LEABHARLANN CHOLÁISTE NA TRÍONÓIDE, BAILE ÁTHA CLIATH | TRINITY COLLEGE LIBRARY DUBLIN
Ollscoil Átha Cliath | The University of Dublin

Terms and Conditions of Use of Digitised Theses from Trinity College Library Dublin

Copyright statement

All material supplied by Trinity College Library is protected by copyright (under the Copyright and Related Rights Act, 2000 as amended) and other relevant Intellectual Property Rights. By accessing and using a Digitised Thesis from Trinity College Library you acknowledge that all Intellectual Property Rights in any Works supplied are the sole and exclusive property of the copyright and/or other IPR holder. Specific copyright holders may not be explicitly identified. Use of materials from other sources within a thesis should not be construed as a claim over them.

A non-exclusive, non-transferable licence is hereby granted to those using or reproducing, in whole or in part, the material for valid purposes, providing the copyright owners are acknowledged using the normal conventions. Where specific permission to use material is required, this is identified and such permission must be sought from the copyright holder or agency cited.

Liability statement

By using a Digitised Thesis, I accept that Trinity College Dublin bears no legal responsibility for the accuracy, legality or comprehensiveness of materials contained within the thesis, and that Trinity College Dublin accepts no liability for indirect, consequential, or incidental, damages or losses arising from use of the thesis for whatever reason. Information located in a thesis may be subject to specific use constraints, details of which may not be explicitly described. It is the responsibility of potential and actual users to be aware of such constraints and to abide by them. By making use of material from a digitised thesis, you accept these copyright and disclaimer provisions. Where it is brought to the attention of Trinity College Library that there may be a breach of copyright or other restraint, it is the policy to withdraw or take down access to a thesis while the issue is being resolved.

Access Agreement

By using a Digitised Thesis from Trinity College Library you are bound by the following Terms & Conditions. Please read them carefully.

I have read and I understand the following statement: All material supplied via a Digitised Thesis from Trinity College Library is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of a thesis is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form providing the copyright owners are acknowledged using the normal conventions. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.

The design, synthesis and application of (thio)urea-based organocatalysts for a range of C-C bond transformations



Trinity College Dublin

A thesis submitted to the University of Dublin for the degree of Doctor of Philosophy 2009

by

Eimear Fleming B.A. (Mod.)

Under the supervision of

Dr. Stephen Connon

Declaration

I declare that this work has not been submitted as an exercise for degree at this or any other university, and that it is entirely my own work. Due acknowledgements and references are given to the work of others. The library of

copy

E. M. F *hedron Letters*, 2006, **47**, 7037

E. M. Fleming, C. Quigley, I. Rozas and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 948

S. A. Kavanagh, A. Piccinini, E. M. Fleming and S. J. Connon, *Org. Biomol. Chem.*, 2008, **6**, 1339

TRINITY COLLEGE
10 AUG 2009
LIBRARY DUBLIN
Thesis 8783

Summary

The identification and development of small chiral organic molecules capable of mimicking the hydrogen-bonding capabilities of enzymes is the main thrust of this thesis concerning the design and application of new (thio)urea containing catalysts for a variety of transformations. Herein we detail the development of a new class of binaphthyl (thio)urea catalysts and the evaluation of same in the asymmetric Friedel-Crafts reaction involving *N*-methyl indole and a range of both activated and deactivated nitrostyrenes. A suite of materials of varying steric and electronic characteristics were employed as catalysts in the enantioselective Friedel-Crafts addition reaction. Whilst enantioselectivity of the Friedel-Crafts adducts was found to be moderate (max. 50% *ee*), this was a significant improvement on the literature precedent, highlighting the difficulty of such a transformation.

Using computational methodologies to elucidate favourable substrate-catalyst interactions we developed a highly acidic urea-based catalyst for a range of Friedel-Crafts type addition reactions to epoxides. This catalyst promoted the smooth addition of a series of nucleophiles to epoxides for the synthesis of densely functionalised compounds. Applying this catalyst in the addition reaction of a range of nucleophiles including *C*-, *O*-, *N*-, and *S*-based nucleophiles to epoxides demonstrated the potential of urea-based molecules as excellent enzyme mimics and the potential of computational modelling for the identification of a suitable catalyst model.

Intrigued by the activity of urea-based catalysts for the promotion of addition reactions and the transition state stabilisation associated with these compounds we applied for the first time a series of urea-derived catalysts in the Johnson-Corey-Chaykovsky epoxidation and cyclopropanation reactions. The ability of the urea-based catalyst to promote the addition of methylene to both aldehydes and enones affirmed a swift and easy route to a range of substituted epoxides and cyclopropanes using the hitherto sluggish yet unexpensive trimethylsulfonium iodide. The design, synthesis and application of new classes of both monofunctional and bifunctional amino-acid derived urea-based catalysts for these reactions was also accomplished and developed as a new method for the aforementioned transformations.

To Mam and Dad

Contents Page

Acknowledgements v
Abstract vi
Abbreviations vii

1.1 General 1
1.1.1 Physical concepts of asymmetric catalysis 2

1.2 Catalyst classification 4
1.2.1 Enzyme mediated catalysis 4
1.2.2 Metal-ion catalysis 6
1.2.3 Organocatalysis 8

1.3 Development of (thio)urea catalysts 9
1.3.1 Early developments-diol organocatalysts 10
1.3.2 *N,N'*–Diaryl urea development 12
1.3.2.1 Summary of *N,N'*-diarylurea catalyst applications 15
1.3.2.2 Recent advances in C-C bond formation using **20** 15
1.3.2.3 3,5-*Bis* trifluoromethylurea **46** catalyst applications 17
1.3.2.4 *N,N'*-diarylurea development: conclusions 18
1.3.3 Chiral (thio)ureas as catalysts 18

1.4 Binaphthyl based catalyst systems 27
1.4.1 BINOL: background 27
1.4.2 BINAM and BINAP: background 28
1.4.3 Asymmetric catalysis by BINAP-, BINOL- and BINAM-based catalysts 29
1.4.3.1 BINAP-derived catalysts in asymmetric synthesis 30
1.4.3.2 BINOL-derived catalysts in asymmetric synthesis 32
1.4.3.3 Asymmetric synthesis using BINAM 36
1.4.4 Asymmetric synthesis by binaphthyl based catalysts: conclusions 36

