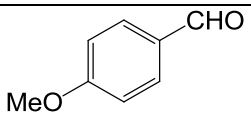
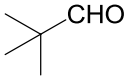
Entry	Chiral imine	% yield	% *ee*
1	**41a**	33.8	41.5
2	**41b**	41.5	34.5
3	**41b**	6.3	19.1
4	**41b**	15.2	7.0
5	**41c**	29.9	2.5

[1] Imine, BCl_3, Et_3N, −45 °C, then aldehyde , CH_2Cl_2, 0 °C, 6 h rt, then H_3O^+.[119]

Table 9 – Boron aza enolates *via* soft enolisation

It was not until approximately another 17 years before this soft enolisation methodology was probed further by Nagao *et al*., who reported the use of Lewis acid-amine base reagents in a similar imine aldol reaction (Table 10).[120] This involved using imine **25** with Et_3N and $MgBr_2$ to form the aza enolate **42**, which then reacts with the aldehyde to form *anti*-**43** and *syn*-**44** products (Table 10).

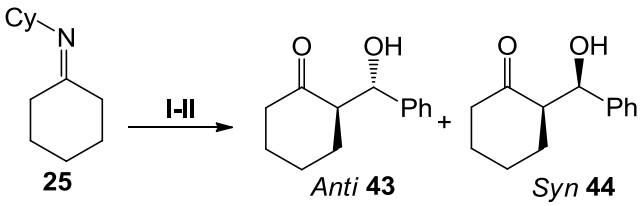


Entry	Aldehyde	Conditions A *anti*/*syn* (% yield)	Conditions B *anti*/*syn* (% yield)
1		83/17 (85)	10/90 (92)
2		90/10 (89)	12/88 (87)
3		69/31 (84)	9/91 (86)
4		70/30 (54)	49/51 (11)

[A] $MgBr_2$, Et_3N, MeCN, −45 °C, 1 h, then ArCHO, −45 °C, 1 h then rt for 11-15 h. [B] $MgBr_2$, Et_3N, MeCN, −45 °C, 1 h, then ArCHO, −45 °C, 11-15 h. Isolated yield is a mixture of anti and syn compounds.

Table 10 – Magnesium aza enolates *via* soft enolisation

Building on this work, Nagao *et al*. reported in 2007 that the stereoselectivity of the reaction could be varied by changing the magnesium salts and amine bases in the imine aldol reaction (Table 11)[121] It was observed that on changing the base from Et_3N to TMEDA the opposite stereoselectivity was observed (Entries 2 and 3, table 11).

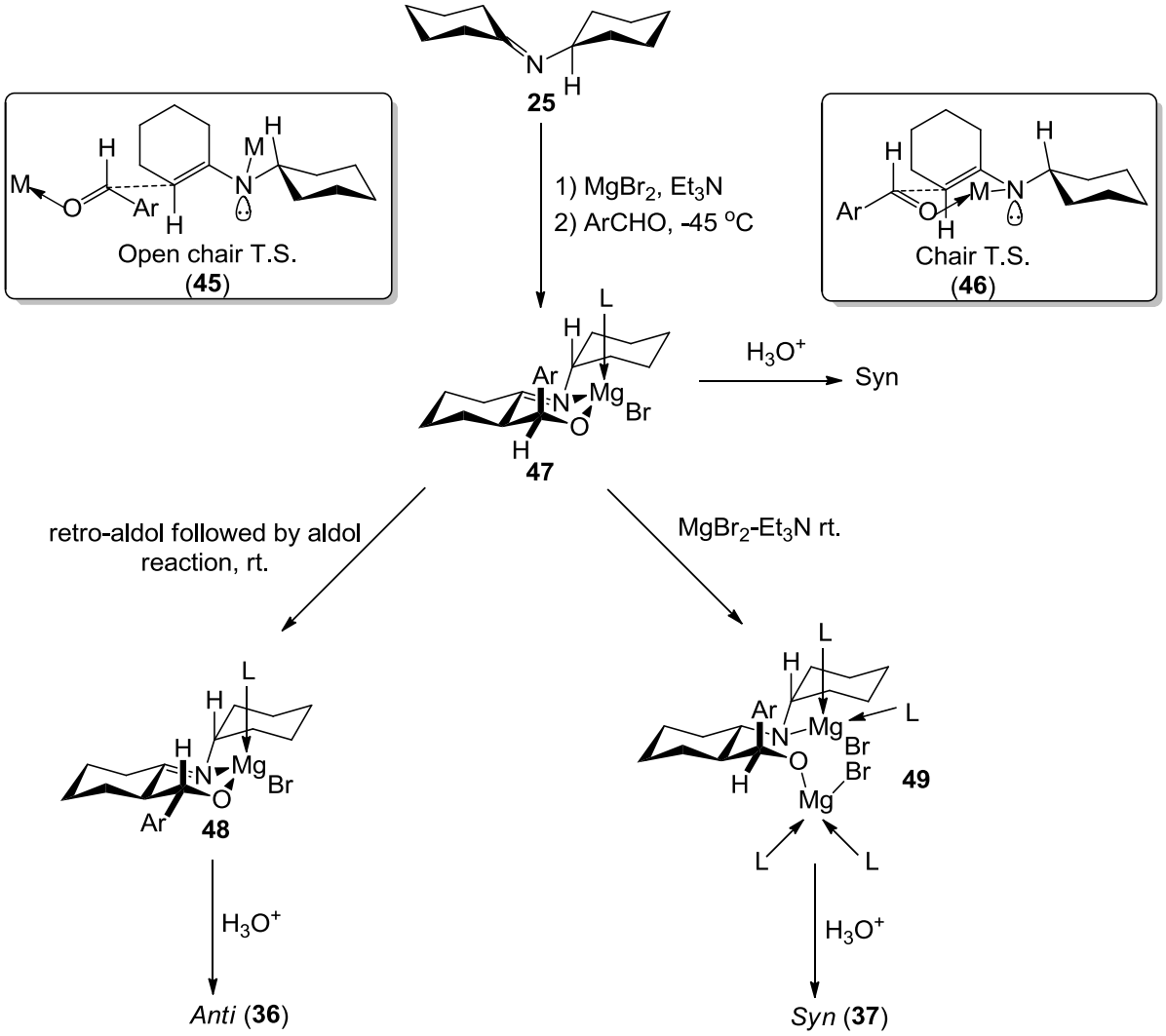


Entry	MgX_2	Et_3N *syn*/*anti* (% yield)	TMEDA *syn*/*anti* (% yield)
1	MgF_2	- (0)	- (0)
2	$MgCl_2$	7/93 (90)	91/9 (93)
3	$MgBr_2$	10/90 (92)	81/19 (82)
4	$Mg(OTf)_2$	5/95 (72)	16/84 (22)
5	$Mg(ClO_4)_2$	75/25 (84)	90/10 (90)

[I] MgX_2, amine base, MeCN, −45 °C, 1 h, then PhCHO, −45 °C, 16 h. [II] 1M AcOH, rt. 1.5 h.

Table 11 – Examples of different magenisum salts influencing stereoselectivity

Nagao *et al.*[120] described a plausible mechanism to explain the stereoselectivity (Scheme 40). This involves reaction of the aza enolate *via* an open chain transition state(s) (**38**) or a chair transition state **45**. The chair transition state **46** will have unfavourable 1,3-diaxial steric hindrance interactions and thus reaction *via* **46** is disfavoured. Therefore, the open chain transition state **45** leading to the unstable imine **47** is favoured. This can then undergo a retro aldol reaction followed by an aldol reaction at room temperature to produce **48**. After hydrolysis this gives the thermodynamic *anti*-product **43**.[122,123] It was also observed that by increasing the amounts of Lewis acid and base, the unstable imine **47** can be stabilised by formation of MgBr-enamine **49** which after hydrolysis produces the kinetic *syn*-product **44** (Scheme 40). This enabled the aldol reaction to be made either reversible or irreversible depending on the base and Lewis acid used (Table 11, Entry 5).[120,124]



Scheme 40 – Nagao's[120] mechanism to explain the observed stereoselectivity

1.2.9 Conclusions

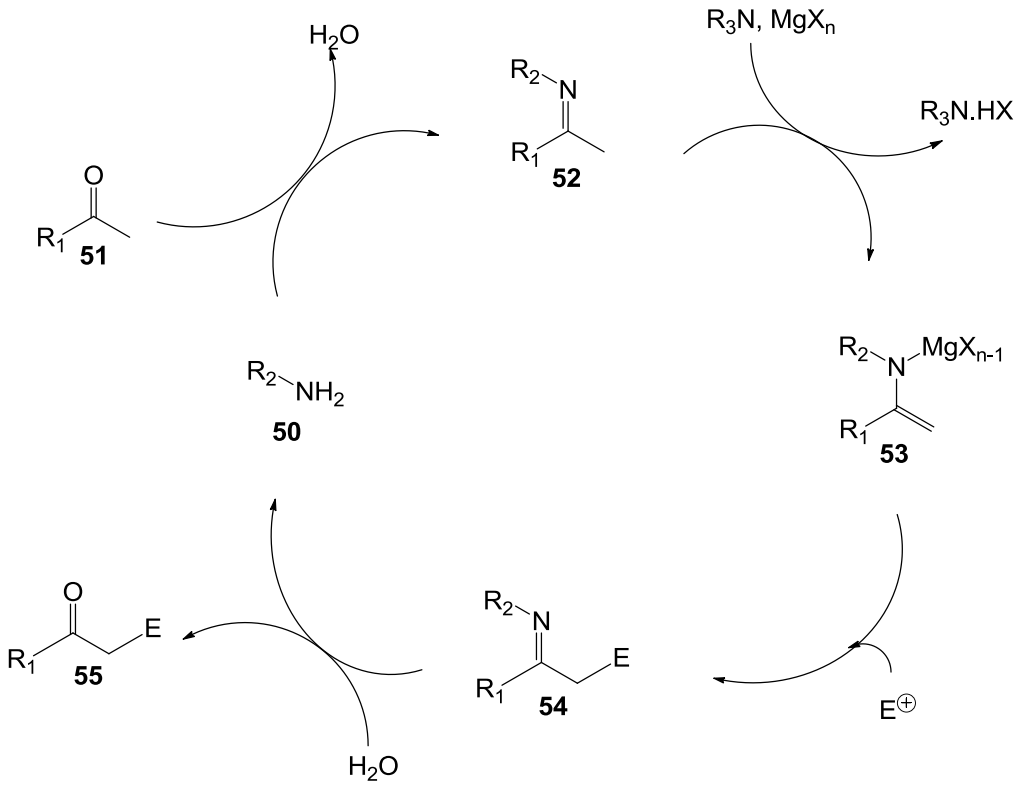
Since the work of Stork in the 1960s, aza enolate reactions have been successfully employed for a range of reactions that cannot be readily achieved with enamines or ketone enolates. This includes alkylation reactions with simple substrates to more interesting reactions involving ring opening of epoxide derivatives.[74] With hydrazone methodology, aza enolate chemistry has grown, particularly in asymmetric synthesis with the use of SAMP/RAMP. Currently, C-heteroatom (Si, Se, S, O, P, N, F) bond formation and C-C bond formation using both achiral and chiral hydrazone methods are well-known synthetic transformations. However, there are still some limitations with hydrazone methodology as stoichiometric amounts of the chiral auxiliary need to be used. This project explores the development of catalytic aza enolate reactions that attempt to combine reversible imine formation with soft enolisation to generate aza enolates directly from carbonyl compounds in a catalytic manner.

It is hoped that this will overcome some of the current limitations of organocatalysis and will enable a range of useful aza enolate reactions to be achieved catalytically for the first time.

1.3 Aim and objectives

At present, organocatalysis is a highly active area of research as it provides new efficient ways of introducing asymmetry with high enantioselectivity. In addition, a catalytic transformation provides the best ‘‘atom economy’’, because the stoichiometric introduction and removal of (chiral) auxiliaries can be avoided.[1,125] However, in the vast majority of these reactions there are a limited number of activation modes; therefore to expand the scope of organocatalysis new activation modes are needed.[58] This project explores the development of a new mode of activation *via* aza enolates intermediates, and its application to catalytic transformations that are not currently viable using existing methods. In particular, this activation mode can potentially be used to achieve reactions with relatively unreactive electrophiles such as epoxides.

It was envisioned that an aza enolate catalytic cycle (Scheme 41) would involve imine formation between a primary amine (**50**) and a ketone/aldehyde (**51**), followed by co-ordination of the resulting imine (**52**) to the Lewis acid (e.g. MgX_2) and subsequent deprotonation to give the aza enolate (**53**). Aza enolate **53** can then undergo a reaction with an electrophile (E^+) to generate the imine (**54**), which can then subsequently be hydrolysed to generate the product ketone (**55**) and regenerate **50**. As a result, this reaction can be catalytic in **50** and depending on the nature of the electrophile, could also be catalytic in Lewis acid and tertiary amine base and therefore this gives several alternative possibilities for introducing asymmetry. Initially, it was decided to investigate Mg salts as they have been demonstrated in the literature to be a suitable Lewis acids for the soft enolisation of imines.



Scheme 41 – Proposed aza enolate catalytic cycle using soft enolisation

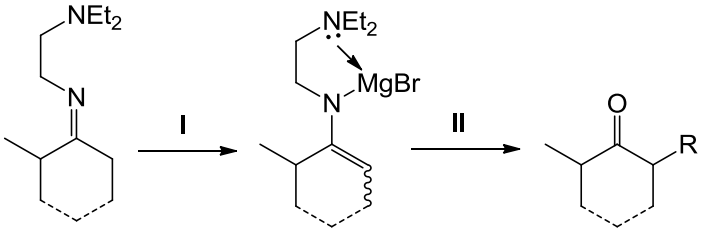
The enolisation of the imine should occur rather than enolisation of the parent ketone as the Lewis acid should preferentially coordinate to the nitrogen of the imine due to its higher basicity. Furthermore, it is desired that the electrophile will react with the aza enolate and not with the amine or base. Initially, it was decided to explore the reaction of pre-formed imines in order to test the feasibility of the aza enolate reactions, before moving on to explore catalytic systems.

Chapter 2 – Development of a catalytic aza enolate aldol reaction

2.1 Results and Discussion

2.1.1 Synthesis of imine derivatives

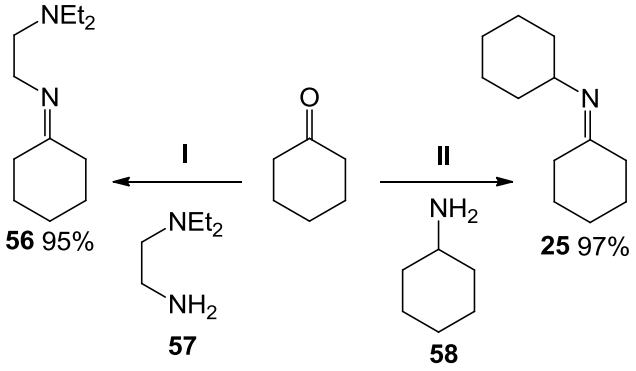
Work in this area began with the synthesis of a number of imine derivatives for use in the proposed methodology (Section 1.3). As described in section 1.2.4, Nakamura *et al*. had employed an imine where the corresponding aza enolate bears an internal nitrogen co-ordination site which significantly alters the reactivity (Scheme 42).[126]



[I] MesMgBr. [II] X-R, H_3O^+.[126]

Scheme 42 – Literature work with internal nitrogen co-ordination site

Therefore, imine **56** was selected alongside the standard imine **25** for initial testing and the two imines were synthesised in excellent yields by reacting cyclohexanone with the corresponding amine **57** or **58** (Scheme 43).

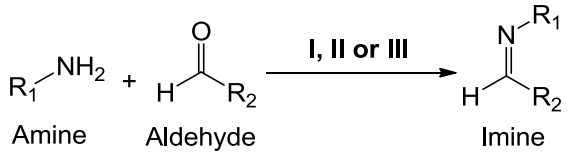


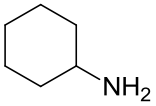
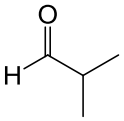
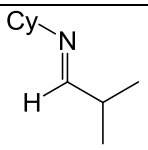
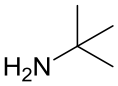
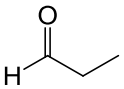
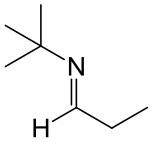
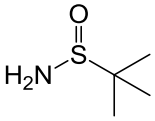
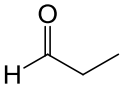
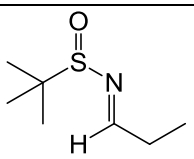
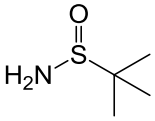
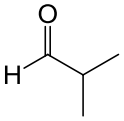
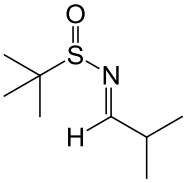
*[I] **57**, 4 Å molecular sieves, 80 °C, 18 h. [II] **58**, Et_2O, 4 Å molecular sieves, rt, 14 h.*

Scheme 43 – Synthesis of imines 25 and 56

Using aldehydes in place of cyclohexanone, several aldehyde derived imines (**59**-**62**) were produced following literature procedures[127-130] (Table 12). Imines **59** and **60** (Entries 1 and 2, Table 12) were chosen together with sulfoximines **61** and **62** (Entries 3 and 4, Table 12). The sulfoximines are more stable systems that can readily be purified chromatographically. These

systems can also be prepared in enantiopure form if needed for the study of enantioselective reactions (Table 12).

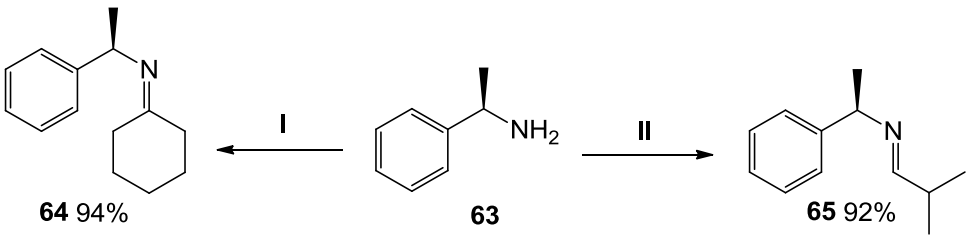


Entry	Amine	Aldehyde	Imine	Procedure
1			 **59** 95%	I
2			 **60** 90%	II
3			 **61** 95%	III
4			 **62** 93%	III

[I] −5 °C, 30 min, rt, KOH pellets, 24 h. [II] CH_2Cl_2, $MgSO_4$, reflux, 2 h. [III] CH_2Cl_2, PPTS, $MgSO_4$, rt., 24 h.

Table 12 – Synthesis of aldehyde derived imines (59-62)

Following a literature procedure,[131] (*R*)-1-phenylethanamine **63** was reacted with cyclohexanone and ^{i}PrCHO to produce chiral imines **64** and **65** respectively (Scheme 44).



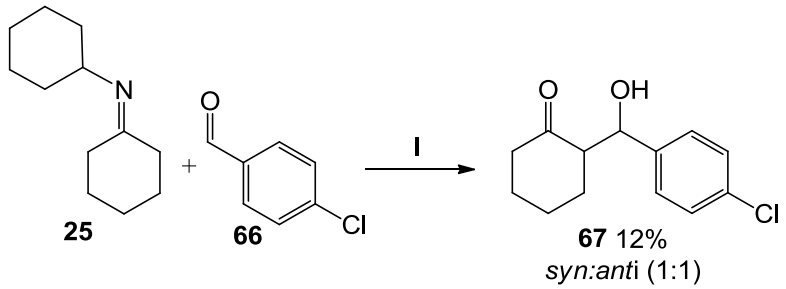
[I] Cyclohexanone, CH_2Cl_2, $MgSO_4$, rt, 14 h. [II] ^{i}PrCHO, CH_2Cl_2, $MgSO_4$, rt, 14 h.

Scheme 44 – Synthesis of chiral imines 64 and 65

With these substrates in hand, it was then possible to begin testing these intermediates in the proposed aza enolate reactions.

2.1.2 Stoichiometric aldol reactions

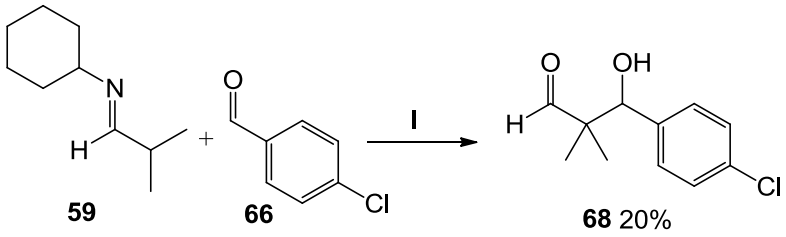
Initial investigations involved examining literature methods for an aza enolate aldol reaction. Firstly, imine **25** was used in an aldol reaction with 4-chlorobenzaldehyde **66** following a literature procedure[120] (Scheme 45). Examination of the crude ^{1}H NMR indicated only a low conversion to the product **67** (19%). Following purification, keto alcohol product **67** was obtained in a low yield of 12%.



*[1] $MgBr_2$, Et_3N, MeCN, −45 °C, 1 h, **66**, MeCN, −45 °C, 1 h; rt, 12 h.*

Scheme 45 – Aldol reaction using imine 25

An analogous reaction was carried out using **59** and aldehyde **66**. Again, examination of the crude ^{1}H NMR indicated only a 25% conversion to the product **68**. Purification produced the corresponding keto alcohol product **68** in a 20% yield (Scheme 46).

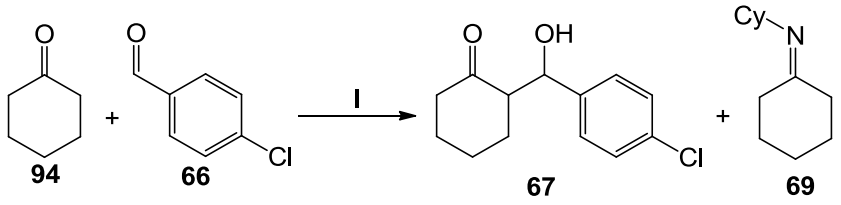


*[1] $MgBr_2$, Et_3N, MeCN, −45 °C, 1 h, **66**, MeCN, −45 °C, 1 h, rt, 12 h.*

Scheme 46 – Aldol reaction using aldehyde derived imine 59

It was then decided to explore whether the imine could be formed *in situ* in the aldol reaction. This involved using cyclohexanone (**94**) directly with aldehyde **66** in the presence of amine, Mg salt and base affording the desired keto alcohol product **67** in 14% yield as a 1:1 mixture of diasteroisomers (Table 13, entry 1). Examination of the crude ^{1}H NMR indicated only a 21% conversion to the product **67**. Large quantities of unreacted imine **69**, derived from

condensation of cyclohexanone with Cy-NH_2, were observed in the crude ^{1}H NMR spectrum. Changing the magnesium counterion from bromide (Table 13, entry 1) to chloride, triflate or perchlorate (Table 13, entries 2-4) had a significant impact on the conversion to the keto alcohol product **67**, with magnesium perchlorate providing the highest conversion, 35%, and cleanest crude ^{1}H NMR. Evidence for an aza-enolate intermediate was provided by control reactions, which excluded one of the three key reagents from the reaction mixture: primary amine, magnesium salt, triethylamine (Table 13, entries 5-7). No apparent conversion to the keto alcohol product **67** was observed in each case, clearly suggesting a synergistic operation of the primary amine, magnesium salt, and triethylamine in the reaction mechanism.

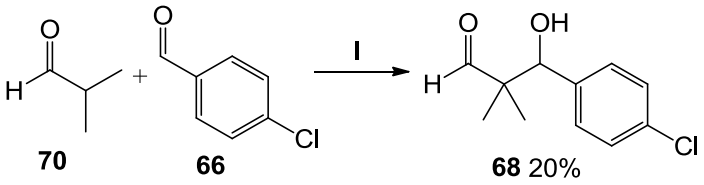


Entry	Et_3N equiv.	Cy-NH_2 equiv.	MgX_2		Conversion[a]	Yield
			X =	equiv.		
1	2.4	1	Br	1.2	19%	14% *syn:anti* (1:1)
2	2.4	1	Cl	1.2	10%	n.d.
3	2.4	1	OTf	1.2	25%	n.d.
4	2.4	1	ClO_4	1.2	35%	n.d.
5	0	1	ClO_4	1.2	<5%	n.d.
6	2.4	0	ClO_4	1.2	<5%	n.d.
7	2.4	1	ClO_4	0	<5%	n.d.

[I] Cy-NH_2, MeCN then MgX_2, Et_3N, MeCN, −45 °C, 1 h then aldehyde (**66**), MeCN, −45 °C, 1 h then rt, 12 h. [a] % conversion determined by ^{1}H NMR ($CDCl_3$). n.d. = not determined

Table 13 – Lewis acid screen and control reactions

With these results (Table 13), a cross-aldol reaction of aldehydes was investigated using aldehyde **70** instead of cyclohexanone under the same reaction conditions and this reaction afforded the aldol product **68** in a 20% yield (Scheme 47).

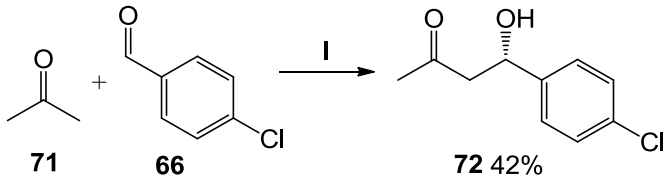


*[I] Cy-NH_2, MeCN then MgX_2, Et_3N, MeCN, −45 °C, 1 h then aldehyde (**66**), MeCN, −45 °C, 1 h then rt, 12 h.*

Scheme 47 - Cross-aldol reaction of aldehydes

2.1.3 Catalytic aza enolate aldol reactions

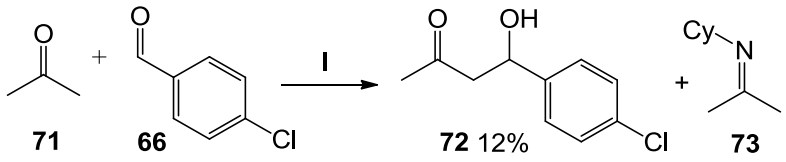
Having demonstrated that stoichiometric aza enolate reactions with MgX_2/Et_3N and a primary amine led to a keto alcohol product (above), the next step was to investigate if a catalytic aza enolate reaction of the imine was possible. Initially, an authentic sample of the keto alcohol product **72** was produced by using *L*-proline as the catalyst in 42% yield and in a 70% *ee* using a literature procedure[132] and analysed by chiral HPLC with the major isomer being determined as 4*R* (Scheme 48).



*[I] L-Proline, DMSO:acetone (4:1), then **66**, 12 h, rt.*

Scheme 48 – Synthesis of authentic sample of 72

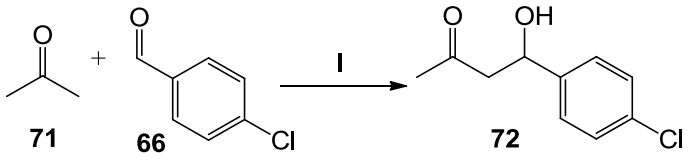
With an authentic sample in hand, a catalytic reaction was investigated. This involved using acetone **71** with catalytic quantities of Cy-NH_2, Et_3N and $Mg(ClO_4)_2$ and 1 equiv. of aldehyde **66**, affording the keto alcohol product **72** in a low isolated yield of 12% (Scheme 49). Inspection of the crude ^{1}H NMR indicated an 18% conversion to the product **72**. Large quantities of unreacted imine **73** derived from condensation of Cy-NH_2 with acetone **71,** were present in the crude ^{1}H NMR spectrum.



*[I] Cy-NH_2 (50 mol %), ($Mg(ClO_4)_2$ (50 mol %), DMSO, Et_3N (50 mol %), then aldehyde (**66**), then rt, 12 h.*

Scheme 49 – Preliminary catalytic reaction

Again, evidence for an aza enolate intermediate was provided by a series of control reactions, which excluded one of the three key reagents from the reaction mixture: Cy-NH_2, $Mg(ClO_4)_2$, Et_3N (Table 14, entries 1-3). No apparent conversion to the keto alcohol product **72** was observed in the absence of any one of the three components, again, clearly suggesting a synergistic operation of the primary amine, magnesium salt, triethylamine in the reaction mechanism.

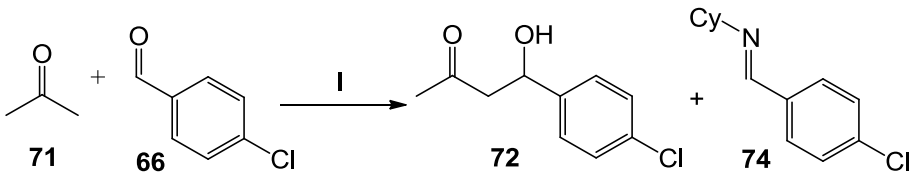


Entry	Et_3N equiv.	Cy-NH_2 equiv.	$Mg(ClO_4)_2$ equiv.	Solvent	Conversion[a]
1	0	0.5	0.5	DMSO	<5%
2	0.5	0	0.5	DMSO	<5%
3	0.5	0.5	0	DMSO	<5%

*[1] Cy-NH_2, ($Mg(ClO_4)_2$, solvent, Et_3N, then aldehyde (**66**), then rt, 12 h. [a] % conversion determined by ^{1}H NMR ($CDCl_3$).*

Table 14 – Catalytic control reactions

To improve the conversion (Scheme 49, above), a solvent screen was attempted with the use of acetone **71** as a reagent and co-solvent in a 4:1 ratio (solvent:acetone) (Table 15, entries 1-8) as this was shown to be the best ratio when using *L*-proline as the catalyst.[132] From these observations, it was a clear that a solvent system involving DMSO and acetone **71** (Table 15, entry 5) led to the best conversion (30%), with an isolated yield of 26%. A range of different co-solvents was then investigated with 1 eq. of acetone **71** being used only as a reagent (Table 15, entries 9-16). It was clear that MeOH and MeCN gave the best conversions of 24% and 26% respectively at room temperature (Table 15, entries 10-11). Importantly, upon inspection of the crude ^{1}H NMR spectra in all of these reactions (Table 15, entries 1 and 4-13), it was apparent that low conversions were due to the formation of large quantities of imine **74**, derived from condensation of Cy-NH_2 with aldehyde **66**. This suggests that the formation of imine **74** maybe irreversible.

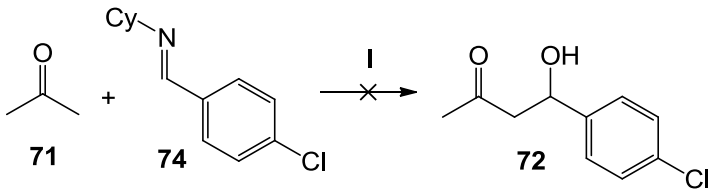


Entry	Acetone eq.	Co-solvent eq.	Solvent	Conversion[a]	Yield
1	-	4:1	MeOH:acetone	21%	
2	-	4:1	CH_2Cl_2:acetone	Intractable mixture	
3	-	4:1	$CHCl_3$:acetone	Intractable mixture	
4	-	4:1	EtOAc:acetone	18%	
5	-	4:1	DMSO:acetone	30%	26%
6	-	4:1	Tol:acetone	5%	
7	-	4:1	THF:acetone	10%	
8	-	4:1	MeCN:acetone	24%	
9	1	0.5	DMSO:EtOAc	18%	
10	1	0.5	DMSO:MeOH	24%	
11	1	0.5	DMSO:MeCN	25%	
12	1	0.5	DMSO:Et_2O	12%	
13	1	0.5	DMSO:THF	12%	
14	1	0.5	DMSO:Tol	Intractable mixture	
15	1	0.5	DMSO:CH_2Cl_2	Intractable mixture	
16	1	0.5	DMSO:$CHCl_3$	Intractable mixture	

*[1] Cy-NH_2 (50 mol %), ($Mg(ClO_4)_2$ (50 mol %), solvent, Et_3N (50 mol %), then aldehyde (**66**), rt, 12 h. [a] % conversion determined by ^1H NMR ($CDCl_3$).*

Table 15 – Solvent screen

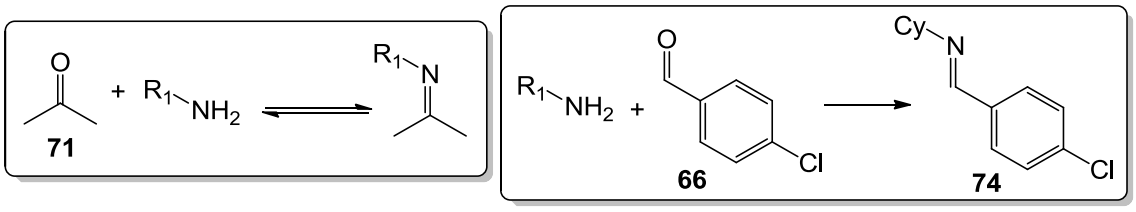
To investigate if the formation of imine **74** was reversible under the reaction conditions and hence whether it is involved further in the catalytic cycle, a pure sample of imine **74** was reacted with acetone **71**. This involved using catalytic quantities of Et_3N and $Mg(ClO_4)_2$ in DMSO:acetone (4:1) to see if any of the keto alcohol product **72** was generated (Scheme 50). Regrettably, the formation of imine **74** appears not to be reversible under these conditions, as the anticipated keto alcohol product **72** was not observed.



[I] ($Mg(ClO_4)_2$ (50 mol %), DMSO:acetone (4:1), Et_3N (50 mol %), rt, 12 h.

Scheme 50 – Reaction to investigate the reversibility of the aldehyde derived imine

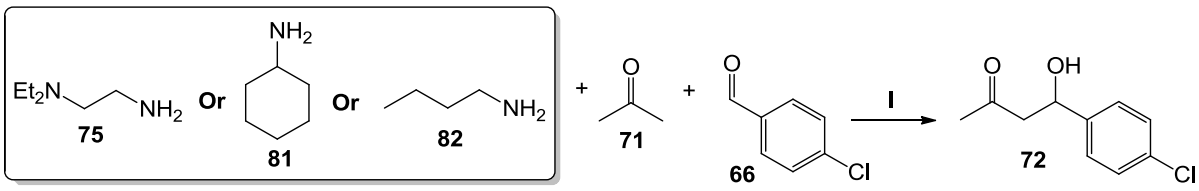
This indicates that due to the (irreversible) formation of imine **74**, the catalytic cycle is inhibited and leads to the primary amine being consumed, leading to lower conversions/yields being obtained (Scheme 51). Thus, to improve conversions/yields and to limit the amount of imine **74** formed; the chosen aldehyde(s) were added dropwise to a mixture of the other reagents in subsequent reactions.



Scheme 51 – Irreversible formation of the aldehyde derived imine

2.1.4 Optimisation of catalytic aza enolate reactions

The next step was to optimise the catalytic aza enolate aldol reaction by investigating the quantities of primary amine, Et_3N and $Mg(ClO_4)_2$ used in the reactions. Preliminary investigations had shown that diamine **75** led to the best conversion to the keto alcohol product **72**, 40%, compared to when **81** (33%) and **82** (25%) were used (Scheme 52).

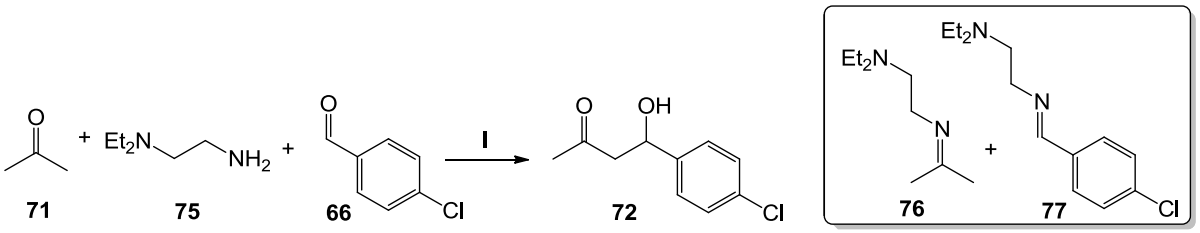


*[I] Amine (50 mol %), ($Mg(ClO_4)_2$ (50 mol %), DMSO:Acetone, Et_3N (50 mol %), then aldehyde (**66**), rt, 12 h.*

Scheme 52 – Preliminary amine screen

Therefore, diamine **75** was chosen for further optimisation of the aza enolate conditions with acetone **71** and aldehyde **66** (Table 16). Interestingly, varying the mol % of the amine **75** from 5 mol % (Table 16, entry 1) to 10 mol % (Table 16, entries 2-8) had a significant impact on the conversion to the keto alcohol product **72**, from 10% to 64% conversion by crude ^1H

NMR spectroscopy analysis. As expected, decreasing the amount of acetone from twenty equivalents to five equivalents leads to lower conversions (Table 16, entries 2 and 3). Increasing the mol % of $Mg(ClO_4)_2$ from 10 mol % to 50 mol % has no real effect on conversions (Table 16, entries 4 and 5). However, increasing the mol % of Et_3N from 10 mol % to 20 mol % increased the conversion from 24% to 52% and increased the isolated yield from 15% to 43% (Table 16, entries 6 and 7). Using 10 mol % of the amine **75** and 20 mol % of Et_3N and $Mg(ClO_4)_2$ with 10 equiv. of acetone **71** provided the highest conversions (Table 16, entries 7-8), 52% and 64% respectively. In addition, due to the volatility of acetone **71**, sealing the reaction vessel also increased the conversion and led to an isolated yield 60% (Table 16, entry 8). Increasing the mol % of the amine **75** by two-fold to 20 mol % decreased the conversion to the keto alcohol product **72**, from 49% to 45% (Table 16, entries 9-14). Reversing the addition of reagents by adding Et_3N first, followed by $Mg(ClO_4)_2$, acetone **71**, amine **75**, and lastly the aldehyde (dropwise) lowered the conversion to 34% from 52% (Table 16, entry 15 *cf.* to entry 7). Increasing the mol % of the amine **75** further to 50 mol %, decreased the conversion of the keto alcohol product **72** to approximately 33% (Table 16, entries 16-17). Greater than 50 mol % of the amine **75**, led to slightly smaller conversion to the keto alcohol product **72** of approximately 29% (Table 16, entries 18-19), the major products observed in these two cases were the two imines **76** and **77** (Table 16). Changing the co-solvent from DMSO:acetone to DMSO:H_2O and DMF:H_2O led to a significant drop in conversion to the keto alcohol product **72** from 52% to 37% respectively (Table 16, entries 20-21 *cf.* to entry 7). In summary, 10 mol % of **75**, 20 mol % of Et_3N, 20 mol % of $Mg(ClO_4)_2$, and 10 equiv. of **71** with a sealed reaction vessel was found to result in the highest conversion.



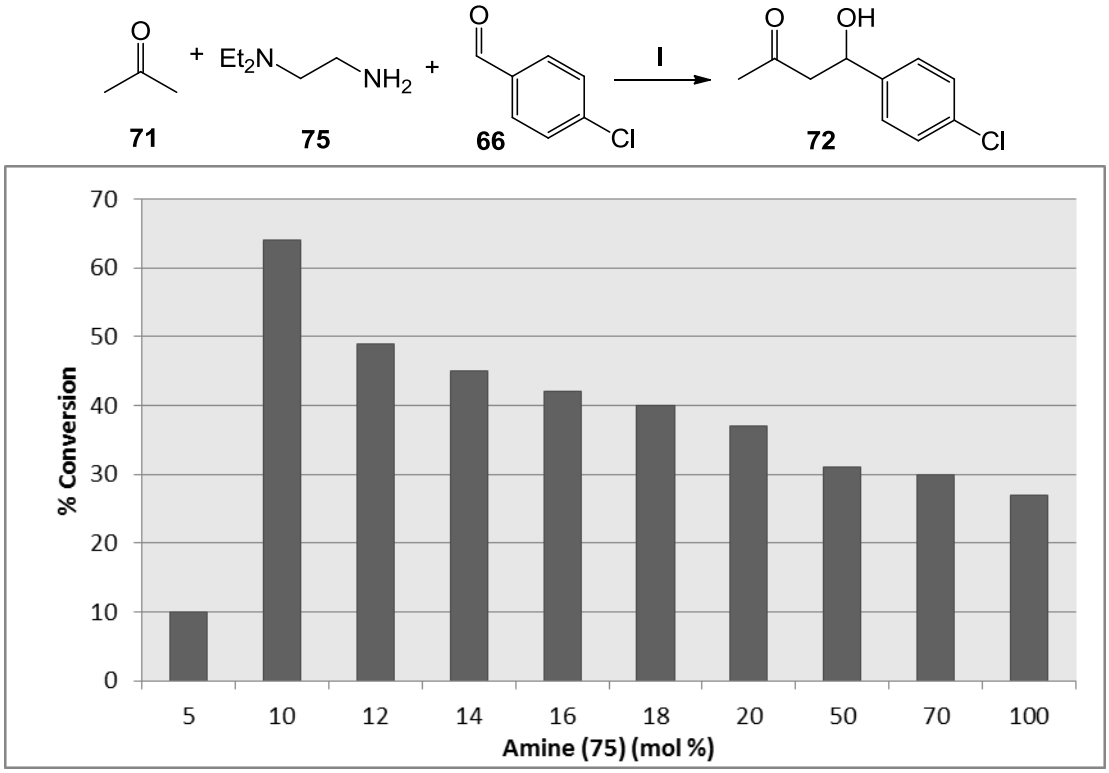
[I] ***75*** *(X mol %),* ***71*** *(X equiv.), ($Mg(ClO_4)_2$ (X mol %), DMSO:acetone (4:1), Et_3N (X mol %), then* ***66****, rt, 12 h.*

Entry	71 (equiv.)	75 (mol %)	$(Mg(ClO_4)_2$ (mol %)	Et_3N (mol %)	conversion*	Yield
1	10	5	20	20	10%	5%
2	5	10	20	20	19%	-
3	20	10	20	20	37%	-
4	10	10	10	20	32%	-
5	10	10	50	20	36%	30%
6	10	10	20	10	24%	15%
7	10	10	20	20	52%	43%
8[a]	**10**	**10**	**20**	**20**	**64%**	**60%**
9	10	12	20	20	49%	38%
10	10	14	20	20	45%	-
11	10	16	20	20	42%	-
12	10	18	20	20	40%	
13	10	20	20	20	37%	
14	20	20	20	20	35%	24%
15[b]	10	20	20	20	34%	-
16	20	50	20	20	33%	9%
17	10	50	20	20	31%	-
18	10	70	20	20	30%	-
19	10	100	20	20	27%	-
20[c]	10	20	20	20	37%	-
21[d]	10	20	20	20	37%	-

[a] *Sealed reaction vessel with argon balloon.* [b] *Reverse addition of reagents.* [c] *Solvent DMSO:H_2O (99:1).* [d] *Solvent DMF:H_2O (99:1). * % conversion determined by ^1H NMR ($CDCl_3$).*

Table 16 – Optimisation of the aza enolate conditions

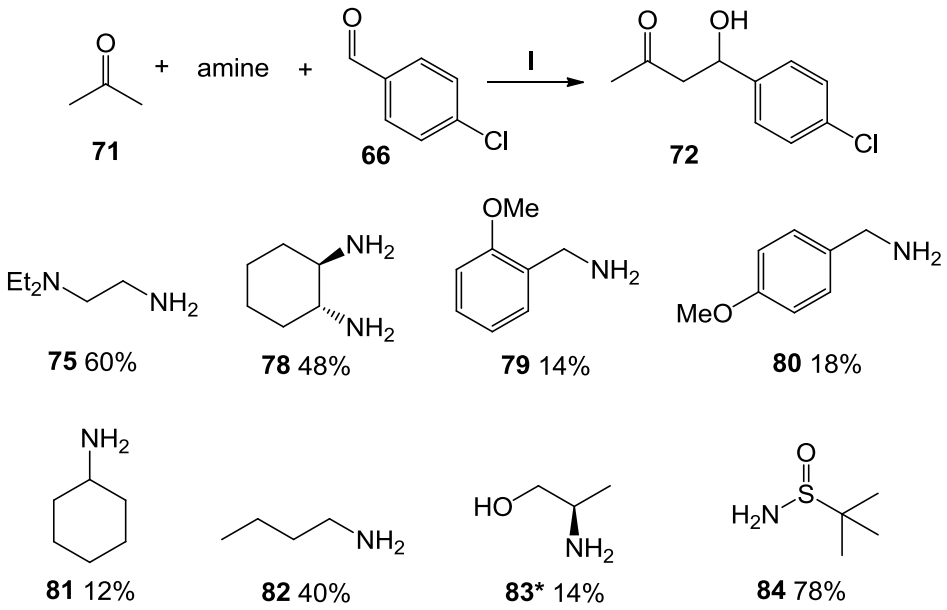
To illustrate the results from increasing the quantity of amine **75** from table 16 in a different format, Graph 1 is shown below. The graph shows that increasing the mol % from 10 mol % to 12 mol % and further to 100 mol % decreased the conversion to the product with 10 mol % being the optimum mol % of amine **75** (Graph 1).



[I] ***75*** *(X mol %),* ***71*** *(10 equiv.), $(Mg(ClO_4)_2$ (20 mol %), DMSO:acetone (4:1), Et_3N (20 mol %), then* ***66****, rt, 12 h.*

Graph 1 – Increasing the quantity of amine 75.

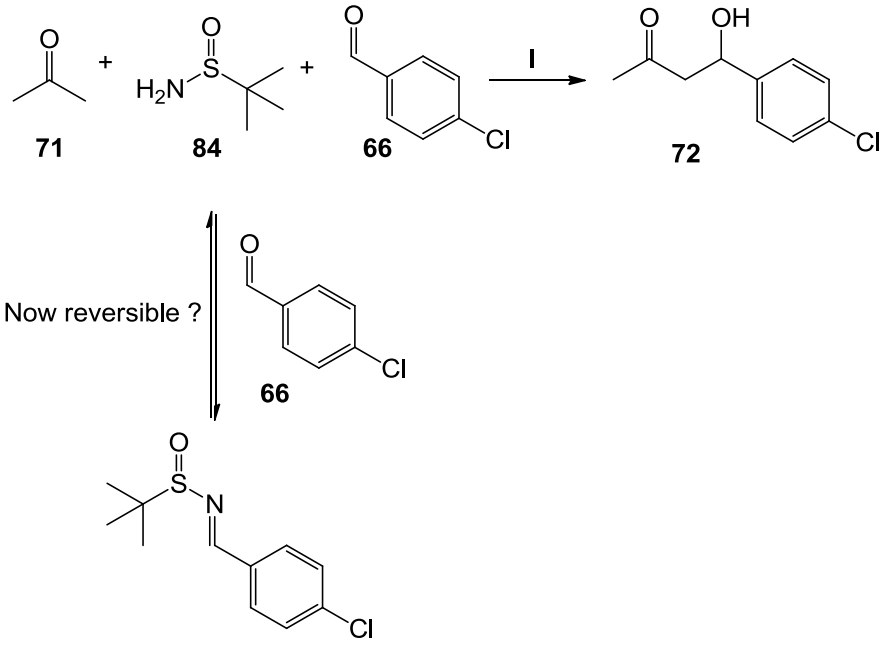
To evaluate the scope of this catalytic reaction, a more in depth amine study was carried out with acetone **71** and aldehyde **66** subjected to the optimised reaction conditions with a variety of amines as catalysts (Scheme 53). The chelating amines **75** and **78** produced moderate to good yields of **72**, 60% and 48%, whereas the aromatic amines **79** and **80** produced **72** in low yields of 14% and 18%, possibly due to the aromatic amines being less nucleophilic. The aliphatic amines **81**, **82** and **83** produced **72** in low to moderate yields of 12%, 40%, and 14% respectively. The commercially available amine **84** was not initially considered, but towards the end of the project a reaction with **84** was carried out, giving an excellent yield of 78% (Scheme 53).