1.5 Friedel-Crafts type reaction: asymmetric addition of indoles to nitroolefins 37
1.5.1 Biological relevance of the asymmetric Friedel-Crafts(FC) reaction 38
1.5.2 Metal-based catalysts for the asymmetric Friedel-Crafts reaction 38
1.5.2.1 Bis(oxazoline)-$Zn(OTf)_2$ catalysed addition of indoles to nitrostyrenes 40
1.5.2.2 $InBr_3$ catalysed Michael addition of indoles to nitrostyrenes 41
1.5.3 Organocatalysts for the asymmetric Friedel-Crafts reaction 42
1.5.4 Organocatalytic asymmetric addition of indoles to nitroolefins 43
1.5.5 Friedel-Crafts additions to nitroolefins: conclusions 47

1.6 Friedel-Crafts reaction: addition of indoles to epoxides 47
1.6.1 Metal(ion)-based catalysts for Friedel-Crafts additions of indoles to epoxides 47
1.6.1.1 Metal-based catalysts for epoxide additions to indoles: conclusions 51
1.6.2 Organocatalytic Friedel-Crafts addition of indoles to epoxides 51
1.6.3 The Friedel-Crafts addition of carbon based nucleophiles to epoxides: Conclusion 51

1.6.4 Metal-based catalysts for Friedel-Crafts additions of non-carbon-based nucleophiles to epoxides 52
1.6.4.1 Metal-catalysed additions of *N*-based nucleophiles to epoxides 52
1.6.4.2 Metal-catalysed additions of *S*-based nucleophiles to epoxides 55
1.6.4.3 Metal-catalysed additions of *O*-based nucleophiles to epoxides 55
1.6.5 Organocatalysis of the addition of *S*-, *N*-, and *O*-based based nucleophiles to epoxides 57
1.6.5.1 Organocatalysed addition of *S*-based nucleophiles to epoxides 57
1.6.5.2 Organocatalysed addition of *N*-based nucleophiles to epoxides 59
1.6.5.3 Organocatalysed addition of *O*-based nucleophiles to epoxides 62
1.6.6 The Friedel-Crafts addition of non-carbon-based nucleophiles to epoxides: Conclusions 65

1.7 The Johnson-Corey-Chaykovsky reaction 65
1.7.1 Historical perspective 65
1.7.2 The mechanism of the Johnson-Corey-Chaykovsky (JCC) reaction 66
1.7.2.1 The effect of reaction conditions on rate and selectivity in the JCC reaction 69
1.7.3 Chiral sulfonium ylides for enantioselective alkylidene transfer 70
1.7.3.1 Chiral sulfonium ylide generation in the presence of metal carbenes 74
1.7.3.2 Conclusions for Section 1.7.3 78
1.7.4 The asymmetric JCC reaction: methylene transfer 78
1.7.4.1 Chiral sulfonium ylides for enantioselective methylene transfer 78
1.7.5 Conclusions for Section 1.7.4 82

1.8 Cyclopropanation *via* Trimethylsulfoxonium iodide reactions 82
1.8.1 The mechanism of the cyclopropanation reaction using trimethylsulfoxonium Iodide 82
1.8.2 Promoters of the cyclopropanation reaction: recent developments 83

2.1 Catalysis of the asymmetric Friedel-Crafts reaction 84
2.1.1 Axially chiral (thio)urea catalysts: design rationale 85
2.1.1.1 Preparation of the binaphthyl *bis*-(thio)urea catalysts 87
2.1.2 Optimisation of reaction conditions for the asymmetric Friedel-Crafts reaction 87
2.1.3 Evaluation of catalysts employed in the asymmetric Friedel-Crafts reaction 90
2.1.4 Design of second generation catalysts 92
2.1.4.1 Preparation of the second generation catalysts 92
2.1.4.2 Evaluation of the second generation catalysts in the asymmetric Friedel-Crafts reaction 94
2.1.5 Broadening the substrate scope of the (*S*)-**291g** catalysed asymmetric Friedel-Crafts addition reaction 96
2.1.6 Examination of the catalytic effect of catalyst (*S*)-**291g** 98
2.1.6.1 Explanation of the origins of enantioselectivity of catalyst (*S*)-**291g** 99
2.1.7 Conclusions for Section 2.1 101

2.2 Catalysis of the Morita-Baylis-Hillman reaction 102
2.2.1 Selected advancement in the asymmetric Morita-Baylis-Hillman reaction: a brief overview 103

2.3 Development of binaphthyl(thiourea) bifunctional organocatalysts 104
2.3.1 Synthesis of catalyst (*S*)-**306** 105
2.3.2 Initial evaluation of (*S*)-**305** and (*S*)-**306** as catalysts in the MBH reaction 106
2.3.3 Catalysis of addition reactions using catalyst (*S*)-**306** 107
2.3.4 Conclusions for Section 2.3 108

2.4 Development of organocatalyst 310 for the asymmetric MBH reaction 109
2.4.1 Design principles and synthesis of catalyst **310** 109
2.4.1.1 Further catalyst screening in the MBH reaction 110
2.4.1.2 Enantiomeric excess of the MBH adducts 112
2.4.2 Conclusions for Section 2.4 113

3.1 The highly active urea-based catalyst 316 113
3.1.2 Catalyst design rationale and its interaction with the substrate based on computational studies 115
3.1.2.1 Epoxide substrate synthesis 119
3.2 Preliminary testing of catalyst **316** 120
3.2.1 Evaluation of catalyst **316** as a catalyst for addition of indoles to various epoxides 122
3.3 Evaluation of nucleophiles other than indole derivatives 124
3.3.1 Catalysis of amine additions to epoxides by **316** 124
3.3.2 The addition of thiols to epoxides catalysed by **316** 129
3.3.3 The addition of alcohols to epoxides catalysed by **316** 130
3.4 Conclusions for Section 3.1 130

4.1 The design of organocatalysts for the Johnson-Corey-Chaykovsky reaction 131
4.1.1 Preliminary catalyst screening in the Johnson-Corey-Chaykovsky reaction 131
4.2 Optimisation of the reaction conditions 133
4.2.1 Base-loading and Base-concentration 134
4.2.2 Ureas and (thio)ureas screened in the Johnson-Corey-Chaykovsky reaction 135
4.2.3 Evaluation of substrate scope of the urea catalysed Johnson-Corey-Chaykovsky reaction 138
4.3 Conclusions for Section 4.1 139

4.4 The asymmetric Johnson-Corey-Chaykovsky reaction 139
4.4.1 Catalyst design rationale 141
4.4.2 Catalyst syntheses 142
4.4.3 Catalysts employed in the asymmetric Johnson-Corey-Chaykovsky reaction 143
4.4.3.1 Mono-, and bifunctional *L*-methionine-derived organocatalysts 143
4.4.3.2 Monofunctional catalyst evaluation requiring a 'methylene' source 147
4.4.4 Second generation catalysts developed for the JCC reaction 151
4.4.4.1 Catalyst **367** design rationale and synthesis 151
4.4.4.2 Synthesis of catalyst (*S,S,S,S*)-**367** 152
4.4.4.3 Evaluation of catalyst **367** under liquid/solid and liquid/liquid reaction conditions 153
4.5 Conclusions for Section 4.4 154

4.6 Application of urea catalysts to the promotion of the cyclopropanation reaction using trimethylsulfoxonium iodide 156
4.6.1 Preliminary evaluation of the urea catalysed cyclopropanation reaction of chalcone 156

4.6.2 Chiral catalysts evaluated in the cyclopropanation reaction using TMSOI 159
4.7 Chapter 4 conclusions 163

5.1 General experimental data 164

Acknowledgements

The first thanks has to go to my Mam and Dad who have been a constant source of support and encouragement to me in my life, a big thanks to you both.

To the rest of the family, Pat, James, Aiden, Clodagh and Debbie thanks for all the support, it was welcomed at times when you probably didn't think so.

To my supervisor Dr Stephen Connon who I am eternally grateful to for the opportunity to pursue this research under his guidance, thanks for your constant encouragement and your enthusiasm in dealing with every unexpected result, I don't know how you do it!

I would like to thank the past and present members of the Connon lab, Shay, Ciaran, Dave Barbara, Sarah O', Conor, Aldo, Jen, Ollie, Sarah K, Louise and Alessandro for time spent with them in the lab. I would especially like to thank everyone who done some proof-reading for me but especially Barbara and Sarah O' for all the extra proof-reading and for been good pals throughout this PhD. I would like to thank the Southern group, a big thanks to Mike, Con, Dave M, Anna and all the past members of the group also.

Thanks to all the staff of the Chemistry department for help along the way. The biggest thanks will have to go to Dr. John O' Brien and Dr. Manuel Ruether for the multitude of NMR's. Thanks to all the staff in the Cocker lab and the Phys.Chem lab for all your help and the use of the equipment. Special thanks to Martin Feeney for all the mass specs, which were all much appreciated.

Thanks to all the people whom I have known in the department since the degree days, those of you who also chose the path of the PhD know exactly who you are so many thanks to you for the good nights out. Special mention has to go to my friend and lunch partner Deirdre for your friendship over the last few years too.

Not forgetting, of course a very big thanks has to go to Johnny, for all your loving support over the last three years, you know more than anyone the highs and lows of my time doing the PhD and have stuck around regardless, words cant express my gratitude for that.

Abstract

The design, synthesis and application of (thio)urea-based organocatalysts for a range of C-C bond transformations

Eimear Fleming

A suite of materials based on the binaphthyl amine backbone were designed and synthesised. These catalysts of varying steric and electronic characteristics were subsequently employed as promoters of the enantioselective Friedel-Crafts addition reaction.

Using computational methodologies to elucidate favourable substrate-catalyst interactions we developed a highly acidic urea-based catalyst for a range of Friedel-Crafts type addition reactions to epoxides.

Also, intrigued by the activity of urea-based catalysts for the promotion of addition reactions and the transition state stabilisation associated with these compounds we applied for the first time a series of urea-derived catalysts in the Johnson-Corey-Chaykovsky epoxidation and cyclopropanation reactions.

Abbreviations

A	Pre-exponential factor
Å	Angstrom
AIM	Atoms In Molecules
atm	atmosphere
bcp	Bond critical point
BINOL	1,1'-Bi-2-naphthol
BINAM	2,2'-Diamino-1,1'-binaphthalene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
cat.	Catalyst
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2] octane
DCM	Dichloromethane
de	Diastereomeric excess
DFT	Density Functional Theory
DKR	Dynamic Kinetic Resolution
DNA	Deoxyribonucleic acid
dr	*diastereomeric ratio*
ee	*enantiomeric excess*
equiv.	Equivalent
FDA	Food and Drug Administration
FC	Friedel-Crafts
GAC	General Acid Catalysis
HDA	Hetero-Diels-Alder
HPLC	High Performance Liquid Chromatography
k	rate constant
k_{rel}	relative rate constant
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*
MBH	Morita-Baylis-Hillman
MeCN	Acetonitrile
o	*ortho*
p	*para*
PTC	Phase Transfer Conditions
q	quaternary centre
qt	quartet
RBF	Round Bottomed Flask
RLS	Rate Limiting Step
RNA	Ribonucleic acid
rt.	Room temperature
THF	Tetrahydrofuran
TMSI	Trimethylsulfonium iodide
TMSOI	Trimethylsulfoxonium iodide
MBH	Morita-Baylis-Hillman
MCPBA	*m*-Chloroperoxybenzoic acid
MS	Molecular sieves
MW	Microwave

NMR	Nuclear Magnetic Resonance
Taddol	α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol
Ts	Tosyl
JCC	Johnson-Corey-Chaykovsky
υ (cm^{-1})Diff	Diffuse reflectance infra-red

1.1 General

The French physicist Biot[1] is credited with the discovery that certain organic compounds have the ability to rotate a plane of polarised light. This astounding observation would lay the foundations for the defining of the term 'chirality' and the future development of asymmetric synthesis. The physical properties of optical and electronic materials often emanates from the ability of chiral molecules to order and communicate effectively intramolecularly. Similarly, on the biological level, the diversity of the natural world could not exist without these intricate communication pathways on the cellular level.