*[1] **71**, $Mg(ClO_4)_2$ (20 mol %), Amine (10 mol %), DMSO:acetone, Et_3N (20 mol %), then **66**, rt, 12 h.* % conversion determined by ^1H NMR ($CDCl_3$).*

Scheme 53 – Amine study

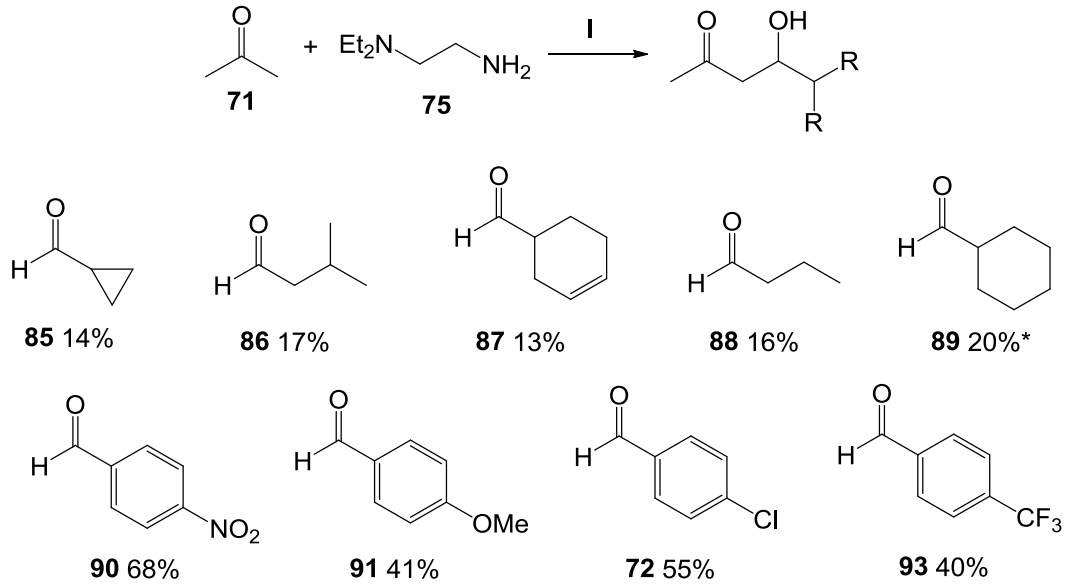
The high yield obtained using sulfinamide **84** may be due to the fact that the reaction between **84** and the aldehyde **66** to form the imine may now be reversible (Scheme 54).



*[1] **71**, $Mg(ClO_4)_2$ (20 mol %), Amine **84** (10 mol %), DMSO:acetone, Et_3N (20 mol %), then **66**, rt, 12 h.*

Scheme 54 – Possible reversibility using sulfinamide 84.

As amine **84** was only investigated later in this project, amine **75** was selected for further optimisation of the aza enolate reaction. Reactions with a variety of different aldehydes were conducted with acetone **71** and chelating amine **75** (Scheme 55). Aliphatic aldehydes produced lower yields (Scheme 55, **85**-**89**), possibly due to the enolisable protons available (not available in the aromatic aldehydes), leading to possible aldehyde-aldehyde cross-reactions. Aromatic aldehydes produced the best yields (Scheme 55, **90**-**93**), presumably as they do not readily undergo competing reactions. Electron withdrawing groups on the aromatic ring make the aldehydes more reactive and lead to greater yields (Scheme 55, **90** and **72**) being obtained. The moderate yield obtained with aldehyde **93** (Scheme 55, **93**) may be due to the low purity of the commercially available aldehyde.

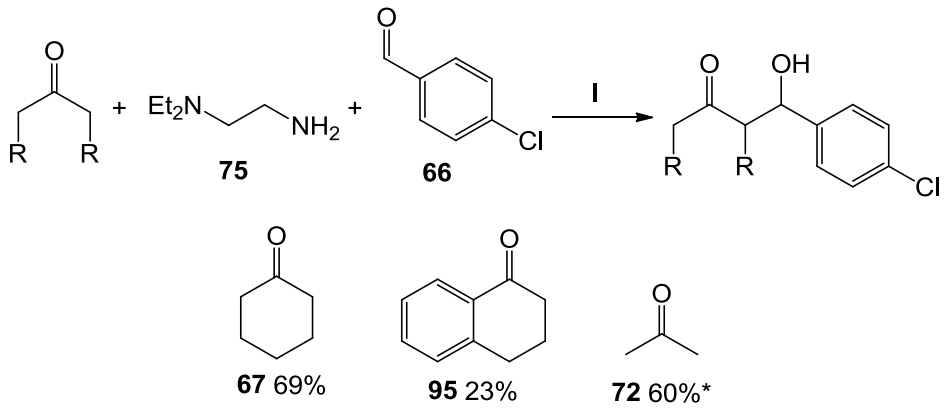


*[I] **71**, $Mg(ClO_4)_2$ (20 mol %), **75** (10 mol %), DMSO:acetone, Et_3N (20 mol %), then aldehyde, rt, 12 h.*

** Isolated as a mixture of aldehyde and product.*

Scheme 55 – Aldehyde study

Following on from these results (Scheme 55), a small study on ketone substrates was conducted with amine **75** and 4-chlorobenzaldehyde **66** as the electrophile (Scheme 56). Cyclohexanone and acetone (Scheme 56) led to the best yields of 69% and 55%. Tetralone **95** gave a moderate yield of 23%, which may be due to i) conjugation of the ketone to the aromatic ring, leading to lower reactivity and ii) fewer enolisable protons compared to ketones **67** and **72**.



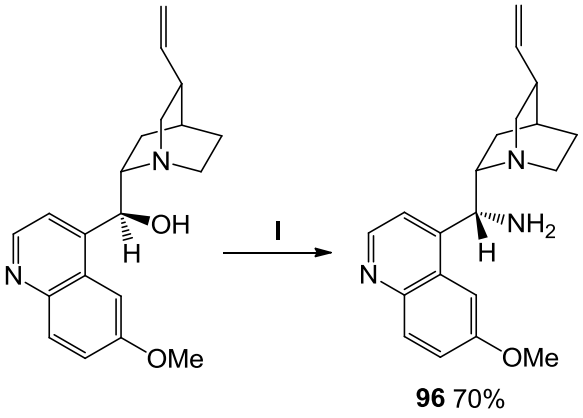
*[I] Ketone, $Mg(ClO_4)_2$ (20 mol %), amine **75** (10 mol %), DMSO, Et_3N (20 mol %), then **66**, rt, 12 h.*

***10 equivalents used*

Scheme 56 – Ketone study

2.1.5 Synthesis of chiral amines

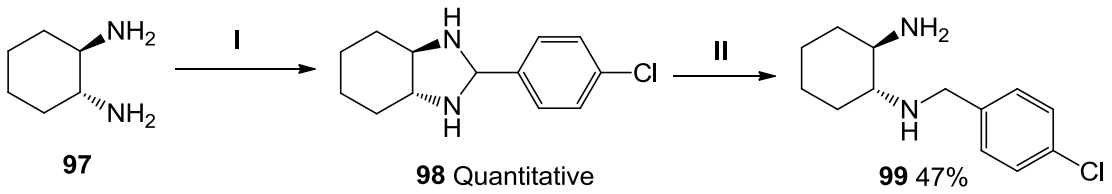
The next logical step was to investigate if asymmetry could be introduced into the catalytic reaction by employing a chiral primary amine. For this a range of chiral amines are required. Initially, chiral amine **96** was selected as it has been shown by Soos *et al*. to catalyse a highly enantioselective conjugate addition reaction.[133] Compound **96** was produced in a 70% yield *via* a Mitsonubu/Staudinger reaction (Scheme 57).



[I] PPh_3, dry THF, 0 °C, then DIAD, Diphenyl phosphoryl azide, THF, 0 °C, then 12 h, rt.

Scheme 57 – Synthesis of chiral amine 96

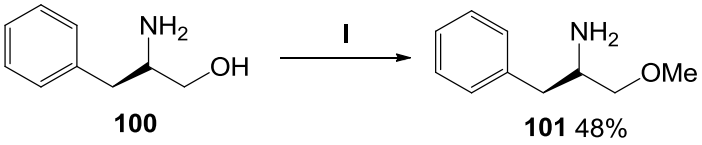
We also wished to explore chiral analogues of the chelating amine **75**. Therefore, commercially available chiral amine **97** was reacted with aldehyde **66** to produce intermediate **98** in a quantitative yield, which was then treated with $NaBH_4$ to produce the diamine **99** in a modest yield of 47% (Scheme 58).



*[I] EtOH, **66**; [II] $NaBH_4$, MeOH, 15 min, rt.*

Scheme 58 – Synthesis of chiral amine 99

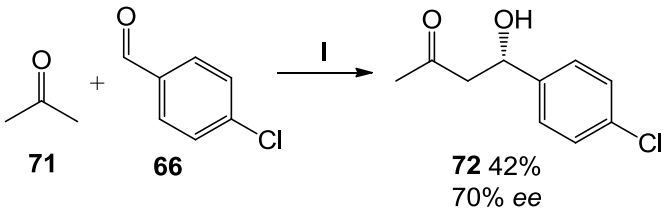
Chiral amine **101** was also synthesised in a 48% yield by methylating commercially available **100** following a literature procedure[134] (Scheme 59).



[I] KH, THF, 0 °C to rt, 12 h, then MeI, THF, 0 °C, rt, 45 min.

Scheme 59 – Synthesis of chiral amine 101

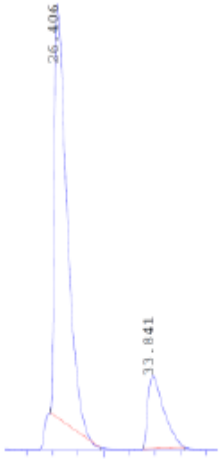
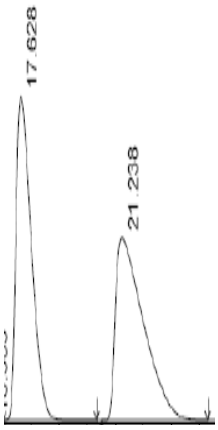
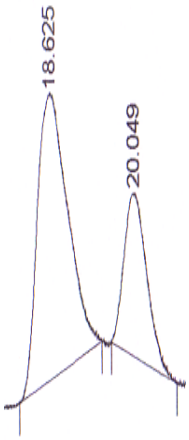
In order to determine whether the chiral amines were providing any level of enantioselectivity we needed to be able to measure the *ee* of the aldol products. We therefore carried out the aldol reaction to form **72** using (*L*)-proline as the organocatalyst to provide an authentic sample (Scheme 60) of the product (with the R isomer as the major enantiomer).



*[I] L-Proline, DMSO:acetone (4:1), then **66**, 12 h, rt.*

Scheme 60 – Synthesis of authentic sample of 72

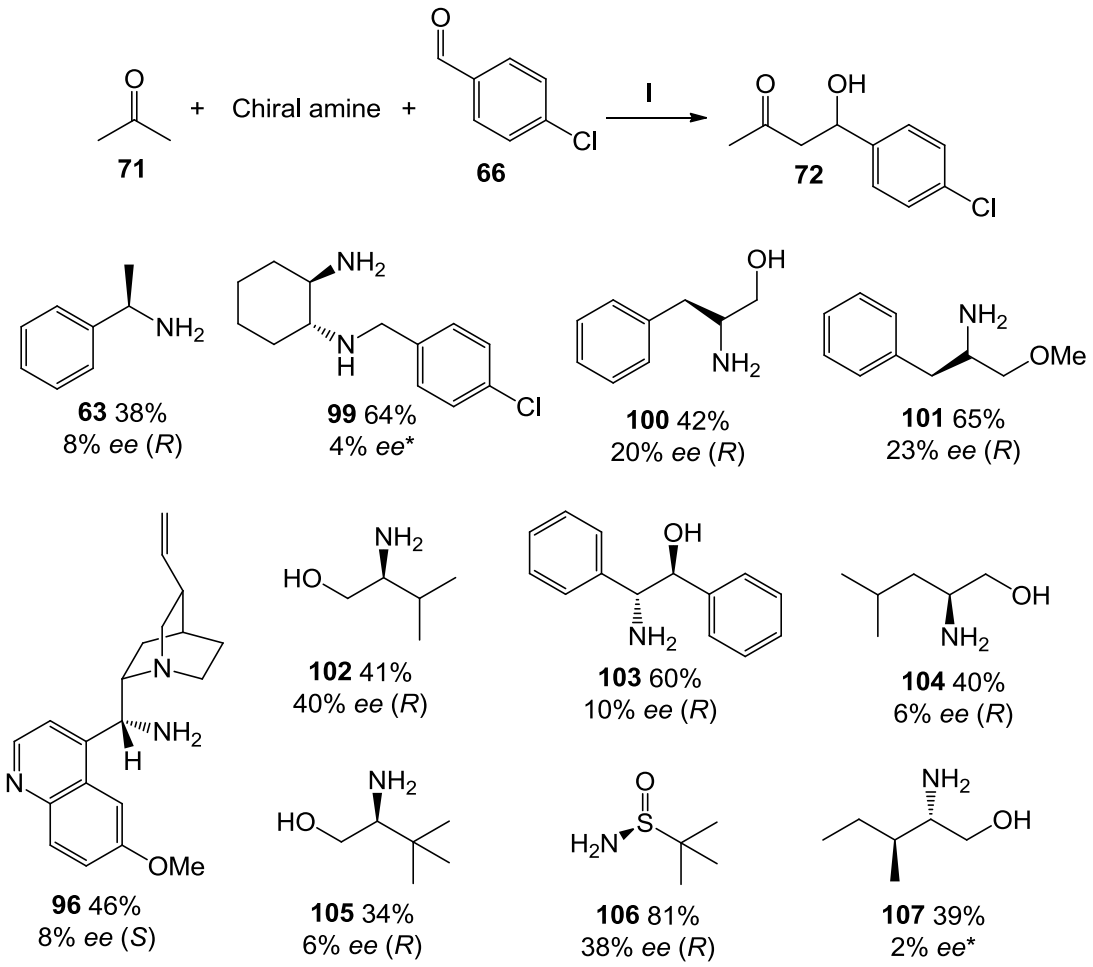
Analysis of the *L*-proline reaction using chiral HPLC enabled us to separate the enantiomers and we obtained a comparable *ee* to the reported reaction (Table 17). Comparison of the HPLC data enabled us to determine that the major product from the aza-enolate reaction with amine **102** had the same absolute configuration as that obtained with *L*-proline as the catalyst (Table 17).

Catalyst, conditions	*L*-Proline	*L*-Proline	Chiral amine **102**
All HPLC samples were columned under the same conditions. CHIRALPAK AD, hexane/*i*-PrOH = 80/20, flow rate = 1 mL.			
ee from HPLC	(*R*)-76%[135]	(*R*)-70% This work	(*R*)-40% This work
$[\alpha]^{22}_{D}$	Lit. +46.2° (*c* = 1, $CHCl_3$).[135]	+38.5° (*c* = 1, $CHCl_3$)	n.d.

n.d. = not determined

Table 17 – How major isomer was determined

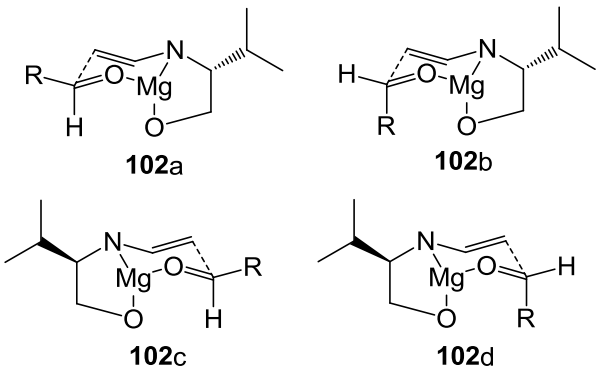
With the above chiral amines in hand and a method to determine the assignment of the major isomer available, it was then possible to begin testing a range of different chiral amines in the aza enolate aldol reaction (Scheme 61). Unfortunately, upon testing eleven different chiral amines gave only low enantioselectivity. However, the best result was obtained with amine **102**, with an *ee* of 40% and an isolated yield of 41% (Scheme 61, **102**). The commercially available chiral sulfinamide (Scheme 61, **106**) also gave a moderate *ee* of 38% and an excellent yield of 81%. The previously prepared amine **96** gave the *S*-isomer as the major product but only gave 8% *ee* which is fairly small. This may be because there is no chelating atom close to the primary amine group in amine **96**.



*[I] **71**, $Mg(ClO_4)_2$ (20 mol %), chiral amine (10 mol %), DMSO:acetone, Et_3N (20 mol %), then **66**, rt, 12 h. [a] ee was determined by chiral HPLC analysis (Chiralpak AD, Daicel Chemical Industries, Ltd.) comparing with the authentic sample **72**.* Any ee below 5% is classed as racemic.*

Scheme 61 – Chiral amine study

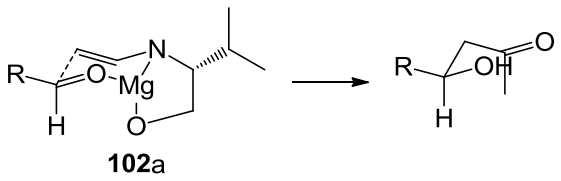
To explain the selectivity in the case of chelating amines such as **102**, we propose a chair transition state for the aldol reaction (Scheme 62). There are four possible chair transition states as shown in Scheme 62. The most favoured transition state would be **102**a as the isopropyl group is facing away from the aldehyde as it approaches the enolate and the 'R' group is equatorial. **102**b does have the isopropyl group facing away from the aldehyde but the aldehyde 'R' group is now axial and this will raise the energy of this transition state. Chair transition states **102**c and **102**d are disfavoured as the isopropyl group is facing towards the aldehyde as it approaches the enolate (Scheme 62).



Note: Methyl groups are removed for clarity

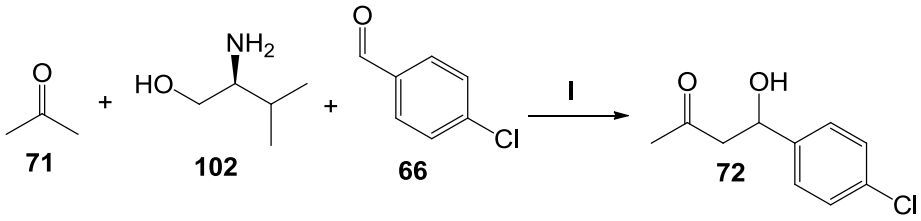
Scheme 62 – Four possible chair transition states using chiral amine 102 as an example

The (R)-product is obtained from transition state **102**a as shown in Scheme 63 in agreement with the observed selectivity from the reactions.



Scheme 63 – Product of transition state 102a

Amine **102** was selected for further optimisation of the asymmetric aza enolate reaction. To enhance the enantioselectivity, a solvent screen was attempted (Table 18). It is clear that polar solvents increase the % conversion (Table 18, entries 2, 3 and 4), however, enantioselectivity is lowered. Encouragingly, with $CHCl_3$ an apparent *ee* of 72% was observed when the crude product was analysed by chiral HPLC (Table 18, entry 8). However, upon purification only a disappointing *ee* of 17% was seen and an isolated yield of 40%. The apparent *ee* of 72% was presumably observed due to by-products having similar retention times to one enantiomer of the product leading to inaccurate peak heights in the HPLC trace obtained from the crude product.



*[1] $Mg(ClO_4)_2$ (20 mol %), **102** (10 mol %), DMSO:acetone, Et_3N (20 mol %), then **66**, rt, 12 h.*

Entry	Solvent	% conversion*/% *ee*	Entry	Solvent	% conversion*/% *ee*
1	MeCN	22%/15%	5	Et_2O	39%/22%
2	EtOAc	50%/16%	6	THF	47%/8%
3	MeOH	58%/12%	7	CH_2Cl_2	34%/23%
4	^{i}PrOH	53%/2%	8	$CHCl_3$	40%[a]/17%

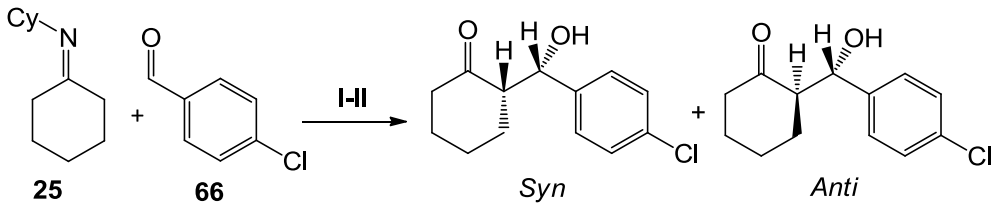
** % conversion determined by ^1H NMR ($CDCl_3$) on crude material. ee determined by chiral HPLC analysis (Chiralpak AD, Daicel Chemical Industries, Ltd.) by comparison to racemic sample of **72**. [a] Isolated yield.*

Table 18 – Solvent screen with amine 102

In summary, after synthesising a variety of chiral amines and testing these intermediates in the aza enolate aldol reaction alongside some commercially available chiral amines, two positive results were obtained. Firstly with amine **102** the reaction gave an *ee* of 40% and an isolated yield of 41% and secondly, sulfinamide **106** gave a moderate *ee* of 38% and an excellent isolated yield of 81%. No further improvement was observed in the *ee* in attempts to optimise the reaction, and hence no further work was carried out with these asymmetric reactions.

2.1.6 Diastereoselectivity of the aza enolate aldol reactions

As previously mentioned in section 1.2.8, Nagao *et al.* reported that variable diastereoselectivity can be observed in aza enolate aldol reactions between a pre formed imine **25** and aromatic aldehydes in the presence of magnesium salts and a base (Et_3N or TMEDA) (Table 19).[120,121]

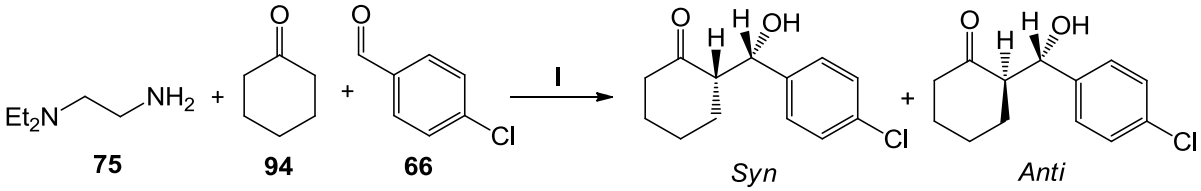


Entry	MgX_2	Et_3N *syn*/*anti* (% yield)	TMEDA *syn*/*anti* (% yield)
1	$Mg(OTf)_2$	92/8 (86)	16/84 (22)
2	$Mg(ClO_4)_2$	33/67 (84)	90/10 (90)

*[I] MgX_2, amine, base, MeCN, −45 °C, 1 h, then aldehyde **66**, −45 °C, 16 h. [II] 1M AcOH, rt, 1.5 h. (Nagao et al.)*[123,124]

Table 19 – Literature example showing diastereoselectivity

With this information, a one-pot catalytic aza enolate aldol reaction was carried out using the optimised conditions developed above (Section 2.2.4) to observe if similar changes in diastereoselectivity are obtained in the catalytic process using amine **75**. It was found that in this case, the diastereoselectivity was similar regardless of which Mg salt was used in the reaction. When the base was changed from Et_3N to TMEDA, the selectivity dropped in each case from 2:1 to around 1:1 (Table 20). The dramatic change in diastereoselectivity from a *syn*-selective reaction to an *anti*-selective reaction was not seen in the catalytic process in sharp contrast to the observations in the stoichiometric reaction of imine **35** (Table 20 *cf* table 19). However, this reaction was not tested with Cy-NH_2 to make it more similar to the stoichiometric reactions reported by Nagao *et al*.



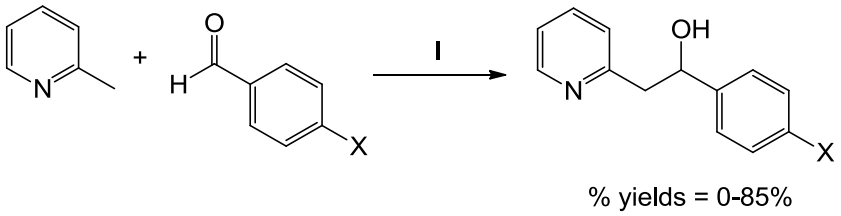
Entry	MgX_2	Et_3N *syn*/*anti* (% yield)	TMEDA *syn*/*anti* (% yield)
1	$Mg(OTf)_2$	67/33 (63)	50/50 (42)
2	$Mg(ClO_4)_2$	67/33 (61)	60/40 (58)

*[I] **75** (10 mol %), DMSO, MgX_2 (20 mol %), base (20 mol %), then aldehyde **65**, then rt, 12 h.*

Table 20 – Diastereoselective aldol reaction

2.1.7 Aza enolate heteroaromatic reactions

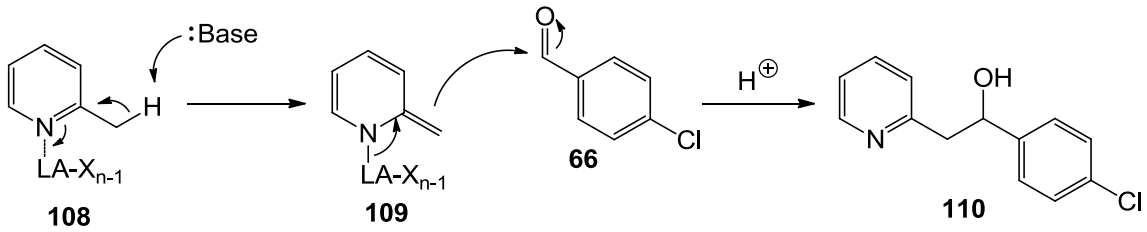
We were interested in discovering whether the catalytic aza enolate reactions could also be applied to reactions of nitrogen heterocycles. Hamana and Sugasawa reported an aldol like reaction of nitrogen containing heteroaromatic compounds with benzaldehydes[136] (Scheme 64). However, there are limitations with their work, as firstly, the use of 9-BBN-OTf leads to a lengthy work-up involving H_2O_2. Secondly, stoichiometric quantities of the reagents are used.



[I] 9-BBN-OTf, $^{i}Pr_2NEt$, CH_2Cl_2, −78 °C, then rt, 17 h. [136]

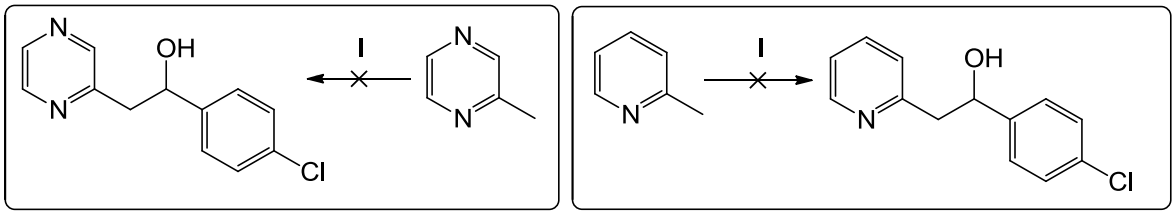
Scheme 64 – Literature example of heteroaromatic reactions

A plausible mechanism similar to an aza enolate reaction could be envisaged where the heteroaromatic compound **108** reacts with a base in the presence of a Lewis acid to form intermediate **109**, which can then undergo an aldol reaction with **66** to produce the product **110** (Scheme 65).



Scheme 65 – Possible mechanism for heteroaromatic compound 108

Initial attempts were made to test if a catalytic aza enolate aldol reaction could take place under our recently developed reaction conditions. Firstly, 2-picoline and pyrazine were tested under the catalytic aza enolate conditions (Scheme 66). Frustratingly, both attempts to form the alcohol product were unsuccessful, with no reaction occurring. Therefore, reactions with stoichiometric quantities of reagents were investigated, which also led to no reaction occurring with complete recovery of starting materials even when carried out neat or in a variety of different solvents (DMSO, MeCN, Et_2O, CH_2Cl_2, THF, $CHCl_3$, and EtOAc).

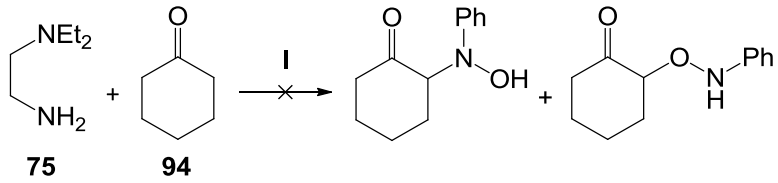


*[1] 2-picoline or pyrazine (50 mol %), $Mg(ClO_4)_2$ (50 mol %), solvent, Et_3N (50 mol %), then **66**, then rt, 12 h.*

Scheme 66 – Attempted heteroaromatic reactions

2.1.8 Reactions of aza enolates with other electrophiles

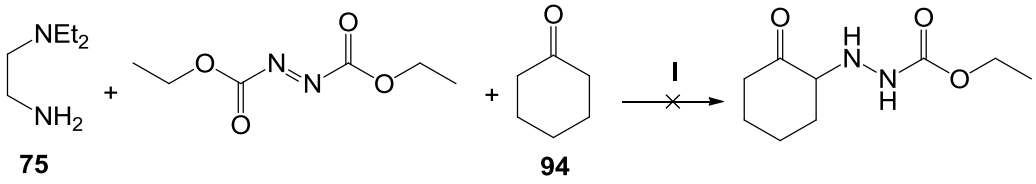
Investigations were conducted into the reaction of aza enolates with nitroso compounds (Scheme 67). The reaction of a range of ketones has been reported in the literature with the use of *L*-proline as a catalyst.[137] Preliminary reactions involved a number of different solvents (DMSO, MeCN, Et_2O, CH_2Cl_2, $CHCl_3$, THF, and EtOAc) with catalytic quantities of amine **75**, $Mg(ClO_4)_2$ and Et_3N and 1 equiv. of ketone **94**. Frustratingly, no isolatable products were observed in any of these reactions and it was found that the majority of the starting materials were still present even upon heating to 50 °C (Scheme 67).



*[1] **75** (10 mol %), **94**, Nitrosobenzene, $Mg(ClO_4)_2$ (20 mol %), Et_3N (20 mol %), DMSO, rt. 12 h.*

Scheme 67 – Attempted aza enolate reaction with nitrosobenzene

An extension to this work was to use azodicarboxylates as electrophiles to analyse if α-functionalisation could occur in the presence of a ketone (Scheme 68) using the same conditions as above. Frustratingly, no α-functionalisation was observed in any of these reactions and it was found that in all reactions the starting materials were still present. This could be due to the mild conditions used and possible heating and/or using a stronger base may produce the α-functionalised product.

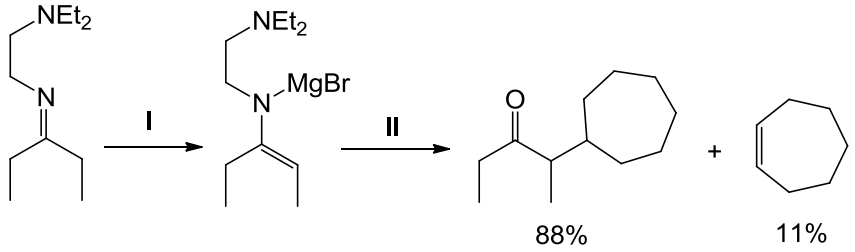


[I] $Mg(ClO_4)_2$ (20 mol %), solvent, Et_3N (20 mol %), then rt, 12 h.

Scheme 68 – Attempted aza enolate reaction with azodicarboxylates

2.1.9 Alkylation reactions

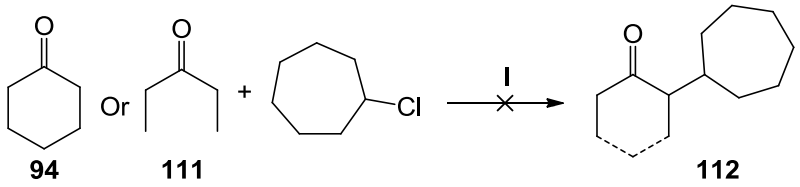
Nakamura *et al.*[69] (Section 1.2.4) had shown that alkylation reactions with pre formed imine derivatives can be achieved with the use of magnesium enamides bearing an internal nitrogen coordination site using stoichiometric conditions (Scheme 69). Interestingly, under these reaction conditions alkylation products could be formed even with poorly reactive alkyl halides such as alkyl chlorides and fluorides.



[I] MesMgBr, THF, rt, then, 80 °C, 1 h; [II] Chlorocycloheptane, THF, 45 °C, 24 h, then, 60 °C, 12 h, then H_3O^+.[69]

Scheme 69 – Literature example of an alkylation reaction

It was envisioned that this transformation might be possible with the catalytic aza enolate conditions (Scheme 70). Frustratingly, all reactions using cyclohexanone **94** and pentan-3-one **111** failed at room temperature and when heated to 40 °C, with starting materials being observed. Leaving the reaction mixtures at 40 °C for 48 h also had no impact on the formation of the product **112** with only starting materials being observed. It seems that aza enolate generation conditions employed in Nakamura's original work are critical for this reaction to be effective.

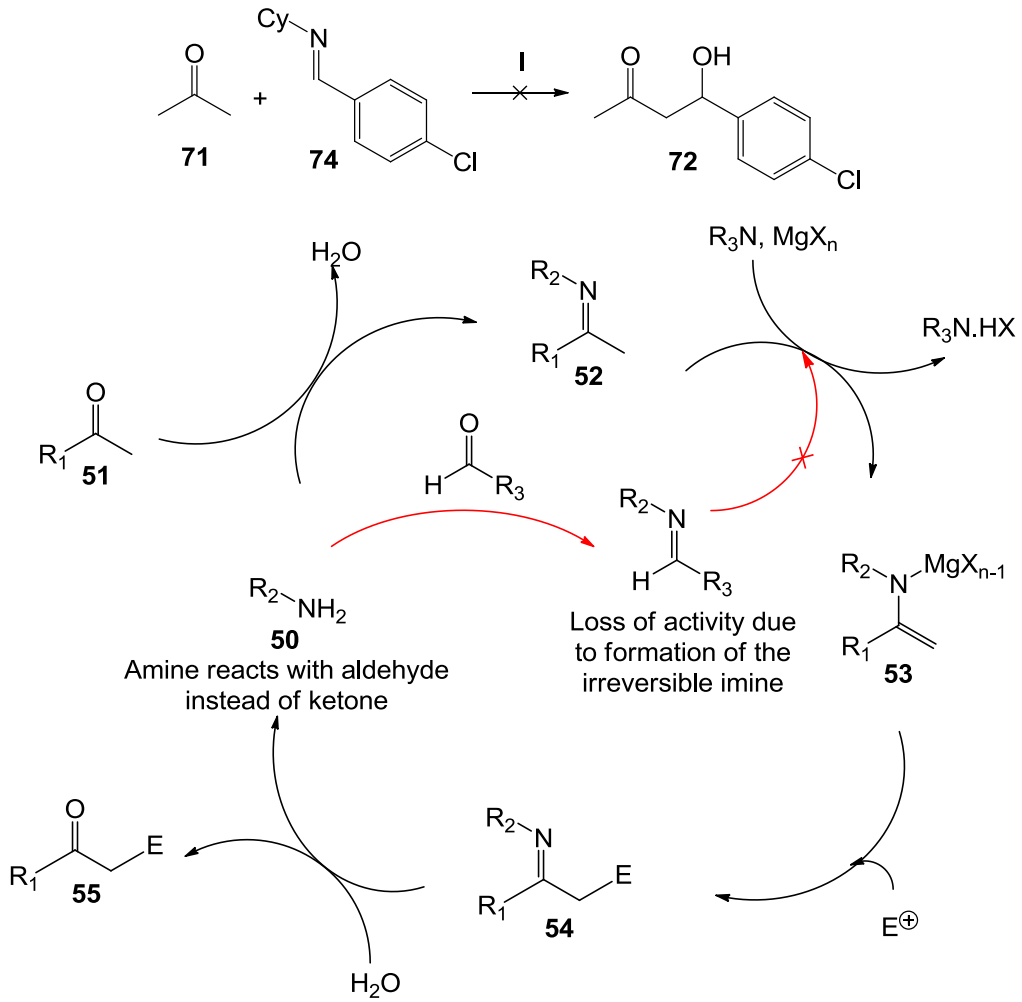


[I] ***94*** *or* ***111****, Chlorocycloheptane, $Mg(ClO_4)_2$ (20 mol %), DMSO, Et_3N (20 mol %), then rt, 12 h.*

Scheme 70 – Attempted alkylation reactions

2.2 Conclusions and future Work

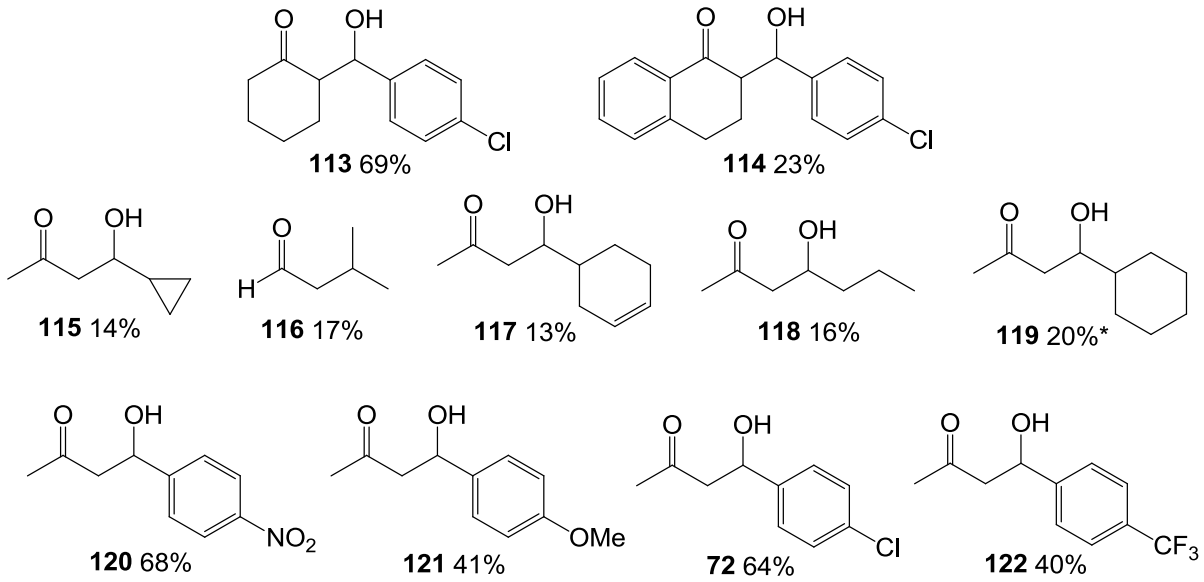
The investigations into a novel catalytic aza enolate aldol reaction have been troublesome in parts. However, the feasibility of a catalytic aza enolate aldol reaction was demonstrated and good yields of aldol products could be obtained in some cases. Particularly in expanding this work into a catalytic reaction, as it was discovered that the formation of imine **74** is not reversible (Scheme 71 – shown in red). This indicates that due to the formation of imine **74** from the condensation of Cy-NH_2 and 4-chlorobenzaldehyde (**66**), the catalytic cycle is inhibited as the imine does not participate further in the catalytic cycle and leads to the primary amine being removed from the reaction, leading to lower conversions/yields being obtained (Scheme 71 – shown in red).



I (Mg(ClO$_4$)$_2$ (50 mol %), DMSO:acetone (4:1), Et$_3$N (50 mol %), then rt, 12 h.

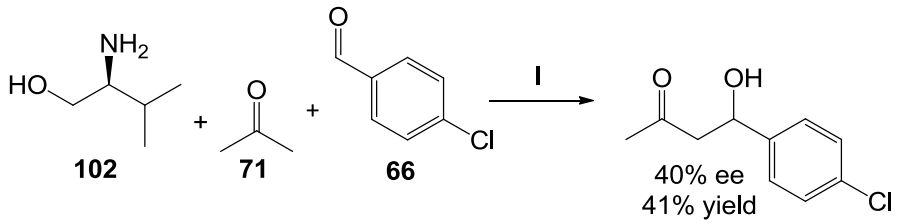
Scheme 71 – Catalytic cycle showing the irreversible formation of the aldehyde derived imine

Optimization, did lead to some interesting results, by adding the aldehyde dropwise the results were improved with good yields being obtained. In addition, 10 mol % of the primary amine was found to be the optimum for achieving the highest conversion (Scheme 72 - selected examples of aldol products with the best yields).



Scheme 72 – Summary of aldol products

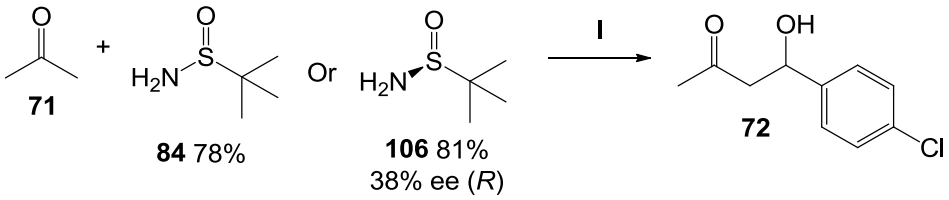
Alongside the development of catalytic aza enolate aldol reactions, a brief investigation of catalytic asymmetric aldol reactions was also carried out, which led to only low to moderate enantioselectivities with valinol **102** producing the best *ee* of 40% (Scheme 73).



[I] ***102*** *(10 mol %), $Mg(ClO_4)_2$ (20 mol %), DMSO:acetone, Et_3N (20 mol %), then* ***66****, then rt, 12 h.*

Scheme 73 – Summary of best chiral amine

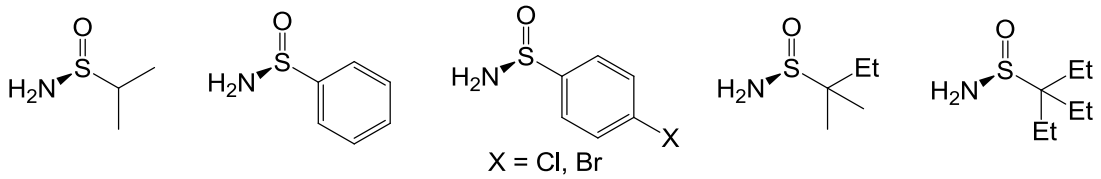
Considerable time was spent on attempting to improve the *ee* by various methods, resulting in no significant improvement. However, with the use of the racemic **84** and chiral sulfinamide **106**, isolated yields did improve and more interestingly, the reaction between **84** or **106** and the aldehyde **66** (Scheme 74) may now be reversible - a possible reason for the higher yields obtained.



[I] ***84*** *or* ***106*** *(10 mol %), $Mg(ClO_4)_2$ (20 mol %), DMSO:acetone, Et_3N (20 mol %), then* ***66****, then rt, 12 h.*

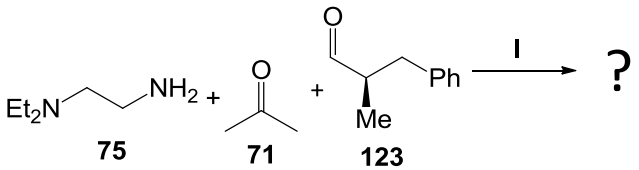
Scheme 74 – Summary of chiral and racemic sulfinamide

However, this work was discovered later in the project and therefore, an interesting area for future work on this would be to investigate the use of chiral sulfinamides further. As the chiral sulfinamide produced a moderate *ee* of 38%, changing the *tert*-butyl to a range of other groups may enhance enantioselectivity. The synthesis of the chiral *iso*-butylsulfinamide in optically pure form has been carried out in high yields and enantioselectivities. Some excellent reviews discussing chiral sulfinamide synthesis are available and the area is well studied.[138-145] Therefore, this would be an interesting avenue to investigate for future work. Possible chiral sulfinamides to synthesise are shown in scheme 75.



Scheme 75 – Future chiral amines to be synthesised

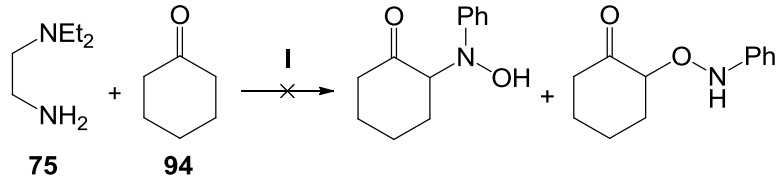
Another area to explore is to investigate if enolization is a significant problem when using enolisable aldehydes as the electrophile. A possible experiment to investigate this is to react the chiral aldehyde **123** under the developed aza enolate conditions. This would show how quickly aldehyde **123** racemizes and by how much (Scheme 76), thus showing if enolization of the electrophile is a significant problem.



[I] ***75*** *(10 mol %), $Mg(ClO_4)_2$ (20 mol %), DMSO:acetone, Et_3N (20 mol %), then* ***123****, then rt, 12 h.*

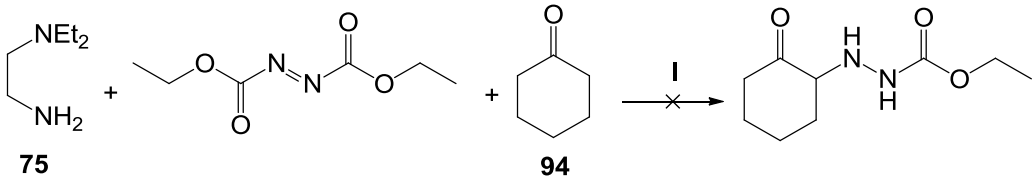
Scheme 76 – Future work to determine if enolisation is a problem

Finally, attempts were made at a heteroaromatic aldol reaction, reactions with nitroso and diazo electrophiles, and α-alkylation reactions, all to no avail (Scheme 77). Nonetheless, a novel catalytic aza enolate reaction has been demonstrated.