It is not surprising therefore that we are now in what has been described as the 'golden age' of organocatalysis.[2] Enantioselective synthesis and organocatalysis in particular have become one of the most competitively researched areas over the last 30 years,[2-9] as the drive to produce enantiopure compounds has gained momentum. In 2006, 80% of small-molecule drugs approved by the Food and Drug Administration (FDA) were chiral and 75% were single enantiomers.[10]

Figure 1.1 Routes to enantiopure compounds

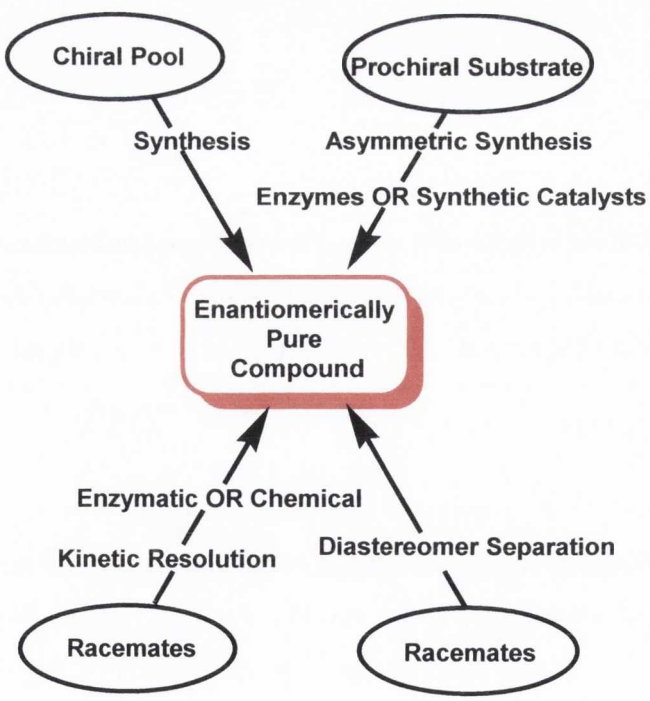


Figure 1.1 outlines the various possible routes available for the synthesis of enantiomerically pure compounds. Nature has provided us with a near endless supply of enantioenriched

compounds also known as the "chiral pool" which includes sugars, alkaloids and amino acids, all of which can be utilised as chiral auxiliaries or reagents in diastereoselective synthesis. Until recently the ability to synthesise enantiopure compounds has been limited, relying upon the purification of enzymes such as hydrolase's and lipases to act as catalysts. In addition, the technique of separating enantiomers which represents the most widespread industrially important method for the production of enantiomerically pure products,[11] a procedure introduced by Pasteur in the 1850's.[12-14] The separation of racemates can only yield a maximum of 50% yield of the desired enantiomer unless the technique of dynamic kinetic resolution (DKR) is utilised whereby the opposite enantiomer can be converted to the desired enantiomer by chemical or enzymatic means. The application of a synthetic catalyst to effect an enantioselective transformation is supremely more efficient than a synthetic strategy involving chiral auxiliaries, chiral reagents or kinetic resolution; because it allows one to aspire towards the synthesis of a product as a single enantiomer from achiral starting materials using a chiral-information-carrying molecule in small amounts.

1.1.1 Physical concepts of asymmetric catalysis

Reacting molecules must bring with them to any collision a certain threshold of energy for reaction to be possible (E_{act}).[15]

$$k = Ae^{-E_{act}/RT} \qquad \textbf{(eq. 1.1)}$$

The Arrhenius equation (eq. 1.1) states the relationship between the rate constant for a reaction (k) with the activation energy (E_{act}) temperature (T), pre-exponential factor (A), and the gas constant (R). In lowering the activation energy for a reaction, a catalyst directly increases the rate of that reaction.

The (*R*) and (*S*) products of an enantioselective process are isodynamic. In the presence of an achiral catalyst the activation energy leading to each enantiomer is equivalent; consequently, the rate constant for each enantiomer is the same *i.e.* k_R is equal to k_S (Figure 1.2). Thus, for a reaction promoted by an achiral catalyst there is no preference for the formation of one enantiomer over the other (eq. 1.2).

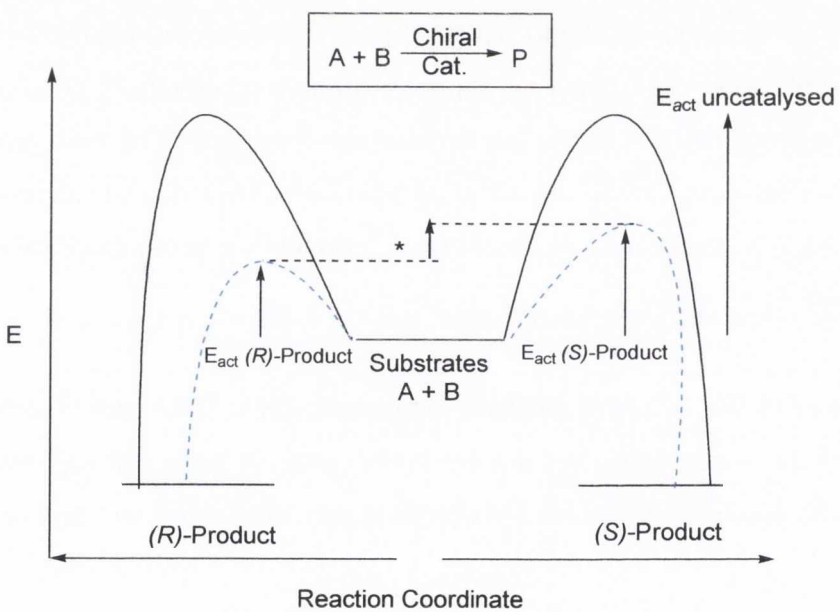
$$\frac{[R]}{[S]} = \frac{k_R}{k_S} = e^{-\Delta\Delta G^{TS}/RT} = 1 \qquad \textbf{(eq. 1.2)}$$

where k_R and k_S are the rate constants for the formation of (*R*) and (*S*) enantiomers, respectively. $\Delta\Delta G^{TS}$ is the difference in the transition state energies for each enantiomer (eq. 1.3).

$$\Delta\Delta G^{TS} = \Delta G_R^{TS} - \Delta G_S^{TS} \qquad \textbf{(eq. 1.3)}$$

where ΔG_R^{TS} and ΔG_S^{TS} are the free energies of activation for the formation of (*R*) and (*S*) enantiomers, respectively. $\Delta\Delta G^{TS}$ is zero in an achiral environment; see (eq. 1.2) above. However, in the presence of a chiral catalyst the activation energy for one enantiomer is reduced relative to the other (Figure 1.2).

Figure 1.2 Potential energy diagram for asymmetric catalysis



* = $\Delta\Delta G^{TS}$ = Energy difference between transition states leading to *(R)* and *(S)* products in the presence of a chiral catalyst.

Of paramount importance in asymmetric catalysis is a large $\Delta\Delta G^{TS}$ value, which translates to significant catalyst selectivity. By reducing the energy available to the system, *i.e* by lowering the temperature, the enantiomeric excess (*ee*) may be increased. The higher activation energy pathway is now less accessible leading to selective formation of one enantiomer, *i.e.* (*R*) in Figure 1.2.

1.2 Catalyst classification

The chemist engaged in asymmetric synthesis has a variety of feasible routes to enantioenriched compounds,[16,17] specifically in the use of:

a) Enzyme-mediated catalysis
b) Catalytic antibodies, RNA/DNA and oligopeptides
c) Metal-ion mediated catalysis
d) Organocatalysts

Categories **a)** and **b)** which are biologically-derived (bio-catalysts) catalytic methods often lack scope in application due to their exceptional substrate specificity.[18] This, coupled with a preference for aqueous reaction media has initiated the development of more tuneable catalyst frameworks. Categories **c)** and **d)**, the "new" synthetically derived catalysts have the greatest potential for general asymmetric synthesis since virtually no constraints exist in terms of molecular design.[11]

Hitherto, the area of bio-catalysts; catalytic antibodies, RNA, DNA and oligopeptides is the least utilised of these categories, yet the deoxyribozymes in particular represent convenient model systems in which the structural and chemical principles of nucleic acid catalysis can be explored.[19]

1.2.1 Enzyme-mediated catalysis

Enzymes are capable of promoting highly chemo-, regio-, diastereo-, and enantioselective reactions, their catalytic efficiency depends immensely on the exploitation of the complex

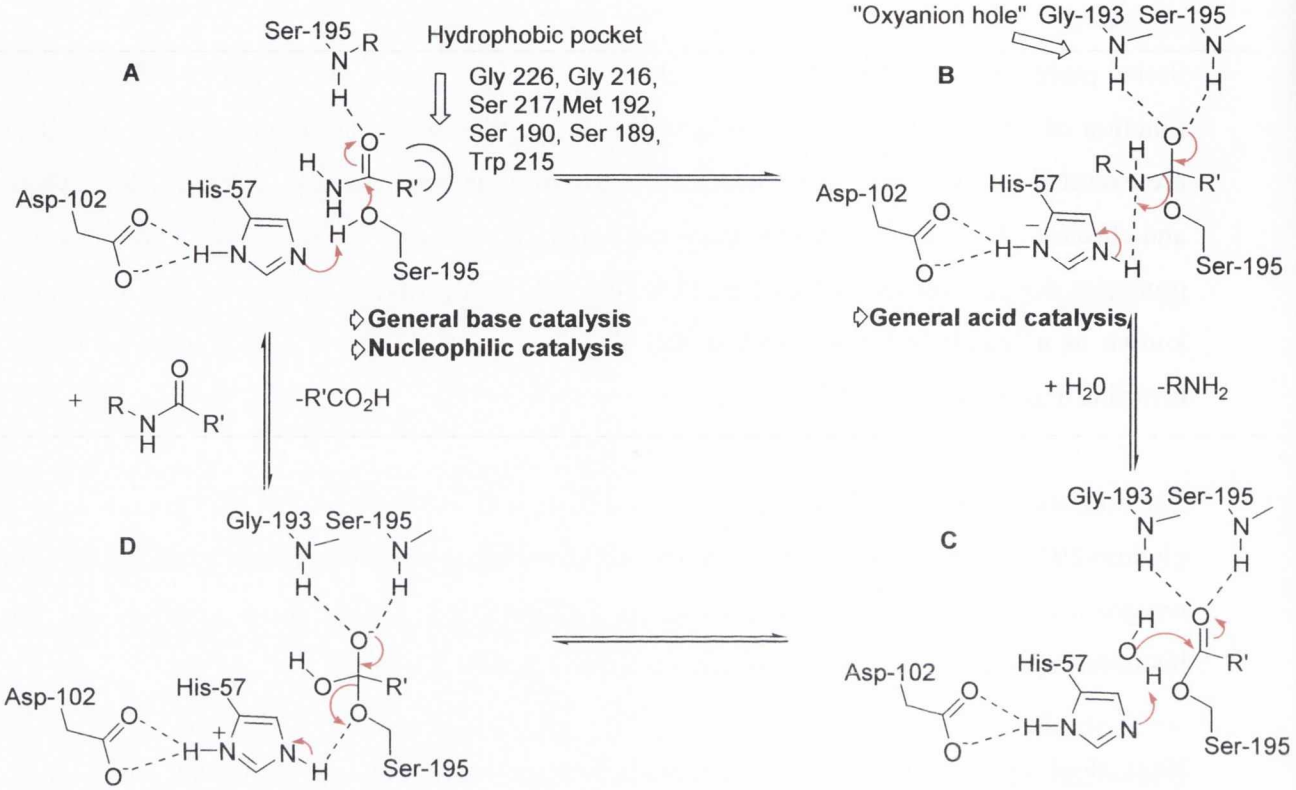
interplay between a multitude of weak forces such as hydrogen bonding, van der Waals interactions and ionic attractions difficult to reverse-engineer in *de-novo* designed synthetic systems.