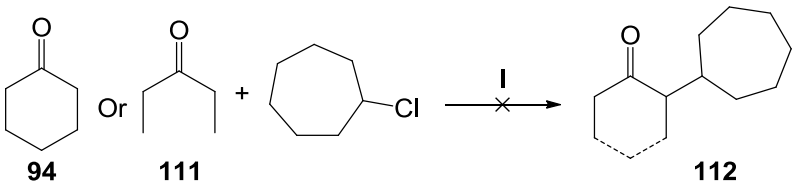
75 **94**

[I] ***75*** *(10 mol %),* ***94****, Nitrosobenzene, $Mg(ClO_4)_2$ (20 mol %), Et_3N (20 mol %), DMSO, rt. 12 h.*



75 **94**

[I] *$Mg(ClO_4)_2$ (20 mol %), solvent, Et_3N (20 mol %), then rt, 12 h.*



94 **111** **112**

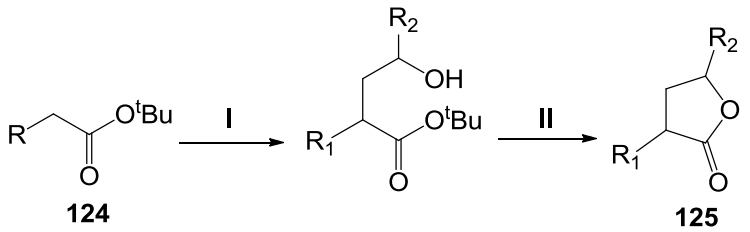
[I] ***94*** *or* ***111****, Chlorocycloheptane, $Mg(ClO_4)_2$ (20 mol %), DMSO, Et_3N (20 mol %), then rt, 12 h.*

Scheme 77 – Summary of other electrophiles that have been used

Chapter 3 - Aza enolate reactions with more challenging electrophiles

3.1 Introduction

The reaction of 'normal' enolates with epoxides is more challenging due to the low reactivity of epoxides, though more reactive enolates such as amide/ester enolates can achieve this transformation, often with additional activation of the epoxide by a Lewis acid. Taylor *et al*. reported the reaction of Al-enolates of esters with various epoxides.[146,147] This involved treating ^{t}Bu-ester **124** with LDA and the Lewis acid Et_2AlCl to form the Al-enolate. This was reacted with the chosen epoxide to form the desired product **125** upon addition of acid (Table 21).



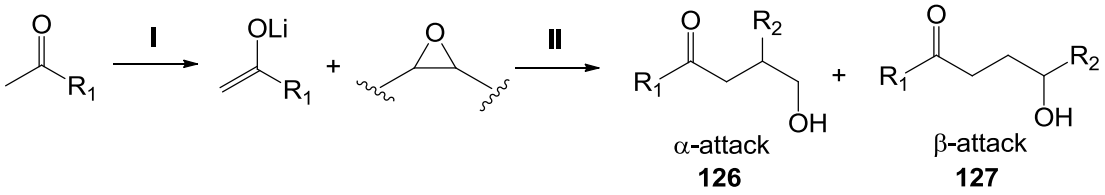
124 **125**

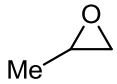
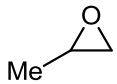
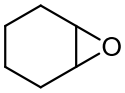
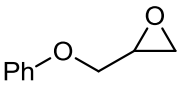
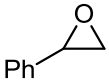
Entry	R_1	R_2	Yield	*syn*:*anti*
1	H	Me	46%	-
2	H	Et	52%	-
3	Me	Me	56%	84:16
4	Me	Et	43%	84:16
5	Me	^{i}Pr	56%	88:12

[I] LDA, THF, ^{n}BuLi, −78 °C, 30 min, then Et_2AlCl, 15 min. then epoxide, then 5 h at −45 °C. [II] p-TsOH.

Table 21 – Ester enolates ring opening epoxides

Crotti *et al*. demonstrated the use of lithium enolates derived from pinacolone and acetaphenone in the presence of $LiClO_4$ to ring open a variety of epoxides to afford in good yields the corresponding γ-hydroxy ketones (Table 22).[148] As expected, the majority of reactions all occur on the least hindered end of the epoxide (Table 22).

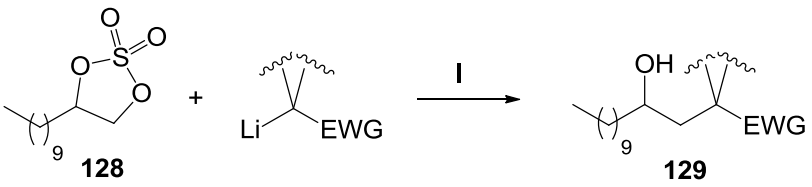


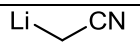
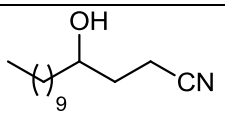
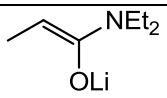
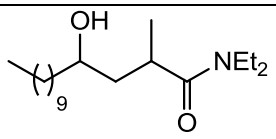
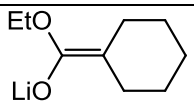
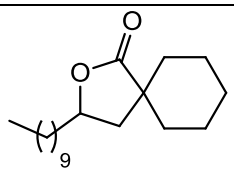
Entry	Epoxide	R_1	R_2	α-attack (**126**)	β-attack (**127**)	Yield
1		^{t}Bu	Me	<1	>99	98%
2		Ph	Me	<1	>99	86%
3		^{t}Bu	*c*-C_4H_8	-	-	80%
4		^{t}Bu	$PhOCH_2$	<1	>99	90%
5		^{t}Bu	Ph	9	91	95%

[I] THF, LHMDS, ketone, 0 °C, 15 min [II] epoxide, THF, 30 min, then $LiClO_4$, 24 h, 50 °C.

Table 22 – Lithium enolates reacting with various epoxides

In 1994, Hoye *et al*. demonstrated the use of enolates of esters and amides to react with the more reactive, cyclic sulfate **128**, to give hydroxylated products **129** in good yields (72-92%) (Table 23 – selected examples).[149]

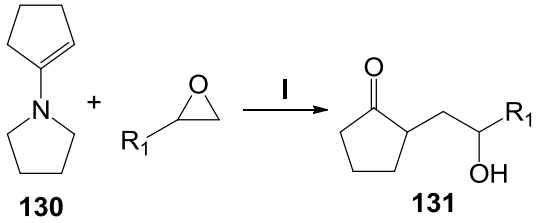


Entry	Nucleophile	Product	Yield
1			73%
2			72%[a]
3			92%

*[1] MeCN, −78 °C, [n]BuLi, 2 h, then **128** in THF, −78 °C, 1 h, then 14 h, rt. a isolated as a 2:1 mixture of diastereomers*

Table 23 – Lithium enolates reacting with cyclic sulfates

Ring opening of epoxides has also been achieved with enamines, demonstrated by Britten *et al.*[150] Britten described the reaction of enamine **130** with an epoxide to afford 1,4-hydroxyketones **131** in moderate yields of 33-60% (Table 24). It is worth pointing out that the conditions used by Britten involve very high temperatures to make the reaction proceed (Table 24).



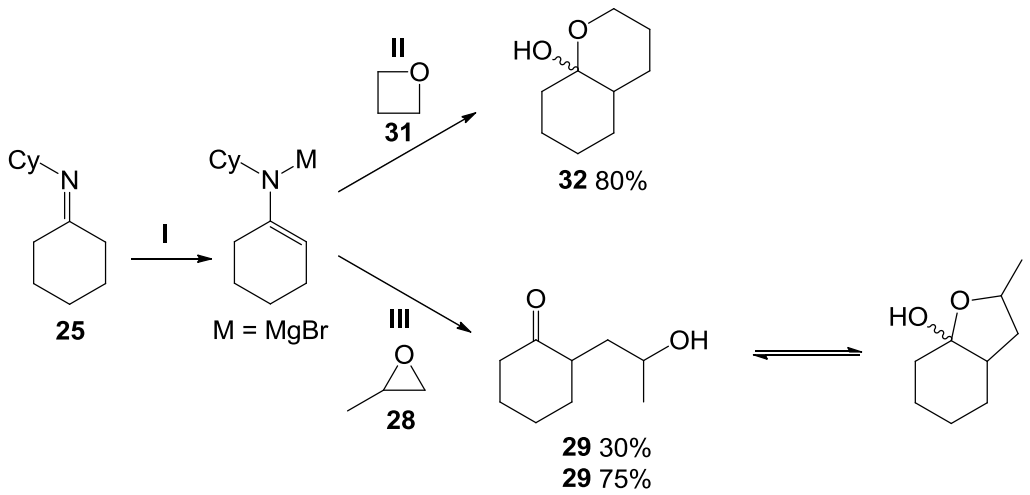
130 **131**

Entry	R_1	Yield
1	Ph	42%
2	H	33%
3	Me	60%
4	Ph	50%
5	Ph	56%

[1] ***130**, DMF, 0 °C, epoxide, 24 h, then reflux, 30 min.*

Table 24 – Ring opening of epoxides with enamines

The use of magnesium aza enolates to ring open epoxide **28** and oxetane **31** was reported by Tarbell *et al.*[87] and Hudrlik *et al.*[88] (Scheme 78). Firstly, Tarbell and Harvey[87] reported the deprotonation of imine **25** with EtMgBr and reaction with epoxide **28** to produce the product **29** (Scheme 78). Reaction with a more challenging electrophile such as oxetane **31** has not been achieved with simple enolates. However, Hudrlik *et al.*[88] reported the use of aza enolates as nucleophiles for the ring opening of oxetane in good yields, using a Grignard reagent as the base, to give the cyclised product **32** (Scheme 78). Hudrlik *et al.*[88] also reported the ring opening of epoxide **28** to give the product **29** in a greater yield of 75% compared to Tarbell and Harvey[87] (Scheme 78). Interestingly, Tarbell and Harvey reported that ring opening of epoxide **28** occurs regioselectivly and produces **29** exclusively. However, characterisation was achieved solely by boiling point and elemental analysis and no NMR data to validate the formation of the product **29** was provided. Hudrlik *et al*. also do not provide any NMR data and simply refer back to the work by Tarbell and Harvey. Therefore, it seems that with the work by Tarbell *et al.*[87] and Hudrlik *et al.*[88] there is some uncertainty that only one isomer of the ring opened product **29** was isolated. Therefore, it was decided to repeat these reactions to explore which product(s) are formed.



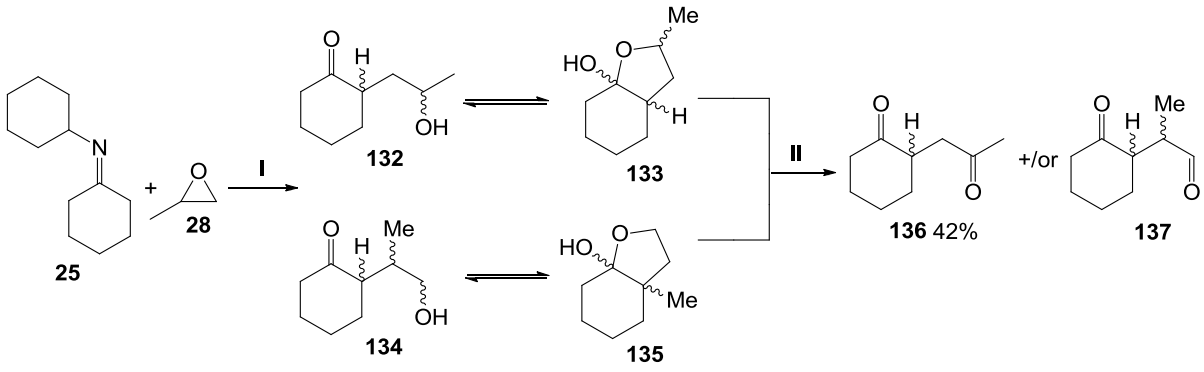
*[I] EtMgBr, THF, reflux, 2 h, then 0 °C then either [II] **31** or [III] **28**, then rt, 25 h.*[87,88,151]

Scheme 78 – Ring opening of oxetane and epoxides

3.2 Results and discussion

3.2.1 Stoichiometric reactions with epoxides

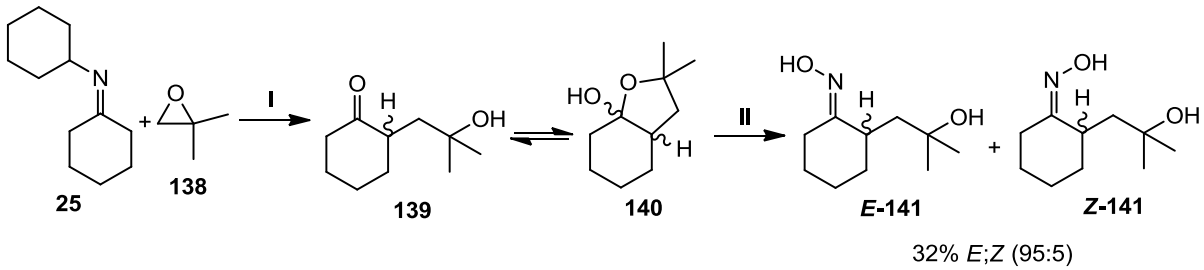
Having developed a catalytic aza enolate aldol reaction (Chapter 2), the next step was to apply this methodology to more challenging electrophiles such as epoxides. At first, the stoichiometric literature procedure by Tarbell and Harvey[87] was repeated with the use of imine **25** and propylene oxide **28** (Scheme 79, step I). Interestingly, all possible regio- and stereo- isomers were produced in a combined 31% yield, in contrast to the literature report (*vide supra*). Due to the mixture of all possible regio- and stereo- isomers being produced, spectroscopic characterisation was extremely difficult. The cyclised lactol form that exists in equilibrium with the γ-hydroxycarbonyl products **132** and **134** is also present as a complex mixture of diastereomers (Scheme 79). To overcome the difficulties in assigning the ^{1}H NMR, it was thought that oxidising the alcohols to the corresponding aldehydes/ketones could simplify the spectrum as only a maximum of two products would be seen (Scheme 79, **136** and **137**). A Swern-Moffatt oxidation was utilised to oxidise the mixture of **132-135** to **136**/**137** (Scheme 79, step II). Pleasingly, upon purification, product **136** was isolated in a yield of 42%. However, product **137** was not isolated cleanly due to the small amounts generated. As expected, this suggests that ring opening occurs preferentially at the least hindered end.



[I] THF, EtMgBr, reflux, 2 h then rt, 30 min, 0 °C, ***28****. [II] SO_3.Py, DMSO, −76 °C, DCM; Et_3N, rt, 5 h.*

Scheme 79 – Repeating literature example

Expanding on this result (Scheme 79), previously prepared imine **25** was reacted with epoxide **138** (Scheme 80). Epoxide **138** was chosen as this is likely to open regioselectively to give only products **139/140**. This too exists as a mixture of the acyclic (**139**) and the cyclic (**140**) lactol forms; however, conversion to the corresponding oxime (**141**) prevents the formation of the cyclised lactol form and thus made spectroscopic analysis simpler. Pleasingly, this successfully led to the isolation of **141** as a mixture of geometric isomers with approximately 95% of ***E*-141** compared to 5% of ***Z*-141** in a modest yield of 32% over two steps (Scheme 80). When changing the epoxide to styrene oxide, no apparent conversion to the γ-hydroxycarbonyl products was observed.

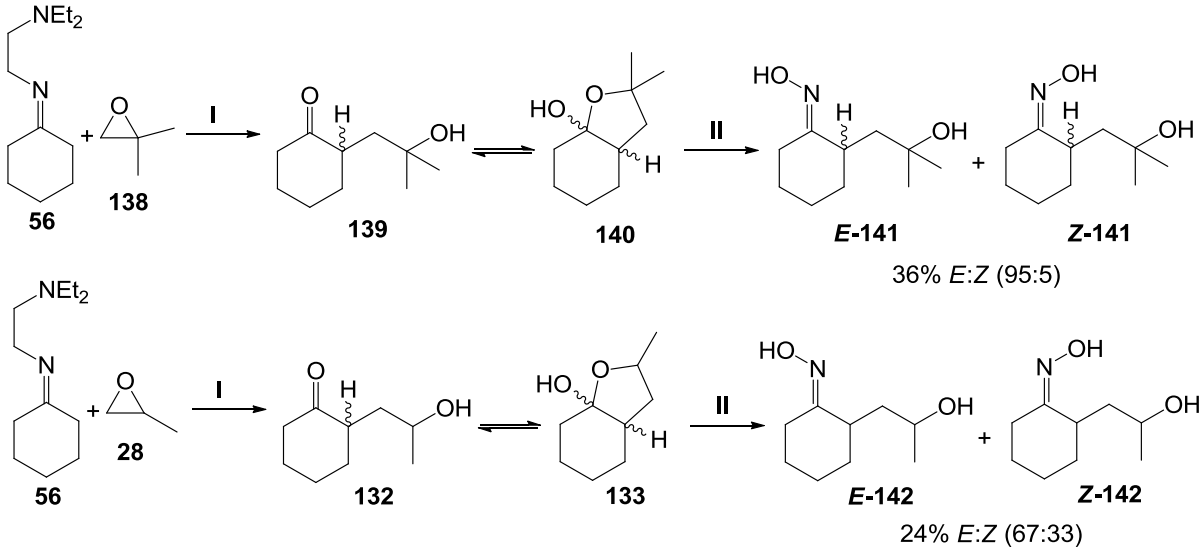


[I] EtMgBr, THF, reflux, then 0 °C, epoxide ***138****; [II] NH_2OH, pyridine, ethanol, reflux, 12 h.*

Scheme 80 – Ring opening of epoxide 138

Changing the imine from **25** (Scheme 80) to the previously prepared chelating imine **56** and reacting this with epoxides **28** and **138**, successfully led to the formation of the desired products (Scheme 81). Using the chelating imine **56** with the more hindered epoxide **138** led to the isolation of the products **141** as a mixture of geometric isomers in a modest yield of 36% (Scheme 81). Changing the epoxide from **138** to the less hindered epoxide **28** leads to a mixture of geometric isomers being obtained over two steps in a 24% isolated yield (Scheme 81). The reason why there is more *cis*-isomer (Scheme 81 - ***Z*-142**) is presumably due to the

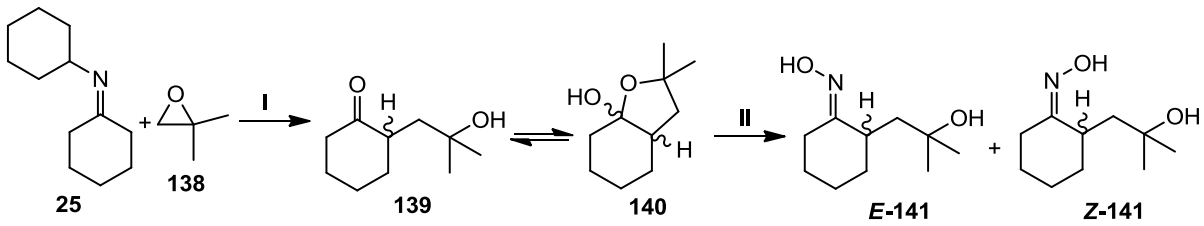
substituent being less bulky than that on ***Z*-141**. The use of the chelating imine **56** compared to the cyclohexyl-imine **25** with epoxide **138** gave a slight improvement in the yield of 36% compared to 32% with imine **25** (Scheme 80 compared to Scheme 81).



*[I] EtMgBr, THF, reflux, then 0 °C, epoxide **28** or **138**; [II] NH_2OH, pyridine, ethanol, reflux, 12 h.*

Scheme 81 – Ring opening of different epoxides

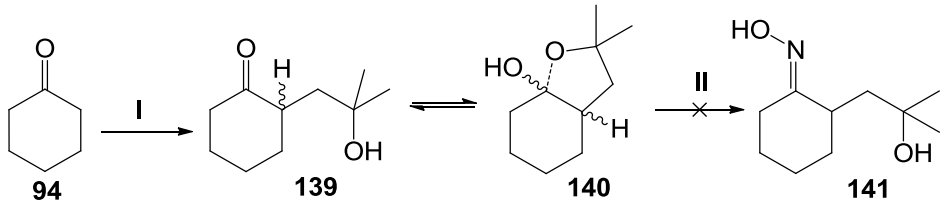
Having demonstrated the use of imines **25** and **56** in the ring opening of epoxides (Scheme 80 and 81), the next step was to investigate if the mild aza enolate methodology developed earlier in the project (Chapter 2) could be applied to the ring opening of epoxides. This would involve the formation of the aza enolate using a Lewis acid and base ($Mg(ClO_4)_2$ and Et_3N) under the mild conditions that were developed earlier, avoiding the use of the harsh conditions previously reported in the literature, i.e. reflux and Grignard reagent (*vide supra*). Firstly, a proof of principle experiment was investigated using imine **25** directly with 2,2-dimethyloxiran (**138**) with stoichiometric quantities of $Mg(ClO_4)_2$ and Et_3N, affording a mixture of the acyclic (**139**) and cyclic (**140**) lactol forms in a conversion yield of 24% and the successful formation of **141** in an isolated yield of 20% as a mixture of geometric isomers (Scheme 82). A test catalytic reaction using catalytic quantities of $Mg(ClO_4)_2$ (50 mol%) and Et_3N (50 mol%) was also attempted. This led to the formation of the hydroxylketone/lactol **139**/**140** in a 12% conversion by ^1H NMR spectrum; regrettably, the subsequent isolation of the oxime **141** was difficult due to the small quantities obtained.



*[I] THF, 0 °C, $Mg(ClO_4)_2$, epoxide **138**, Et_3N, then rt, 12 h. [II] Hydroxylamine, pyridine, ethanol, reflux, 2 h.*

Scheme 82 – Ring opening of epoxide 138 using milder aza enolate conditions

Having discovered that an aza enolate reaction with imine **25** and epoxide **138** takes place using the milder Lewis Acid conditions, the next step was to investigate if a reaction could be achieved in which the imine was generated *in situ* (Scheme 83). This involved using cyclohexanone (**94**) directly with epoxide (**138**) and Cy-NH_2 in a one-pot procedure. Examination of the crude ^{1}H NMR indicated only a low conversion, 11%, to the acyclic (**139**) and cyclic (**140**) lactol forms. Unfortunately, attempted isolation of the oxime **141** was unsuccessful (Scheme 83).

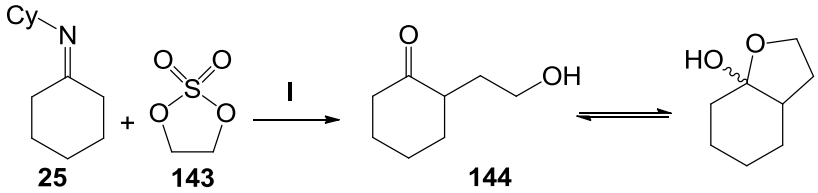


*[I] Cy-NH_2, THF, $Mg(ClO_4)_2$, **138**, Et_3N then rt, 12 h. [II] NH_2OH, pyridine, ethanol, reflux, 2 h.*

Scheme 83 – *In situ* imine generation and reaction with epoxide 138

Having learnt that reactions with epoxides using the mild aza enolate generation method do take place, albeit not very efficiently, the next step was to investigate a simpler more reactive electrophile. Cyclic sulfate **143** is an interesting electrophile to investigate as it is known to be more reactive than an epoxide and also gives a product with only one chiral centre, meaning interpretation of the ^{1}H NMR should be simpler. The high reactivity of cyclic sulfates has been attributed to both ring strain and the good leaving group ($ROSO_3^-$ *c.f.* to epoxide RO^-).[152] Therefore, a reaction involving imine **25** with cyclic sulfate **143** was investigated using stoichiometric quantities of base (Et_3N or DIPEA) and MgX_2 (Table 25). Changing the magnesium counterion from bromide (Table 25, entries 1 and 4) to triflate or perchlorate (Table 25, entries 2, 3, 5 and 6) had a significant impact on the conversion to the γ-hydroxycarbonyl product **144**, with magnesium perchlorate providing the highest conversion, 47%, and cleanest crude ^{1}H NMR spectrum when using Et_3N as the base (Table

25, entry 6). Pleasingly, the products were isolated in low to moderate yields of 18 and 31% from these reactions (Table 25, entries 3 and 6).



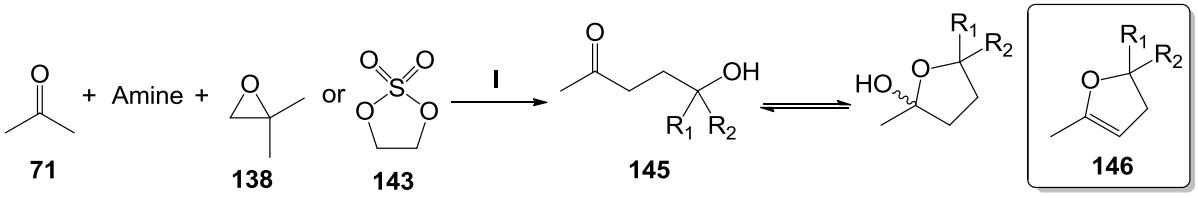
Entry	Base	MgX_2 X =	Conversion[a]	Yield
1	DIPEA	Br	<5%	n.d.
2	DIPEA	OTf	<5%	n.d.
3	DIPEA	ClO_4	30%	18%
4	Et_3N	Br	<5%	n.d.
5	Et_3N	OTf	40%	n.d.
6	Et_3N	ClO_4	47%	31%

*[1] MeCN, MgX_2 (1.2 equiv.), Base (2 equiv.), −76 °C, then **143**, then rt, 11 h. [a] % conversion determined by ^1H NMR ($CDCl_3$).*

Table 25 – Ring opening of cyclic sulfate 143 using milder aza enolate conditions

3.2.2 Catalytic reactions with epoxides

Having shown that ring opening of epoxides using stoichiometric quantities of reagents could be achieved (Section 3.2.1), the next step was to investigate if a catalytic aza enolate reaction could work, with catalytic quantities of amine (10 mol %), $Mg(ClO_4)_2$ (20 mol %) and Et_3N (20 mol %). Initially, a proof of principle experiment was investigated. This involved a small amine screen with acetone (**71**) and cyclic sulfate (**143**) or epoxide (**138**) in a one-pot procedure (Table 26). Pleasingly, reactions using cyclic sulfate **143** produced moderate conversions by crude ^1H NMR (Table 26, entries 4-6), with the chelating amine producing the highest conversion of 35% and an isolated yield of 29% (Table 26, entry 4). Interestingly, on changing the epoxide from **143** to **138**, no apparent conversion to the product **145** was seen with the dehydrated product **146** being observed (Table 26, entries 1-3), with approximately 35% conversion by ^1H NMR. The dehydrated product **146** was confirmed by comparing to the literature[153].



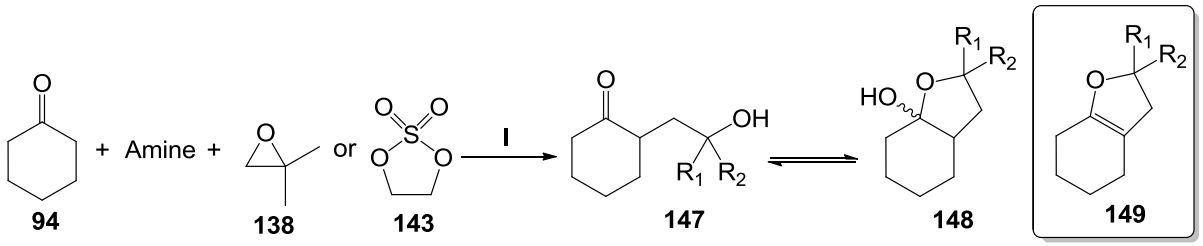
R_1, R_2 = Me = 2,2-Dimethyloxiran (**138**)
R_1, R_2 = H = Cyclic sulfate (**143**)

Entry	Amine	Epoxide	Product (145)		By-product (146)	
			Conversion[a]	Yield	Conversion[a]	Yield
1	Et_2N NH_2	**138**	<5%	n.d.	35%	n.d.
2	Cy-NH_2	**138**	<5%	n.d.	34%	n.d.
3	NH_2	**138**	<5%	n.d.	35%	n.d.
4	Et_2N NH_2	**143**	35%	29%	<5%	n.d.
5	Cy-NH_2	**143**	25%	n.d.	<5%	n.d.
6	NH_2	**143**	26%	21%	<5%	n.d.

*[I] Amine (10 mol %), $Mg(ClO_4)_2$ (20 mol %), DMSO:acetone, Et_3N (20 mol %) then **138** or **143**, then rt, 12 h. [a] % conversion determined by ^1H NMR ($CDCl_3$). n.d. = not determined.*

Table 26 – Catalytic ring opening of epoxide 138 and cyclic sulfate 143 using ketone 71

To test the scope of this reaction, the ketone was changed from acetone **71** to cyclohexanone **94**. Unfortunately, in the majority of these reactions when using epoxide **138**, an intractable mixture was obtained and no apparent conversion to the desired product **147**/**148** was seen (Table 27, entries 1-3). However, again the by-product **149** was observed in one case, with a conversion of 10% by crude ^{1}H NMR (Table 27, entry 3). Upon changing the epoxide **138** to the cyclic sulfate **143**, low conversions to the desired product **147**/**148** were observed by crude ^{1}H NMR analysis (Table 27, entries 4-6) with no apparent conversion to the side product **149**.



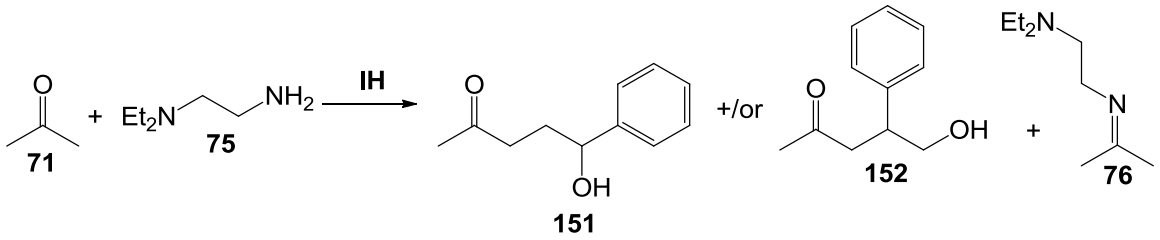
R_1, R_2 = Me = 2,2-dimethyloxiran (**138**)
R_1, R_2 = H = cyclic sulfate (**143**)

Entry	Amine	Epoxide	Product (147)		By-product (149)	
			Conversion[a]	Yield	Conversion[a]	Yield
1	Et_2N⁄⁄NH_2	**138**	<5%	n.d.	<5%	n.d.
2	Cy-NH_2	**138**	<5%	n.d.	<5%	n.d.
3	⁄⁄NH_2	**138**	<5%	n.d.	10%	n.d.
4	Et_2N⁄⁄NH_2	**143**	15%	n.d.	<5%	n.d.
5	Cy-NH_2	**143**	10%	n.d.	<5%	n.d.
6	⁄⁄NH_2	**143**	10%	n.d.	<5%	n.d.

*[1] Amine (10 mol %), $Mg(ClO_4)_2$ (20 mol %), DMSO, Et_3N (20 mol %) then **138** or **143**, then rt, 12 h. [a] % conversion determined by ^1H NMR ($CDCl_3$). n.d. = not determined.*

Table 27 - Catalytic ring opening of epoxide 138 and cyclic sulfate 143 using ketone 94

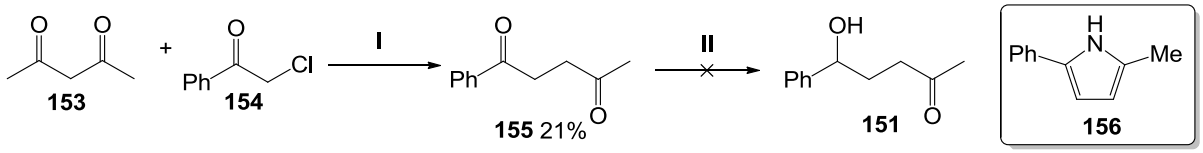
With these preliminary results (Tables 26 and 27), chelating amine (**75**) produced the best yield of 29% when using acetone as the ketone (Table 26, entry 4), and therefore, chelating amine **75** was selected for further examination. This involved using acetone **71** directly with styrene oxide (**150**) in a one-pot procedure using the same conditions as earlier (Scheme 84). Examination of the crude ^1H NMR spectrum indicated that starting material and imine **76** were present. Varying the solvent had no significant outcome on the formation of **151**/**152**, in addition, the crude NMR was difficult to interpret, and therefore it was decided to prepare an authentic sample of the product.



*[I] Amine (10 mol %), $Mg(ClO_4)_2$ (20 mol %), Solvent:Acetone (4:1), Et_3N (20 mol %) then **150**, then rt, 12 h.*

Scheme 84 – Ring opening of styrene oxide

Attention was focused on synthesising an authentic sample of **151**. Dione **153** was reacted with 2-chloro-1-phenylethanone (**154**) in the presence of potassium carbonate to produce the ketone (**155**) in an acceptable yield of 21% (Scheme 85, step I). The ketone **155** was subjected to selective reduction of the benzylic carbonyl *via* $TiCl_3$ and aq. NH_3 following a literature procedure[154] (Scheme 85, step II). However, on examination of the crude ^{1}H NMR, the ketone **155** had cyclised into pyrrole **156**.

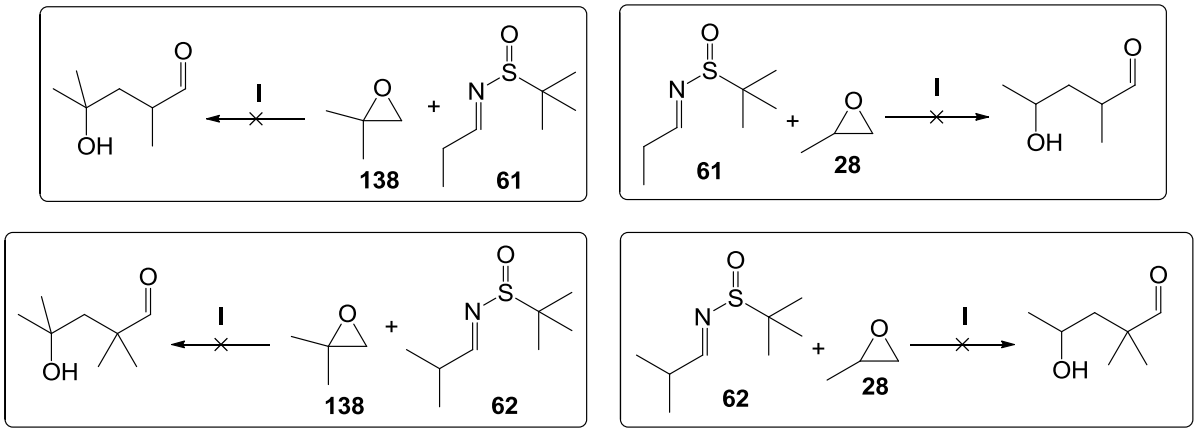


[I] Potassium carbonate, ethanol, reflux, 12 h. [II] aq. NH_3, $TiCl_3$, MeOH, 0 ^oC, 12 h.

Scheme 85 – Attempted synthesis of authentic sample 151

3.2.3 Stoichiometric reactions of aldehyde-derived imines with epoxides

It was thought with the limited success of imines ring opening challenging substrates (*vide supra*) that it would be interesting to investigate the use of aldehyde-derived imines with epoxides to see if any ring opening occurs. The previously prepared imines **61** and **62** were reacted with epoxides **28** and **138** (Scheme 86). Unfortunately, all attempts resulted in unreacted starting material remaining.

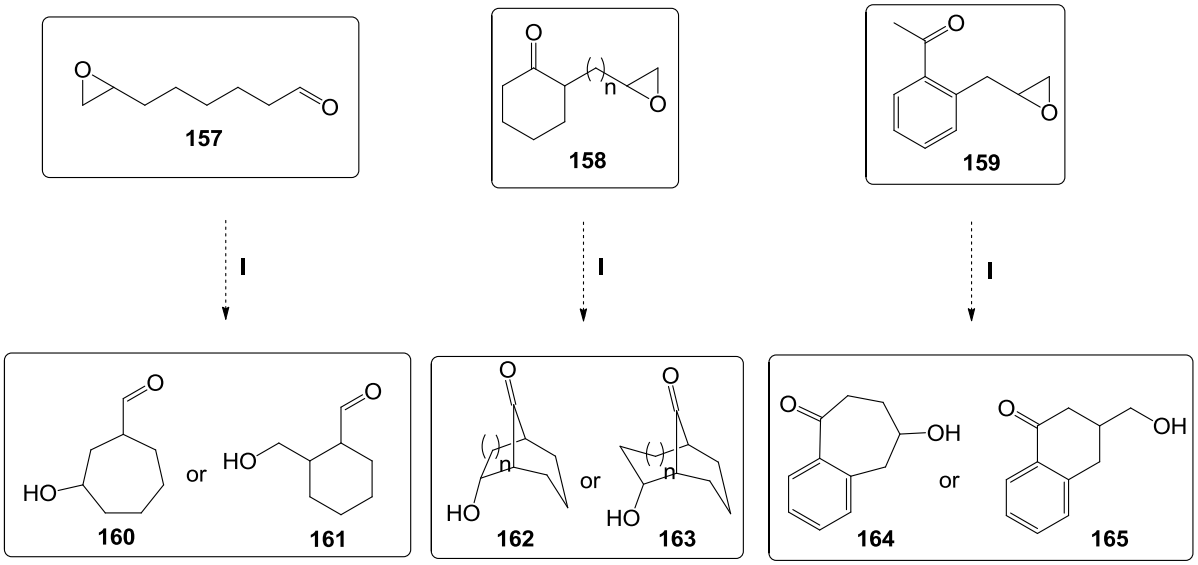


[1] *Et_3N, $Mg(ClO_4)_2$, aldehyde, MeCN, 12 h, rt.*

Scheme 86 – Attempted reactions of aldehyde-derived imines with epoxides

3.2.4 Investigating intramolecular reactions

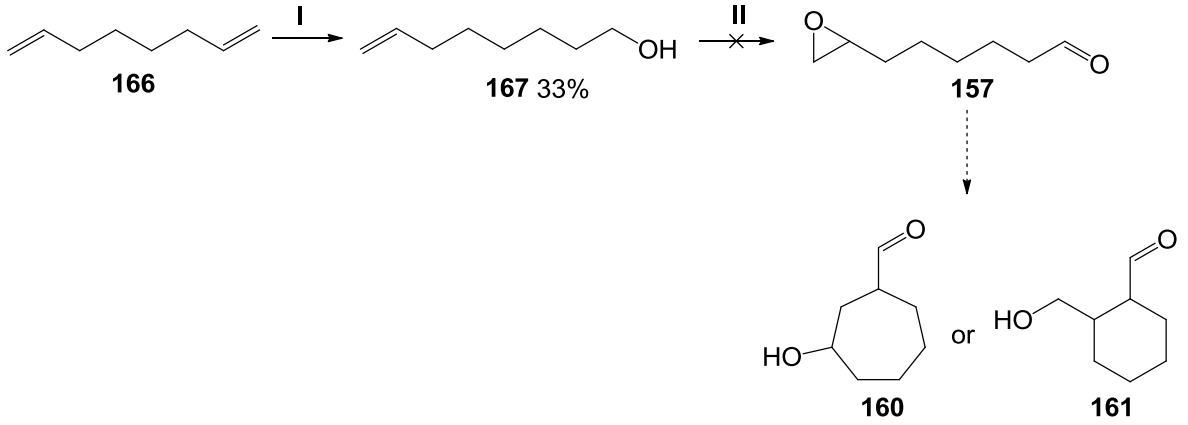
Given the problems and low conversions that were obtained in these reactions with catalytic/stoichiometric quantities (Sections 3.2.1 - 3.2.3); intramolecular reactions were then investigated, as it was hoped this would be more successful. In order to investigate intramolecular reactions, compounds containing both a carbonyl and an epoxide were required. Possible compounds to synthesise are outlined in scheme 87. These substrates would then undergo the aza enolate reactions as previously (Section 2.1). The formation of intramolecular substrates might give useful information regarding stereocontrol/regioselectivity and the geometry of the aza enolate intermediates. Furthermore, a major advantage is that intramolecular substrates could be designed to enable multiple stereocentres to be created in a single aza enolate reaction.



[I] Amine, Base, Lewis acid, DMSO, rt, 12 h.

Scheme 87 – Possible compounds to synthesise

Therefore, to form **157** diene **166** was selected and underwent a hydroboration to afford the alcohol **167** in 33% yield after oxidative work-up (Scheme 88, step I). Nooy *et al.*[155] reported that the use of *m*-CPBA in conjunction with TEMPO could lead to oxidation of the alkene and alcohol in a one-pot procedure. Therefore, attempts were made to use this procedure to generate the desired epoxy-aldehyde **157** (Scheme 88, step II), However, ^{1}H NMR analysis revealed that no reaction had taken place even when adding excess *m*-CPBA and TEMPO with starting materials being recovered.

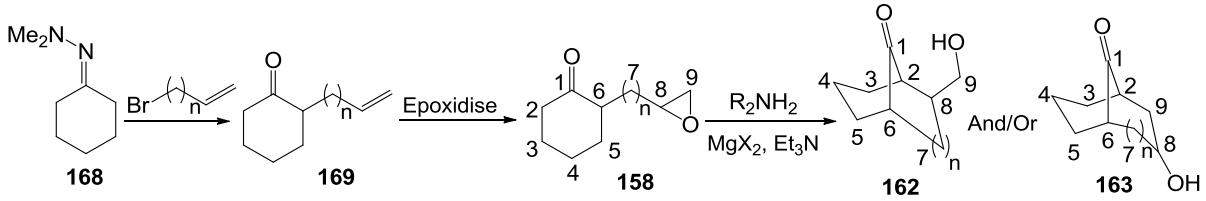


[I] BH_3.THF, 0^{o}C, 1 h, then H_2O_2, NaOH, rt, 12 h. [II] m-CPBA, CH_2Cl_2, rt, then TEMPO, rt.12 h.

Scheme 88 – Attempted synthesis of 157

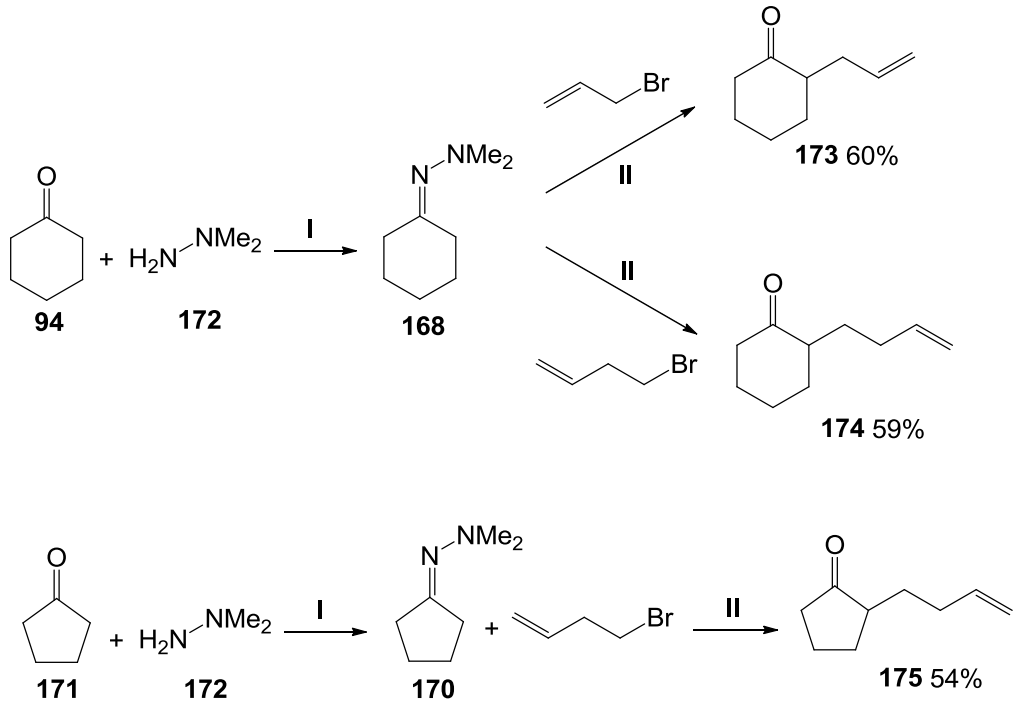
With the problems associated with the proposed synthesis of **160** and **161** (Scheme 86), it was decided that compound **158** should be synthesised instead (Scheme 89). This involved using hydrazone aza enolate methodology (See chapter 1) to alkylate **168** and form **169** (Scheme

89), which would then undergo epoxidation to form the epoxy-ketone **158**. We could then explore using an aza enolate reaction for the formation of the bicyclic products **162** and/or **163** (Scheme 89).



Scheme 89 – Proposed synthesis of 158

Hydrazones **168** and **170** were prepared using a literature procedure[156] from cyclohexanone (**94**) or cyclopentanone (**171**) and dimethylhydrazine **172** in quantitative yield (Scheme 90). This was followed by alkylation to furnish ketones **173, 174** and **175** in reasonable yields of 60 %, 59 % and 54 % respectively (Scheme 90).

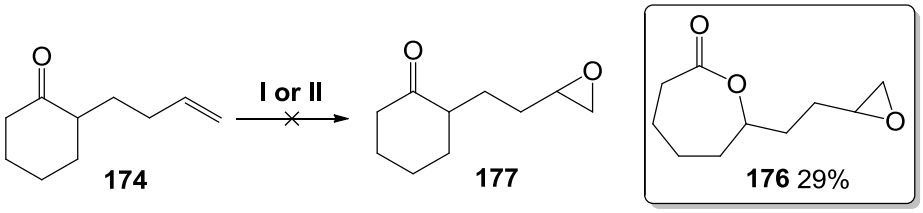


*[I] **168** or **170**, 80 °C, 14 h. [II] THF, 0 °C, [n]BuLi, 45 min, allyl bromide, then rt, 3 h.*

Scheme 90 – Synthesis of compounds 173, 174 and 175

With sufficient alkene compounds **173**, **174** and **175** in hand, **174** was epoxidised using commercially available *m*-CPBA (Scheme 91). Unfortunately, lactone **176** was isolated in a 29% yield as the major product in place of the desired epoxy-ketone **177** (Scheme 91). To overcome this problem, an alternative procedure was attempted using $NaHCO_3$ as epoxidation of an alkene in the presence of a ketone has been shown to work with a similar

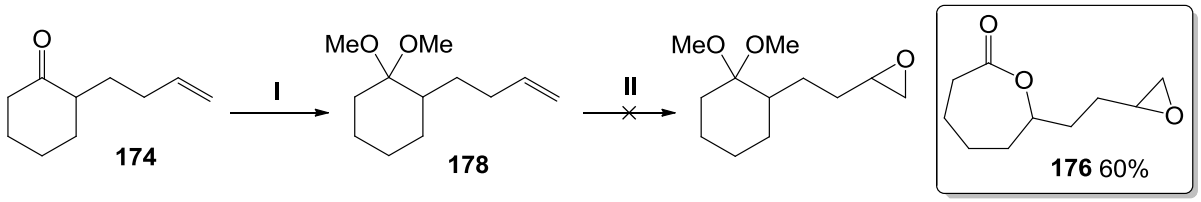
substrate.[157] Therefore, an attempt was made to use **174** in a 1:1 mixture of CH_2Cl_2:$NaHCO_3$, unfortunately, again, the Baeyer–Villiger product **176** was observed.