Serine proteases are a class of enzymes characterised by a serine residue in the active site, the function of which is to assist in the hydrolysis of peptide bonds in proteins. Serine proteases are excreted by the pancreas, of which there are three general classes, chymotrypsin, trypsin and elastase which have similar primary and tertiary structures.[20] The catalytic action of serine proteases depends on the cooperation of a nucleophile, a general base and an acid in what is known as a 'catalytic triad' which in the aforementioned proteases is composed of serine, histidine and aspartate residues.

The mechanism is outlined in Scheme 1.1 and starts with substrate binding and activation by a glycine-193 residue *via* hydrogen bonding, followed by nucleophilic attack of the side chain oxygen of a serine-195 residue, which is facilitated by general base catalysis *via* the histidine/aspartate proton shuttle system (Scheme 1.1, part A).

Next, alcoholysis of the amide bond proceeds through the high-energy tetrahedral intermediate (stabilised by the 'oxyanion hole' which is two hydrogen bond donating amino acid residues: glycine 193 and serine 195) assisted by general acid catalysis by the catalytic triad (Scheme 1.1, part B). Binding in the 'oxyanion hole' is specific for the acyl-enzyme intermediate due to van der Waals interactions, which guarantees specificity for binding but also for cleavage at the correct aromatic residues in the subsequent step. Nucleophilic attack of a water molecule on the acyl-enzyme intermediate (assisted by the catalytic triad) hydrolyses the acylenzyme intermediate and regenerates the active site serine moiety while releasing the product (Scheme 1.1, part C/D).

Scheme 1.1 Acceleration of amide hydrolysis in serine protease by double weak H-bonding, multiple noncovalent catalyst-substrate interactions and bifunctional catalysis.[6]

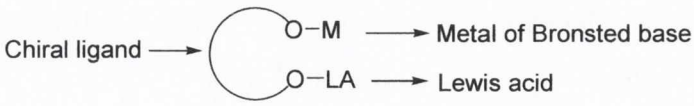


The simultaneous activation of the nucleophile and electrophile and the use of weak hydrogen bonding by enzyme active sites, as shown in the serine proteases above, has served as inspiration for many synthetic catalyst systems designed to promote addition reactions to carbonyl and other electrophiles.

1.2.2 Metal-ion catalysis

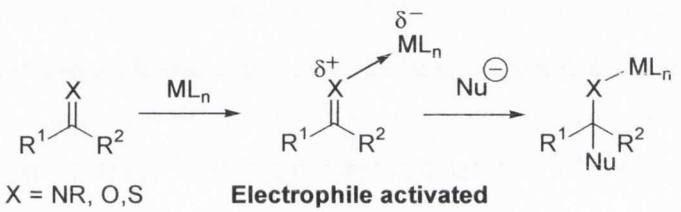
By coupling the Lewis-acidic nature of metals with an adjacent Lewis-basic group on the same molecule in a controlled asymmetric environment, it could be possible to mimic the active site of an enzyme. (Figure 1.3) The more recent design of bifunctional small molecule catalysts for asymmetric reactions has arisen (based on the monofunctional metal-ion based catalysts originating in the 1950's), due to the unique capabilities of Lewis acidic metal ions.[21]

Figure 1.3 Bifunctional catalyst model involving a metal-ion centre



Lewis acidic metal-ion catalysts are highly adaptable; [6] variation of the metal-ion (M) and modification of the (chiral) ligand backbone (L) enables alteration of the steric and electronic properties of the catalyst (Scheme 1.2).

Scheme 1.2 Electrophile activation by a metal-ion centre



Metal-ion based catalysts most usually operate by coordinating to the Lewis basic carbonyl electrophile, the result of which is a decrease in energy of the lowest unoccupied molecular orbital, the C=O π* orbital, activating the group towards cycloaddition/nucleophilic attack. This, together with strong enthalpic substrate binding leads to reaction rate enhancement. The strong Lewis acidic nature of the metal-ion centre does however have associated disadvantages, including a) product inhibition due to non-specific binding (ideally the catalyst should bind selectively to the transition state of the rate-determining reaction step) b) strong oxophilicity of the metal-ions (in particular group I and II metals and the early transition metals) which can necessitate rigorous exclusion of air and moisture, and c) limited functional group compatibilities.[5] Regardless of these drawbacks the excellent activity of well designed metal-based catalysts and the high levels of stereo-induction (possible through the use of chiral ligands capable of using the steric and electronic characteristics of the metal coordination sphere) have revolutionised asymmetric synthesis and the area remains a prolific area of study in the area of asymmetric synthesis today.[22-24]

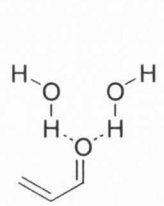
1.2.3 Organocatalysis

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound which does not contain a metal atom.[2]

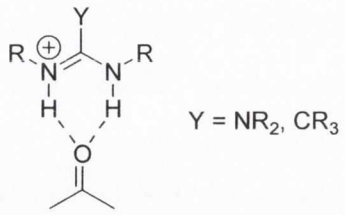
In an attempt to design more environmentally friendly, selective, robust and functional group tolerant catalysts the scientific community has focused its attention on the potential of the simplest of Lewis acids, the proton.[5] Strong protic acids are not required as catalysts in carbonyl addition reactions if the reaction proceeds under general acid catalysis (GAC), whereby the proton transfer occurs only in the transition state or the catalyst is instrumental in stabilising the transition state through hydrogen bonding. GAC systems lack the strong enthalpic substrate-binding capabilities of the metal-ion based Lewis acid catalysts, thereby leading to diminished turnover frequencies (TOF) relative to benchmark metal-based systems, this however need not be viewed as inauspicious.[5] The weaker hydrogen bonding of the organocatalyst and increased catalyst stability effectively allows for more specific substrate binding, dramatically reducing the problem of product inhibition. The absence of a strongly oxophilic metal-ion centre alleviates some of the difficulties of functional group and solvent incompatibilities as well as moisture sensitivity.