*[I] **174**, CH_2Cl_2, m-CPBA, 0°C, 20 min, then rt, 12 h. [II] **174**, CH_2Cl_2, 1M $NaHCO_3$ m-CPBA, rt. 12 h.*

Scheme 91 – Attempted synthesis of 177

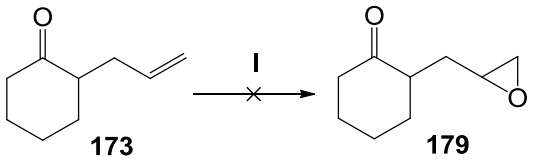
To prevent the formation of undesired lactone **176**, the carbonyl group of **174** was acetal protected prior to *m*-CPBA oxidation to give **178** in a quantitative yield (Scheme 90). However, upon addition of *m*-CPBA the acetal was hydrolysed and frustratingly again, the Baeyer–Villiger product **176** was observed in a 60% yield (Scheme 92).



*[I] trimethyl orthoformate, amberlyst-15, petrol, rt. 1 h. [II] **178**, m-CPBA, CH_2Cl_2, 0 °C.*

Scheme 92 – Synthesis of unwanted Baeyer–Villiger product 176

To overcome these problems, other literature procedures that have been shown to epoxidise alkenes in the presence of ketones were investigated. Alkene **173** was reacted with a freshly prepared solution of potassium peroxomonosulfate (Oxone®) in water/$EDTANa_2$ following a literature procedure[158] (Scheme 93). Unfortunately, upon examination of the crude ^{1}H NMR, no apparent conversion to the product **179** was observed, with starting material **173** still present.

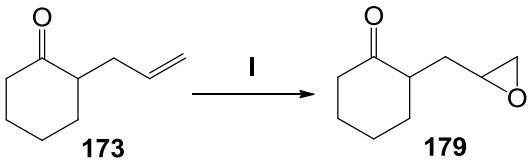


[I] Potassium peroxomonosulfate, acetone, 2 °C. pH maintained at 7.5 by additions of 0.5M KOH.

Scheme 93 – Attempted synthesis of 179

With no reaction occurring with Oxone® (Scheme 93), Baertschi *et al*.[159,160] has reported that 3,3-Dimethyldioxirane (DMDO) has been successful in epoxidising an alkene in the presence

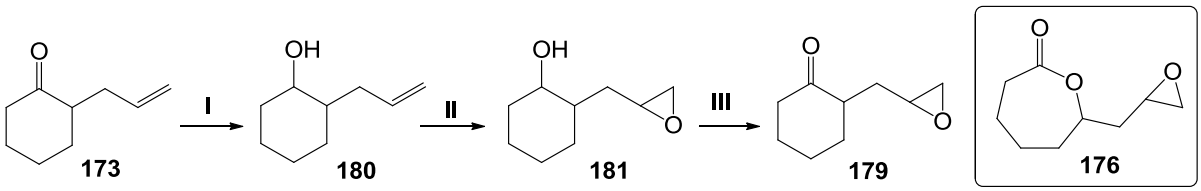
of a ketone where other conventional methods such as *m*-CPBA and Oxone® had failed. Furthermore, the by-product of oxidation with DMDO is acetone, a fairly innocuous and volatile compound making purification of the products straightforward. Therefore, DMDO was synthesised using a literature procedure[161] and subsequently reacted with alkene **173** (Scheme 94). Examination of the crude ^{1}H NMR spectrum indicated a very low conversion, 10%, to the product **179**. Unfortunately, due to this low conversion, this reaction was abandoned.



[I] DMDO, acetone, 0 °C, 1 h.

Scheme 94 – Synthesis of 179

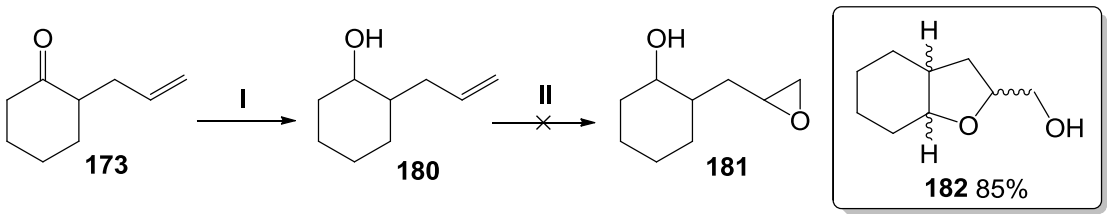
From encountering numerous problems with the epoxidation of the alkene **173**, it was thought that reducing the ketone **173** to the alcohol **180**, followed by subsequent epoxidation would lead to the epoxy alcohol **181**. Oxidation would give the desired product **179** and this route should avoid the formation of the undesired Baeyer-Villiger product **176** (Scheme 95).



[I] MeOH/THF (1:1), $NaBH_4$, 1 h, rt. [II] CH_2Cl_2, 0 °C, m-CPBA, 2 h. [III] Swern oxidation.

Scheme 95 – Proposed synthesis of 179 which avoids the unwanted product 176

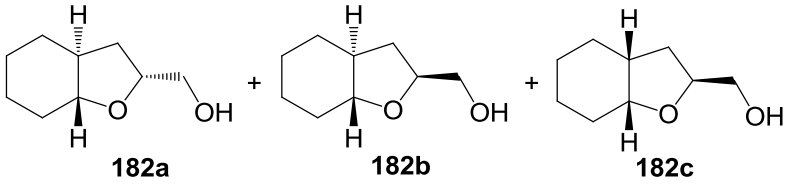
Therefore, the ketone **173** was reduced with sodium borohydride to form the alcohol **180** in quantitative yield (Scheme 96, step I). However, subsequent epoxidation failed to produce **181**; instead, the cyclic ether **182** was formed in 85% yield (Scheme 96).



[I] MeOH/THF (1:1), $NaBH_4$, 1 h, rt. [II] CH_2Cl_2, 0 °C, m-CPBA, 2 h.

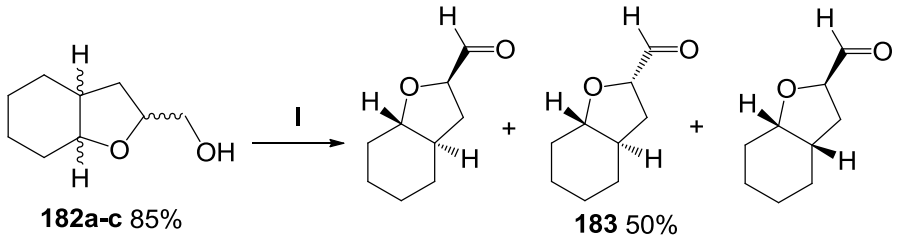
Scheme 96 – Attempted synthesis of 181

Comparing with the literature data from Hartung *et al.*[162] and Gravel *et al.*[163], it appears that **182** was formed as a mixture of three diastereomers (**182a-182c**) plus another unidentified product (Scheme 97).



Scheme 97 – Diasteromers of 182

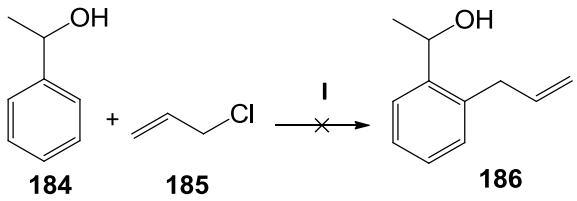
Initially, upon examination of the crude ^{1}H NMR spectra it was thought that the desired epoxide **181** had been formed (Scheme 96). Therefore, subsequent oxidation was attempted to generate the ketone **179**. Upon analysis of the NMR spectra and comparing to the literature data from Gravel *et al.*[163] it was clear that an aldehyde had been formed, and the cyclic ether **183** was isolated in a 50% (Swern) or 30% (PCC) yield(s) as a mixture of three diastereomers and an unidentified product (Scheme 98).



[1] oxalyl chloride, DMSO, −76 °C, CH_2Cl_2, Et_3N, then, rt, 2 h or CH_2Cl_2 4 Å ms, PCC, 10 min, then rt, 12 h.

Scheme 98 – Diasteromers of 183

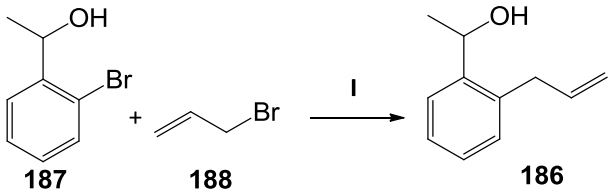
With the difficulties in synthesising the two original targets **157** and **158** (Scheme 87), efforts were then diverted to synthesising a substrate with an aromatic ring **159**. Taber *et al.*[164] have achieved the formation of **159**, directly from the commercially available alcohol **184**. This involved using 1-phenylethanol **184** directly with allyl chloride **185** in an *ortho*-allylation reaction (Scheme 99). Unfortunately, the formation of the product **186** was not observed with numerous attempts and in all cases unreacted starting material remained.



[I] TMEDA (4 equiv.), Et_2O, 0 °C, ^nBuLi, 5 min, then reflux, 1 h, then rt, −5 °C, CuCN, 30 min, allyl chloride, 10 min, rt, 30 min.

Scheme 99 – Attempted *ortho*-allylation reaction

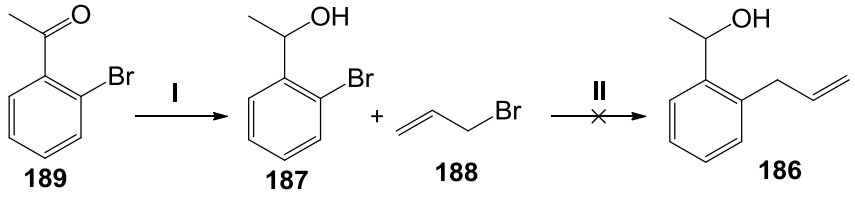
Sälinger and Brückner[165] recently reported that the use of bromo-alcohol **187** in a lithiation with a catalytic amount of CuCN·2LiCl and allyl bromide **188** could lead to the formation of the desired product **186** (Scheme 100).



*[I] $^iPr_2Mg$, Et_2O, TMEDA, then **187**, −40 °C, 10 min, then rt, 30 min, **188**, CuCN·2LiCl, 1.5 h.[165]*

Scheme 100 – Literature example of formation of 186

Therefore, **187** was synthesised in a quantitative yield from the commercially available **189** *via* a $NaBH_4$ reduction. The alcohol was then reacted with allyl bromide **188** using the Sälinger and Brückner[165] procedure. Frustratingly, product **186** was not observed in crude ^1H NMR with starting material and an intractable mixture being obtained (Scheme 101).



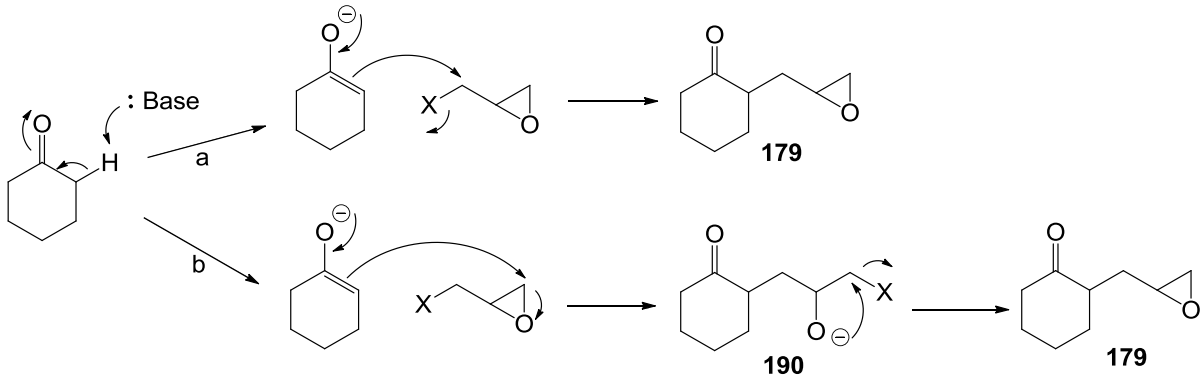
*[I] MeOH/THF (1:1), $NaBH_4$, 1 h, rt. [II] $^iPr_2Mg$, Et_2O, TMEDA, then **187**, −40 °C, 10 min, then rt, 30 min, **188**, CuCN·2LiCl, 1.5 h.*

Scheme 101 – Attempted synthesis of 186

3.2.5 Formation of Oxazolidines

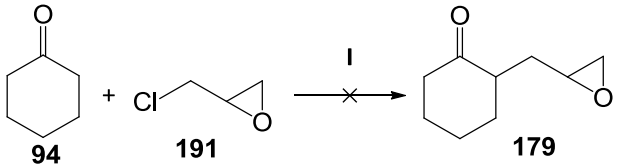
After encountering all of these problems in forming the desired epoxide substrate in the presence of a ketone, it was decided to consider another strategy. Although ketone enolates do no normally react with epoxides, it was thought that using the more reactive *epi*-halohydrin reagents could overcome this obstacle. It was envisioned that by reacting an

enolate with an *epi*-halohydrin it may be possible to produce the desired epoxy-ketone **179** (Scheme 100, step a). However, the enolate could ring open the epoxide as the epoxide is now more reactive with a halogen group pulling electron density away from the ring making the less substituted carbon more δ^+ electron deficient, leading to **190**. This could then undergo an 'S_N2'-like reaction and lead to the product **179** (Scheme 102, step b).



Scheme 102 – Proposed mechanisms for formation of 179

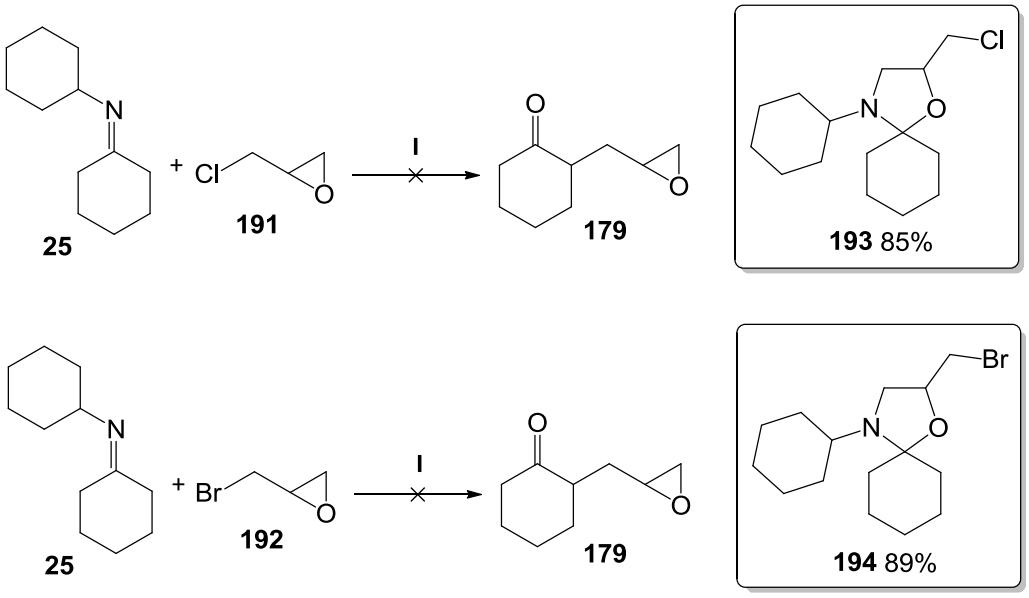
With this plan (Scheme 102), cyclohexanone **94** was deprotonated with LDA to form the enolate, which was reacted with *epi*-chlorohydrin **191** (Scheme 103); unfortunately, the desired product (**179**) was not formed with starting materials being recovered.



[I] *THF, -76 °C, LDA, 30 min, then rt, 1.5 h.*

Scheme 103 – Attempted synthesis of 179

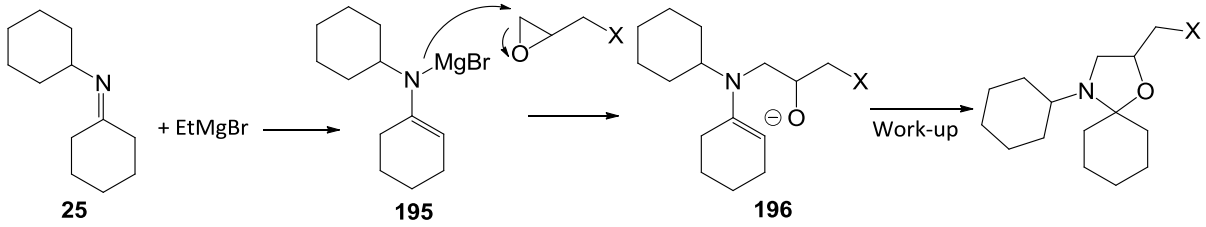
It was thought that the enolate might not have been reactive enough. Therefore, it was thought that the use of an aza enolate could possibly overcome this problem as we had already demonstrated that aza enolates could ring open epoxides (Section 3.2.1). Hence, imine **25** was reacted with *epi*-chloro and bromohydrin (**191** and **192**) using a Grignard reagent to generate the aza enolate (Scheme 104). Unfortunately, the epoxide **179** failed to form. However, interestingly, oxazolidines were formed in excellent yields [85% when X = Cl (**193**) and 89% when X = Br (**194**)] and there appear to be no products formed by the attack of the aza enolate carbon on the epoxide possibly due the change in reactivity of the epoxide equivalent compared to earlier work (Section 3.2.1) (Scheme 104).



[I] *3M EtMgBr (1.15 equiv.), THF, reflux, 2 h, then 0 °C, epi-chloro or bromohydrin, 1 h, then rt, 12 h.*

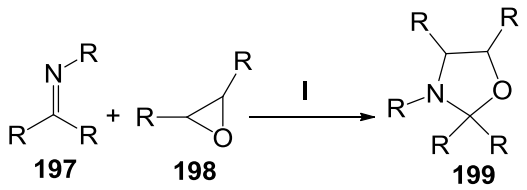
Scheme 104 – Formation of oxazolidines 193 and 194

A possible mechanism involves deprotonating imine **25** with the Grignard reagent to form the aza enolate (**195**), this could then ring open the epoxide by attack of the nitrogen to give **196**, which cyclises upon work-up to form the oxazolidine (Scheme 105).

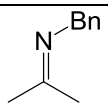
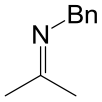
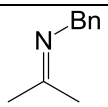
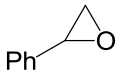
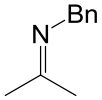
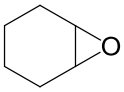
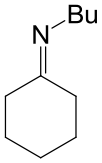
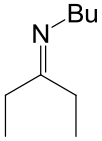


Scheme 105 – Proposed mechanism of oxazolidine formation

Given the high yields obtained, this might offer a useful way of making 1,3-oxozolidines, therefore, a brief literature search was carried out to see if any similar reactions had been previously reported. It was found that generally the synthesis of 1,3-oxozolidines is normally achieved by the condensation of 1,2-amino alcohols with carbonyl compounds in the presence of acid catalysts[166,167]. In recent years, several so-called [3+2] cycloaddition reactions have been reported to produce 1,3-oxazolidines,[168,169] particularly, by the groups of Nishitani and Su. Nishitani *et al.*[170] demonstrated that a variety of 1,3-oxazolidines can be synthesised by reacting imines and epoxides with the use of samarium iodide (Table 28, selected examples).



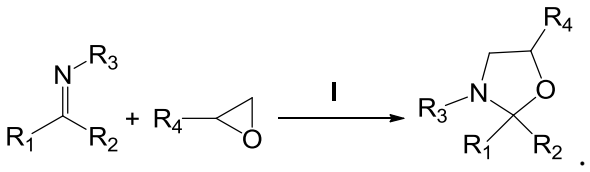
197 **198** **199**

Entry	Imine (**197**)	Epoxide (**198**)	Oxazolidine (**199**) % yield
1			93
2			83
3			81
4			6
5			82
6			85

[1] *Imine, epoxide, SmI_2 (5 mol%), THF, rt, Ar atmosphere, 5 h.*[170]

Table 28 – Literature examples of oxazolidine formation using different epoxides

Su *et al.*[171] has demonstrated that *N*-arylimines can react with epoxides under mild conditions in the presence of a catalytic amount of $Yb(OTf)_3$ (5 mol %) to give 1,3-oxazolidine derivatives in good yields (Table 29 – selected examples).

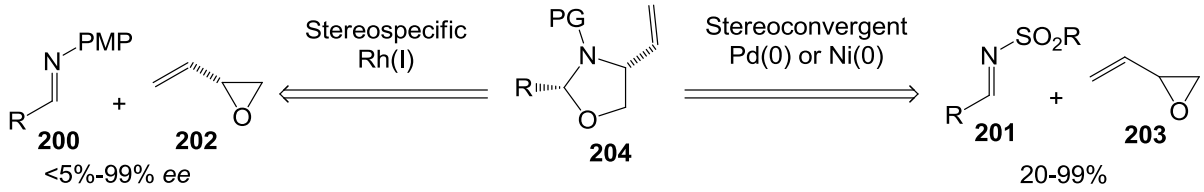


Entry	R_1	R_2	R_3	R_4	Yield (%)
1	H	C_6H_5	C_6H_5	CH_2Cl	85
2	H	*p*-NO_2-C_6H_4	C_6H_5	CH_2Cl	89
3	H	*p*-MeO-C_6H_4	C_6H_5	CH_2Cl	77
4	C_6H_5	C_6H_5	C_6H_5	CH_2Cl	95
5	C_6H_5	C_6H_5	C_6H_5	CH_2OCH_2Ph	83
6	C_6H_5	C_6H_5	*p*-Cl-C_6H_4	CH_2OCH_2Ph	90

[I] CH_2Cl_2, Yb(OTf)3 (5 mol %), 40 °C, 2 h.[171]

Table 29 – Literature example of different oxazolidine derivatives

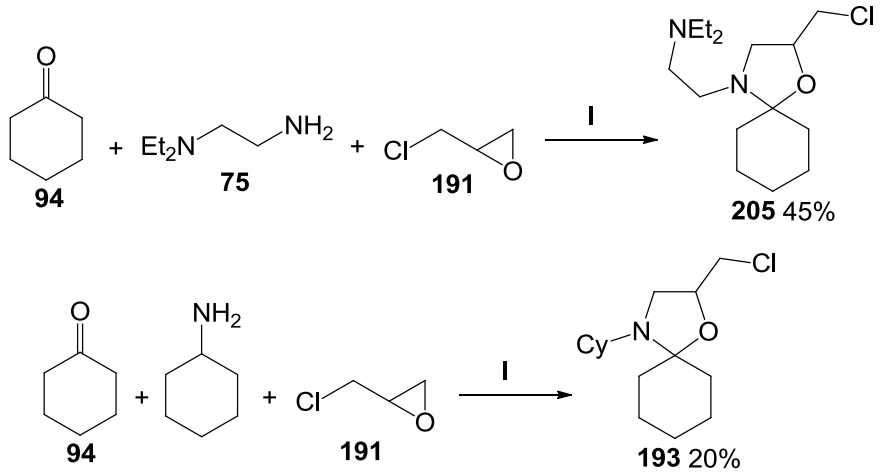
Another recent example is from Jarvo *et al*.[172] who reported the use of a rhodium, palladium or nickel catalyst in the formation of 1,3-oxazolidines (Scheme 106). This involved using either imine **200** or **201** with epoxide **202** (enantiopure) or **203** (racemic) to form the corresponding 1,3-oxazolidines **204** (Scheme 106).



Scheme 106 – Literature example of enanatiopure oxazolidines

All of these examples have advantages in that good yields are obtained and catalytic quantities of metal salt are used. However, there are some disadvantages; in the case of Nishitani *et al*. SmI_2 has to be used, which is difficult to prepare, is air sensitive and expensive. The majority of reactions that Su *et al*. reports involve *epi*-chlorohydrin, aromatic substituents on the imine (no enolizable ketones/aldehydes), heat at 40 °C and only a small number of epoxides were investigated. With Jarvo *et al*. protecting groups have to be used on the nitrogen and only one epoxide is utilised in this chemistry as the unsaturated epoxide is necessary for the catalytic reaction to work. In addition, in all cases pre-formed imines are employed, therefore, these imines have to be synthesised before being used. With these disadvantages, it was thought if a magnesium aza enolate method could be developed with *in-*

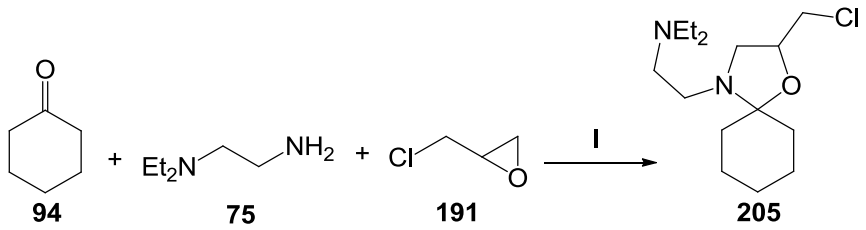
situ formation of the imine and subsequent reaction with an epoxide it would be a more effective method of preparing oxazolidines. This would involve the use of the earlier developed aza enolate methodology. A proof of principle experiment was carried out, which involved the use of cyclohexanone **94** with chelating amine **75** or Cy-NH_2 and *epi*-chlorohydrin **191** (Scheme 107). Oxazolidine product(s) **193**/**205** were isolated in a 47 and 20% yield respectively (Scheme 107).



[I] *Amine **75** or Cy-NH_2, **94**, THF, $Mg(ClO_4)_2$, chloromethyloxirane **191**, Et_3N, rt, 12 h.*

Scheme 107 – Synthesis of oxazolidines 193 and 205

With these promising results (Scheme 107), a small solvent screen was attempted using the same conditions with cyclohexanone **94** and the chelating amine **75** (Table 30). With the use of DMSO (Table 30, entry 1), no apparent conversion by ^{1}H NMR was observed, however, the use of CH_2Cl_2, MeCN and THF (Table 30, entries 2-4) all produced conversions varying from 30-66%. Isolated yields were obtained with MeCN and THF (Table 30, entries 3-4) of 31% and 50% respectively. Evidence for an aza enolate intermediate was provided by control reactions, which excluded one of the two key reagents from the reaction mixture: magnesium salt and triethylamine (Table 30, entries 5-6). No apparent conversion to the oxazolidine product **205** was observed in each case, clearly suggesting a synergistic operation of the primary amine, magnesium salt and triethylamine in the reaction mechanism.

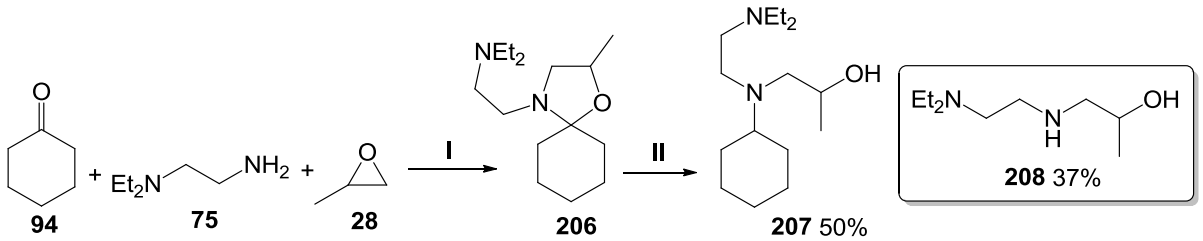


Entry	Ketone (**94**) equiv.	Amine (**75**) equiv.	Epoxide (**191**) equiv.	Solvent	Conversion*	Yield (**205**)
1	1	1	1	DMSO	<5%	n.d.
2	1	1	1	CH_2Cl_2	30%	n.d.
3	1	1	1	MeCN	45%	31
4	1	1	1	THF	66%	50
5[a]	1	1	1	THF	<5%	n.d.
6[b]	1	1	1	THF	<5%	n.d.

*[1] Solvent, $Mg(ClO_4)_2$, chloromethyloxirane, Et_3N, rt, 12 h. * % conversion determined by ^1H NMR ($CDCl_3$). [a] No Et_3N. [b] No $Mg(ClO_4)_2$.*

Table 30 - Evidence for an aza enolate intermediate was provided by control reactions

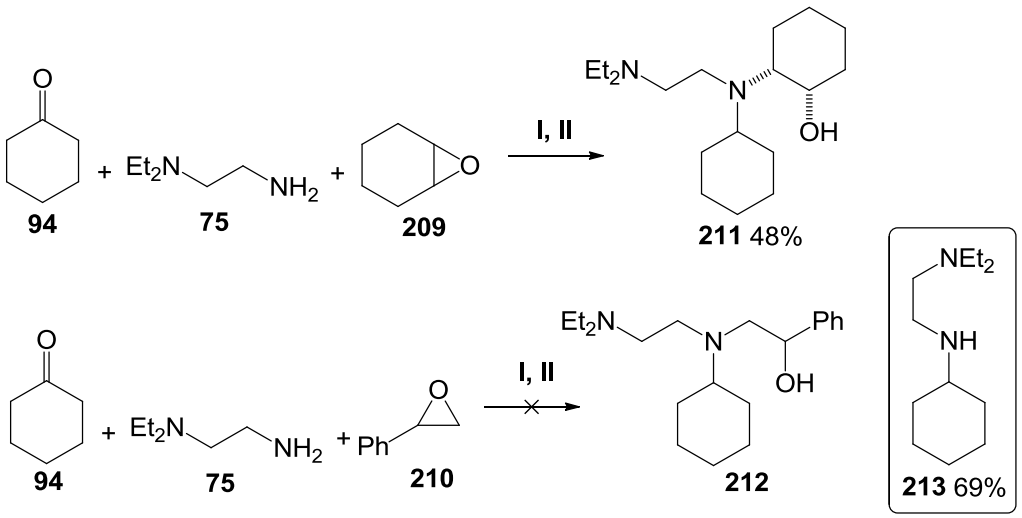
With these promising results, the next step was to investigate different epoxide substrates. Therefore, epoxide **28** was reacted with ketone **94** and chelating amine **75** (Scheme 108). With changing the epoxide from **191** to **28**, it was discovered that the product **206** was degrading on silica and produced a low yield of 20%. Therefore, it was thought that reducing the C-O bond of product **206** with $NaBH_4$ to give the corresponding alcohol product **207** might lead to a product that is easier to purify. Therefore, a reduction was attempted and pleasingly, the alcohol product was isolated in 50% over the two steps. However, it was discovered that the undesirable product **208** was also isolated in a 37% yield (Scheme 108). When comparing the ^1H NMR spectra of the oxazolidine product **206** (Scheme 107) with the earlier reactions **139** and **140** involving epoxide ring opening *via* aza enolates (Section 3.2.1), there appears to be some peaks in the earlier reactions with **139** and **140** (Scheme 82) which correspond to the oxazolidine products and could explain why the yields for those reactions (**139** and **140**, Scheme 82) were low. However, there is a slight change in reaction conditions, the earlier reactions were done at 0 °C and then warmed to room temperature compared to these reaction conditions which were done at room temperature with no cooling.



*[I] THF, **94**, **75**, $Mg(ClO_4)_2$, **28**, Et_3N, rt, 12 h; [II] $NaBH_4$, MeOH:THF (1:1), rt, 2 h.*

Scheme 108 – Formation of 207

With this promising result (Scheme 108), the next step was to test if a different epoxide could be utilized in this methodology. Earlier, Nishitani *et al.*[170] described that the reaction of cyclohexene oxide **209** gave only a very low yield of 6% of the corresponding oxazolidine (Table 25). Therefore, it was believed that the use of cyclohexene oxide **209** would be an interesting epoxide to test under our conditions. In addition, they also use styrene oxide **210** and produce a good yield of 81% of the corresponding oxozolidine (Table 25) Thus, cyclohexanone **94** was reacted with the chelating amine **75** and cyclohexene oxide **209** or styrene oxide **210** (Scheme 109). Pleasingly, with cyclohexene oxide **209** the oxazolidine derived product **211** was isolated as a mixture of diastereomers (2:1) in a modest yield of 48%. Unfortunately, with the use of epoxide **210** the major isolated product was that of the reduced imine **213** in a yield of 69% and not the desired product **212** (Scheme 109).

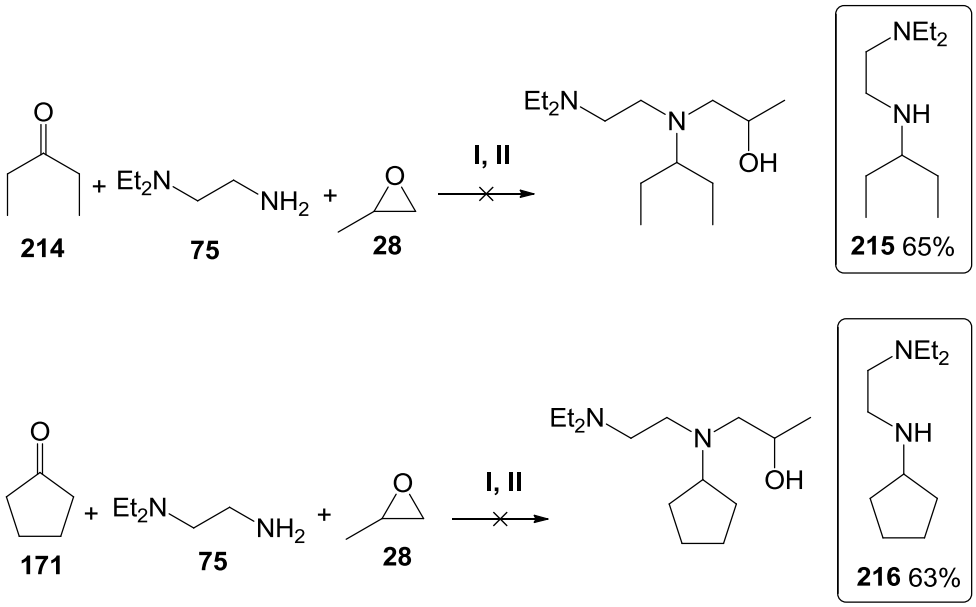


[I] THF, $Mg(ClO_4)_2$, Et_3N, rt, 12 h; [II] $NaBH_4$, MeOH:THF (1:1), rt, 2 h.

Scheme 109 – Formation of 211 and by-product 213

To expand the scope of this reaction, a small ketone screen was carried out. This involved using linear ketone **214** and cyclopentanone **171** with the chelating amine **75** and epoxide **28**

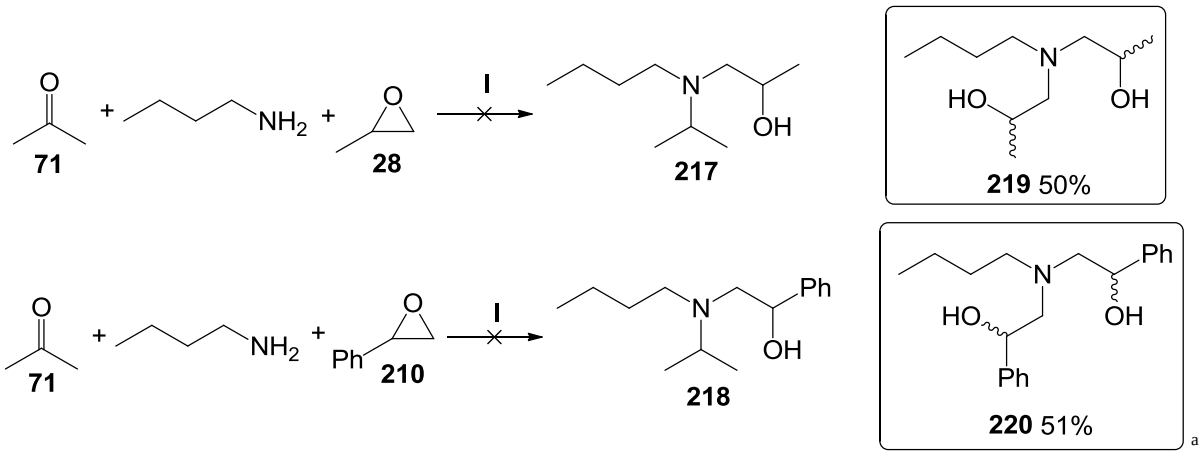
(Scheme 110). Unfortunately, in both cases the major product isolated was the reduced imine. Amines **215** and **216** were obtained in 65 and 63% yields respectively.



[I] THF, $Mg(ClO_4)_2$, Et_3N, rt, 12 h; [II] $NaBH_4$, MeOH:THF (1:1), rt, 2 h.

Scheme 110 – Formation of by-products 215 and 216

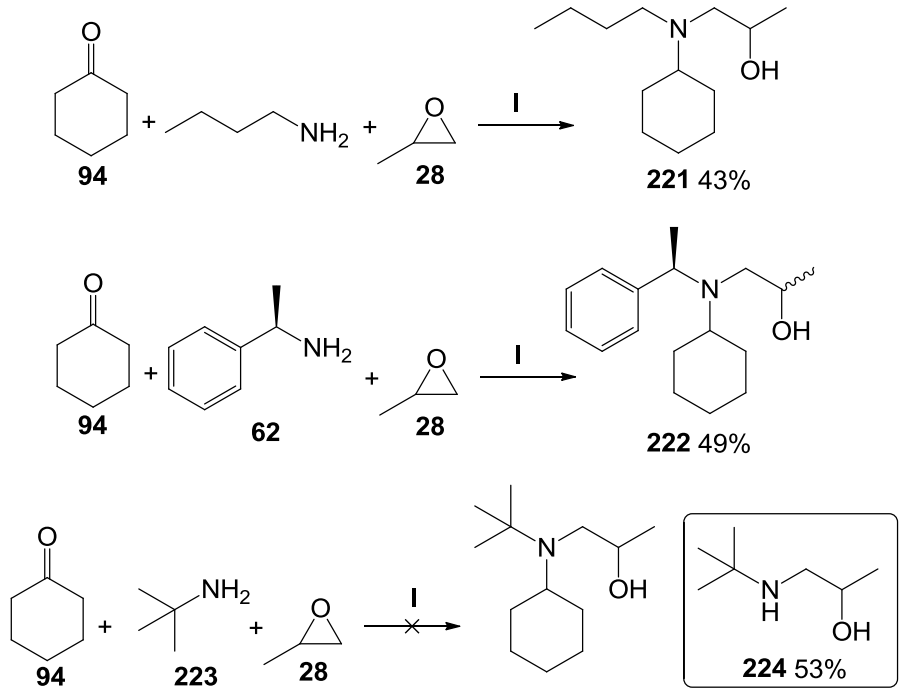
Moving on from these results (Scheme 110), it was thought that the use of a simple amine and a simple ketone might lead to easier interpretation of the data. Therefore, *n*-butylamine was selected and reacted with epoxides **28** and **210** using acetone **71** as the ketone (Scheme 111). Unfortunately, in both reactions the desired products **217** and **218** were not observed, with the undesired products **219** and **220** being isolated in yields of 50% and 51% as a mixture of diastereomers (Scheme 111). A possible reason for these reactions not to have formed the desired products is that the volatile acetone **71** may be evaporating. Therefore, it was decided for subsequent reactions to revert to cyclohexanone **94** as it has already proven to work.



[1] THF, $Mg(ClO_4)_2$, n-butylamine, Et_3N, rt, 12 h, then $NaBH_4$, MeOH:THF (1:1), rt, 2 h.

Scheme 111 – Attempted formation of 217 and 218

Lastly, a small amine study was investigated with cyclohexanone **94** and epoxide **28** (Scheme 112). Both *n*-butylamine and chiral amine **63** produced the corresponding product **221** and **222** (mixture of diastereomers, 1:1) after reduction *via* $NaBH_4$ in moderate yield (43% and 49% yield respectively). However, the use of the more hindered amine **223**, led to undesired product **224** being produced in a 53% yield *via* the amine ring opening the epoxide (Scheme 112).

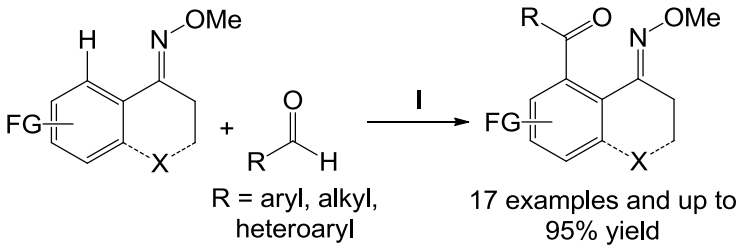


[1] THF, $Mg(ClO_4)_2$, amine, Et_3N, rt, 12 h, then $NaBH_4$, MeOH:THF (1:1), rt, 2 h.

Scheme 112 – Synthesis of different alcohols

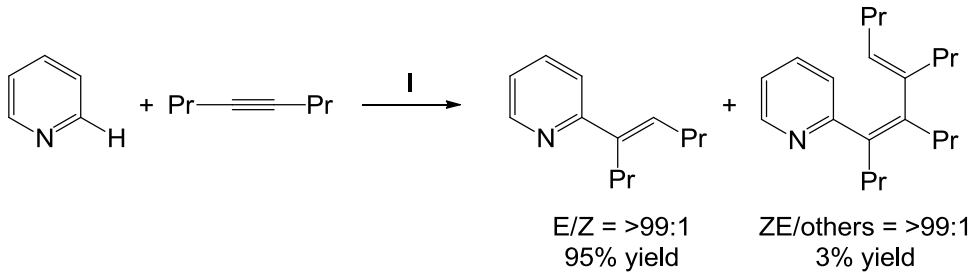
3.2.6 C-H activation

The use of cyclo-palladated imines with various electrophiles has not been widely explored with regard to C-H activation; however, it has been explored with other very similar systems such as oximes[173,174] (Scheme 113) and pyridines[175] (Scheme 114).



[1] $Pd(OAc)_2$ (5 mol %), TBHP (2 equiv.), AcOH (0.5 equiv.), Tol, 100 °C, 2 h.[173]

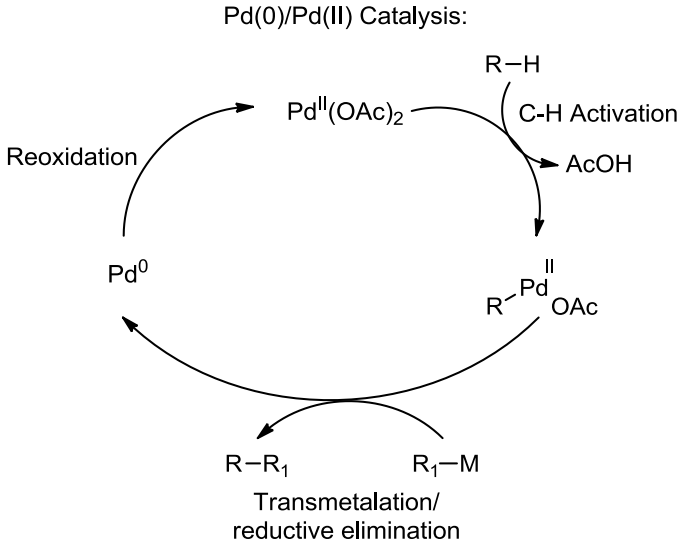
Scheme 113 - Literature example of C-H activation using oximes



[1] $Ni(cod)_2$ (3 mol %), $P(^iPr)_3$ (12 mol %), $ZnMe_2$ (6 mol %), Tol, 50 °C, 24 h.[175]

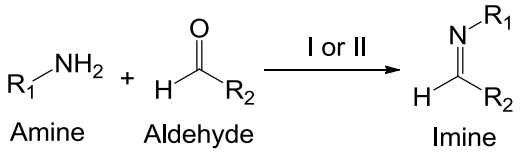
Scheme 114 – Literature example of C-H activation using pyridines

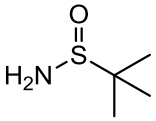
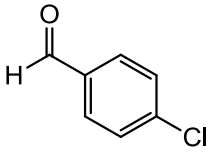
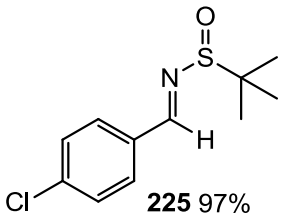
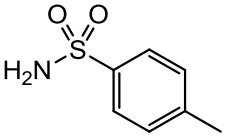
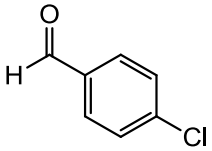
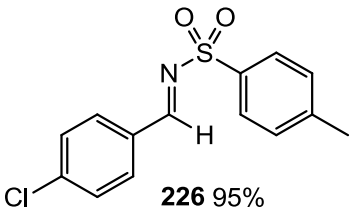
Therefore, it was envisioned that the use of a pre-formed imine with a palladium source could produce an imine-palladium complex, which could then be used for *ortho*-halogenation (Scheme 115 – example of palladium(II) catalysis).



Scheme 115 - Example of palladium(II) catalysis

Firstly, imines **225** and **226** were chosen as they offer another coordination site from the lone pair of the oxygen atom (or the sulphur atom in the case of **225**). Imines **225** and **226** were prepared using literature procedures[176,177] (Table 31).

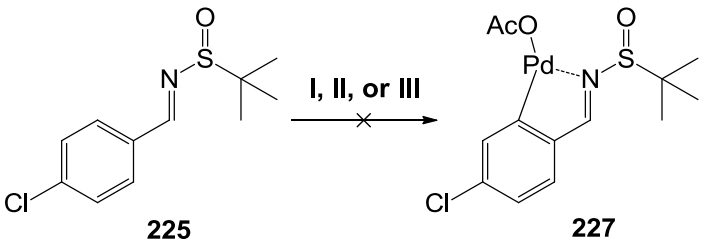


Entry	Amine	Aldehyde	Imine	Procedure
1			 **225** 97%	I
2			 **226** 95%	II

[I] CH_2Cl_2, PPTS, $MgSO_4$, rt., 24 h. [II] Tol, 4 Å molecular sieves, reflux, 16 h.

Table 31 – Synthesis of imines 225 and 226

With these substrates in hand, imine **225** was subjected to a literature palladation procedure[178] to see if the imine-palladium complex **227** could be produced (Scheme 116), which could then be used for *ortho*-halogenation. This involved using $Pd(OAc)_2$, AcOH at 100 °C for 1 h (Scheme 116), however, the desired product was not isolated with an intractable mixture being obtained. It was thought that the conditions used were too harsh, therefore, milder conditions were utilised with imine **225** dissolved in deuterated MeOH with $Pd(OAc)_2$ for 6 h (Scheme 116). This also did not produce the imine-palladium complex **227** with only starting material being observed. It was then thought that use of a different palladium species could overcome this problem, therefore, imine **225** was subjected to another literature procedure[179] which involved using imine **225** with Na_2PdCl_4, NaOAc and AcOH for 24 h at room temperature (Scheme 116). Unfortunately, this also led to no reaction being observed with a mixture of starting material and an intractable mixture being obtained.

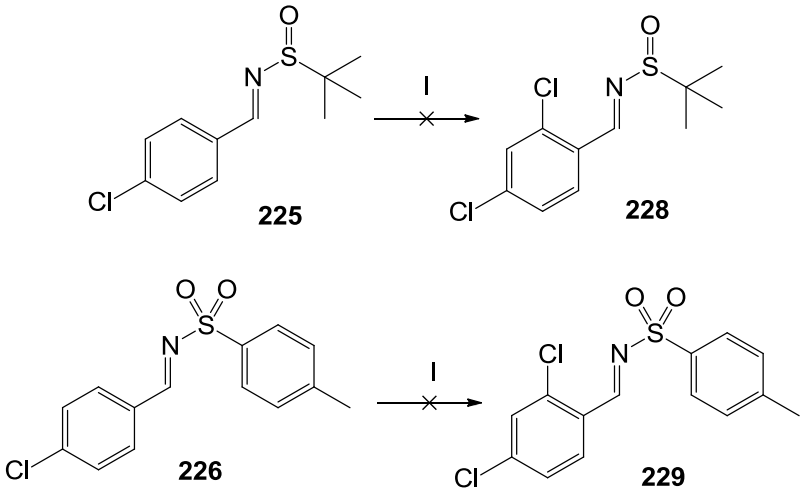


225 **227**

*[I] Imine **224**, $Pd(OAc)_2$, AcOH, 100 °C, 1 h. [II] Imine **224**, $Pd(OAc)_2$, CD_3OD, 6 h, rt. [III] Imine **224**, Na_2PdCl_4, NaOAc, AcOH, 24 h, rt.*

Scheme 116 – Attempted synthesis of imine 227

Having difficulties in obtaining the desired product (Scheme 116), we then explored whether direct halogenation could occur with *in-situ* formation of the imine-palladium complex (one-pot). Therefore, following a literature procedure[180] imines **225** and **226** were examined in a halogenation reaction. Unfortunately, in both cases no reaction had taken place with starting material imine **225** or imine **226** being observed (Scheme 117).



225 **228**

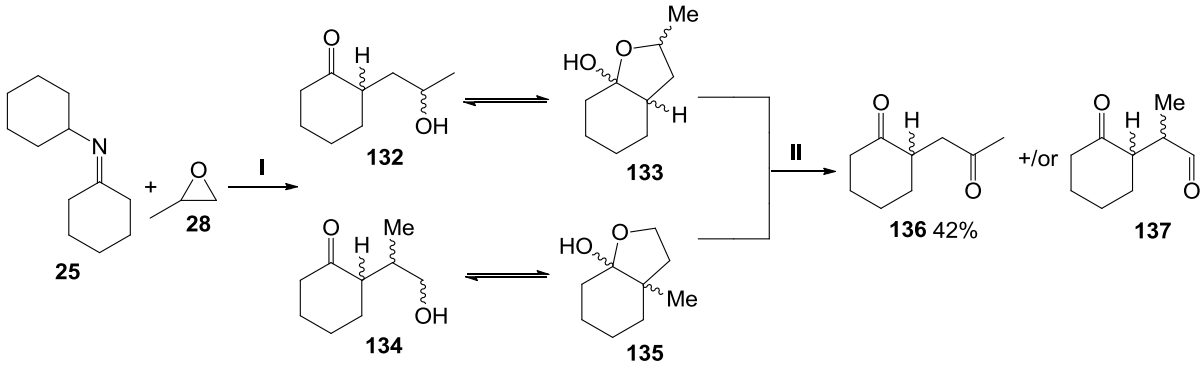
226 **229**

*[I] Imine **113** or **114**, $Cu(OAc)_2$, $CuCl_2$, $Pd(OAc)_2$, 120 °C, 2 h.*

Scheme 117 – Attempted synthesis of imines 228 and 229

3.3 Conclusions and Future Work

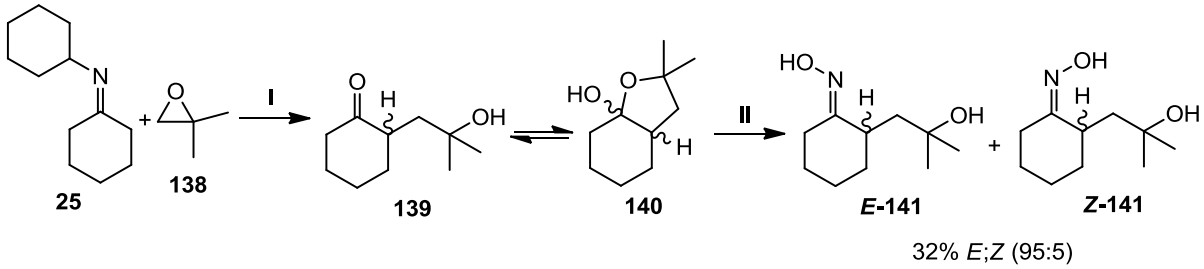
The investigation into using the developed aza enolate chemistry with more challenging electrophiles has been troublesome in parts. Firstly, stoichiometric reactions were investigated. Tarbell and Harvey reported that the ring opening of epoxide **28** occurs regioselectively and produces **132** exclusively (Scheme 118). However, characterisation was achieved solely by boiling point and elemental analysis and no NMR data to validate the formation of the product **132** was provided (Scheme 118). When this reaction was investigated, all possible regio- and stereo- isomers were produced in a combined 31% yield which was in contrast to the reported literature by Tarbell and Harvey (Scheme 118). With the difficulties in assigning the ^{1}H NMR, the alcohols were oxidised to the corresponding aldehyde/ketone (**136**/**137**), with product **136** being isolated in a yield of 42% (Scheme 118).



[I] THF, EtMgBr, reflux, 2 h then rt, 30 min, 0 °C, ***28****. [II] SO_3.Py, DMSO, −76 °C, DCM; Et_3N, rt, 5 h.*

Scheme 118 – Summary of ring opening of epoxide 28

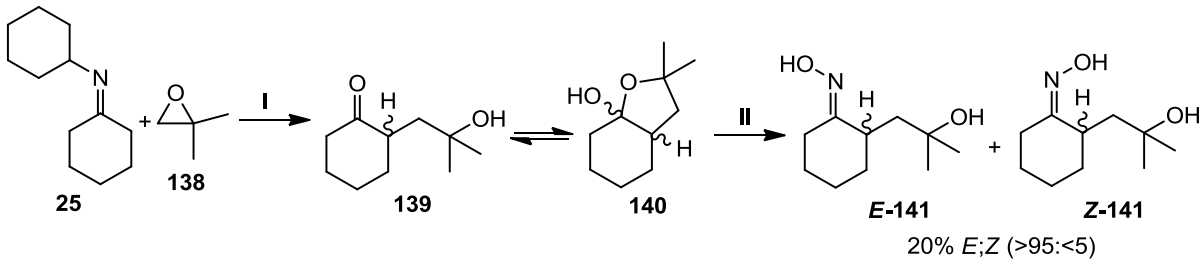
When expanding on this result with epoxide **138**, which was selected due to its likelihood to open regioselectively, there were still problems due to the mixture of the acyclic (**139**) and the cyclic (**140**) lactol forms which made characterisation difficult. Pleasingly this was overcome with the use of oxime formation and led to the successful isolation of the desired products in a 32% yield over two steps (Scheme 119).



[I] EtMgBr, THF, reflux, then 0 °C, epoxide ***138****; [II] NH_2OH, pyridine, ethanol, reflux, 12 h.*

Scheme 119 – Summary of ring opening of epoxide 138

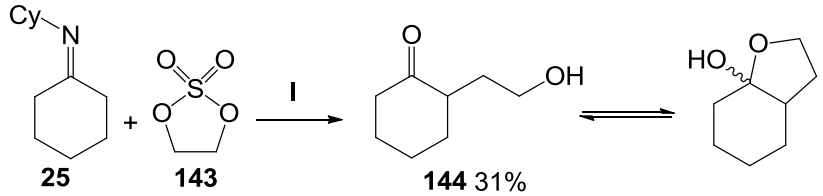
Secondly, the use of the earlier developed aza enolate methodology using a Lewis acid and base was applied to epoxides and led to the successful formation of the desired products, albeit in low yield of 20% over two steps (Scheme 120). Nonetheless, a novel method to ring open an epoxide using the mild aza enolate generation method developed earlier was demonstrated.



*[I] THF, 0 °C, $Mg(ClO_4)_2$, epoxide **138**, Et_3N, then rt, 12 h. [II] Hydroxylamine, pyridine, ethanol, reflux, 2 h.*

Scheme 120 – Summary of ring opening of 138 using the milder aza enolate chemistry

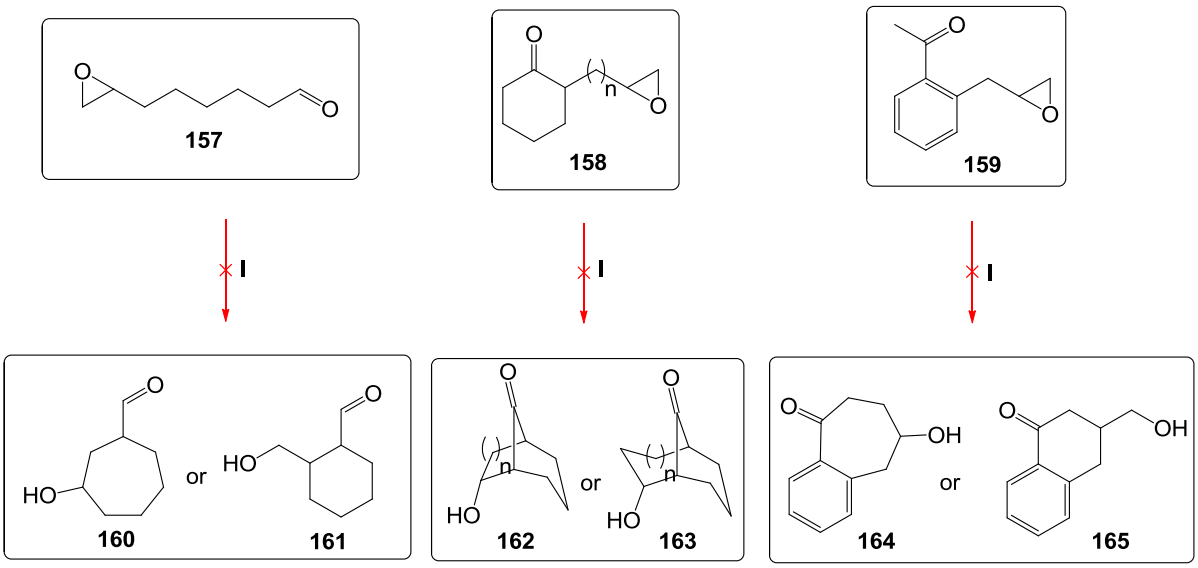
From demonstrating that reactions with epoxides using the mild aza enolate generation method do take place, investigations into a simpler more reactive electrophile the cyclic sulfate **143** were undertaken. It was discovered that the use of magnesium perchlorate provided the highest conversion, 47%, and cleanest crude ^{1}H NMR when using Et_3N as the base. The product **144** was isolated in a yield of 31% (Scheme 121).



*[I] MeCN, MgX_2 (1.2 equiv.), Base (2 equiv.), −76 °C, then **143**, then rt, 11 h.*

Scheme 121 – Summary of ring opening of cyclic sulfate 143

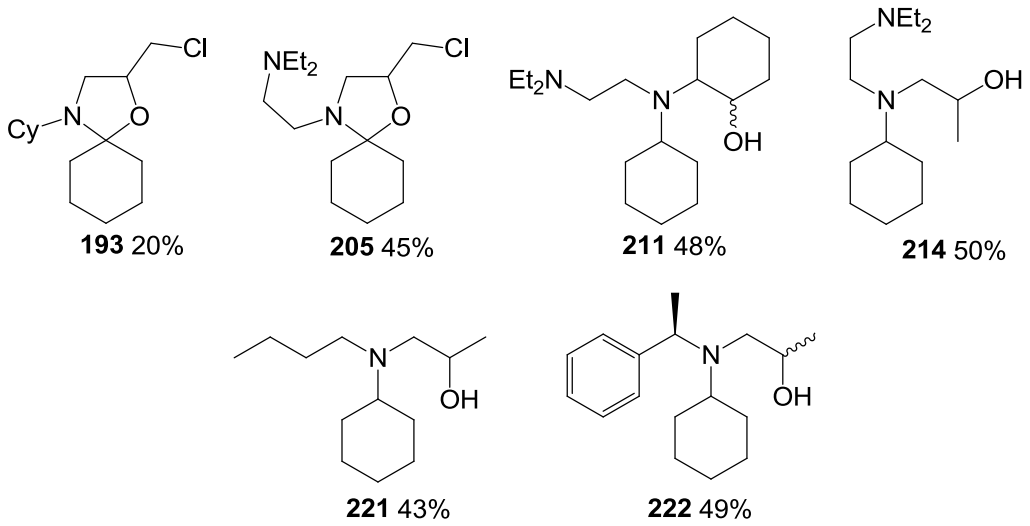
Catalytic reactions using epoxides and their derivatives were also investigated, unfortunately, low conversions were obtained, and characterisation was difficult. This led to investigations into intramolecular substrates that would include an epoxide in the presence of a ketone, which was hoped to be more successful (Scheme 122). Unfortunately, all attempts to form the desired targets have thus far proved unsuccessful.



[I] *Amine, Base, Lewis acid, DMSO, rt, 12 h.*

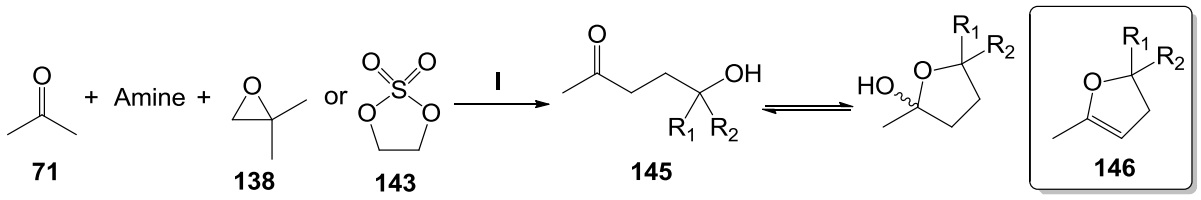
Scheme 122 – Summary of attempted synthesis of target products

Lastly, the use of different epoxides led to the serendipitous discovery of a method for the formation of oxazolidines using aza enolate chemistry. Pleasingly this led to good yields being obtained with a variety of electrophiles (Scheme 123), with some associated problems as described.



Scheme 123 – Summary of different oxazolidine/alcohol products

Future work on this project will focus on two areas. The first being, to explore the catalytic reactions further, particularly, the formation of the undesired by product **146** and improve on the yields of the product **145** (Table 32).



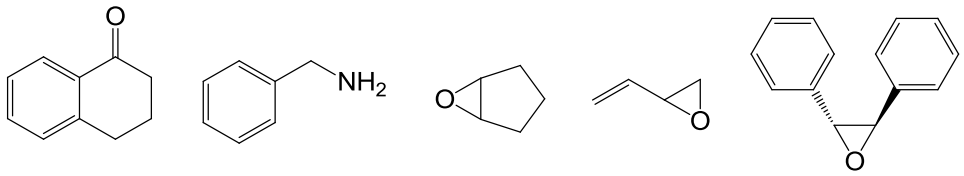
R_1, R_2 = Me = 2,2-dimethyloxiran (**138**)
R_1, R_2 = H = cyclic sulfate (**143**)

Entry	Amine	Epoxide	Product (145)		By-product (146)	
			Conversion[a]	Yield	Conversion[a]	Yield
1	Et_2N NH_2	**138**	<5%	n.d.	35%	n.d.
2	Cy-NH_2	**138**	<5%	n.d.	34%	n.d.
3	NH_2	**138**	<5%	n.d.	35%	n.d.
4	Et_2N NH_2	**143**	35%	29%	<5%	n.d.
5	Cy-NH_2	**143**	25%	n.d.	<5%	n.d.
6	NH_2	**143**	26%	21%	<5%	n.d.

*[1] Amine (10 mol %), $Mg(ClO_4)_2$ (20 mol %), DMSO:acetone, Et_3N (20 mol %) then **138** or **143**, then rt, 12 h. [a] % conversion determined by ^1H NMR ($CDCl_3$). n.d. = not determined.*

Table 32 – Summary of catalytic ring opening reactions

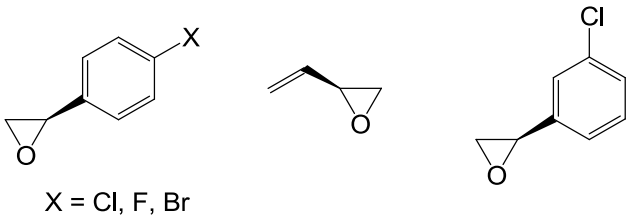
Secondly, the optimisation of the oxazolidine reaction to improve the yields, as well as the synthesis of a more diverse range of amines, ketones and epoxides (Scheme 124). A catalytic version of the oxazolidine formation could also be attempted with catalytic quantities of base and Lewis acid.



Scheme 124 – Potential substrates to use

Finally, a more in depth study in asymmetry could be investigated with the oxazolidine reactions using chiral epoxides (Scheme 125). In addition, as molecules containing oxazolidine ring systems exhibit many activities such as antibacterial activity and anti-

tuberculosis activity,[181] efforts may be concentrated on forming a variety of different oxazolidine structures and testing their biological activity.



Scheme 125 – Potential chiral substrates to use

Chapter 4 - Experimental Section

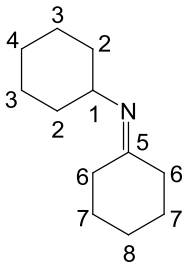
4.1 General Methods

All the reagents and solvents were used as received without further purification, unless otherwise stated. Where necessary, reactions were carried out under argon unless otherwise stated, and laboratory reagent grade solvents were used unless otherwise stated. Petroleum ether 40-60 °C is reported as petrol and was purchased from Fisher. Reactions were monitored by TLC on SIL G/UV_{254} silica plates purchased from VWR, and were visualized under UV lamp operating at short and long wavelength ranges with alkaline potassium permanganate solution or phosphomolybdic acid (PMA). Flash column chromatography was carried out with Kieselgel 60M 0.04/0.063nm (230-240 mesh) silica gel. All yields quoted are isolated yields, and when multiple products are obtained, data are presented in terms of the order of compounds isolated.

^{1}H NMR spectra were recorded at 300 MHz, 400 MHz, 500 MHz or 600 MHz on a Bruker AMX300, Bruker AMX400, Bruker AMX500, or Bruker AMX600 MHz spectrometer operating at ambient temperature using an internal deuterium lock. Chemical shifts are reported in parts per million using the following abbreviations: *s* singlet, *d* doublet, *t* triplet, *q* quartet, *qn* quintet, *sx* sextet, *sept* septet, *m* multiplet, *br* broad; or a combination thereof. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AMX300, 100 MHz on a Bruker AMX400 MHz, 125 MHz on a Bruker AMX500 MHz and 150 MHz on a Bruker AMX600 MHz spectrometer and are reported in ppm using $CDCl_3$ or DMSO-d_6 as an internal standard. Mass spectra (EI, CI and ES) were obtained from VG70-SE or a MAT 900 XP spectrometer by Dr. Lisa Haigh (UCL Chemistry Department). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 operating in ATR mode and are quoted in cm^{-1}. Optical rotations were determined from an average of five measurements at ambient temperature using a 1 mL, 1 dm cell and were measured using Perkin–Elmer 343 polarimeter (sodium D-line, 529 nm). $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}, *c* is concentration (g/100 mL). The following chiral column was used: CHIRALPAK® AD column (0.46cm × 25cm) purchased from Daicel Chemical Industries, Ltd.

4.2 Experimental procedures

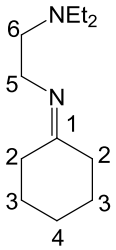
N-Cyclohexylidenecyclohexanamine[182,183] (25)



Cyclohexylamine (23.30 mL, 204 mmol) was added to a stirred solution of cyclohexanone (21.10 mL, 204 mmol) in dry Et_2O (150 mL) containing 4 Å molecular sieves for 10 min. The solution was left to stand for 14 h at room temperature. The solvent was removed under reduced pressure to obtain the crude product as pale orange liquid. Purification by vacuum distillation gave the title compound as a colourless oil (20.6 g, 97%).

bp 110-116 °C, 1 Torr (Lit. bp 111-115 °C, 8 Torr[182]): ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 3.14 (1H, m, 1-H), 2.46-2.07 (4H, m, 6-H), 1.59-1.41 (16H, m, cyclohexyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 170.6 (C-5), 57.8 (C-1), 36.6 (C-6), 33.8 (C-2), 29.0 (C-8), 27.5 (C-7), 26.1 (C-4), 24.9 (C-3); LRMS (ES^+): 180 (100%, $[M+H]^+$), 83 (75); υ_{max} (film/cm^{-1}) 2984 (C-H), 1660 (C=N), 1448 (CH_2).

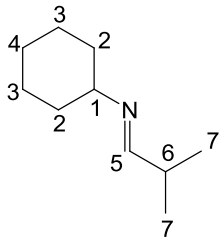
N^1-Cyclohexylidene-N^2,N^2-diethylethane-1,2-diamine[69] (56)



N,*N*-Diethylethylenediamine (80 mL, 100 mmol) was added to cyclohexanone (70 mL, 100 mmol) containing 4 Å molecular sieves. The solution was heated to 80 °C for 18 h. The reaction mixture was filtered through a pad of Celite® and washed with Et_2O (5 × 30 mL). The solvent was removed under reduced pressure to obtain the title compound as a pale brown oil (9.5 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 3.33 (2H, t, *J* = 7.2 Hz, 5-H), 2.57 (2H, t, *J* = 7.2, 6-H), 2.45 (4H, q, *J* = 7.2 Hz, CH_2CH_3), 2.24-2.34 (4H, m, 3-H), 1.60-1.75 (6H, m, 2-H and 4-H), 1.04 (6H, t, *J* = 7.2 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 173.6 (C-1), 53.9 (C-6), 48.7 (CH_2CH_3), 39.9 (C-5), 29.0 (C-2), 27.6 (C-2), 26.9 (C-3), 26.0 (C-4), 11.8 (CH_2CH_3); LRMS (ES^+): 197 (100%, $[M+H]^+$); υ_{max} (film/cm^{-1}) 2928 (C-H), 1661 (C=N).

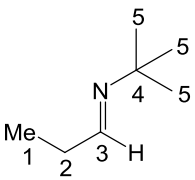
_N_-(2-Methylpropylidene)cyclohexanamine[127,184] (59)



Butanal (25.30 mL, 201 mmol) was added drop-wise to cyclohexylamine (23.10 mL, 201 mmol) at −5 °C in an ice-salt bath. The mixture was stirred for 30 min, and then allowed to warm to room temperature. The water layer was removed and the organic extract was left to stand for 24 h in the presence of KOH pellets. This mixture was filtered and concentrated under reduced pressure to obtain the title compound as a light orange oil (19 g, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.35 (1H, d, *J* = 5.8 Hz, 5-H), 2.75-2.68 (1H, m, 1-H), 2.28-2.19 (1H, m, 6-H), 1.58-1.28 (10H, m, 2-H, 3-H and 4-H), 0.90-0.87 (6H, m, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 167.4 (C-5), 69.3 (C-1), 34.3 (C-6), 33.8 (C-2), 25.5 (C-4), 24.8 (C-3), 19.5 (C-7); LRMS (CI): 154 (100%, $[M+H]^+$); HRMS (CI) observed $[M+H]^+$: 154.15914; $C_{10}H_{20}N$ requires 154.15957; υ_{max} (film/cm^{-1}) 2927 (C-H), 1668 (C=N).

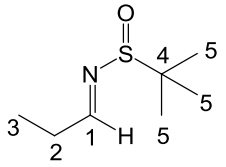
2-Methyl-_N_-propylidenepropan-2-amine[128,185] (60)



2-Methylpropan-2-amine (10.90 mL, 103 mmol) was added to a stirred solution of propanal (6.20 mL, 86 mmol) in CH_2Cl_2 (15 mL) containing $MgSO_4$ (1.50 g). The solution was refluxed for 12 h. The reaction mixture was filtered and the solvent was removed under reduced pressure to obtain the crude product as a yellow liquid. Purification by vacuum distillation produced the title compound as a pale yellow oil (5.50 mL, 90%).

bp 100-103 °C, 1 Torr (Lit. bp 99-100 °C, 1 Torr[128]): ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.70 (1H, t, *J* = 4.9 Hz, 3-H), 2.12 (2H, qd, *J* = 7.7, 4.9 Hz, 2-H), 1.11 (9H, s, 5-H), 0.91 (3H, t, *J* = 7.7 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 159.8 (C-3), 56.5 (C-4), 32.5 (C-5), 29.5 (C-2), 10.7 (C-1); LRMS (EI): 113 (100%, $[M]^{+\bullet}$); υ_{max} (film/cm^{-1}) 2970 (C-H), 1628 (C=N).

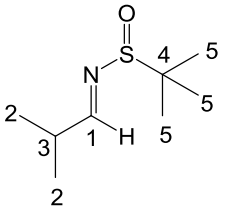
2-Methyl-*N*-propylidenepropane-2-sulfinamide[129,186] (61)



2-Methylpropane-2-sulfinamide (1.00 g, 8.26 mmol) was added to a stirred solution of PPTS (0.10 g, 0.41 mmol) in CH_2Cl_2 (13.8 mL) containing $MgSO_4$ (5.00 g, 41.30 mmol). Propanal (1.20 mL, 16.50 mmol) was added to the stirred solution. The solution was stirred for 14 h at room temperature. The reaction mixture was filtered through Celite© and washed with CH_2Cl_2 (2 × 15 mL). The solvent was removed under reduced pressure to obtain the crude product. Purification by column chromatography eluting with CH_2Cl_2:petrol (5:1) gave the title compound as a colourless oil (0.95 g, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.70 (1H, t, *J* = 4.9 Hz, 1-H), 2.12 (2H, qd, *J* = 7.7, 4.9 Hz, 2-H), 1.11 (9H, s, 5-H), 0.91 (3H, t, *J* = 7.7 Hz, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 159.8 (C-1), 56.5 (C-4), 32.5 (C-5), 29.5 (C-2), 10.7 (C-3); LRMS (CI): 162 (100%, $[M+H]^{+}$); HRMS (CI) observed ($[M+H]^{+}$): 162.09571; $C_7H_{16}ONS$ requires 162.09526.

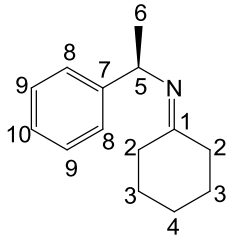
2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide[130,187] (62)



2-Methylpropane-2-sulfinamide (1.00 g, 8.26 mmol) was added to a stirred solution of PPTS (0.10 g, 0.41 mmol) in CH_2Cl_2 (13.80 mL) containing $MgSO_4$ (5.00 g, 41.30 mmol). 2-Methylpropanal (2.30 mL, 24.80 mmol) was added to the stirred solution. The solution was stirred for 14 h at room temperature. The reaction mixture was filtered through Celite© and washed with CH_2Cl_2 (2 × 15 mL). The solvent was removed under reduced pressure to obtain the title compound as a colourless oil (930 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.96 (1H, d, *J* = 4.4 Hz, 1-H), 2.74-2.65 (1H, m, 3-H), 1.16 (9H, s, 5-H), 1.14 (3H, d, *J* = 3.1 Hz, 2-H), 1.13 (3H, d, *J* = 3.1 Hz, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 173.8 (C-1), 56.5 (C-4), 34.9 (C-3), 22.3 (C-5), 18.9 (C-2); LRMS (CI): 176 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 176.11030; $C_8H_{18}ONS$ requires 176.11091.

(*R*)-*N*-Cyclohexylidene-1-phenylethanamine (64)

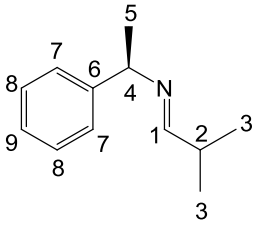


(*R*)-1-Phenylethylamine (0.60 mL, 4.5 mmol) was added to a stirred solution of cyclohexanone (0.50 mL, 5.1 mmol) in CH_2Cl_2 (5 mL) containing $MgSO_4$ (0.20 g). The solution was stirred for 14 h at room temperature. The reaction mixture was filtered and the solvent was removed under reduced pressure to obtain the title compound as a green oil (470 mg, 94%).

Data in agreement with the literature[188,189]

Green oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.56-7.33 (2H, m, 9-H), 7.28-7.25 (3H, m, 8-H and 10-H), 4.68 (1H, q, *J* = 6.5 Hz, 5-H), 2.31 (4H, m, 2-H), 1.81 (3H, d, *J* = 6.5 Hz, 6-H), 1.73-1.47 (4H, m, 3-H), 1.46-1.44 (2H, m, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 172.2 (C-1), 146.3 (C-7), 128.4 (C-9), 126.6 (C-8), 126.2 (C-10), 57.8 (C-5), 40.3 (C-2), 29.6 (C-2 or C-3), 28.0 (C-2 or C-3), 26.2 (C-3), 25.2 (C-4); LRMS (EI): 201 (100%, $[M]^{+\bullet}$), 186 (48%, $[M^{+\bullet}$-Me]), 105 (21% $[M^{+\bullet}$-$C_6H_{10}N]$); HRMS (EI) observed ($[M]^{+\bullet}$): 201.15069; $C_{14}H_{19}N$ requires 201.15120; υ_{max} (film/cm^{-1}) 1670 (C=N); $[\alpha]^{22}_D$ = +17.6° (*c* = 1, $CHCl_3$).

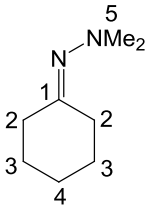
(*R*)-*N*-(2-Methylpropylidene)-1-phenylethanamine[131,190] (65)



(*R*)-1-Phenylethylamine (1.30 mL, 9.90 mmol) was added to a stirred solution of isobutyraldehyde (0.80 mL, 9 mmol) in CH_2Cl_2 (5 mL) containing $MgSO_4$ (0.30 g). The solution was stirred for 14 h at room temperature. The reaction mixture was filtered and the solvent was removed under reduced pressure to obtain the title compound as a yellow oil (460 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.63 (1H, d, *J* = 5.4 Hz, 1-H), 7.40-7.32 (5H, m, 7-H, 8-H and 9-H), 4.30 (1H, q, *J* = 6.8 Hz, 4-H), 2.52 (1H, m, 2-H), 1.52 (3H, d, *J* = 6.8 Hz, 5-H), 1.12 (6H, t, *J* = 7.5 Hz, 3-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 168.4 (C-1), 145.3 (C-6), 128.4 (C-8), 126.7 (C-7), 126.5 (C-9), 69.4 (C-4), 34.1 (C-2), 24.9 (C-5), 19.5 (C-3); LRMS (CI): 176 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 176.14426; $C_{12}H_{17}N$ requires 176.14338; υ_{max} (film/cm^{-1}) 1665 (C=N); $[\alpha]^{22}_D$ = +48.5° (*c* = 1, $CHCl_3$), Lit. $[\alpha]^{22}_D$ = +82.3° (*c* = 1, $CHCl_3$)[131].

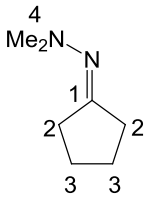
2-Cyclohexylidene-1,1-dimethylhydrazine[191] (168)



Cyclohexanone (42.50 mL, 408 mmol), was added to hydrazine (34.10 mL, 448 mmol) and heated together at 80 °C for 12 h. Upon cooling to room temperature, solid NaOH pellets (12 g) was added and the mixture was stirred for 30 min. The reaction mixture was extracted with ether (3 × 50 mL) and the combined organic extracts were washed with saturated NaCl solution (60 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the title compound as a brown oil (40 g, quantitative).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 2.26-2.17 (2H, m, H-2), 2.17-2.07 (6H, m, H-5), 1.98-1.90 (2H, m, H-2), 1.45-1.28 (6H, m, H-3 and H-4); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm}; 170.1 (C-1), 47.5 (C-5), 35.9 (C-2), 28.5 (C-2), 27.4 (C-3), 25.9 (C-4); LRMS (CI): 141 (100%, $[M+H]^+$), 96 (7); HRMS (CI) observed ($[M+H]^+$): 141.13980; $C_8H_{17}N_2$ requires 141.13917; υ_{max} (film/cm^{-1}) 2920 (C-H), 2840 (N-CH_3), 1665 (C=N).

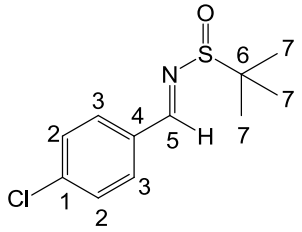
2-Cyclopentylidene-1,1-dimethylhydrazine[191] (170)



Cyclopentanone (28.40 mL, 297 mmol), was added to hydrazine (31 mL, 386 mmol) and heated together at 80 °C for 12 h. Upon cooling to room temperature, solid NaOH pellets (8 g) was added and the mixture was stirred for 30 min. The reaction mixture was extracted with ether (3 × 45 mL) and the combined organic extracts were washed with saturated NaCl solution (60 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the title compound as a brown oil (27 g, quantitative).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 2.53 (6H, s, 4-H), 2.45 (2H, m, 2-H), 2.37 (2H, m, 2-H), 1.70-1.81 (4H, complex m, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm}; 177.5 (C-1), 47.9 (C-4), 33.4 (C-2), 29.5 (C-2), 24.8 (C-3); LRMS (CI): 127 (100%, $[M+H]^+$), 96 (1); HRMS (CI) observed ($[M+H]^+$): 127.12412; $C_7H_{15}N_2$ requires 127.12352; υ_{max} (film/cm^{-1}) 2970 (C-H), 1660 (C=N).

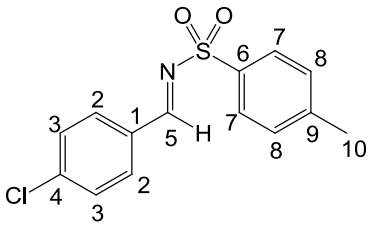
_N_-(4-Chlorobenzylidene)-2-methylpropane-2-sulfinamide[176] (225)



(±)^{t}Butyl sulfinamide (0.50 g, 4.1 mmol) was added to CH_2Cl_2 (5 mL), followed by pyridinium *p*-toluenesulfonate (PPTS) (104 mg, 4.1 mmol), $MgSO_4$ (5.00 g, 41.3 mmol) and 4-chlorobenzaldehyde (0.90 g, 6.2 mmol). The mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through a pad of Celite® and the filter cake was washed with CH_2Cl_2 (4 × 10 mL). Purification by column chromatography eluting with petrol:EtOAc (2:1) gave the title compound as a white solid (0.49 g, 97%).

mp = 39–41 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 8.37 (1H, s, 5-H), 7.60 (2H, m, 3-H), 7.20 (2H, m, 2-H), 1.08 (9H, s, 7-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 181.4 (C-5), 138.5 (C-1), 132.5 (C-4), 130.5 (C-3), 129.2 (C-2), 57.7 (C-6), 22.5 (C-7); LRMS (CI): 244 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 244.05580; $C_{11}H_{15}ClNOS$ requires 244.05628; υ_{max} (film/cm^{-1}) 1740 (C=N), 1090 (S=O).

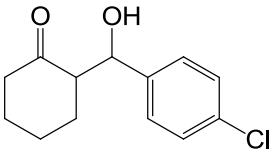
_N_-(4-Chlorobenzylidene)-4-methylbenzenesulfonamide[177] (226)



4-Methylbenzenesulfonamide (1.30 g, 7.8 mmol) was added to toluene (10 mL), followed by 4-chlorobenzaldehyde (1.00 g, 7.1 mmol). The mixture was heated with a Dean–Stark apparatus in the presence of activated molecular sieve 4 Å and a catalytic amount of amberlyst®-15 for 16 h. The mixture was cooled to room temperature without stirring, filtered, washed with toluene (2 × 25 mL) and the filtrate was concentrated under reduced pressure. The solid obtained was then triturated in pentane to give the crude product. Purification by column chromatography eluting with petrol:EtOAc (8:1) gave the title compound as a white solid (0.95 g, 95%).

mp = 170-173 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 9.15 (1H, s, 5-H), 8.04 (2H, d, *J* = 8.5 Hz, 2-H), 7.93 (2H, d, *J* = 8.5 Hz, 3-H), 7.84 (2H, d, *J* = 8.2 Hz, 8-H), 7.70 (2H, d, *J* = 8.2 Hz, 7-H), 3.37 (3H, s, 10-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 170.5 (C-5), 144.8 (C-6), 141.9 (C-9), 141.4 (C-4), 140.0 (C-1), 134.7 (C-2), 132.9 (C-3), 131.2 (C-7), 130.1 (C-8), 20.8 (C-10); LRMS (CI): 294 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 294.03571; $C_{14}H_{13}O_2NSCl$ requires 294.03500; υ_{max} (film/cm^{-1}) 1738 (C=N), 1366 $(S=O)_2$).

2-((4-Chlorophenyl)(hydroxy)methyl)cyclohexanone (67)



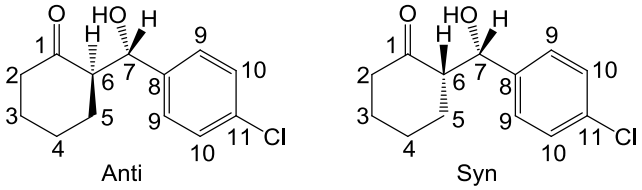
Representative procedure using N-cyclohexylidenecyclohexanamine as amine

N-Cyclohexylidenecyclohexanamine (**25**) (1 eq.) was added to MeCN (6 mL). The mixture was stirred for 5 min and sequentially a suspension of $MgBr_2$ (1.2 eq.) in MeCN (6 mL) was added, followed by Et_3N (2.5 eq.) at −45 °C. The solution was stirred for 1 h at −45 °C. A solution of 4-chlorobenzaldehyde (1 eq.) in MeCN (3 mL) was added and the mixture was stirred for 1 h at −45 °C. The mixture was then stirred for 12 h at room temperature. The reaction mixture was treated with 1M AcOH (10 mL) and stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a brown oil. Purification by column chromatography eluting with petrol:Et_2O (4:1), gave the title compound as a brown oil (14%) and as a mixture of *syn*:*anti* (1:1).

Representative procedure using N,N-diethylethylenediamine as amine

N,N-Diethylethylenediamine (0.1 eq.), was added to a stirred solution of cyclohexanone (1 eq.) in DMSO (2.50 mL) followed by $Mg(ClO_4)_2$ (0.2 eq.), and Et_3N (0.10 mL, 0.2 eq.). 4-Chlorobenzaldehyde (1 eq.) was added to DMSO and this mixture was added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon. The reaction mixture was quenched with water (30 mL) and then extracted with Et_2O (2 × 35 mL). The combined organic extracts were washed with saturated NaCl solution (30 mL), dried over $MgSO_4$ and filtered. The solvent was removed under

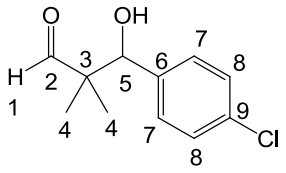
reduced pressure to obtain the crude product as a colourless oil. Purification by column chromatography eluting with petrol:Et_2O (3:1) gave the title compound as a colourless oil (69%) and as a mixture of *syn*:*anti* (67:33).



Data in agreement with the literature[192,193]

Anti-diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.32 (2H, d, *J* = 8.6 Hz, 10-H), 7.27 (2H, d, *J* = 8.6 Hz, 9-H), 4.76 (1H, d, *J* = 8.7 Hz, 7-H), 3.98 (1H, s, O-H), 2.57 (1H, dddd, *J* = 13.7, 9.8, 5.8, 4.2 Hz, 5-*H*H), 2.48 (1H, dddd, *J* = 13.7, 8.7, 5.8, 4.4 Hz, 5-H*H*), 2.35 (1H, td, *J* = 8.7, 5.8 Hz, 6-H), 2.09 (1H, dt, *J* = 11.9, 6.2 Hz, 2-*H*H), 1.80 (1H, ddd, *J* = 11.9, 8.7, 5.1 Hz, 2-H*H*), 1.70-1.26 (4H, m, 3-H and 4-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_{ppm} 215.6 (C-1), 140.5 (C-8), 140.0 (C-11), 128.9 (C-10), 128.8 (C-10), 74.5 (C-7), 57.8 (C-6), 43.0 (C-2), 31.1 (C-3), 28.1 (C-4), 25.1 (C-5); *Syn*-diasteromer: ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.30 (2H, d, *J* = 8.6 Hz, H-10), 7.26 (2H, d, *J* = 8.6 Hz, H-9), 5.37 (1H, d, *J* = 2.4 Hz, H-7), 3.00 (1H, s, O-H), 2.70-2.60 (2H, m, H-2), 1.86-1.75 (5H, m H-4, H-5 and H-6), 1.65-1.55 (2H, m, H-3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 212.6 (C-1), 139.9 (C-8), 131.3 (C-11), 128.7 (C-10), 127.6 (C-9), 70.5 (C-7), 57.4 (C-6), 42.4 (C-2), 28.2 (C-3), 27.4 (C-4), 25.4 (C-5); LRMS (EI): 238 (100%, $[M]^{+\bullet}$), 141 (66%, $[M]^{+\bullet}$-Aryl-CHOCl); HRMS (EI) observed ($[M]^{+\bullet}$): 238.07639; $C_{13}H_{15}O_2Cl$ requires 238.07551; υ_{max} (film/cm^{-1}) 3440 (O-H), 1695 (C=O).

3-(4-Chlorophenyl)-3-hydroxy-2,2-dimethylpropanal (68)



Procedure 1

N-(2-Methylpropylidene)cyclohexanamine (**59**) (0.20 g, 1.1 mmol) was added to MeCN (6 mL). The mixture was stirred for 5 min and sequentially a suspension of $MgBr_2$ (0.20 g, 1.3 mmol) in MeCN (6 mL) was added, followed by Et_3N (0.40 mL, 2.8 mmol) at −45 °C. The solution was stirred for 1 h at −45 °C. A solution of 4-chlorobenzaldehyde (0.15 g, 1.1

mmol) in MeCN (3 mL) was added and the mixture was stirred for 1 h at −45 °C. The mixture was then stirred for 12 h at room temperature. The reaction mixture was treated with 1M AcOH (10 mL) and stirred for 1.5 h. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a brown oil. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as a colourless oil (40 mg, 20%).

Procedure 2

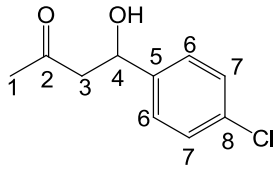
2-Methylpropanal (0.10 mL, 1.1 mmol) was added to a solution containing cyclohexylamine (0.13 mL, 1.1 mmol) MeCN (4 mL). The mixture was stirred for 5 min and sequentially a suspension of $Mg(ClO_4)_2$ (0.25 g, 1.1 mmol) in MeCN (3 mL) was added, followed by Et_3N (0.15 mL, 1.1 mmol) at −45 °C. The solution was stirred for 1 h at −45 °C. A solution of 4-chlorobenzaldehyde (0.15 g, 1.1 mmol) in MeCN (3 mL) was added and the mixture was stirred for 1 h at −45 °C. The mixture was then stirred for 12 h at room temperature. The reaction mixture was treated with 1M AcOH (10 mL) and stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a brown oil. The crude product was purified by column chromatography eluted with 4:1 petrol:Et_2O, to obtain the title compound as a colourless oil (30 mg, 20%).

Data in agreement with the literature[194]

OH peak not seen in ^{1}H NMR

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 9.91 (1H, s, 1-H), 7.65 (2H, d, *J* = 8.2 Hz, 8-H), 7.47 (2H, d, *J* = 8.2 Hz, 7-H), 4.87 (1H, s, 5-H), 1.01 (3H, s, 4-H), 0.91 (3H, s, 4-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 206.4 (C-2), 138.2 (C-6), 131.6 (C-9), 128.9 (C-7 or C-8), 128.2 (C-7 or C-8), 76.7 (C-5), 50.9 (C-3), 20.0 (C-4), 18.3 (C-4); LRMS (EI): 195 (100%, $[M\text{-}OH]^{+\bullet}$); HRMS (EI) observed ($[M\text{-}OH]^{+\bullet}$): 195.05810; $C_{11}H_{12}OCl$ requires 195.05712; υ_{max} (film/cm^{-1}) 3458 (O-H), 1728 (C=O)-H).

4-(4-Chlorophenyl)-4-hydroxybutan-2-one (72)



Authentic sample procedure[132]

L-proline (0.30 g, 2.1 mmol) was added to a stirred solution of acetone (0.10 mL, 1.4 mmol) in DMSO:acetone (4:1, 5 mL). 4-Chlorobenzaldehyde (1.00 g, 7.1 mmol) was added to the stirred mixture. The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with NH_4Cl (20 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as pale yellow oil. Purification by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a colourless oil (420 mg, 42%, 70% *ee*, major isomer *R*). HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 17.6 min (*R* major), t_R = 21.2 min (*S* minor). $[\alpha]^{22}_D$ = +38.5° (*c* = 1, $CHCl_3$), Lit. $[\alpha]^{22}_D$ = +51.0° (*c* = 1, $CHCl_3$)[132].

Unoptimised procedure

4-Chlorobenzaldehyde (1 eq.) was added to a stirred solution of DMSO (4 mL), followed by; Cyclohexylamine (0.5 eq.), acetone (10 eq.), $Mg(ClO_4)_2$ (0.5 eq.), and Et_3N (0.5 eq.). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a yellow oil. Purification by column chromatography eluting with petrol:Et_2O (3:1) gave the title compound as a colourless oil.