Organic chemists have discovered that low molecular weight synthetic molecules bearing a H-bonding motif can catalyse an array of C-C and C-heteronuclear bond forming reactions with high enantioselectivity and broad substrate scope.[2,5,6,25-27] Jørgensen *et al.* showed that two water molecules could act as hydrogen bond activators of a carbonyl group, in effect rigidifying the transition state and promoting rate enhancement in the Diels Alder[28,29] and other pericyclic reactions (Figure 1.4). Catalysts capable of donating two hydrogen bonds have since emerged as a class of "privileged"[30] catalyst structures capable of catalysing mechanistically diverse reactions such as 1,2 and 1,4 additions, acyl-transfer and cycloaddition reactions.[6] Figure 1.4 also schematically represents the rigid double hydrogen bond activation of a carbonyl electrophile by guanidinium[31]/ amidinium ions[32], diol[33] and (thio)urea classes of catalyst.

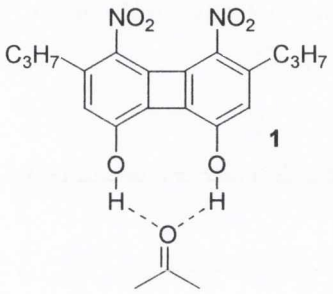
Figure 1.4 Examples of double hydrogen bond activation of a carbonyl electrophile by various rigid catalyst frameworks.



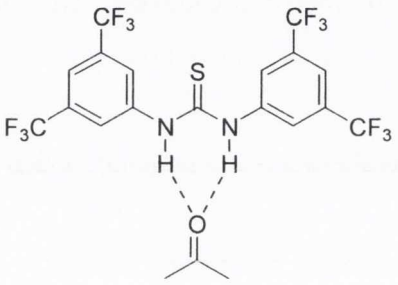
Jorgensen's diol model



Corey's guanidinium ion catalysts
Gobel's amidinium ion catalysts



Kelly's biphenylenediol



Schreiner's diaryl(thio)urea catalysts

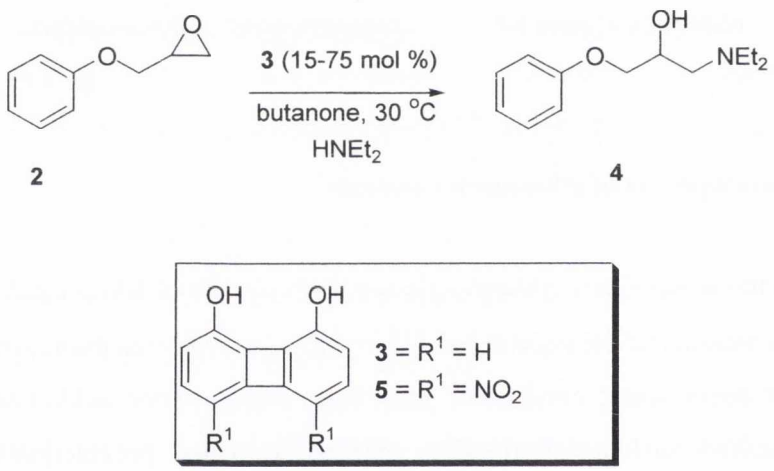
1.3 Development of (thio)urea catalysts

As mentioned earlier in Section 1.2.3 strong protic acids are not efficient catalysts for many C-C bond-forming reactions as the necessary nucleophiles (enolates, enamines and cyanides) are rapidly quenched under acidic conditions. Moreover, strong protic acids can in some cases promote side-reactions such as elimination, epimerisation and polymerisation reactions of starting materials and products.[27] The multitude of enzymes operating through general acid catalysis by hydrogen bond activation of the carbonyl group has inspired the use of Lewis acids capable of similar hydrogen bonding techniques in catalyst systems. The utilisation of functional groups capable of donating hydrogen bonds as general acid catalysts is the one of the current strategies being employed in asymmetric organocatalysis.[34-36]

1.3.1 Early developments-diol organocatalysts

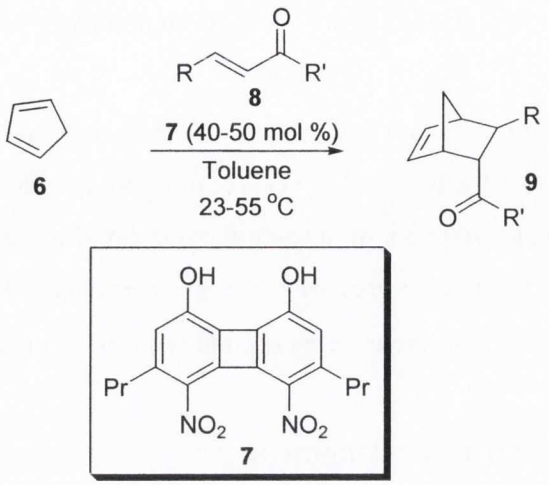
Hine *et al.*[37] published a seminal paper in 1984 that demonstrated the catalytic ability of diols as double hydrogen bond donating molecules in the addition reaction of nucleophiles to epoxides. 1,8-Biphenylenediol **3** was found to be a significantly better catalyst than either mono-substituted phenols or *meta* and *para*-substituted phenols for the addition reaction to phenyl glycidyl ether **2** (Scheme 1.3). The overall superiority of **3** motivated the authors to propose (based on experimental evidence and X-ray crystal structure data[38]) that both hydroxyl groups participated in catalysis. The catalytic activity per hydroxyl group of **3** was found to be that expected of a phenol 600 times as acidic.[5]