Optimised procedure

Primary amine (0.1 equiv.) was added to a stirred solution of acetone (10 equiv.) in DMSO:acetone (4:1, 2.5 mL) followed by; $Mg(ClO_4)_2$ (0.2 eq.), and Et_3N (0.2 eq.). 4-Chlorobenzaldehyde (1 eq.) was added to a solution mixture of DMSO:acetone (4:1, 2.5 mL) and added dropwise *via* a syringe pump (1.59 cc/hr) to the stirred mixture. The mixture was stirred for 12 h at room temperature under argon. The reaction mixture was

quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as pale yellow oil. Purification by column chromatography eluting with petrol:Et_2O (3:1) gave the title compound as a colourless oil.

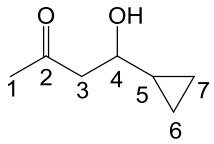
Primary amine	**Yield (%)/ee (%)**	**Major isomer *R* or *S***
N,*N*-Diethylethylenediamine (**75**)	60%	
2-Methoxyphenyl)methanamine (**79**)	14%	
(1*R*,2*R*)-Cyclohexane-1,2-diamine (**78**)	48%	
2-Methylpropane-2-sulfinamide (**84**)	78%	
4-(Methoxyphenyl)methanamine (**79**)	18%	
Butylamine (**82**)	40%	
(*R*)-1-Phenylethanamine (**62**)	38%/8%	***R***
(1*R*,2*S*)-2-Amino-1,2-diphenylethanol (**103**)	60%/10%	***R***
(*R*)-2-Amino-4-methylpentan-1-ol (**104**)	40%/6%	***R***
(*R*)-2-Amino-3,3-dimethylbutan-1-ol (**105**)	34%/6%	***R***
9-Amino(9-deoxy)epihydroquinine (**96**)	46%/8%	***S***
(*R*)-1-Methoxy-3-phenylpropan-2-amine (**101**)	65%/23%	***R***
(*R*)-2-Amino-3-phenylpropan-1-ol (**100**)	42%/16%	***R***
(*R*)-2-Amino-3-methylbutan-1-ol (**102**)	41%/40%	***R***
(*R*)-2-Methylpropane-2-sulfinamide (**106**)	81%/38%	***R***
(1*R*,2*R*)-N^1-(4-Chlorobenzyl)cyclohexane-1,2-diamine (**99**)	64%/4%	
(2*S*,3*S*)-2-Amino-3-methylpentan-1-ol (**107**)	39%/2%	

Data in agreement with the literature[195,196]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.36-7.32 (4H, m, 6-H and 7-H), 5.08 (1H, d, *J* = 4.4 Hz, 4-H), 3.57 (1H, s, OH), 3.00 (1H, d, *J* = 5.5 Hz, 3-*H*H), 2.70 (1H, dd, *J* = 5.5, 4.4 Hz, 3-H*H*), 2.15 (3H, s, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 208.9 (C-2), 141.5 (C-5), 131.9 (C-6 and C-8), 129.0 (C-7), 69.2 (C-4), 51.9 (C-3), 30.8 (C-1); LRMS (ES^+): 200 (^{37}Cl, 14%,

$[M]^+$), 198 (^{35}Cl, 43%, $[M]^+$), 181 (95%, $[M]^+$-OH), 141 (100%, $[M]^+$-C_3H_5O); υ_{max}/cm^{-1} 3407 (O-H), 1703 (C=O).

4-Cyclopropyl-4-hydroxybutan-2-one (85)

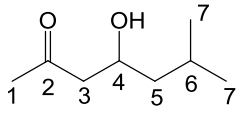


N,*N*-Diethylethylenediamine (0.20 mL, 1.4 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and stirred followed by the addition of; acetone (10.50 mL, 143 mmol), $Mg(ClO_4)_2$ (0.60 g, 2.9 mmol), and Et_3N (0.40 mL, 2.85 mmol). Cyclopropanecarboxaldehyde (1.10 mL, 14.3 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon, quenched with water (25 mL), and then extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a colourless oil. Purification by column chromatography eluting with petrol:EtOAc (3:1) gave the title compound as a colourless oil (140 mg, 14%).

Data in agreement with the literature[197]

^1H NMR (500 MHz, $CDCl_3$): δ_{ppm} 3.27 (1H, ddd, *J* = 11.2, 7.1, 4.9 Hz, 4-H), 3.01 (1H, s, OH), 2.68 (2H, m, 3-H), 2.13 (3H, s, 1-H), 0.86 (1H, qt, *J* = 7.1, 5.0 Hz, 5-H), 0.31 (1H, td, *J* = 9.7, 5.0 Hz, 6-H), 0.12 (1H, td, *J* = 9.4, 4.9 Hz, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 209.9 (C-2), 72.6 (C-4), 50.3 (C-3), 31.1 (C-1), 17.2 (C-5), 3.6 (C-6), 2.5 (C-7); LRMS (EI): 127 (100%, $[M-H]^{+\bullet}$); HRMS (EI) observed ($M^{+\bullet}$-H): 127.07581; $C_7H_{11}O_2$ requires 127.07536; υ_{max} (film/cm^{-1}) 3457 (O-H), 3016 (C-H), 1740 (C=O).

4-Hydroxy-6-methylheptan-2-one (86)

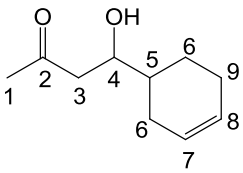


N,*N*-Diethylethylenediamine (0.20 mL, 1.2 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and stirred followed by the addition of; acetone (8.50 mL, 116 mmol), $Mg(ClO_4)_2$ (0.50 g, 2.3 mmol), and Et_3N (0.30 mL, 2.3 mmol). 3-methylbutanal (1.30 mL, 11.6 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon, quenched with water (25 mL), and then extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a colourless oil. Purification by column chromatography eluting with petrol:EtOAc (3:1) gave the title compound as a colourless oil (170 mg, 17%).

Data in agreement with the literature[198,199]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 4.11 (1H, m, 4-H), 3.03 (1H, s, OH), 2.59 (1H, dd, *J* = 9.9, 3.6 Hz, 3-*H*H), 2.52 (1H, dd, *J* = 8.7, 3.6 Hz, 3-H*H*), 2.17 (3H, s, 1-H), 1.71-1.78 (1H, m, 6-H), 1.45 (1H, ddd, *J* = 12.5, 8.9, 5.3 Hz, 5-*H*H), 1.12 (1H, ddd, *J* = 11.5, 8.9, 5.3 Hz, 5-H*H*), 0.90 (6H, dd, *J* = 7.6, 6.6 Hz, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 210.3 (C-2), 65.7 (C-4), 50.5 (C-3), 44.9 (C-5), 30.8 (C-1), 24.4 (C-6), 23.3 (C-7), 22.0 (C-7); LRMS (CI): 145 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 145.12326; $C_8H_{17}O_2$ requires 145.12285; υ_{max} (film/cm^{-1}) 3448 (O-H), 2957 (C-H), 1730 (C=O).

4-(Cyclohex-3-enyl)-4-hydroxybutan-2-one (87)

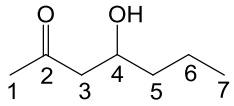


N,*N*–Diethylethylenediamine (0.10 mL, 0.9 mmol) was added to a solvent mixture of DMSO/acetone (4:1, 5 mL) and stirred followed by the addition of; acetone (6.70 mL, 90.8 mmol), $Mg(ClO_4)_2$ (0.40 g, 1.8 mmol), and Et_3N (0.30 mL, 1.8 mmol). Cyclohex-3-enecarbaldehyde (1.00 mL, 9.1 mmol) was added to a solvent mixture of DMSO/acetone

(4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon. The reaction mixture was quenched with water (25 mL) and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a pale yellow oil. Purification by column chromatography eluting with petrol:EtOAc (3:1) gave the title compound as a colourless oil and as a mixture of diastereomers *syn*:*anti* (1:1) (130 mg, 13%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 5.66-5.62 (2H, m, 7-H and 8-H), 3.92 (0.5H, ddd, *J* = 9.0, 5.9, 2.6 Hz, 4-H), 3.83 (0.5H, ddd, *J* = 9.8, 6.9, 2.6 Hz, 4-H), 3.00 (0.5H, s, OH), 2.98 (0.5H, s, OH), 2.66 (1H, dd, *J* = 5.9, 4.3 Hz, 3-H), 2.63 (1H, dd, *J* = 6.9, 4.3 Hz, 3-H), 2.58 (0.5H, dd, *J* = 9.0, 4.7 Hz, 5-H), 2.54 (0.5H, dd, *J* = 9.8, 4.7 Hz, 5-H), 2.12 (3H, s, 1-H), 2.10-1.40 (6H, m, 6-H and 9-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 210.4 (C-2), 210.3 (C-2), 127.4 (C-7 or C-8), 126.9 (C-7 or C-8), 126.4 (C-7 or C-8), 125.7 (C-7 or C-8), 71.5 (C-4), 71.0 (C-4), 47.7 (C-3), 47.6 (C-3), 39.3 (C-5), 39.3 (C-5), 30.9 (C-6) 30.9 (C-6), 28.4 (C-1), 27.8 (C-1), 25.2 (C-9), 25.1 (C-9); LRMS (CI): 169 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 169.12353; $C_{10}H_{17}O_2$ requires 169.12285; υ_{max} (film/cm^{-1}) 3424 (O-H), 1708 (C=O), 1365 (C=C).

4-Hydroxyheptan-2-one (88)



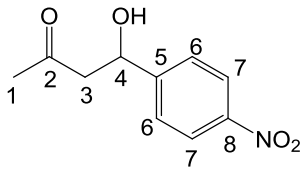
N,*N*-Diethylethylenediamine (0.10 mL, 0.7 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 2.5 mL) and stirred followed by the addition of; acetone (4.0 mL, 69.3 mmol), $Mg(ClO_4)_2$ (0.30 g, 1.4 mmol), and Et_3N (0.10 mL, 1.4 mmol). Butanal (0.50 g, 7.0 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 2.5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon. The reaction mixture was quenched with water (25 mL) and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as yellow oil. Purification

by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a colourless oil (0.14 g, 16%).

Data in agreement with the literature[200]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 4.10-4.07 (1H, m, 4-H), 2.97 (1H, s, OH), 2.63 (2H, m, 3-H), 2.11 (3H, s, 1-H), 1.51-1.34 (4H, m, 5-H and 6-H), 0.93 (3H, s, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 207.7 (C-2), 67.1 (C-4), 52.6 (C-3), 39.5 (C-5), 30.1 (C-1), 18.5 (C-6), 14.4 (C-7); υ_{max} (film/cm^{-1}) 3405 (O-H), 1743 (C=O).

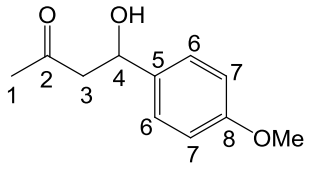
4-Hydroxy-4-(4-nitrophenyl)butan-2-one[201,202] (90)



N,*N*-Diethylethylenediamine (60 µL, 0.3 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) followed by; acetone (2.40 mL, 31.0 mmol), $Mg(ClO_4)_2$ (150 mg, 0.7 mmol), Et_3N (92 µL, 0.7 mmol). 4-Nitrobenzaldehyde (0.50 g, 3.3 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon, quenched with water (15 mL), and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a colourless oil. Purification by column chromatography eluting with petrol:EtOAc (3:1) gave the title compound as a colourless oil (0.34 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 8.20 (2H, d, *J* = 8.8 Hz, 7-H), 7.54 (2H, d, *J* = 8.8 Hz, 6-H), 5.26 (1H, dd, *J* = 8.4, 4.6 Hz, 4-H), 3.60 (1H, d, *J* = 2.4 Hz, OH), 2.85 (1H, dd, *J* = 8.4, 3.9 Hz, 3-H), 2.82 (1H, dd, *J* = 4.6, 3.9 Hz, 3-H), 2.22 (3H, s, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 208.8 (C-2), 150.0 (C-5), 145.0 (C-8), 126.5 (C-6), 123.9 (C-7), 69.0 (C-4), 51.6 (C-3), 30.8 (C-1); LRMS (EI): 209 (100%, $[M]^{+\bullet}$); HRMS (EI) observed ($[M+Na]^{+\bullet}$): 232.05770; $C_{10}H_{11}NO_4$ requires 223.05800; υ_{max} (film/cm^{-1}) 3449 (O-H), 3118 (C-H), 1713 (C=O).

4-Hydroxy-4-(4-methoxyphenyl)butan-2-one (91)

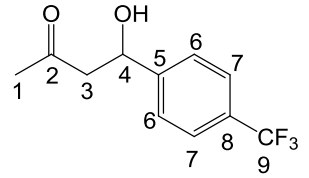


N,*N*–Diethylethylenediamine (0.10 mL, 0.7 mmol) was added to a solvent mixture of DMSO/acetone (4:1, 5 mL) and stirred followed by the addition of; acetone (5.40 mL, 73.5 mmol), $Mg(ClO_4)_2$ (0.30 g, 1.5 mmol), and Et_3N (0.20 mL, 1.47 mmol). 4-Methoxybenzaldehyde (0.90 mL, 7.4 mmol) was added to a solvent mixture of DMSO/acetone (4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon. The reaction mixture was quenched with water (25 mL) and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as yellow oil. Purification by column chromatography eluting with petrol:Et_2O (3:1) gave the title compound as a colourless oil (0.59 g, 41%).

Data in agreement with the literature[203]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.26 (2H, d, *J* = 8.4 Hz, 6-H), 6.86 (2H, d, *J* = 8.4 Hz, 7-H), 5.07 (1H, dd, *J* = 8.4, 6.8 Hz, 4-H), 3.76 (3H, s, OMe), 3.30 (1H, s, OH), 2.87 (1H, dd, *J* = 8.4, 4.6 Hz, 3-H), 2.84 (1H, dd, *J* = 6.8, 4.6 Hz, 3-H), 2.15 (3H, s, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 210.0 (C-2), 158.9 (C-8), 134.9 (C-5), 126.8 (C-6), 113.7 (C-7), 69.4 (C-4), 55.1 (O-Me), 51.9 (C-3), 30.6 (C-1); LRMS (EI): 194 (100%, $[M]^{+\bullet}$), 77 (80%, $M^{+\bullet}$-C_6H_4); HRMS (EI) observed ($M^{+\bullet}$): 194.09452; $C_{11}H_{14}O_3$ requires 194.09375; υ_{max} (film/cm^{-1}) 3420 (O-H), 2921 (Ar-H), 1705 (C=O), 1361 (C-OMe).

4-Hydroxy-4-(4-(trifluoromethyl)phenyl)butan-2-one (93)



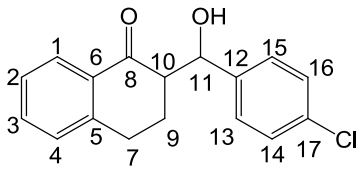
N,*N*-Diethylethylenediamine (20 µL, 0.1 mmol) was added to a stirred mixture of DMSO:acetone (4:1, 5 mL) followed by; acetone (1.00 mL, 14.0 mmol), $Mg(ClO_4)_2$ (60 mg, 0.3 mmol), and Et_3N (40 µL, 0.3 mmol). 4-(Trifluoromethyl)benzaldehyde (30 mg, 1.4

mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.02 cc/hr). The mixture was stirred for 12 h at room temperature under argon, quenched with water (25 mL), and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a colourless oil. Purification by column chromatography eluting with petrol:EtOAc (3:1) gave the title compound as a colourless oil (100 mg, 40%).

Data in agreement with the literature[204]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.60 (2H, d, *J* = 8.2 Hz, H-7), 7.47 (2H, d, *J* = 8.2 Hz, H-6), 5.20 (1H, dd, *J* = 7.9, 4.4 Hz, H-4), 3.55, (1H, s, OH), 2.83 (2H, dd, *J* = 8.1, 4.4 Hz, H-3), 2.20 (3H, s, Me); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 208.8 (C-2), 146.8 (C-5), 129.9 (q, *J* = 40.6 Hz, C-8), 126.0 (C-6), 125.5 (C-7), 124.2 (q, *J* = 40.7 Hz, C-9), 69.3 (C-4), 51.8 (C-3), 30.8 (C-1); LRMS (CI): 233 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 233.07912; $C_{11}H_{12}O_2F_3$ requires 233.07894; υ_{max} (film/cm^{-1}) 3431 (O-H), 2918 (C-H), 1711 (C=O).

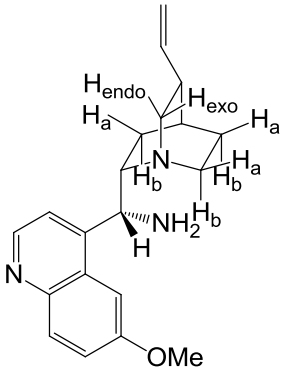
2-((4-Chlorophenyl)(hydroxy)methyl)-3,4-dihydronaphthalen-1(2H)-one (95)



N,*N*-Diethylethylenediamine (0.10 mL, 0.7 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and stirred followed by the addition of; 3,4-Dihydro-1(2*H*)-naphthalenone (1.00 mL, 7.8 mmol), $Mg(ClO_4)_2$ (0.30 g, 0.1 mmol), and Et_3N (0.20 mL, 0.1 mmol). 4-Chlorobenzaldehyde (1.00 g, 7.1 mmol) was added to a solvent mixture of DMSO:acetone (4:1, 5 mL) and added dropwise to the stirred mixture *via* a syringe pump (1.59 cc/hr). The mixture was stirred for 12 h at room temperature under argon, quenched with water (25 mL), and then extracted with Et_2O (2 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (35 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a yellow oil. Purification by column chromatography eluting with petrol:EtOAc (3:1) gave the title compound as a pale yellow oil (0.23 g, 23%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 8.06 (1H, d, *J* = 7.9 Hz, 15-H), 7.50 (1H, d, *J* = 7.5, Hz, 1-H), 7.34-7.30 (5H, m, 2-H, 3-H, 13-H, 14-H, 16-H), 7.22 (1H, d, *J* = 7.5 Hz, 4-H), 4.95, (1H, d, *J* = 8.7 Hz, 11-H), 2.88 (2H, dd, *J* = 9.1, 4.3 Hz, 9-H), 2.75-2.67 (1H, m, 10-H), 1.70-1.64 (2H, m, 7-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 202.1 (C-8), 144.4 (C-5), 139.8 (C-12), 134.3 (C-6), 132.3 (C-3), 132.0 (C-17), 128.7 (C-14 and C-16), 127.6 (C-13 and C-15), 127.0 (C-2), 75.0 (C-11), 54.0 (C-10), 28.8 (C-7), 26.1 (C-9); LRMS (CI): 289 (^{37}Cl, 25%, $[M+H]^+$), 287 (^{35}Cl, 75%, $[M+H]^+$); HRMS (CI) observed (^{35}Cl, $[M+H]^+$): 287.08263; $C_{17}H_{16}O_2{}^{35}Cl$ requires 287.08388; υ_{max} (film/cm^{-1}) 3449 (O-H), 2929 (C-H), 1738 (C=O).

9-Amino(9-deoxy)epihydroquinine[133] (96)



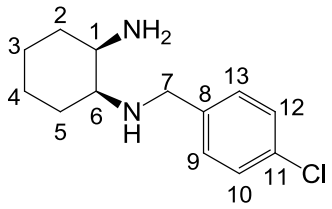
Hydroquinine (1.00 g, 3.1 mmol) and triphenylphosphine (960 mg, 3.7 mmol) were dissolved in dry THF (20 mL) and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (0.70 g, 3.7 mmol) was added in one portion. A solution of diphenyl phosphoryl azide (0.80 mL, 3.7 mmol) in dry THF (8 mL) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and then stirred for 12 h at this temperature. The mixture was heated to 50 °C for 2 h and then triphenylphosphine (1.00 g, 4.0 mmol) was slowly added portion-wise, the heating was maintained until gas evolution had ceased (2 h). The solution was cooled to room temperature, water (2 mL) was added, and the solution was stirred for 3 h. The solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2 and 10% HCl (1:1, 50 mL). The aqueous phase was washed with CH_2Cl_2 (4 × 20 mL), basified with excess aqueous NH_4OH solution and washed with CH_2Cl_2 (4 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography eluting with EtOAc:MeOH:aq. NH_4OH (50:50:1) affording the title compound as a yellow viscous oil (0.70 g, 70%).

Data in agreement with the literature[133]

NH_2 peak not seen

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 8.69 (1H, d, *J* = 4.7 Hz, 13-H), 7.98 (1H, d, *J* = 9.2 Hz, 19-H), 7.61 (1H, d, *J* = 4.7, Hz, 12-H), 7.42 (1H, s, 16-H), 7.33 (1H, dd, *J* = 9.2, 2.6 Hz, 18-H), 4.54 (1H, d, *J* = 10.9 Hz, 10-H), 3.91 (3H, s, O*CH*$_3$), 3.38 (1H, dddd, *J* = 15.6, 10.3, 7.8, 2.7 Hz, 8-H_b), 3.18 (1H, dd, *J* = 13.6, 10.0 Hz, 4-H_{exo}), 3.03-2.98 (1H, m, 9-H), 2.71 (1H, ddd, *J* = 15.6, 13.7, 4.8 Hz, 8-H_a), 2.46 (1H, ddd, *J* = 13.6, 10.0, 2.7 Hz, 4-H_{endo}), 2.40-2.35 (2H, m, 7-H_b), 1.68 (1H, dd, *J* = 13.4, 10.4 Hz, 5-H_b), 1.60-1.55 (1H, m, 6-H), 1.53 (1H, unresolved partly overlapping signal, 7-H_a), 1.53 (1H, ddd, *J* = 13.4, 10.4, 2.8 Hz, 5-H_a), 1.40-1.35 (1H, m, 3-H), 1.28-1.20 (1H, m, 2-H), 0.69 (2H, d, *J* = 7.4 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 157.7 (C-17), 147.9 (C-11), 147.3 (C-13), 144.8 (C-14), 141.2 (C-2), 131.9 (C-19), 128.9 (C-15), 121.3 (C-18), 120.0 (C-12), 112.1 (C-1), 102.0 (C-16), 71.9 (C-9) 58.0 (C-4), 55.6 (O*CH*$_3$), 41.1 (C-10), 37.5 (C-8), 28.9 (C-3), 27.7 (C-5), 25.9 (C-7), 25.3 (C-6).

(1*R*,2*R*)-*N*^{1}-(4-Chlorobenzyl)cyclohexane-1,2-diamine (99)

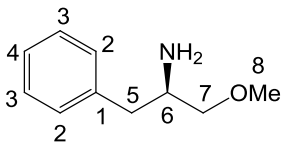


(1*R*,2*R*)-cyclohexane-1,2-diamine (0.40 g, 3.6 mmol) was added to a solution of 4-Chlorobenzaldehyde (0.50 g, 3.6 mmol) in 15mL of ethanol and stirred for 15 min at room temperature. The solvent was removed under reduced pressure and this procedure was repeated three times to obtain the crude product as a pale yellow oil. The crude mixture was dissolved in MeOH:THF (1:1, 6 mL), then $NaBH_4$ (0.30 g, 8.4 mmol) was added. The mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with water (15 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a pale yellow oil. Purification by column chromatography eluting with Et_2O:MeOH:Et_3N (30:9:1) gave the title compound as a colourless oil (0.35 g, 70%).

NH and NH_2 peaks not seen

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 7.19-7.15 (4H, m, 9-H, 10-H, 12-H and 13-H), 3.73 (1H, dd, *J* = 13.4, 10.4 Hz, 7-H), 3.50 (1H, dd, *J* = 11.2, 10.4 Hz, 7-H), 2.29-2.21 (2H, m, 1-H and 6-H), 2.13-2.08 (2H, m, 2-H), 2.04-1.96 (4H, m, 3-H and 4-H), 1.01-0.8 (2H, m, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 139.7 (C-1), 132.3 (C-8), 129.4 (C-9 and C-13), 128.4 (C-10 and C-12), 62.8 (C-1), 60.9 (C-6), 55.3 (C-4), 35.2 (C-5), 31.5 (C-2), 25.23 (C-3), 25.18 (C-4); LRMS (CI): 239 (100%, $[M+H]^+$); HRMS (CI) observed (^{35}Cl, $[M+H]^+$): 239.13158; $C_{13}H_{20}N_2Cl$ requires 239.13150; υ_{max} (film/cm^{-1}) 3299 (N-H), 2925 (C-H).

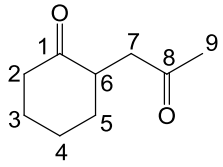
(*R*)-1-Methoxy-3-phenylpropan-2-amine[134] (101)



Potassium hydride (120 mg, 2.9 mmol, 35 wt % oil dispersion) was placed in a flame dried flask, washed with pentane (3 × 5 mL) and decanted. Dry THF (4 mL) was added, and a solution of (*S*)-(-)-2-amino-3-phenyl-1-propanol (0.40 g, 2.6 mmol) in dry THF (3 mL) was added dropwise. The mixture was stirred overnight at room temperature and then cooled to 0 °C. A solution of iodomethane (0.20 mL, 2.9 mmol) in THF (10 mL) was added dropwise over 30 min. After 1 h of stirring, the mixture was poured into ice, followed by addition of water (10 mL). The organic solvent was removed by evaporation, and the aqueous mixture was extracted with hexane (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a colourless oil. Purification by column chromatography eluting with petrol:EtOAc (4:1) gave the title compound as a colourless oil (192 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 7.28 (2H, dd, *J* = 12.1, 5.6 Hz, 3-H), 7.18 (2H, partly unresolved, dd, *J* = 12.1, 5.6, Hz, 2-H), 7.19-7.17 (1H, m, 4-H), 3.37-3.29 (4H, m, 6-H and 8-H), 3.25-3.18 (2H, m, 7-H), 2.76 (1H, dd, *J* = 14.1, 5.5 Hz, 5-H), 2.52 (1H, dd, *J* = 14.1, 7.8 Hz, 5-H), 1.44 (2H, br, NH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 138.8 (C-1), 129.3 (C-3), 128.5 (C-2), 126.4 (C-4), 77.4 (C-7), 59.0 (C-8), 52.4 (C-6), 40.9 (C-5); LRMS (ES^+): 166 (100%, $[M+H]^+$), 156 (31%), 133 (12%, $[M]^+$-NOH_3); HRMS (ES^+) observed $[M+H]^+$): 166.1230; $C_{10}H_{16}NO$ requires 166.1232; υ_{max} (film/cm^{-1}) 3420 (NH_2) 2952 (C-H).

2-(2-Oxopropyl)cyclohexanone (136)

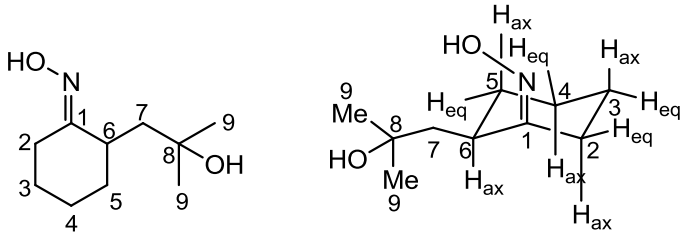


N-Cyclohexylidenecyclohexanamine (**25**) (11.00 g, 61.0 mmol) was dissolved in dry THF (40 mL). Ethylmagnesium bromide (35 ml, 3M in THF) was added to the solution dropwise and the reaction mixture was heated at reflux for 2 h. The solution was cooled to 0 °C and propylene oxide (6.40 mL, 95 mmol) was added. The resulting dark green solution was stirred at 0 °C for 1 h, then for 1 h at room temperature. The solution was partitioned between Et_2O (40 mL) and brine (40 mL). The layers were separated and the aqueous layer was extracted twice with Et_2O (2 x 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Petrol (25 mL) was added to the residue and l M acetic acid (35 mL) for 2 h at room temperature. Saturated NaCl was added and the layers were separated, the aqueous layer was extracted twice with Et_2O (2 x 25 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), brine (25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the alcohol (**132**) as a light brown oil (3.37 g, 31%). The alcohol (**132**) (200 mg, 1.28 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to −10 °C. Et_3N (0.54 mL, 3.84 mmol) was added to the mixture followed by a solution of sulfur trioxide pyridine complex (SO_3•Py) (0.60 g, 3.83 mmol) in DMSO (0.27 mL). The mixture was stirred for 30 min at −10 °C and allowed to warm to room temperature over 30 min. The reaction mixture was quenched with saturated NaCl solution (20 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with 10% citric acid solution (5 mL), saturated NaCl solution (10 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as colourless oil. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as colourless oil (84 mg, 42%).

Data in agreement with the literature[205]

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 2.97 (2H, d, *J* = 5.4 Hz, 7-H), 2.37 (2H, t, *J* = 5.9 Hz, 2-H), 2.20 (3H, s, 9-H), 2.15-2.06 (3H, m, cyclohexyl), 1.45-1.05 (6H, m, 3-H, 4-H and 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 211.6 (C-1), 207.4 (C-8), 46.5 (C-7), 43.2 (C-6), 41.9 (C-2), 34.1 (C-9), 30.5 (C-3), 27.7 (C-4), 25.4 (C-5); υ_{max} (film/cm^{-1}) 1720 (C=O), 1715 (C=O).

2-(2-Hydroxy-2-methylpropyl)cyclohexanone oxime[88] (141)



Representative procedure using Grignard reagent

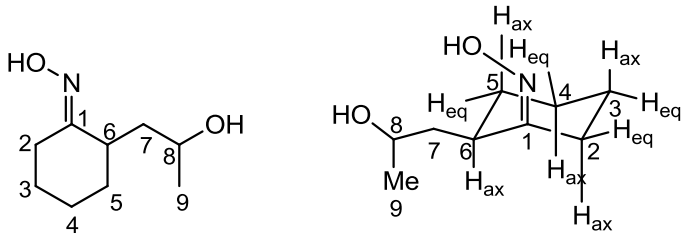
N^1-Cyclohexylidene-N^2,N^2-diethylethane-1,2-diamine (**56**) (5.00 g, 28.0 mmol) was dissolved in dry THF (20 mL). Ethylmagnesium bromide (17.5 mL, 3 M solution in THF) was added to the solution dropwise and the reaction mixture was heated at reflux. After 2 h, the solution was cooled to 0 °C, and 2,2-dimethyloxiran (4.00 mL, 45.0 mmol) was added. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature. The reaction mixture was quenched with saturated NaCl solution (20 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give a brown residue. The residue was treated with petroleum ether (25 mL) and l M acetic acid (35 mL) for 2 h at room temperature. Saturated NaCl solution was added, the aqueous layer was re-extracted twice with Et_2O (2 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (25 mL), saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography eluted with EtOAc:Petrol (2:1), to obtain ketone **139** as a light brown oil (2.15 g, 43%). Hydroxylamine hydrochloride (0.40 g, 5.76 mmol) was added to a solution containing **139** (652 mg, 3.84 mmol), ethanol (15 mL) and pyridine (0.6 mL, 7.59 mmol). The mixture was refluxed for 2 h. The reaction mixture was quenched with water (15 mL) and then extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude oxime product as pale brown oil. Purification by column chromatography eluting with EtOAc:petrol (4:1) gave the title compound as a colourless oil over two steps in a *anti*:*syn* ratio of 95:5 as determined by ^{1}H NMR (235 mg, 36%).

Representative procedure using aza enolate methodology

N^1-Cyclohexylidene-N^2,N^2-diethylethane-1,2-diamine (**56**) (100 mg, 0.6 mmol) was dissolved in dry THF (5 mL). The solution was cooled to 0 °C and $Mg(ClO_4)_2$ (0.12 g, 0.6 mmol) was added, followed by 2,2-dimethyloxiran (0.06 mL, 0.67 mmol) and Et_3N (0.12 mL, 0.8 mmol). The resulting solution was stirred at 0 °C for 1 h, then for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (10 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to afford the crude product. Hydroxylamine hydrochloride (100 mg, 1.32 mmol) was added to a solution containing **139** (150 mg, 0.88 mmol), ethanol (5 mL) and pyridine (0.14 mL, 1.76 mmol). The mixture was refluxed for 2 h. The reaction mixture was quenched with water (15 mL) and then extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude oxime product as pale brown oil. Purification by column chromatography eluting with EtOAc:Petrol (1:1) gave the title compound as a mixture of geometric isomers as a colourless oil over two steps in a *anti*:*syn* ratio of 95:5 as determined by ^{1}H NMR (20 mg, 20%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 3.37 (1H, ddd, *J* = 14.4, 4.3, 3.1 Hz, 2-H_{eq}), 2.33 (1H, dddd, *J* = 12.2, 11.0, 4.6, 2.8 Hz, 6-H), 2.07 (1H, dd, *J* = 11.0, 10.9 Hz, 7-H), 1.83-1.79 (1H, m, 3-H_{eq}), 1.77-1.73 (1H, m, 4-H_{eq}), 1.73-1.69 (1H, m, 5-H_{eq}), 1.63 (1H, ddd, *J* = 14.4, 13.1, 5.2 Hz, 2-H_{ax}), 1.47-1.43 (1H, m, 4-H_{ax}), 1.42 (1H, dd, *J* = 10.9, 2.8 Hz, 7`-H), 1.34-1.29 (1H, m, 3-$H_{ax}$), 1.28-1.22 (1H, m, 5-$H_{ax}$), 1.22 (3H, s, 9-H), 1.14 (3H, s, 9`-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 162.0 (C-1), 69.6 (C-8), 46.5 (C-7), 40.1 (C-6), 36.1 (C-5), 32.1 (C-9), 27.7 (C-3), 26.0 (C-2), 25.7 (C-4); LRMS (ES^+): 208 (100 %, $[M+Na]^+$); HRMS (ES^+) observed $[M+Na]^+$): 208.1313; $C_{10}H_{19}NO_2Na$ requires 208.1313; υ_{max} (film/cm^{-1}) 3225 (O-H), 2900 (C-H), 1670 (C=N).

2-(2-Hydroxypropyl)cyclohexanone oxime (142)

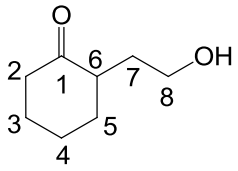


N^1-Cyclohexylidene-N^2,N^2-diethylethane-1,2-diamine (**56**) (5.00 g, 28.0 mmol) was dissolved in dry THF (20 mL). Ethylmagnesium bromide (17.50 ml, 3 M solution in THF) was added to the solution dropwise and the reaction mixture was heated at reflux. After 2 h, the solution was cooled to 0 °C, and 2,2-dimethyloxiran (4 mL, 45 mmol) was added. The resulting yellow solution was stirred at 0 °C for 1 h, then for 1 h at room temperature. The reaction mixture was quenched with saturated NaCl solution (20 mL) and extracted with Et_2O (2 × 15 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to give a brown residue. The residue was treated with petroleum ether (25 mL) and l M acetic acid (35 mL) for 2 h at room temperature. Saturated NaCl solution was added, the aqueous layer was extracted twice with Et_2O (2 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (25 mL), saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product. The crude product was purified by column chromatography eluted with EtOAc:Petrol (2:1), to obtain ketone **132** as a brown oil (1.80 g, 36%). Hydroxylamine hydrochloride (0.40 g, 5.76 mmol) was added to a solution containing **132** (662 mg, 3.84 mmol), ethanol (15 mL) and pyridine (0.60 mL, 7.59 mmol). The mixture was refluxed for 2 h. The reaction mixture was quenched with water (15 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to afford the crude oxime product as a brown oil. Purification by column chromatography eluting with EtOAc:Petrol (4:1) gave the title compound as a colourless oil over two steps in a *anti*:*syn* ratio of 67:33 as determined by ^{1}H NMR (159 mg, 24%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 4.33-4.28 (1H, m, 8-H), 3.41 (1H, ddd, *J* = 14.2, 5.1, 4.1 Hz, 2-H_{eq}), 2.34 (1H, dddd, *J* = 12.4, 10.7, 9.1, 6.9 Hz, 6-H), 2.30 (1H, ddd, *J* = 10.7, 8.9, 7.8 Hz, 7-H), 1.93-1.90 (1H, m, 3-H_{eq}), 1.80-1.77 (1H, m, 4-H_{eq}), 1.75-1.70 (1H, m, 5-H_{eq}), 1.69-1.60 (1H, m, 2-H_{ax}), 1.49-1.45 (1H, m, 4-H_{ax}), 1.42 (1H, ddd, *J* = 9.1, 7.8, 6.6 Hz, 7`-H), 1.37-1.34 (1H, m, 3-H_{ax}), 1.30-1.27 (1H, m, 5-H_{ax}), 1.22 (3H, d, *J* = 6.9 Hz, 9-H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ_{ppm} 162.6 (C-1), 66.7 (C-8), 40.1 (C-6), 37.2 (C-7), 34.5 (C-5), 26.6 (C-3), 26.0 (C-4), 25.1 (C-2), 23.5 (C-9); υ_{max} (film/cm^{-1}) 3223 (O-H), 2900 (C-H), 1670 (C=N).

2-(2-Hydroxyethyl)cyclohexanone (144)



Procedure 1

N-Cyclohexylidenecyclohexanamine (**25**) (0.50 g, 2.8 mmol) was added to MeCN (10 mL), followed by $Mg(ClO_4)_2$ (0.74 g, 3.3 mmol) and DIPEA (1.16 mL, 8.3 mmol). The mixture was stirred at −45 °C for 1 h, followed by the addition of a solution of 1,3,2-dioxathiolane 2,2-dioxide (0.50 g, 2.8 mmol) in MeCN (10 mL). The mixture was stirred for 1 h at −45 °C, then allowed to warm to room temperature over 12 h. The reaction mixture was treated with 1M AcOH (6 mL) and stirred for 1 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a yellow oil. Purification by column chromatography eluting with petrol:Et_2O (4:1), gave the title compound as a pale yellow oil (9 mg, 18%).

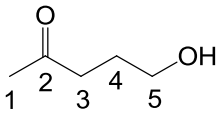
Procedure 2

N-Cyclohexylidenecyclohexanamine (**25**) (0.50 g, 2.8 mmol) was added to MeCN (10 mL), followed by $Mg(ClO_4)_2$ (0.74 g, 3.3 mmol) and Et_3N (1.16 mL, 8.3 mmol). The mixture was stirred at −45 °C for 1 h, followed by the addition of a solution of 1,3,2-dioxathiolane 2,2-dioxide (0.50 g, 2.77 mmol) in MeCN (10 mL). The mixture was stirred for 1 h at −45 °C, then allowed to warm to room temperature over 12 h. The reaction mixture was treated with 1M AcOH (6 mL) and stirred for 1 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a yellow oil. Purification by column chromatography eluting with petrol:Et_2O (4:1), gave the title compound as a pale yellow oil (155 mg, 31%).

Data in agreement with the literature[87,206]

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 4.60 (1H, s, OH), 3.60-3.40 (2H, m, 8-H), 3.00 (1H, td, *J* = 7.4, 4.4 Hz, 6-H), 2.21 (2H, dd, *J* = 6.5, 4.4 Hz, 4-H), 2.10-2.01 (2H, m, 7-H), 1.97-1.85 (2H, m, 2-H), 1.71-1.55 (4H, m, 3-H and 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 212.5 (C-1), 54.6 (C-8), 42.9 (C-6), 41.8 (C-2), 26.9 (C-5), 24.7 (C-7), 24.2 (C-3), 17.6 (C-4); LRMS (EI): 142 (100%, $[M-H]^{+\bullet}$); HRMS (EI) observed ($[M-H]^{+\bullet}$): 141.09174; $C_8H_{13}O_2$ requires 141.09109; υ_{max} (film/cm^{-1}) 3429 (O-H), 2943 (C-H), 1738 (C=O).

5-Hydroxypentan-2-one (145)



Procedure 1

1,3,2-Dioxathiolane 2,2-dioxide (1.00 g, 8.1 mmol) was added to a stirred solution of DMSO:acetone (4:1, 5 mL) followed by *N*,*N*-diethylethylenediamine (82 µL, 0.8 mmol), acetone (5.92 mL, 80.6 mmol), $Mg(ClO_4)_2$ (0.36 g, 1.61 mmol), and Et_3N (0.22 mL, 1.6 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as yellow oil. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as a colourless oil (290 mg, 29%).

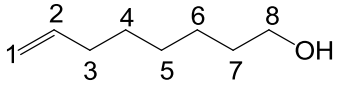
Procedure 2

1,3,2-Dioxathiolane 2,2-dioxide (1.00 g, 8.1 mmol) was added to a stirred solution of DMSO:acetone (4:1, 5 mL) followed by *n*-butylamine (80 µL, 0.8 mmol), acetone (5.92 mL, 80.6 mmol), $Mg(ClO_4)_2$ (0.36 g, 1.6 mmol), and Et_3N (0.22 mL, 1.6 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as yellow oil. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as a colourless oil (210 mg, 21%).

Data in agreement with the literature[207]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 3.51 (2H, t, *J* = 6.2 Hz, 5-H), 2.46 (2H, t, *J* = 6.9 Hz, 3-H), 2.12 (3H, s, 1-H), 1.79 (2H, tt, *J* = 6.9, 6.2 Hz, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 207.0 (C-2), 68.8 (C-5), 47.2 (C-3), 30.9 (C-1), 25.4 (C-4); LRMS (EI): 102 (100%, $[M]^{+\bullet}$); HRMS (EI) observed ($[M]^{+\bullet}$): 102.06770; $C_5H_{10}O_2$ requires 102.06808; υ_{max} (film/cm^{-1}) 3459 (O-H), 2971 (C-H), 1740 (C=O).

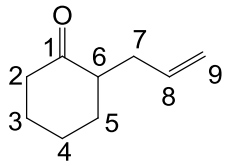
Oct-7-en-1-ol[208,209] (167).



BH_3.THF solution (1M, 71.50 mL, 65 mmol) was added drop-wise over 30 minutes to a stirred solution of octadiene (27 mL, 181 mmol). The solution was left to stir for 1 h at room temperature. A solution of 30% H_2O_2 (42.6 mL, 1810 mmol) in 1M NaOH (70 mL, 1810 mmol) was added drop-wise to the solution and left to stir for 12 h. The reaction mixture was quenched with water (50 mL) and then extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with saturated NaCl solution (60 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a colourless oil (9.8 g). Purification by column chromatography eluting with petrol:Et_2O (5:1) gave the title compound as a colourless oil (8.87 g, 33%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 5.77 (1H, ddt, *J* = 17.1, 10.2, 6.6 Hz, 2-H), 4.99 (1H, ddt, *J* = 17.1, 2.2, 1.2 Hz, 1-H_{trans}), 4.93 (1H, ddt, *J* = 10.2, 2.0, 1.1 Hz, 1-H_{cis}), 3.75 (2H, t, *J* = 7.0 Hz, 8-H), 3.45 (2H, apparent q, *J* = 7.0 Hz, 3-H), 2.17, (1H, s, O-H), 1.57 (2H, quint, *J* = 7.0 Hz, 7-H), 1.36-1.23 (6H, m, 3-H and 5-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 139.0 (C-2), 114.2 (C-1), 62.6 (C-8), 34.8 (C-3), 33.7 (C-7), 28.9 (C-4, C-5 and C-6); LRMS (CI): 129 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 129.12807; $C_8H_{17}O$ requires 129.12793; υ_{max} (film/cm^{-1}) 3400 (O-H), 1640 (C=C).

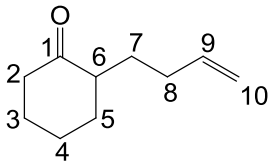
2-Allylcyclohexanone[156] (173)



2-Cyclohexylidene-1,1-dimethylhydrazine (**168**) (2.45 mL, 15.7 mmol) was dissolved in dry THF (20 mL) under argon at room temperature. The solution was then cooled to 0 °C, n-BuLi (12 mL, 19.2 mmol) was added over 20 min and the mixture was then stirred for 45 min at 0 °C. 1-Bromoprop-2-ene (1.72 mL, 19.5 mmol) was added to the mixture, and then the solution was warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with water (20 mL), stirred for 15 min, and then extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was treated with acetone (20 mL) and wet amberlyst®-15 (2.00 g) and stirred for 12 h at room temperature. Amberlyst®-15 was removed by filtration through Celite®, acetone (15 mL) was added to the reaction mixture. The organic solvent was removed under reduced pressure. The residue was partitioned and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product. Purification by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a brown oil (1.32 g, 60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 5.73 (1H, dddd, *J* = 17.9, 10.1, 3.7, 1.2 Hz, 8-H), 5.01-4.93 (2H, m, 9-H), 2.53-2.48 (1H, m, 6-H), 2.38-2.32 (2H, m, 7-H), 2.10-1.80 (8H, complex m, 2-H, 3-H, 4-H and 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 212.5 (C-1), 136.4 (C-8), 116.1 (C-9), 50.2 (C-6), 42.0 (C-2), 33.8 (C-4), 27.9 (C-3), 25.0 (C-5 and C-7); LRMS (EI): 138 (100%, $[M]^{+\bullet}$); HRMS (EI) observed ($[M]^{+\bullet}$): 138.10357; $C_9H_{14}O$ requires 138.10392; υ_{max} (film/cm^{-1}) 2930 (C-H), 1740 (C=O).

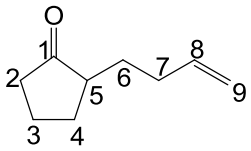
2-(But-3-en-1-yl)cyclohexanone[156] (174)



2-Cyclohexylidene-1,1-dimethylhydrazine (**168**) (2.20 mL, 15.7 mmol) was dissolved in dry THF (20 mL) under argon at room temperature. The flask was then cooled to 0 °C, ^{n}BuLi (12 mL, 19.2 mmol) was added over 20 min and the mixture was then stirred for 45 min at 0 °C. 4-Bromobut-1-ene (1.72 mL, 19.5 mmol) was then added to the mixture and the solution was warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with water (20 mL), stirred for 15 min, and then extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was treated with acetone (20 mL) and wet amberlsyt®-15 (2 g) and stirred for 12 h at room temperature. Amberlyst®-15 was removed by filtration through Celite® and the solution was washed with acetone (15 mL). The organic solvent was removed under reduced pressure. The residue was partitioned and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product. Purification by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a brown oil (1.3 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 5.80 (1H, ddt, *J* = 17.4, 10.4, 6.5 Hz, 9-H), 5.02-4.80 (2H, m, 10-H), 2.80-2.70 (1H, m, 6-H), 2.30-1.33 (12H, m, 2-H, 3-H, 4-H, 5-H, 7-H and 8-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 213.2 (C-1), 138.5 (C-9), 114.7 (C-10), 49.8 (C-6), 42.1 (C-2), 33.9 (C-5), 31.2 (C-8), 28.5 (C-7), 28.0 (C-3), 24.9 (C-4). LRMS (CI): 153 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 153.12831; $C_{10}H_{17}O$ requires 153.12794; υ_{max} (film/cm^{-1}) 2933 (C-H), 1710 (C=O), 1640 (C=C).

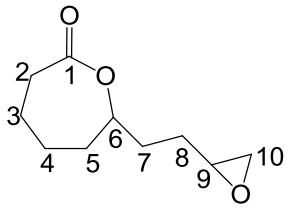
2-(But-3-enyl)cyclopentanone[210] (175)



2-Cyclopentylidene-1,1-dimethylhydrazine (**168**) (5 mL, 39 mmol) was dissolved in dry THF (35 mL) under argon at room temperature. The solution was then cooled to 0 °C, ^{n}BuLi (2.49 mL, 39 mmol) was added over 25 min and the mixture was then stirred for 45 min at 0 °C. 4-Bromobut-1-ene (4.75 mL, 47 mmol) was then added to the mixture and the solution was warmed to room temperature and stirred for 3 h. The reaction mixture was quenched with water (25 mL), stirred for 15 min, and then extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure and the residue was treated with acetone (20 mL) and wet amberlyst®-15 (1.5 g) and stirred for 12 h at room temperature. Amberlyst®-15 was removed by filtration through Celite® and the solution was washed with acetone (15 mL). The organic solvent was removed under reduced pressure. The residue was partitioned and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as a colourless oil (2.7 g, 54%).

^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} 5.76 (1H, ddt, *J* = 16.9, 10.4, 6.7 Hz, 8-H), 5.05-4.90 (2H, m, 9-H), 2.33-1.95 (7H, m, 2-H, 3-H, 4-H and 5-H), 1.92-1.65 (2H, m, 7-H), 1.65-1.22 (2H, m, 6-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 220.5 (C-1), 136.0 (C-8), 115.1 (C-9), 48.5 (C-5), 38.2 (C-2), 31.6 (C-7), 30.0 (C-4), 28.8 (C-6), 20.7 (C-3); υ_{max} (film/cm^{-1}) 2927 (C-H), 1740 (C=O), 1702 (C=C).

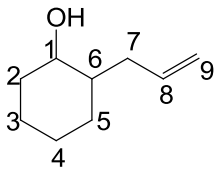
7-(2-(Oxiran-2-yl)ethyl)oxepan-2-one (176)



2-(But-3-enyl)cyclopentanone (**175**) (0.20 mL, 1.3 mmol) was dissolved in CH_2Cl_2 (10 mL) and stirred for 5 min at 0 °C. *m*-CPBA (0.24 g, 1.4 mmol) was added in several portions at 0 °C over 20 min and the reaction was allowed to warm up to room temperature, then stirred for 12 h at this temperature. The reaction mixture was quenched with saturated $Na_2S_2O_3$ (2 mL) and stirred for 1 h at room temperature. The mixture was extracted with EtOAc (3 × 15 mL) and washed with saturated $NaHCO_3$ solution (20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and then concentrated under reduced pressure to give the crude product. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as a colourless oil and as a mixture of diastereomers (58 mg, 29%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.25 (1H, dddd, *J* = 12.6, 10.1, 7.9, 4.1 Hz, 6-H), 2.87-2.81 (1H, m, 9-H), 2.66 (1H, dd, *J* = 9.6, 4.3 Hz, 10-H), 2.59-2.51 (2H, m, 2-H), 2.39 (1H, dd, *J* = 11.1, 4.3 Hz, 10-H), 1.88-1.81 (2H, m, 7-H), 1.80-1.73 (6H, m, 3-H, 4-H and 5-H), 1.71-1.65 (1H, m, 8-H), 1.64-1.59 (1H, m, 8-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_{ppm} 175.7 (C-1), 79.7 (C-6), 52.2 (C-9), 47.0 (C-10), 34.5 (C-2 and C-5), 33.2 (C-7), 32.4 (C-4), 28.7 (C-8), 23.0 (C-3); LRMS (EI): 183 (100%, $[M-H]^{+\bullet}$); HRMS (EI) observed ($[M-H]^{+\bullet}$): 183.10213; $C_{10}H_{15}O_3$ requires 183.10157; υ_{max} (film/cm^{-1}) 1750 (CO-O), 1230 (epoxide).

2-Allylcyclohexanol[163] (180)

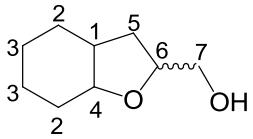


2-Allylcyclohexanone (**173**) (1.50 g, 11 mmol) was dissolved in a solution of MeOH/THF (1:1, 10 mL/10 mL) and cooled to 0 °C. $NaBH_4$ (0.45 g, 12 mmol) was added portion wise over 20 min, the resulting solution was stirred at 0 °C for 20 min and allowed to warm up to room temperature, then stirred for 12 h at room temperature. The reaction mixture was quenched with water (25 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered.

The solvent was removed under reduced pressure to obtain the product as a colourless oil in a quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} 5.89-5.77 (1H, m, 8-H), 5.07-4.99 (2H, m, 9-H), 3.91 (1H, s, OH), 3.28-3.24 (1H, m, 1-H), 2.45 (1H, dd, *J* = 13.7, 6.2 Hz, 7-H), 2.19 (1H, dt, *J* = 14.1, 13.7 Hz, 7-H), 2.08-1.94 (3H, complex m, 6-H and cyclohexyl), 1.83-1.25 (6H, complex m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 137.7 (C-8), 116.2 (C-9), 74.8 (C-1), 45.0 (C-6), 41.3 (C-2), 37.3 (C-7), 26.5 (C-3), 25.6 (C-5), 25.0 (C-4); LRMS (CI): 123 (100%, $[M\text{-}OH]^+$); HRMS (CI) observed ($[M\text{-}OH]^+$): 123.11616; C_9H_{15} requires 123.11683; υ_{max} (film/cm^{-1}) 3377 (O-H), 3000 (C-H), 1640 (C=C).

Octahydrobenzofuran-2-yl methanol (182)



Procedure 1

2-Allylcyclohexanol (**180**) (1.00 g, 7.2 mmol) was added to CH_2Cl_2 (20 mL) and cooled to 0 °C. *m*-CPBA (1.74 g, 10 mmol) was added portion wise over 20 min and the resulting solution was stirred at 0 °C for 2 h. The solution was allowed to warm up to room temperature, then stirred for 12 h at room temperature. The reaction mixture was cooled to 0 °C and quenched with aqueous Na_2SO_3 (20 mL) and saturated $NaHCO_3$ solution (20 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and filtered, then concentrated under reduced pressure to give the crude product as a colourless oil. Purification by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a colourless oil and as a mixture of diastereomers but was not isolated pure as there is an additional unidentified product (66:34) (850 mg, 85%).

Procedure 2

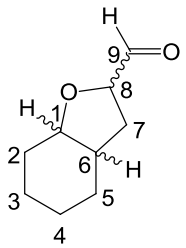
2-Allylcyclohexanol (**180**) (240 mg, 1.7 mmol) was dissolved in a 1:1 mixture of CH_2Cl_2 (5 mL) and 1M $NaHCO_3$ solutiin (5 mL). The resulting solution was cooled to 0 °C and *m*-CPBA (330 mg, 1.9 mmol) was added portion wise over 20 min, the resulting solution was stirred at 0 °C for 2 h and allowed to warm up to room temperature, then stirred for 12 h. The

reaction mixture was cooled to 0 °C and quenched with aqueous H_2O (20 mL) and extracted with Et_2O (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$ and then concentrated under reduced pressure to give the crude product as a mixture of diastereomers (66:34) (168 mg, 70%), which was compared to the product from procedure 1.

Data in agreement with the literature[162,163]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} (major diastereomer) 4.22 (1H, dddd, *J* = 11.7, 7.5, 5.1, 4.5 Hz, 6-H), 3.68 (1H, dd, *J* = 11.7, 3.9 Hz, 7-H), 3.64 (1H, dd, *J* = 4.5, 3.9 Hz, 7-H), 2.10-1.95 (1H, m, 4-H), 1.92-1.85 (1H, m, 1-H), 1.75 (2H, dd, *J* = 7.5, 4.2 Hz, 5-H), 1.70-1.35 (5H, m, 2-H and O-H), 1.34-1.12 (4H, m, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 78.0 (C-4), 77.9 (C-6), 66.0 (C-7), 38.2 (C-1), 34.2 (C-5), 28.2 (C-2), 27.7 (C-2), 24.1 (C-3), 20.6 (C-3); ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} (minor diastereomer) 4.14 (1H, dddd, *J* = 9.0, 6.8, 4.1, 3.0 Hz, 6-H), 3.93 (1H, dd, *J* = 9.0, 3.9 Hz, 7-H), 3.85-3.80 (1H, m, 7-H), 3.10-2.99 (1H, m, 4-H), 2.10-2.40 (1H, m, 1-H), 1.81-1.75 (2H, m, 5-H), 1.70-1.35 (4H, m, 2-H), 1.34-1.12 (4H, m, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 82.6 (C-4), 79.0 (C-6), 65.6 (C-7), 45.9 (C-1), 33.2 (C-5), 31.3 (C-2), 29.0 (C-2), 25.7 (C-3), 24.4 (C-3); LRMS (CI): 157 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 157.12241; $C_9H_{17}O_2$ requires 157.12285;. υ_{max} (film/cm^{-1}) 3412 (O-H), 2928 (C-H), 1055 (C-O).

Octahydrobenzofuran-2-carbaldehyde (183)



Procedure 1

DMSO (1.21 mL, 17.1 mmol) was added to dry CH_2Cl_2 (25 mL), followed by dropwise addition of oxalyl chloride (0.36 mL, 8.6 mmol) at -78 °C under argon. The mixture was stirred at −78 °C for 20 min. Octahydrobenzofuran-2-yl methanol (**182**) (1 g, 6.6 mmol) was added dropwise over 15 min, followed by 20 min stirring at -78 °C. Triethylamine (4.6 mL, 33 mmol) was added dropwise over 10 min at −78 °C. The mixture was allowed to warm to room temperature for 12 h. The reaction mixture was quenched with water (20 mL), stirred for 15 min, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were

washed with saturated NaCl solution (25 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to give the crude product as a mixture of diastereomers but was not isolated pure as there is an additional unidentified product (500 mg, 50%) (66:34).

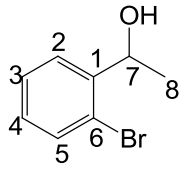
Procedure 2

Dry CH_2Cl_2 (25 mL) was added to activated molecular sieves (4 Å). Octahydrobenzofuran-2-yl methanol (**182**) (0.05 g, 0.3 mmol) was added to the mixture followed by pyridinium chlorochromate (0.17 g, 0.8 mmol) portion wise over 10 min. The mixture was stirred for 12 h at room temperature. The reaction mixture was diluted with Et_2O (10 mL) with vigorous stirring of the reaction mixture. The mixture was filtered through a pad of Celite® and washed with Et_2O (3 × 15 mL). The solvent was removed under reduced pressure to give the crude product. Purification by column chromatography eluting with petrol:Et_2O (4:1) gave the title compound as a colourless oil and a mixture of diastereomers but was not isolated pure as there is an additional unidentified product (15 mg, 30%) (66:34).

Data in agreement with the literature[163]

^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} (major diastereomer) 9.71 (1H, s, 9-H), 4.35 (1H, dd, *J* = 10.7, 8.8 Hz, 8-H), 3.21 (1H, dd, *J* = 10.7, 3.9 Hz, 1-H), 2.22-2.15 (2H, m, 7-H), 2.13-1.90 (4H, complex m, 6-H and cyclohexyl), 1.60-1.00 (5H, complex m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 204.0 (C-9), 94.9 (C-1), 91.9 (C-8), 46.8 (C-6), 34.3 (C-7 or C-2), 31.8 (C-7 or C-2), 29.6 (C-5), 27.8 (C-4), 24.4 (C-3). ^{1}H NMR (500 MHz, $CDCl_3$): δ_{ppm} (minor diastereomer) 9.68 (1H, s, 9-H), 4.42 (1H, d, *J* = 8.3 Hz, 8-H), 3.16 (1H, dd, *J* = 10.6, 3.9, Hz, 1-H), 2.00-1.70 (6H, complex m, 6-H, 7-H and cyclohexyl), 1.5-0.8 (5H, complex m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 202.0 (C-9), 85.0 (C-1), 81.6 (C-8), 45.5 (C-6), 32.3 (C-7 or C-2), 31.2 (C-7 or C-2), 29.2 (C-5), 26.8 (C-4), 24.3 (C-3); LRMS (EI): 154 (100 %, $[M]^{+\bullet}$); HRMS (EI) observed ($[M]^{+\bullet}$): 154.09812; $C_9H_{14}O_2$ requires 154.09883; υ_{max} (film/cm^{-1}) 2933 (C-H), 1715 (C=O), 1058 (C-O).

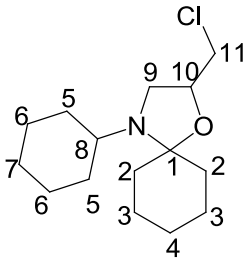
1-(2-Bromophenyl)ethanol[211] (187)



2-bromoacetophenone (5.00 g, 25 mmol) was dissolved in a solution of MeOH:THF (1:1, 10 mL) and cooled to 0 °C. $NaBH_4$ (1.04 g, 28 mmol) was added portion wise over 20 min and the resulting solution was stirred at 0 °C for 20 min and allowed to warm up to room temperature, then stirred for 12 h at room temperature. The reaction mixture was quenched with water (20 mL) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the product as a colourless oil in a quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$ δ_{ppm} 7.55 (1H, d, *J* = 7.8 Hz, 5-H), 7.49 (1H, d, *J* = 7.9 Hz, 4-H), 7.31 (1H, d, *J* = 7.6 Hz, 2-H), 7.11 (1H, *J* = 7.6 Hz, 3-H), 5.19 (1H, dq, *J* = 6.4, 3.2 Hz, 7-H), 2.78 (1H, d, *J* = 3.2 Hz, OH), 1.43 (3H, d, *J* = 6.4 Hz, 8-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 144.8 (C-1), 132.7 (C-5), 128.9 (C-4), 128.0 (C-3), 126.8 (C-2), 121.7 (C-6), 69.2 (C-7), 23.7 (C-8); LRMS (EI): 199 (100%, $[M]^{+\bullet}$); HRMS (EI) observed ($[M]^{+\bullet}$): 199.98362; C_8H_9OBr requires 199.98313; υ_{max} (film/cm^{-1}) 3331 (O-H), 740 (C-Br).

2-(Chloromethyl)-4-cyclohexyl-1-oxa-4-azaspiro[4.5]decane (193)



Procedure 1

N-Cyclohexylidenecyclohexanamine (**25**) (0.20 g, 1.1 mmol) was added to dry THF (7 mL). Ethylmagnesium bromide (0.17 mL, 3M solution in Et_2O) was added to the solution dropwise and heated at reflux. After 2 h, the solution was cooled to 0 °C; chloromethyloxirane (0.16 mL, 1.5 mmol) was added. The resulting colourless solution was stirred at 0 °C for 1 h, then for 12 h at room temperature. The reaction mixture was quenched with water (20 mL) and extracted with Et_2O (20 mL). The combined organic extracts were washed with saturated

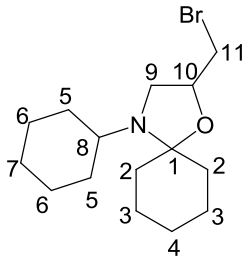
NaCl solution (25 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to give a colourless residue. The residue was stirred with petrol (20 mL) and lM acetic acid (25 mL) for 2 h at room temperature. NaCl was added to saturate the aqueous layer, the layers were separated, and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), saturated NaCl solution (20 mL), and were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a colourless oil (170 mg, 85%).

Procedure 2

Cyclohexylamine (0.23 mL, 2.0 mmol) was added to THF (4 mL), followed by cyclohexanone (0.21 mL, 2.0 mmol), $Mg(ClO_4)_2$ (0.46 g, 2.0 mmol), chloromethyloxirane (0.16 mL, 2.0 mmol) and Et_3N (0.28 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to obtain the crude product as a pale yellow oil. Purification by column chromatography eluting with petrol:EtOAc:MeOH (20:5:1) gave the title compound as a pale yellow oil (46 mg, 20%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.08 (1H, dddd, *J* = 12.7, 9.6, 7.7, 5.0 Hz, 10-H), 3.56 (1H, dd, *J* = 9.6, 7.1 Hz, 11-H), 3.30 (1H, dd, *J* = 12.7, 7.1 Hz, 11-H), 3.22 (1H, dd, *J* = 7.7, 6.8 Hz, 9-H), 2.95 (1H, dd, *J* = 6.8, 5.0 Hz, 9-H), 2.56-2.50 (1H, m, 8-H), 1.77-1.72 (5H, m, cyclohexyl), 1.64-1.55 (7H, m, cyclohexyl), 1.49-1.44 (2H, m, cyclohexyl), 1.35-1.20 (6H, m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 96.8 (C-1), 74.7 (C-10), 54.3 (C-8), 47.9 (C-9), 36.8 (C-11), 33.8 (C-5), 33.7 (C-5), 32.7 (2 × C-2), 26.4 (C-4 or C-7), 26.1 (C-4 or C-7), 25.6 (2 × C-6), 23.7 (C-3), 23.6 (C-3); LRMS (CI): 272 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 272.17844; $C_{15}H_{27}ONCl$ requires 272.17812; υ_{max} (film/cm^{-1}) 2930 (C-H), 1092 (C-O).

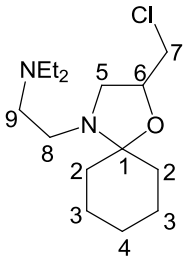
2-(Bromomethyl)-4-cyclohexyl-1-oxa-4-azaspiro[4.5]decane (194)



N-Cyclohexylidenecyclohexanamine (**25**) (0.20 g, 1.1 mmol) was added to dry THF (7 mL). Ethylmagnesium bromide (0.17 ml, 3M solution in Et_2O) was added to the solution dropwise and heated at reflux. After 2 h, the solution was cooled to 0 °C; bromomethyloxirane (0.13 mL, 1.5 mmol) was added. The resulting colourless solution was stirred at 0 °C for 1 h, then for 12 h at room temperature. The reaction mixture was quenched with water (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (25 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to give a colourless residue. The residue was stirred with petrol (20 mL) and lM acetic acid (25 mL) for 2 h at room temperature. NaCl was added to saturate the aqueous layer, the layers were separated, and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by column chromatography eluting with petrol:Et_2O (2:1) gave the title compound as a colourless oil (178 mg, 89%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.12 (1H, dddd, *J* = 10.4, 9.5, 8.4, 7.1 Hz, 10-H), 3.43 (1H, dd, *J* = 9.5, 6.5 Hz, 11-H), 3.30 (1H, dd, *J* = 10.4, 6.5 Hz, 11-H), 3.25 (1H, dd, *J* = 8.4, 6.2 Hz, 9-H), 2.94 (1H, dd, *J* = 7.1, 6.2 Hz, 9-H), 2.54-2.52 (1H, m, 8-H), 1.80-1.63 (5H, m, cyclohexyl), 1.61-1.48 (7H, m, cyclohexyl), 1.46-1.42 (2H, m, cyclohexyl), 1.28-1.22 (6H, m, cyclohexyl); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 97.1 (C-1), 74.8 (C-10), 54.3 (C-8), 48.7 (C-9), 37.6 (C-11), 35.56 (C-5), 35.07 (C-2), 33.9 (C-4 and C-7), 33.7 (C-6), 32.8 (C-3); LRMS (ES^+): 316 (^{79}Br, 100%, $[M]^+$); HRMS (ES^+) observed (^{79}Br, $[M]^+$): 316.1276; $C_{15}H_{27}NO^{79}Br$ requires 316.1272; υ_{max} (film/cm^{-1}) 2970 (C-H), 1092 (C-O).

2-(2-(Chloromethyl)-1-oxa-4-azaspiro[4.5]decan-4-yl)-N,N-diethylethanamine (205)



Procedure 1

N,*N*-Diethylethylenediamine (0.25 mL, 1.8 mmol) was added to MeCN (4 mL), followed by cyclohexanone (0.19 mL, 1.8 mmol), $Mg(ClO_4)_2$ (0.4 g, 1.8 mmol), chloromethyloxirane (0.14 mL, 1.8 mmol) and Et_3N (0.25 mL, 1.8 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to obtain the crude product as a pale yellow oil. Purification by column chromatography eluting with petrol:EtOAc:MeOH (20:5:1) gave the title compound as a pale yellow oil (89 mg, 47%).

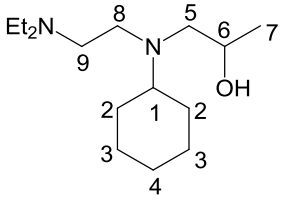
Procedure 2

N,*N*-Diethylethylenediamine (0.25 mL, 1.8 mmol) was added to MeCN (4 mL), followed by cyclohexanone (0.19 mL, 1.8 mmol), $Mg(ClO_4)_2$ (0.4 g, 1.8 mmol), chloromethyloxirane (0.14 mL, 1.8 mmol) and Et_3N (0.25 mL, 1.8 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure to obtain the crude product as a pale yellow oil. Purification by column chromatography eluting with petrol:EtOAc:MeOH (20:5:1) gave the title compound as a pale yellow oil (95 mg, 50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.20 (1H, dddd, *J* = 11.4, 9.8, 8.2, 4.9 Hz, 6-H), 3.57 (1H, dd, *J* = 9.8, 7.2 Hz, 7-H), 3.44 (1H, dd, *J* = 11.4, 7.2 Hz, 7-H), 3.07 (1H, dd, *J* = 8.2, 5.9 Hz, 5-H), 2.95 (1H, dd, *J* = 5.9, 4.9 Hz, 5-H), 2.64-2.51 (8H, m, 8-H, 9-H and 2 × CH_2CH_3), 1.65-1.50 (7H, m, cyclohexyl), 1.46-1.42 (2H, m, cyclohexyl), 1.36-1.29 (1H, m, cyclohexyl), 1.03 (1H, t, *J* = 7.2 Hz, 2 × CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 96.9

(C-1), 74.7 (C-6), 53.4 (C-5), 52.8 (C-9), 47.6 (*CH*$_2$CH$_3$), 47.2 (C-8), 46.2 (C-7), 34.3 (C-2), 31.7 (C-2), 25.7 (C-4), 23.4 (C-3), 23.3 (C-3), 11.8 (CH$_2$*CH*$_3$); LRMS (CI): 289 (100%, [M+H]$^+$); HRMS (CI) observed ([M+H]$^+$): 289.20410; $C_{15}H_{30}ON_2Cl$ requires 289.20467; υ_{max} (film/cm^{-1}) 2970 (C-H), 1091 (C-O).

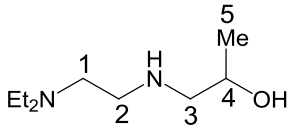
1-(Cyclohexyl(2-(diethylamino)ethyl)amino)propan-2-ol (207)



N,*N*-Diethylethylenediamine (0.29 mL, 2.0 mmol) was added to THF (4 mL), followed by cyclohexanone (0.21 mL, 2.0 mmol), Mg(ClO$_4$)$_2$ (0.46 g, 2.0 mmol), 2-methyloxirane (0.13 mL, 2.0 mmol) and Et$_3$N (0.28 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et$_2$O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over MgSO$_4$ and filtered. The solvent was removed under reduced pressure and MeOH:THF (1:1, 6 mL) was added followed by NaBH$_4$ (0.13 g, 4.1 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et$_2$O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over MgSO$_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a pale yellow oil (105 mg, 50%).

^{1}H NMR (600 MHz, CDCl$_3$): δ_{ppm} 4.08 (1H, s, OH), 3.70-3.64 (1H, m, 6-H), 2.76-2.67 (4H, m, 2 × *CH*$_2$CH$_3$), 2.65 (1H, d, *J* = 5.9 Hz, 5-H), 2.61 (2H, dt, *J* = 6.9, 5.1 Hz, 9-H), 2.59-2.54 (1H, partly unresolved, m, 8-H), 2.57 (4H, t, *J* = 7.1 Hz, 2 × CH$_2$*CH*$_3$), 2.53-2.51 (1H, partly unresolved, m, 8-H), 2.39-2.33 (1H, m, cyclohexyl), 2.18 (1H, d, *J* = 9.3 Hz, 5-H), 1.79-1.72 (3H, m, cyclohexyl), 1.67-1.64 (1H, m, cyclohexyl), 1.60-1.52 (2H, m, cyclohexyl), 1.24-1.12 (3H, m, cyclohexyl), 1.08 (6H, t, *J* = 7.1 Hz, 2 × CH$_2$*CH*$_3$), 1.05 (3H, d, *J* = 6.5 Hz, 7-H); ^{13}C NMR (125 MHz, CDCl$_3$): δ_{ppm} 66.5 (C-6), 61.8 (C-1), 58.2 (C-5), 52.5 (C-9), 47.9 (C-8), 46.5 (2 × *CH*$_2$CH$_3$), 29.6 (C-2), 28.7 (C-3), 26.3 (C-4), 20.3 (C-7), 10.3 (2 × CH$_2$*CH*$_3$); LRMS (ES$^+$): 257 (100%, [M]$^+$); HRMS (ES$^+$) observed ([M]$^+$): 257.2603; $C_{15}H_{33}N_2O$ requires 257.2593; υ_{max} (film/cm^{-1}) 3456 (O-H), 2929 (C-H).

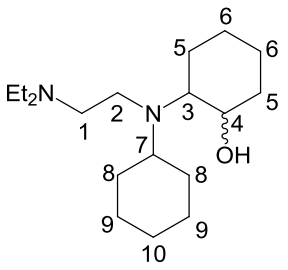
1-((2-(Diethylamino)ethyl)amino)propan-2-ol (208)



N,*N*-Diethylethylenediamine (0.29 mL, 2.0 mmol) was added to THF (4 mL), followed by cyclohexanone (0.21 mL, 2.0 mmol), $Mg(ClO_4)_2$ (0.46 g, 2.0 mmol), 2-methyloxirane (0.13 mL, 2.0 mmol) and Et_3N (0.28 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried ($MgSO_4$) and filtered. The solvent was removed under reduced pressure and MeOH:THF (1:1, 6 mL) was added followed by $NaBH_4$ (0.13 g, 4.1 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried ($MgSO_4$) and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil (78 mg, 37%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.27 (2H, s, OH and NH), 3.85 (1H, dqt, *J* = 10.9, 9.5, 6.3 Hz, 4-H), 2.83-2.79 (1H, m, 2-H), 2.73-2.69 (2H, m, 1-H), 2.61 (2H, t, *J* = 6.3 Hz, 3-H), 2.57 (4H, q, *J* = 7.1 Hz, 2 × CH_2CH_3), 2.48 (1H, dd, *J* = 10.9, 7.9 Hz, 2-H), 1.13 (3H, d, *J* = 6.3 Hz, 5-H), 1.03 (6H, t, *J* = 7.1 Hz, 2 × CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 65.0 (C-4), 56.5 (C-3), 51.9 (C-2), 46.9 (2 × CH_2CH_3), 46.4 (C-1), 20.7 (C-5), 11.4 (2 × CH_2CH_3); LRMS (CI): 175 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 175.18040; $C_9H_{23}ON_2$ requires 175.18104; υ_{max} (film/cm^{-1}) 3456 (O-H), 2971 (C-H).

2-(Cyclohexyl(2-(diethylamino)ethyl)amino)cyclohexanol (211)

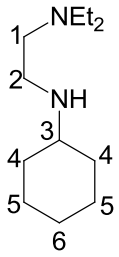


N,*N*-Diethylethylenediamine (0.72 mL, 5.1 mmol) was added to THF (5 mL), followed by cyclohexanone (0.53 mL, 5.1 mmol), $Mg(ClO_4)_2$ (1.14 g, 5.1 mmol), cyclohexene oxide (0.52

mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol). The mixture was stirred for 12 h at room temperature. MeOH:THF (1:1, 8 mL) was added followed by $NaBH_4$ (0.26 g, 8.2 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried ($MgSO_4$) and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil and as a mixture of diastereomers (2:1) (254 mg, 48%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.06 (0.5H, td, *J* = 10.3, 4.3 Hz, 4-H), 3.45 (0.5H, td, *J* = 14.8, 4.3 Hz, 4-H), 2.57-2.43 (8H, m, 1-H, 2-H and 2 × CH_2CH_3), 2.53 (0.5H, dd, *J* = 10.3, 7.2 Hz, 3-H), 2.45 (0.5H, dd, *J* = 14.8, 7.2 Hz, 3-H), 1.95-1.85 (1H, m, 7-H), 1.80-1.51 (8H, m, cyclohexyl), 1.36-1.17 (10H, m, cyclohexyl), 1.07 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 0.97 (3H, t, *J* = 7.1 Hz, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 69.2 (C-5), 69.1 (C-5), 54.3 (C-4), 54.2 (C-4), 51.8 (C-2), 51.0 (C-2), 48.3 (C-8), 48.3 (C-8), 47.5 (C-3), 47.5 (C-3), 46.39 (CH_2CH_3), 46.38 (CH_2CH_3), 28.5 (C-9), 28.4 (C-9), 25.5 (C-6), 24.4 (C-10), 23.3 (C-7), 22.8 (C-7), 20.0 (C-7), 19.9 (C-7), 11.9 (CH_2CH_3), 11.8 (CH_2CH_3); LRMS (CI): 279 (100%, $[M\text{-}OH]^+$); HRMS (CI) observed ($[M\text{-}OH]^+$): 279.27992; $C_{18}H_{35}N_2$ requires 279.28002; υ_{max} (film/cm^{-1}) 3460 (O-H), 2924 (C-H).

N^1-Cyclohexyl-N^2,N^2-diethylethane-1,2-diamine (213)



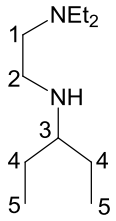
N,*N*-Diethylethylenediamine (0.72 mL, 5.1 mmol) was added to THF (5 mL), followed by cyclohexanone (0.53 mL, 5.1 mmol), $Mg(ClO_4)_2$ (1.14 g, 5.1 mmol), 2-phenyloxirane (0.58 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol). The mixture was stirred for 12 h at room temperature. MeOH:THF (1:1, 8 mL) was added followed by $NaBH_4$ (0.26 g, 8.2 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered.

Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil (366 mg, 69%).

Data in agreement with the literature

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.50 (1H, s, NH), 2.92-2.89 (1H, m, 3-H), 2.72 (2H, t, *J* = 6.1 Hz, 2-H), 2.60-2.44 (2H, m, 1-H), 2.54 (2H, dq, *J* = 13.3, 7.1 Hz, CH_2CH_3), 2.47 (2H, dq, *J* = 13.2, 7.1 Hz, CH_2CH_3), 2.01-1.80 (3H, m, cyclohexyl), 1.73-1.61 (2H, m, cyclohexyl), 1.58-1.56 (2H, m, cyclohexyl), 1.46-1.43 (2H, m, cyclohexyl), 1.26-1.22 (1H, m, cyclohexyl), 0.99 (6H, t, *J* = 7.1 Hz, 2 × CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 62.8 (C-3), 48.9 (C-1), 48.4 (C-2), 46.4 (2 × CH_2CH_3), 28.7 (2 × C-4), 28.6 (2 × C-5), 25.4 (C-6), 11.9 (2 × CH_2CH_3); LRMS (CI): 199 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 199.21783; $C_{12}H_{27}N_2$ requires 199.21742; υ_{max} (film/cm^{-1}) 3160 (N-H), 2933 (C-H).

N^1,N^1-Diethyl-N^2-(pentan-3-yl)ethane-1,2-diamine (215)

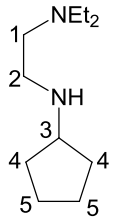


N,*N*-Diethylethylenediamine (0.72 mL, 5.1 mmol) was added to THF (5 mL), followed by pentan-3-one (0.54 mL, 5.1 mmol), $Mg(ClO_4)_2$ (1.14 g, 5.1 mmol), 2-methyloxirane (0.28 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol). The mixture was stirred for 12 h at room temperature. MeOH:THF (1:1, 8 mL) was added followed by $NaBH_4$ (0.26 g, 8.2 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil (351 mg, 65%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.80 (1H, s, NH), 3.00 (1H, dt, *J* = 8.5, 5.7 Hz, 3-H), 2.66 (2H, t, *J* = 7.8 Hz, 1-H), 2.60 (2H, dq, *J* = 11.4, 7.2 Hz, CH_2CH_3), 2.49 (2H, dq, *J* = 11.4, 7.2 Hz, CH_2CH_3), 2.46-2.43 (2H, m, 2-H), 1.56-1.52 (2H, m, 4-H), 1.45-1.40 (2H, m, 4-H), 1.01 (6H, t, *J* = 7.2 Hz, CH_2CH_3), 0.97-0.93 (6H, m, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 68.0 (C-3), 49.8 (C-1), 49.3 (C-2), 46.3 (2 × CH_2CH_3), 22.9 (C-4), 22.3 (C-4), 11.7 (2 × CH_2CH_3),

11.5 (C-5), 11.3 (C-5); LRMS (CI): 187 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 187.21705; $C_{11}H_{27}N_2$ requires 187.21742; υ_{max} (film/cm^{-1}) 3155 (N-H), 2970 (C-H).

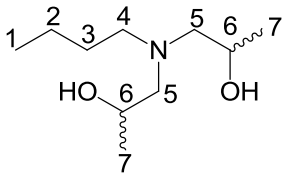
N^1-Cyclopentyl-N^2,N^2-diethylethane-1,2-diamine (216)



N,*N*-Diethylethylenediamine (0.72 mL, 5.1 mmol) was added to THF (5 mL), followed by cyclopentanone (0.45 mL, 5.1 mmol), $Mg(ClO_4)_2$ (1.14 g, 5.1 mmol), 2-methyloxirane (0.28 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol). The mixture was stirred for 12 h at room temperature. MeOH:THF (1:1, 8 mL) was added followed by $NaBH_4$ (0.26 g, 8.2 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil (284 mg, 63%).

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 4.38 (1H, s, NH), 3.25 (1H, dt, *J* = 8.3, 7.1, 3-H), 2.76 (2H, t, *J* = 7.8 Hz, 2-H), 2.65 (2H, dq, *J* = 11.4, 7.4 Hz, CH_2CH_3), 2.58 (2H, dq, *J* = 11.4, 7.4 Hz, CH_2CH_3), 2.50-2.45 (2H, m, 1-H), 1.70-1.54 (8H, m, 4-H and 5-H), 1.01 (6H, t, *J* = 7.4 Hz, 2 × CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 65.1 (C-3), 50.4 (C-2), 49.0 (C-1), 46.5 (2 × CH_2CH_3), 29.4 (C-4), 29.3 (C-4), 24.4 (C-5), 24.2 (C-5), 11.90 (2 × CH_2CH_3); LRMS (CI): 185 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 185.20164; $C_{11}H_{25}N_2$ requires 185.20177; υ_{max} (film/cm^{-1}) 3155 (N-H), 2920 (C-H).

1,1'-(Butylazanediyl)bis(propan-2-ol) (219)

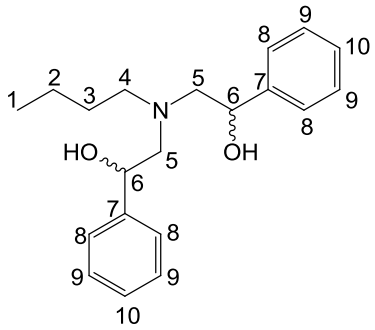


Butylamine (0.20 mL, 2.0 mmol) was added to THF (4 mL), followed by acetone (0.15 mL, 2.0 mmol), $Mg(ClO_4)_2$ (0.46 g, 2.0 mmol), 2-methyloxirane (0.13 mL, 2.0 mmol) and Et_3N (0.28 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and MeOH:THF (1:1, 6 mL) was added followed by $NaBH_4$ (0.13 g, 4.1 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil and as a mixture of diastereomers (51 mg, 50%).

OH peaks not seen

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 3.82-3.74 (4H, m, 6-H), 2.53-2.47 (8H, m, 5-H), 2.38-2.32 (4H, m, 4-H), 1.44-1.37 (4H, m, 3-H), 1.28-1.21 (4H, m, 2-H), 1.10-1.01 (12H, m, 7-H), 0.94-0.90 (6H, m, 1-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ_{ppm} 65.4 (C-6), 64.0 (C-6), 63.9 (C-5), 62.6 (C-5), 55.6 (C-4), 55.1 (C-4), 29.3 (C-3), 29.2 (C-3), 20.6 (C-7), 20.3 (C-2), 14.1 (C-1); LRMS (CI): 190 (100 %, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 190.18030; $C_{10}H_{24}O_2N$ requires 190.18070; υ_{max} (film/cm^{-1}) 3360 (O-H), 2961 (C-H).

2,2'-(Butylazanediyl)bis(1-phenylethanol) (220)



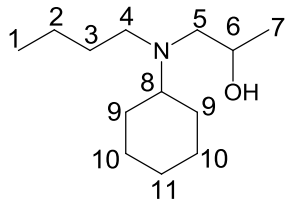
Butylamine (0.20 mL, 2.0 mmol) was added to THF (4 mL), followed by acetone (0.15 mL, 2.0 mmol), $Mg(ClO_4)_2$ (0.46 g, 2.0 mmol), 2-phenyloxirane (0.25 mL, 2.0 mmol) and Et_3N

(0.28 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and MeOH:THF (1:1, 6 mL) was added followed by $NaBH_4$ (0.13 g, 4.1 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil as a mixture of diastereomers (102 mg, 51%).

OH peaks not seen

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 7.36-7.32 (4H, m, 8-H), 7.30-7.25 (6H, m, 9-H and 10-H), 3.76 (2H, dd, *J* = 8.6, 4.6 Hz, 6-H), 3.70 (2H, dd, *J* = 10.8, 4.6 Hz, 5-H), 3.53 (2H, dd, *J* = 10.8, 8.6 Hz, 5-H), 2.56-2.50 (1H, m, 4-H), 2.48-2.43 (1H, m, 4-H), 1.49-1.41 (2H, m, 3-H), 1.35-1.27 (2H, m, 2-H), 0.87 (3H, t, *J* = 7.3 Hz, 1-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 141.0 (C-7), 128.7 (C-8), 127.6 (C-10), 127.3 (C-9), 66.7 (C-6), 64.7 (C-5), 47.2 (C-4), 32.4 (C-3), 20.5 (C-2), 14.1 (C-1); LRMS (CI): 314 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 314.21246; $C_{20}H_{28}O_2N$ requires 314.21200; υ_{max} (film/cm^{-1}) 3285 (O-H), 2928 (C-H), 1739 (C=C).

1-(Butyl(cyclohexyl)amino)propan-2-ol (221)

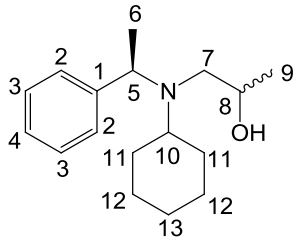


Butylamine (0.20 mL, 2.0 mmol) was added to THF (4 mL), followed by cyclohexanone (0.21 mL, 2.0 mmol), $Mg(ClO_4)_2$ (0.46 g, 2.0 mmol), propylene oxide (0.13 mL, 2.0 mmol) and Et_3N (0.28 mL, 2.0 mmol). The mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure and MeOH:THF (1:1, 6 mL) was added followed by $NaBH_4$ (0.13 g, 4.1 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil (90 mg, 43%).

OH peaks not seen

^{1}H NMR (400 MHz, $CDCl_3$): δ_{ppm} 3.65 (1H, dqd, *J* = 12.4, 9.4, 6.2 Hz, 6-H), 2.48 (1H, d, *J* = 9.4 Hz, 5-H), 2.44 (1H, partly unresolved, d, *J* = 12.4 Hz, 5-H), 2.44-2.40 (2H, m, 4-H), 2.20-2.15 (1H, m, 8-H), 1.85-1.61 (6H, m, cyclohexyl), 1.40-1.13 (8H, m, 2-H, 3-H and cyclohexyl), 1.10 (3H, d, *J* = 6.2 Hz, 7-H), 0.90 (3H, t, *J* = 7.4 Hz, 1-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ_{ppm} 63.0 (C-8), 60.0 (C-6), 58.3 (C-5), 50.6 (C-4), 31.7 (C-3), 31.5 (C-9), 26.9 (C-11), 26.4 (C-10), 26.2 (C-10), 20.6 (C-7), 19.9 (C-2), 14.2 (C-1); LRMS (CI): 214 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 214.21684; $C_{13}H_{28}ON$ requires 214.21709; υ_{max} (film/cm^{-1}) 3458 (O-H), 2928 (C-H).

1-(Cyclohexyl((*R*)-1-phenylethyl)amino)propan-2-ol (222)



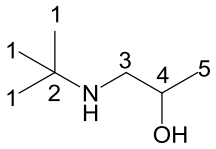
(*R*)-1-Phenylethanamine (0.65 mL, 5.1 mmol) was added to THF (5 mL), followed by cyclohexanone (0.54 mL, 5.1 mmol), $Mg(ClO_4)_2$ (1.14 g, 5.1 mmol), 2-methyloxirane (0.28 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol). The mixture was stirred for 12 h at room temperature. MeOH:THF (1:1, 8 mL) was added followed by $NaBH_4$ (0.26 g, 8.2 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil and as a mixture of diastereomers (1:1) (265 mg, 49%).

OH peak missing

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 7.34 (3H, m, 2-H and 4-H), 7.28-7.20 (2H, m, 3-H), 3.96 (0.5H, partly unresolved, q, *J* = 6.9 Hz, 5-H), 3.98-3.94 (0.5H, m, 5-H), 3.68-3.65 (1H, m, 8-H), 2.47 (1H, dd, *J* = 10.2, 4.8 Hz, 7-H), 2.35 (1H, dd, *J* = 10.1, 4.8 Hz, 7-H), 2.28-2.23 (1H, m, 10-H), 1.45-1.31 (10H, m, cyclohexyl), 1.03 (3H, d, *J* = 6.3 Hz, 9-H), 0.9 (3H, d, *J* = 6.9 Hz, 6-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 143.2 (C-1), 142.6 (C-1), 128.5 (C-2), 128.44

(C-2) 128.36 (C-3), 128.3 (C-3), 128.0 (C-4), 127.9 (C-4), 64.6 (C-5), 64.3 (C-5), 60.3 (C-7), 60.2 (C-8), 60.0 (C-8), 59.7 (C-7), 54.5 (C-10), 53.7 (C-10), 34.5 (C-11), 33.0 (C-11), 26.2 (C-13), 25.3 (C-13), 25.0 (C-12), 24.9 (C-12), 26.2 (C-6), 24.9 (C-6), 20.5 (C-9), 20.4 (C-9); LRMS (CI): 262 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 261.20890; $C_{17}H_{28}NO$ requires 261.20926; υ_{max} (film/cm^{-1}) 3425 (O-H), 2931 (C-H).

1-(^{t}Butylamino)propan-2-ol (224)



2-Methylpropan-2-amine (0.54 mL, 5.1 mmol) was added to THF (5 mL), followed by cyclohexanone (0.54 mL, 5.1 mmol), $Mg(ClO_4)_2$ (1.14 g, 5.1 mmol), 2-methyloxirane (0.28 mL, 5.1 mmol) and Et_3N (0.71 mL, 5.1 mmol). The mixture was stirred for 12 h at room temperature. MeOH:THF (1:1, 8 mL) was added followed by $NaBH_4$ (0.26 g, 8.2 mmol). The mixture was stirred for 1.5 h at room temperature. The reaction mixture was quenched with water (10 mL) and then extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with saturated NaCl solution (15 mL), dried over $MgSO_4$ and filtered. Purification by column chromatography eluting with petrol:EtOAc:MeOH (4:2:1) gave the title compound as a colourless oil (281 mg, 52%).

OH peak missing

^{1}H NMR (600 MHz, $CDCl_3$): δ_{ppm} 5.54 (1H, s, NH), 4.10 (1H, tq, *J* = 11.9, 6.3 Hz, 4-H), 3.06 (1H, dd, *J* = 11.9, 5.9 Hz, 3-H), 2.85 (1H, d, *J* = 6.3 Hz, 3-H), 1.38 (9H, s, 1-H), 1.26 (3H, d, *J* = 6.4 Hz, 5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_{ppm} 64.2 (C-4), 60.6 (C-2), 58.3 (C-3), 26.0 (C-1), 20.9 (C-5); LRMS (CI): 132 (100%, $[M+H]^+$); HRMS (CI) observed ($[M+H]^+$): 132.13864; $C_7H_{18}NO$ requires 132.13884; υ_{max} (film/cm^{-1}) 3395 (O-H), 3295 (N-H), 2971 (C-H).

Chapter 5 – References

5.1 References

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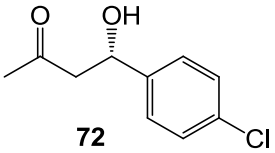
Appendix: HPLC data

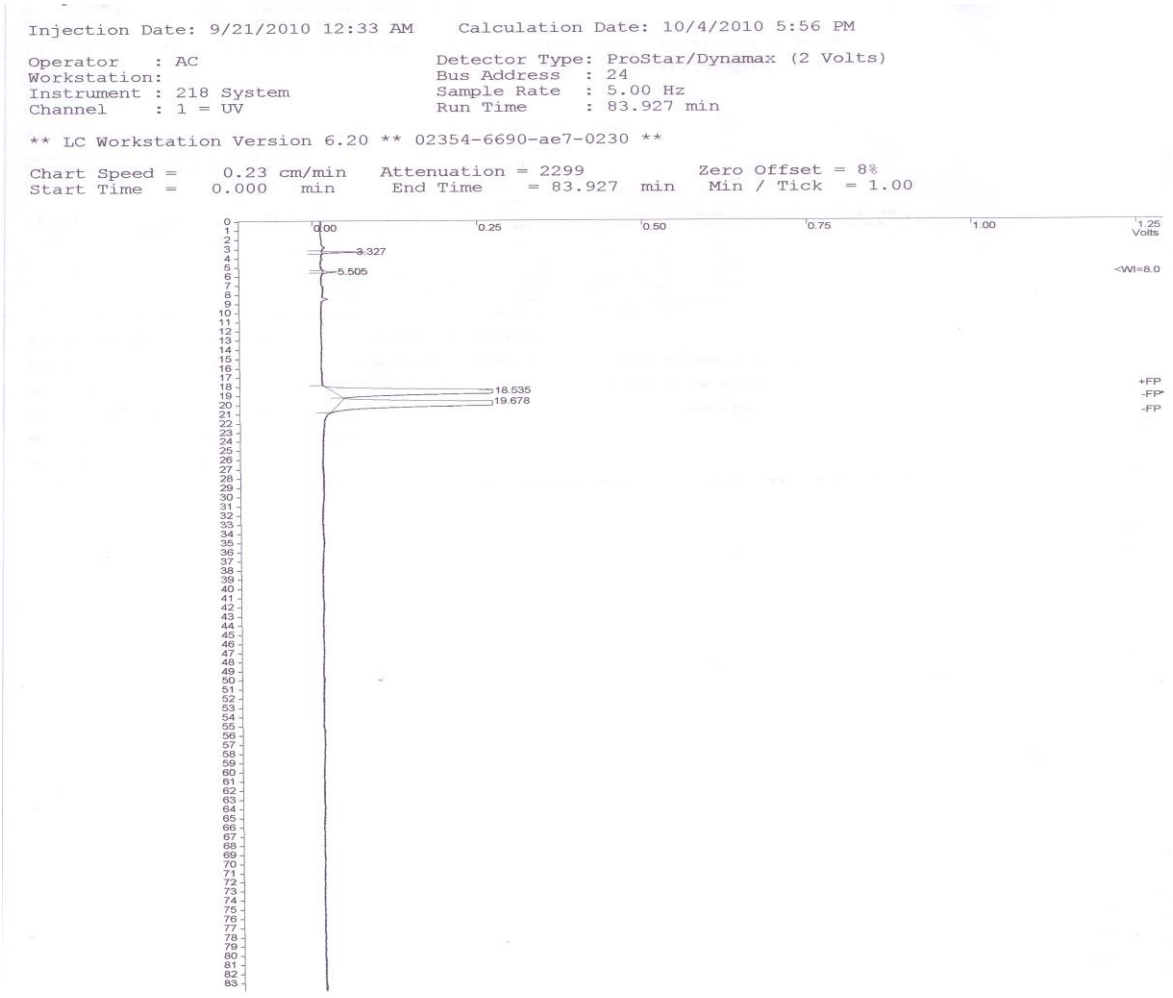
HPLC data for 4-(4-chlorophenyl)-4-hydroxybutan-2-one (72) using different chiral amines



72

Racemic compound of **72**

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 18.5 min (*R*), t_R = 19.7 min (*S*).



Appendix

Method File : wtc5alkynedibenz 0012-1.mth
Sample ID : Manual Sample

Injection Date: 9/21/2010 12:33 AM Calculation Date: 10/4/2010 5:56 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 83.927 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.9882	3.327	0.000	419953	BB	5.6	
2		0.7573	5.505	0.000	159964	BB	7.8	
3		47.9764	18.535	0.000	10133731	BB	40.8	
4		49.2780	19.678	0.000	10408656	BB	40.7	
	Totals:	99.9999		0.000	21122304			

Total Unidentified Counts : 21122304 counts

Detected Peaks: 4 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 12595 microVolts LSB: 1 microVolts

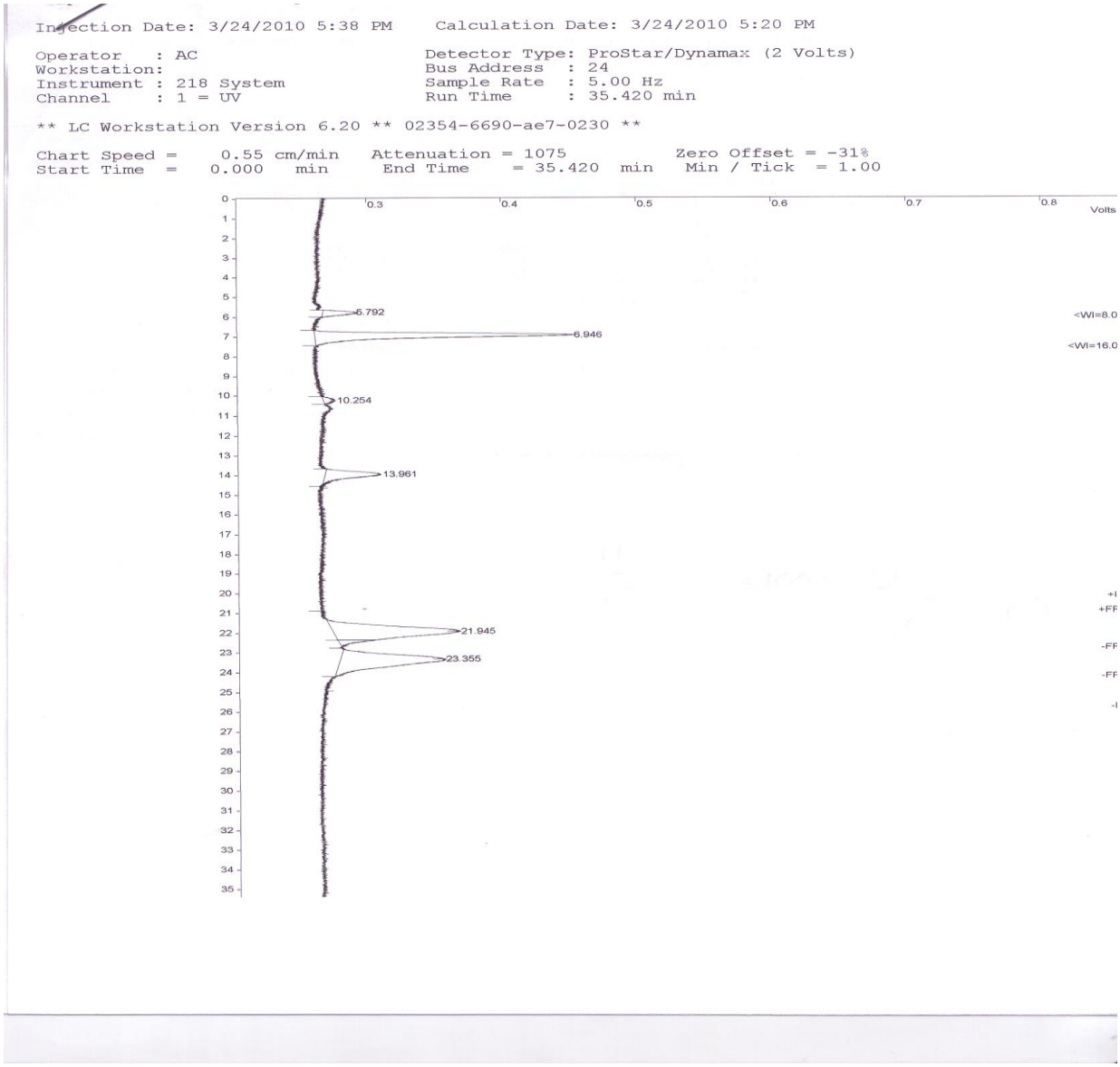
Noise (used): 2666 microVolts - monitored before this run

Manual injection

****

(*R*)-1-Phenylethanamine (**62**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 21.9 min (*R* major), t_R = 23.4 min (*S* minor).



Appendix

File : 03-24-20105;38;28 pm-1.mth
le ID : Manual Sample

njection Date: 3/24/2010 5:38 PM Calculation Date: 3/24/2010 5:20 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 35.420 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		2.9172	5.792	0.000	309682	BB	12.4	
2		28.0602	6.946	0.000	2978746	BB	13.7	
3		1.0840	10.254	0.000	115075	BB	15.5	
4		8.2960	13.961	0.000	880666	BB	19.6	
5		32.1069	21.945	0.000	3408322	BB	36.8	
6		27.5356	23.355	0.000	2923050	BB	34.4	
	Totals:	99.9999		0.000	10615541			

Total Unidentified Counts : 10615540 counts

Detected Peaks: 6 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 267389 microVolts LSB: 1 microVolts

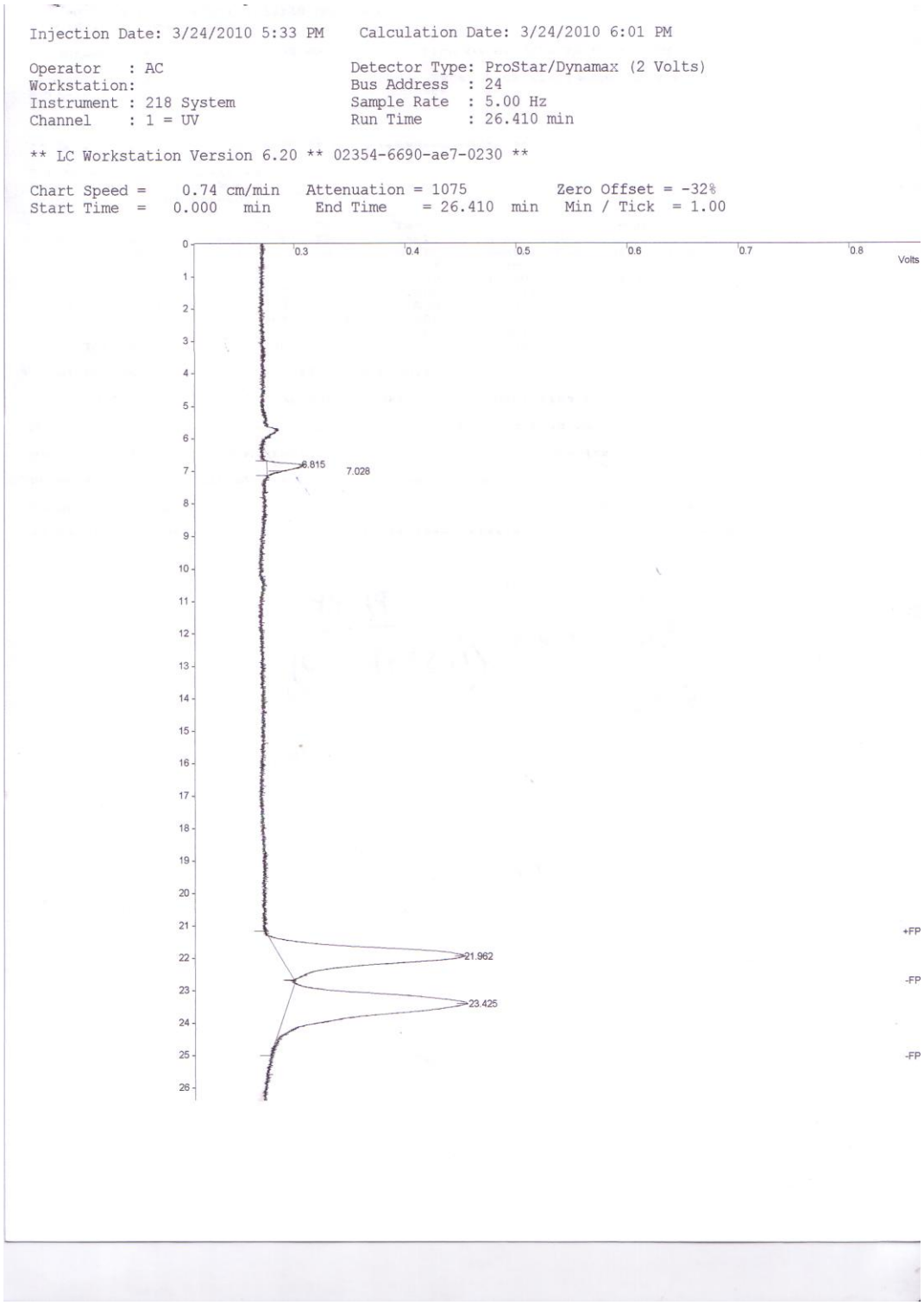
Noise (used): 4865 microVolts - monitored before this run

Manual injection

****

9-Amino(9-deoxy)epihydroquinine (**96**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 22.0 min (*R* minor), t_R = 23.4 min (*S* major).



Appendix

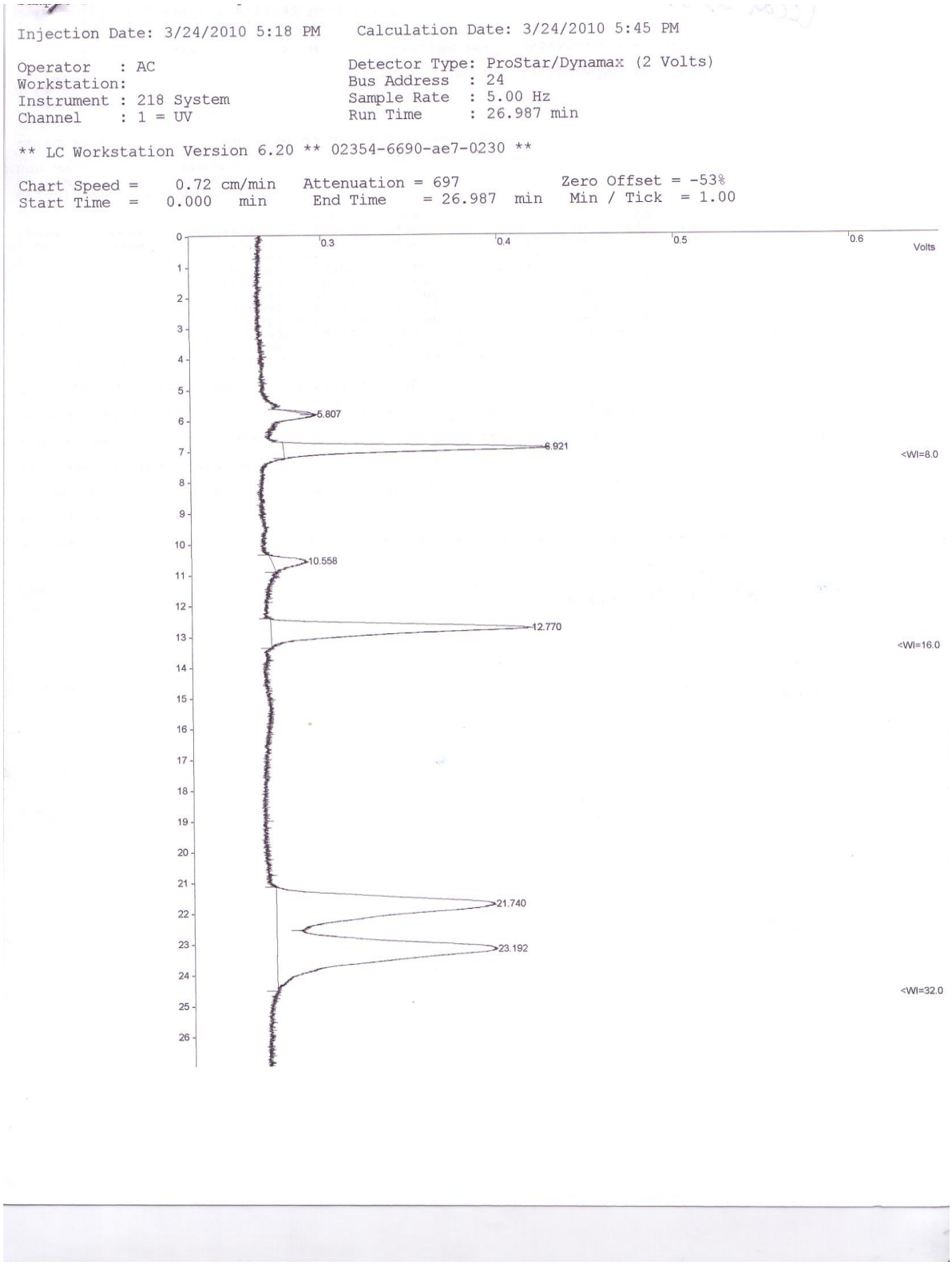
```
hod File : 03-24-20105;33;30 pm-1.mth
mple ID   : Manual Sample

Injection Date: 3/24/2010 5:33 PM     Calculation Date: 3/24/2010 6:01 PM

Operator    : AC                      Detector Type: ProStar/Dynamax (2 Volts)
Workstation:                          Bus Address  : 24
Instrument : 218 System               Sample Rate  : 5.00 Hz
Channel     : 1 = UV                  Run Time     : 26.410 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		3.2166	6.815	0.000	420902	BV	6.6	
2		0.3837	7.028	0.000	50211	VB	0.0	
3		44.1933	21.962	0.000	5782825	BB	33.7	
4		52.2064	23.425	0.000	6831371	BB	38.4	
	Totals:	100.0000		0.000	13085309			

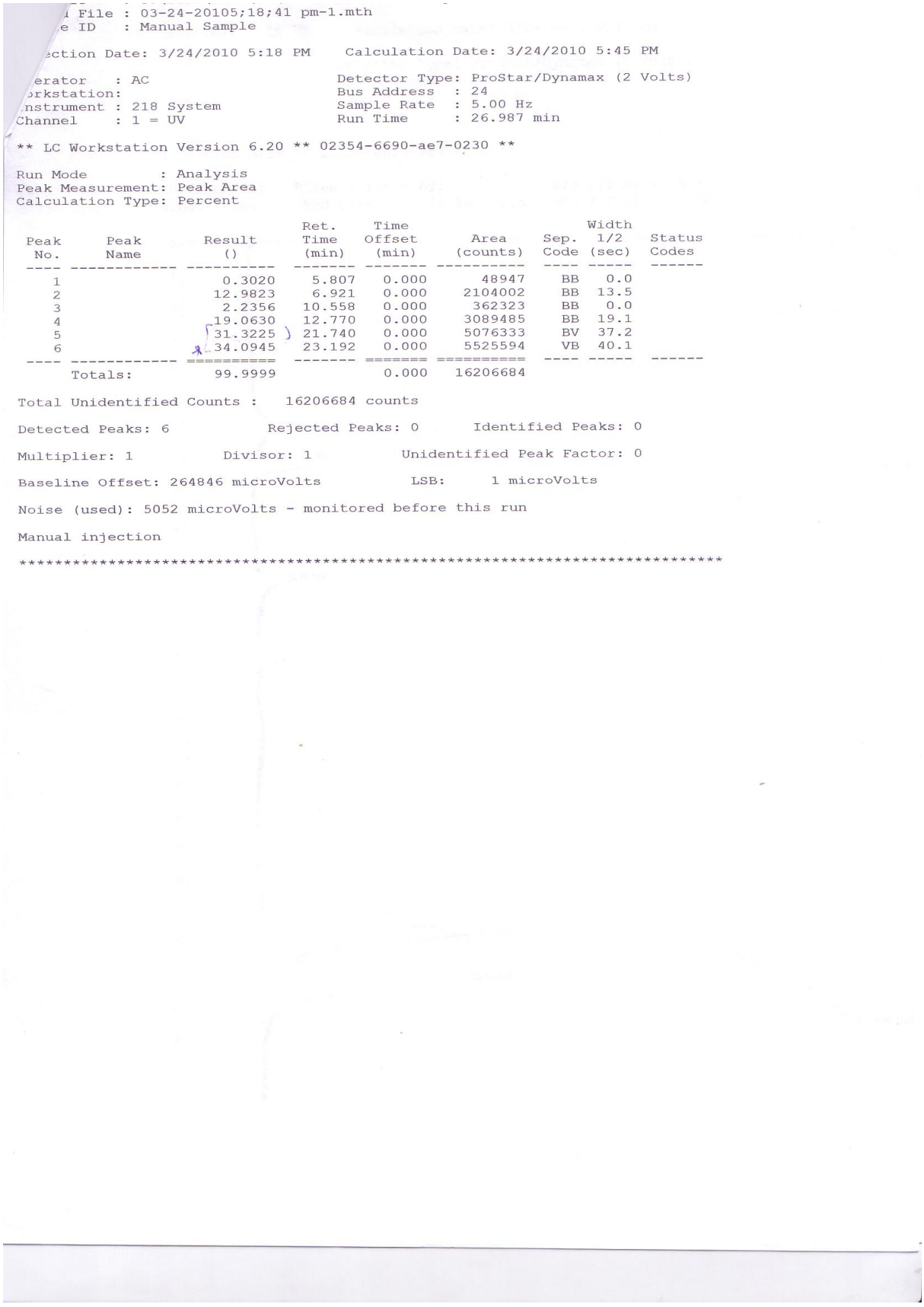
```
Total Unidentified Counts :    13085308 counts

Detected Peaks: 4            Rejected Peaks: 0       Identified Peaks: 0

Multiplier: 1           Divisor: 1           Unidentified Peak Factor: 0

Baseline Offset: 269663 microVolts           LSB:      1 microVolts

Noise (used): 4616 microVolts - monitored before this run

Manual injection

*******************************************************************************
```

(1*R*,2*R*)-N^1-(4-Chlorobenzyl)cyclohexane-1,2-diamine (**99**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 21.7 min (*R* minor), t_R = 23.2 min (*S* major).



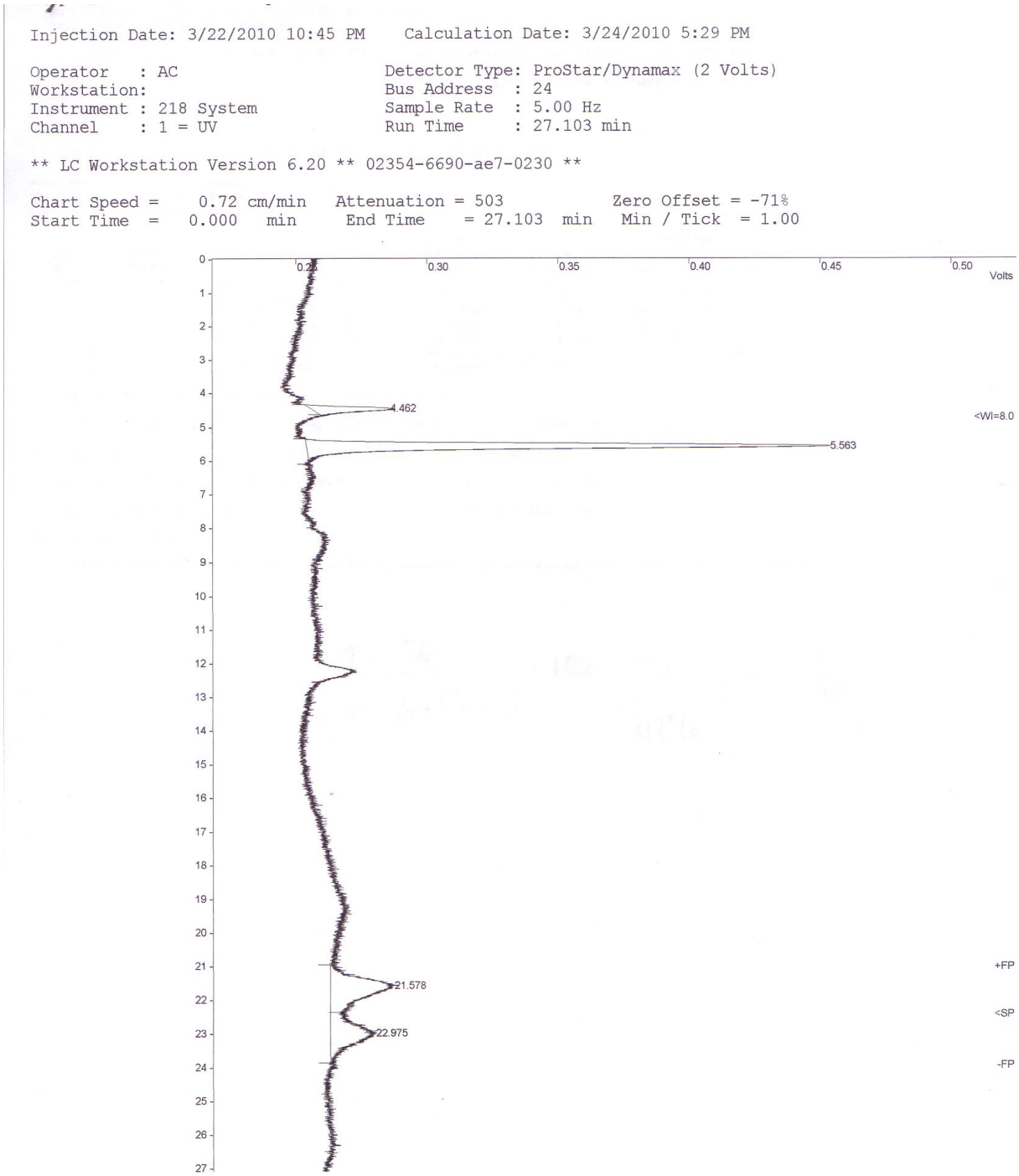
Appendix



```
 1 File : 03-24-20105;18;41 pm-1.mth
 e ID   : Manual Sample

ection Date: 3/24/2010 5:18 PM     Calculation Date: 3/24/2010 5:45 PM

erator    : AC                          Detector Type: ProStar/Dynamax (2 Volts)
orkstation:                             Bus Address  : 24
nstrument : 218 System                  Sample Rate  : 5.00 Hz
Channel   : 1 = UV                      Run Time     : 26.987 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

                                 Ret.     Time                          Width
 Peak      Peak        Result    Time    Offset       Area     Sep.     1/2    Status
  No.      Name          ()      (min)    (min)     (counts)  Code    (sec)   Codes
 ---- ------------ ---------- ------- -------- ---------- ---- -----  ------
    1                  0.3020    5.807    0.000      48947   BB    0.0
    2                 12.9823    6.921    0.000    2104002   BB   13.5
    3                  2.2356   10.558    0.000     362323   BB    0.0
    4                 19.0630   12.770    0.000    3089485   BB   19.1
    5                 31.3225   21.740    0.000    5076333   BV   37.2
    6                 34.0945   23.192    0.000    5525594   VB   40.1
 ---- ------------ ========== ------- ======== ========== ---- -----  ------
      Totals:         99.9999             0.000   16206684

Total Unidentified Counts :   16206684 counts

Detected Peaks: 6            Rejected Peaks: 0       Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 264846 microVolts          LSB:     1 microVolts

Noise (used): 5052 microVolts - monitored before this run

Manual injection

*******************************************************************************
```

(*R*)-2-Amino-3-phenylpropan-1-ol (**100**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 21.6 min (*R* major), t_R = 23.0 min (*S* minor).

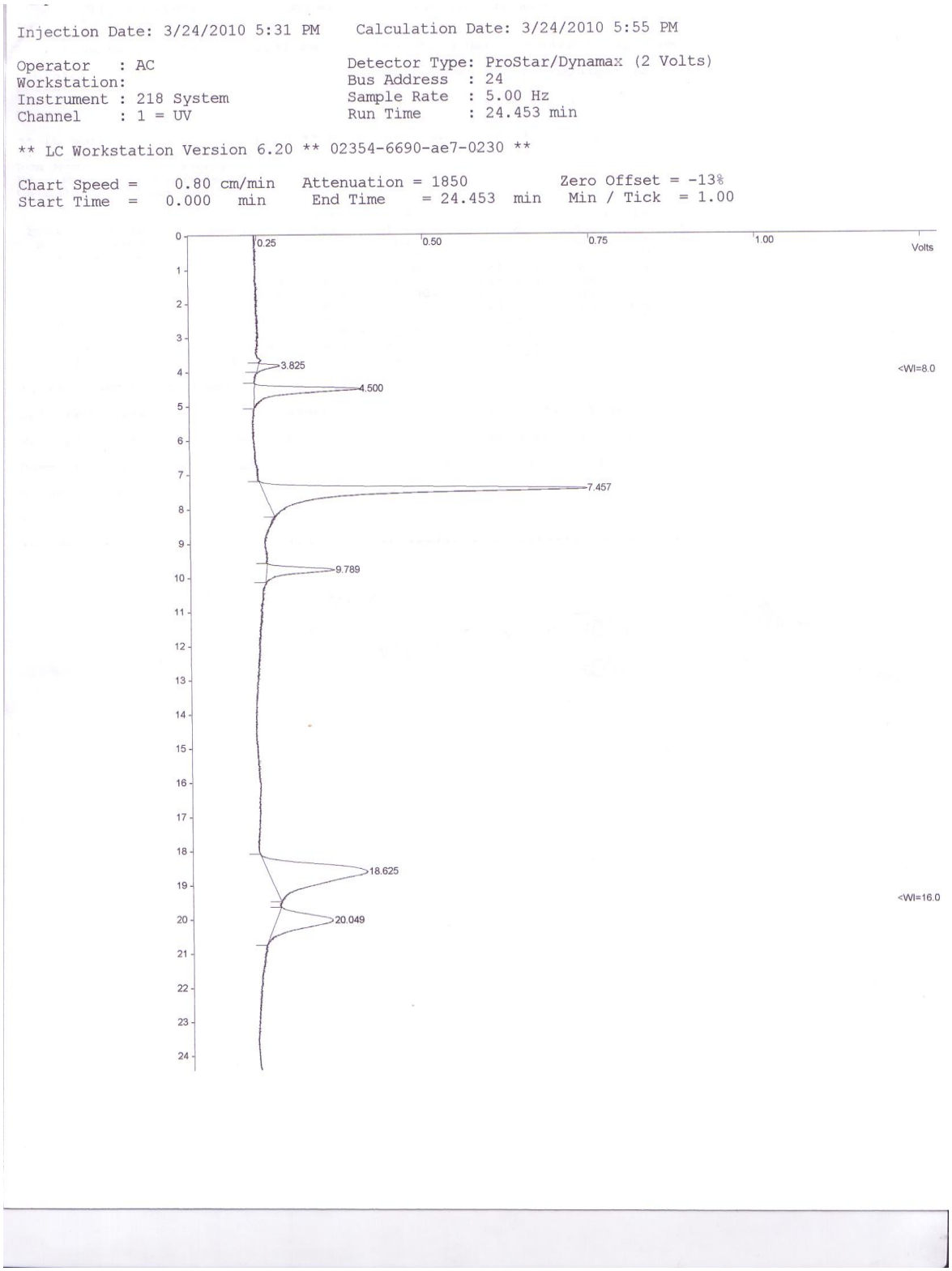


Appendix

```
od File : 03-24-20105;59;33 pm-1.mth
ple ID   : Manual Sample

jection Date: 3/22/2010 10:45 PM    Calculation Date: 3/24/2010 5:29 PM

Operator    : AC                        Detector Type: ProStar/Dynamax (2 Volts)
Workstation:                            Bus Address  : 24
Instrument : 218 System                 Sample Rate  : 5.00 Hz
Channel     : 1 = UV                    Run Time     : 27.103 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

                                Ret.     Time                      Width
 Peak      Peak        Result   Time   Offset       Area    Sep.   1/2   Status
  No.      Name          ()     (min)   (min)     (counts)  Code  (sec)  Codes
 ---- ------------ ---------- ------- ------- ---------- ---- -----  ------
    1                  7.1574   4.462   0.000     296085   BB    9.7
    2                 52.1604   5.563   0.000    2157755   BB    9.7
    3                 23.5623  21.578   0.000     974719   BV    0.0
    4                 17.1199  22.975   0.000     708210   VB   27.1
 ---- ------------ ========== ======= ======= ========== ---- -----  ------
      Totals:        100.0000             0.000    4136769

Total Unidentified Counts :    4136769 counts

Detected Peaks: 4           Rejected Peaks: 0      Identified Peaks: 0

Multiplier: 1          Divisor: 1          Unidentified Peak Factor: 0

Baseline Offset: 256785 microVolts          LSB:     1 microVolts

Noise (used): 4557 microVolts - monitored before this run

Manual injection

*******************************************************************************
```

(*R*)-2-Amino-3-methylbutan-1-ol (**102**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 18.6 min (*R* major), t_R = 20.0 min (*S* minor).



hod File : C:\star\methods\AC Methods\210nm 97-3-12.mth
mple ID : Manual Sample

Injection Date: 3/24/2010 5:31 PM Calculation Date: 3/24/2010 5:55 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 24.453 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.3815	3.825	0.000	244631	BB	6.7	
2		10.5013	4.500	0.000	1859484	BB	9.9	
3		37.7413	7.457	0.000	6682894	BB	10.2	
4		7.0059	9.789	0.000	1240534	BB	10.9	
5		30.5426	18.625	0.000	5408212	BB	38.5	
6		12.8273	20.049	0.000	2271353	BB	23.5	
	Totals:	99.9999		0.000	17707108			

Total Unidentified Counts : 17707108 counts

Detected Peaks: 6 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 246913 microVolts LSB: 1 microVolts

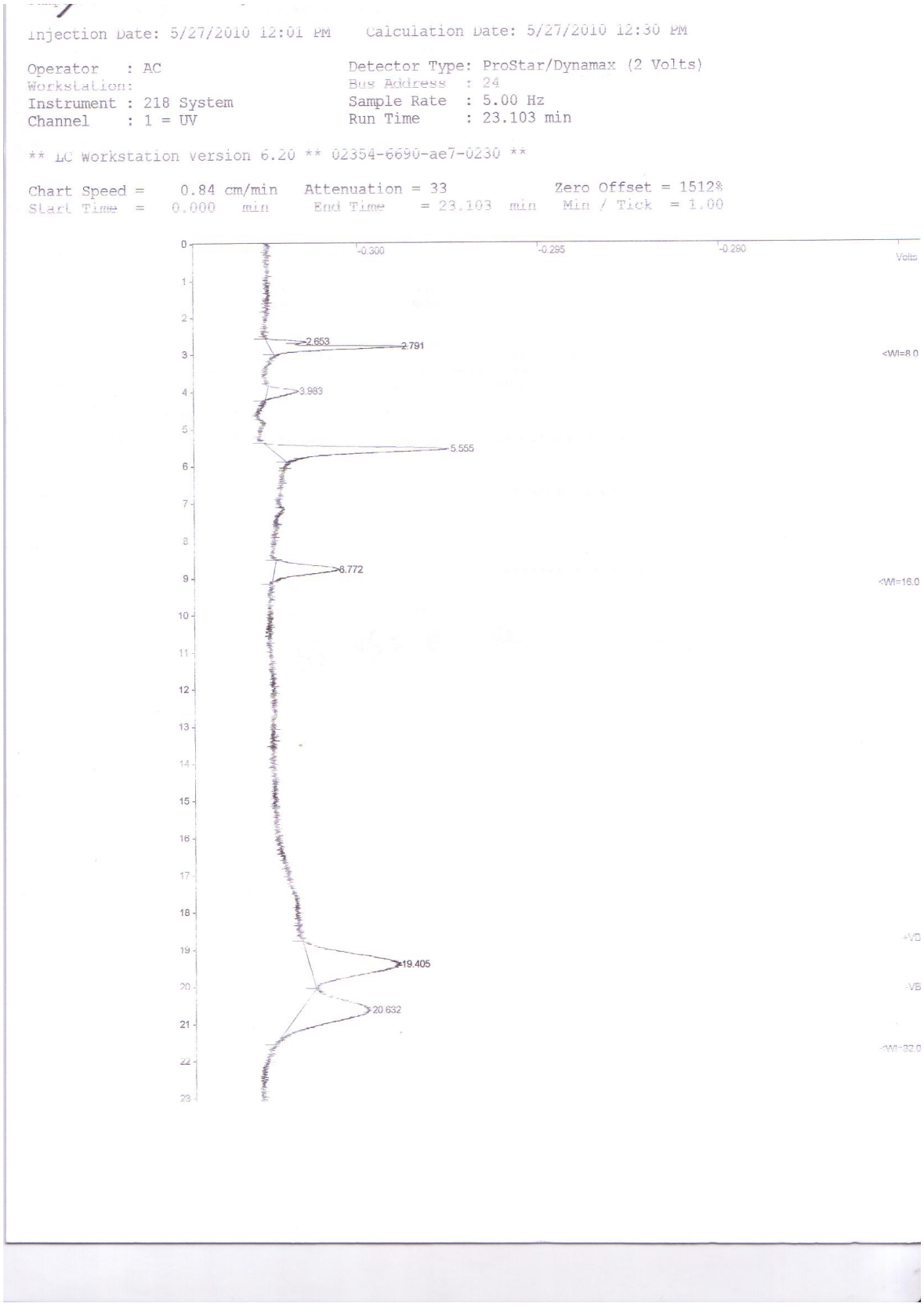
Noise (used): 5354 microVolts - monitored before this run

Manual injection

****

(1*R*,2*S*)-2-Amino-1,2-diphenylethanol (**103**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 19.4 min (*R* major), t_R = 20.6 min (*S* minor).



Appendix

File : nc in 10% aq.etoh014-1.mth
ID : Manual Sample

ction Date: 5/27/2010 12:01 PM Calculation Date: 5/27/2010 12:30 PM

erator : AC
orkstation:
nstrument : 218 System
Channel : 1 = UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 23.103 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Rel. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.9277	2.653	0.000	5744	BV	5.4	
2		9.6484	2.791	0.000	28751	VB	6.4	
3		3.2569	3.983	0.000	9705	BB	11.1	
4		19.0883	5.555	0.000	56880	BB	11.0	
5		8.8508	8.772	0.000	26364	BB	15.3	
6		30.8174	19.405	0.000	91831	BB	38.4	
7		25.4105	20.632	0.000	75719	BB	37.0	
	Totals:	100.0000		0.000	297984			

Total Unidentified Counts : 297984 counts

Detected Peaks: 7 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: -302493 microVolts LSB: 1 microVolts

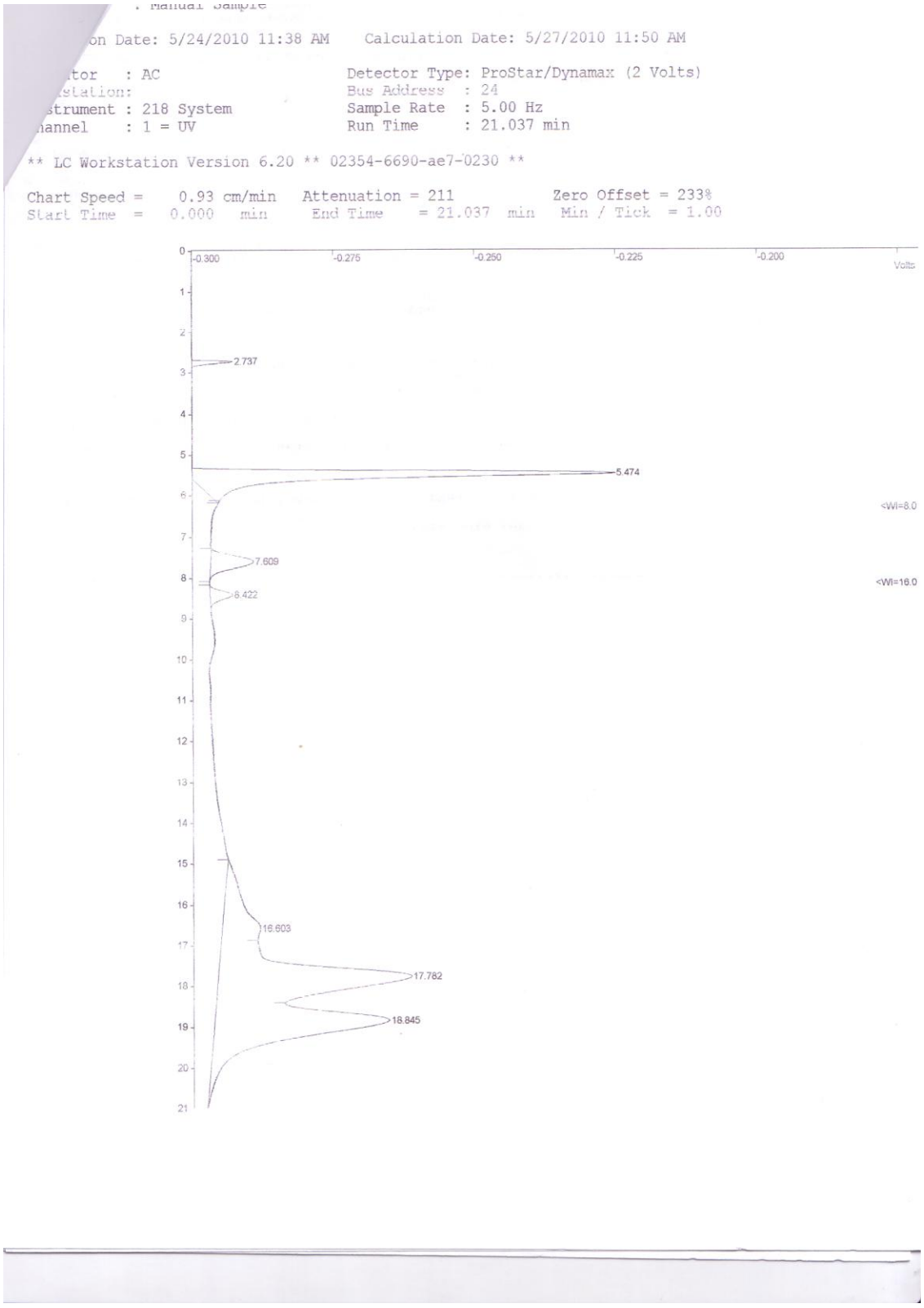
Noise (used): 100 microVolts (monitored before this run

Manual injection

****

(*R*)-2-Amino-4-methylpentan-1-ol (**104**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 17.8 min (*R* major), t_R = 18.8 min (*S* minor).



le : C:\star\methods\AC Methods\254nm 97-3-12.mth
D : Manual Sample

ion Date: 5/24/2010 11:38 AM Calculation Date: 5/27/2010 11:50 AM

itor : AC
station:
trument : 218 System
annel : 1 = UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 21.037 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Rel. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.4012	2.737	0.000	67596	BB	6.1	
2		21.4257	5.474	0.000	1033584	BB	11.1	
3		3.2664	7.609	0.000	157572	BB	19.9	
4		1.2302	8.422	0.000	59346	BB	14.0	
5		8.5641	16.603	0.000	413136	BV	66.8	
6		33.7866	17.782	0.000	1629874	VV	40.0	
7		30.3258	18.845	0.000	1462925	VB	39.3	
	Totals:	100.0000		0.000	4824033			

Total Unidentified Counts : 4824032 counts

Detected Peaks: 8 Rejected Peaks: 1 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: -302927 microVolts LSB: 1 microVolts

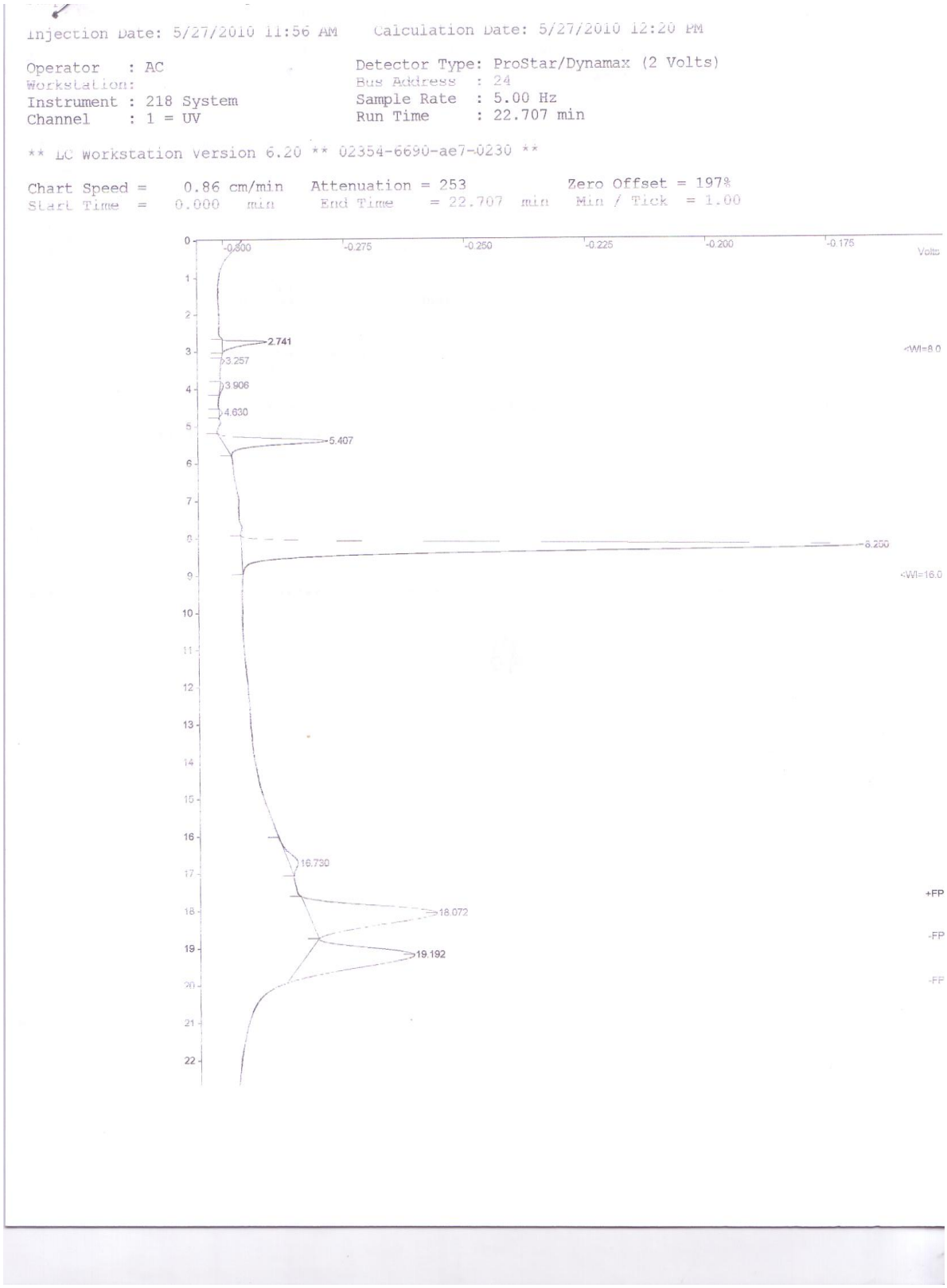
Noise (used): 198 microVolts - monitored before this run

Manual injection

****

(*R*)-2-Amino-3,3-dimethylbutan-1-ol (**105**)

HPLC (Daicel Chiralpack AD, hexane/*i*-PrOH, 80/20, flow rate 1 mL/min, λ = 254 nm), t_R = 18.1 min (*R* major), t_R = 19.2 min (*S* minor).



Appendix

File : nc in 10% aq.etoh017-1.mth
ID : Manual Sample

tion Date: 5/27/2010 11:56 AM Calculation Date: 5/27/2010 12:20 PM

rator : AC
kstation:
strument : 218 System
hannel : 1 = UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 22.707 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.8490	2.741	0.000	75833	BB	7.4	
2		0.0914	3.257	0.000	3748	BB	4.8	
3		0.2033	3.906	0.000	8340	BB	0.0	
4		0.0948	4.630	0.000	3890	BB	7.2	
5		6.2940	5.407	0.000	258133	BB	11.1	
6		49.1521	8.250	0.000	2015834	BB	14.3	
7		1.2209	16.730	0.000	50070	BB	0.0	
8		21.8823	18.072	0.000	897439	BB	35.3	
9		19.2121	19.192	0.000	787932	BB	30.8	
	Totals:	99.9999		0.000	4101219			

Total Unidentified Counts : 4101219 counts

Detected Peaks: 9 Rejected Peaks: 0 Identified Peaks: 0

Multiplier: 1 Divisor: 1 Unidentified Peak Factor: 0

Baseline Offset: 296191 microVolts LSB: 1 microVolts

Noise (used): 294 microVolts - monitored before this run

Manual injection

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