Scheme 1.3 Epoxide ring opening using biphenylene derivatives as catalysts



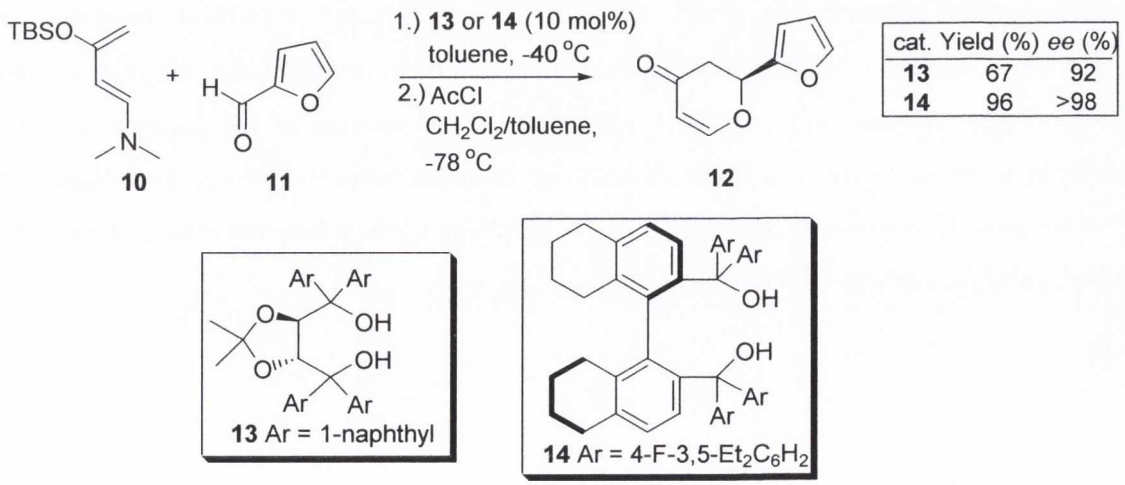
Subsequent work in the Hine group identified dinitrophenylenediol derivative **5** as an appreciably more efficient hydrogen-bond donator.[39] Later Kelly and co-workers[33] disclosed the successful catalysis of the Diels-Alder reaction between cyclopentadiene **6** and α,β-unsaturated aldehydes and ketones by a 3,6-dipropyl derivative **7** (Scheme 1.4). The binding mode of catalysis outlined by Kelly in Figure 1.4 (*vide supra*), was subsequently confirmed by computational modelling carried out by the Jørgensen group to explain rate acceleration in the Diels-Alder reactions and Claisen rearrangements in water relative to non-protic solvents.[28,40]

Scheme 1.4 Kelly *et al.* promotion of the Diels-Alder reaction



Rawal *et al.*'s investigations into the hydrogen-bond-promoted hetero-Diels-Alder (HDA) reaction not only discovered that hydrogen bond donating solvents such as 2-butanol and chloroform were capable of accelerating reaction rates by nearly three orders of magnitude,[41] but also led to the development of the first α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL)-based chiral promoter **13** of the HDA.[42] **13** Was found to catalyse HDA reactions of aminodienes **10** with aliphatic and aromatic aldehydes *e.g* **11** in excellent yields and enantioselectivities (Scheme 1.5).[6]

Scheme 1.5 Enantioselective TADDOL derivatives as promoters of cycloaddition reactions



Yamamoto and Rawal *et al.* subsequently made modifications to the chiral backbone, utilising the axially chiral characteristics of 1,1'-bi-2-naphthol (BINOL, **14)** which also proved to be an excellent promoter of the HDA reaction with a variety of aldehyde substrates (Scheme 1.5).[42]

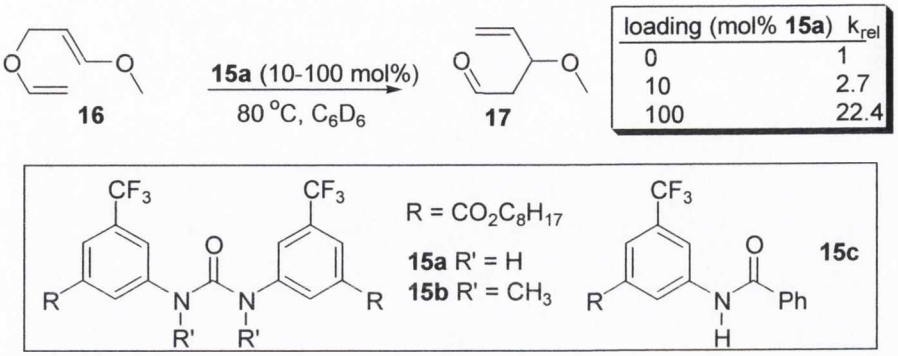
X-ray crystallographic studies of a variety of TADDOL derivatives have been shown to exhibit an intramolecular hydrogen bond between both hydroxyl groups, the remaining proton on the hydroxyl group not involved in intramolecular bonding is therefore acidified and orientationally distinct. Crystal structures of inclusion complexes have shown that the free hydroxyl group participates in a single hydrogen bond with the substrate.[38,39]

1.3.2 *N,N'*-Diaryl urea development

Theses early studies by Hine[39] and Kelly[33] recognised that GAC by conformationally restricted metal-free diprotic acids were a good template on which to base future organocatalyst design on. Etter *et al.* developed those concepts with studies on the co-crystallisation of *N,N'*-diarylureas with a range of compounds with Lewis basic functional groups such as nitroaromatics and ethers.[43,44] The crystal complexes confirmed the binary mode of binding by each urea component (*i.e.* one Lewis basic substrate binds by accepting a Hydrogen bond from each urea hydrogen) and provided the foundation for the development of chiral urea-based organocatalysts.

Curran *et al.* were the first group to use *N,N'*-diarylureas as catalysts. **15** When used in substoichiometric amounts promoted the allylation of cyclic α-sulfinyl radicals with allyltributylstannane.[45] The inclusion of an electron-withdrawing group (*i.e.*, CF_3) in the *meta* positions of the aromatic substituents to minimise self-association of the catalyst and alkyl side chains in order to aid catalyst solubility in common solvents proved advantageous.[46] *N,N'*-diarylurea **15** also found utility as a promoter of the Claisen rearrangement of **16**, albeit with high catalyst loadings (Scheme 1.6).[47]

Scheme 1.6 Curran's *N,N'*-diarylurea catalysed Claisen rearrangement of **16**[47]

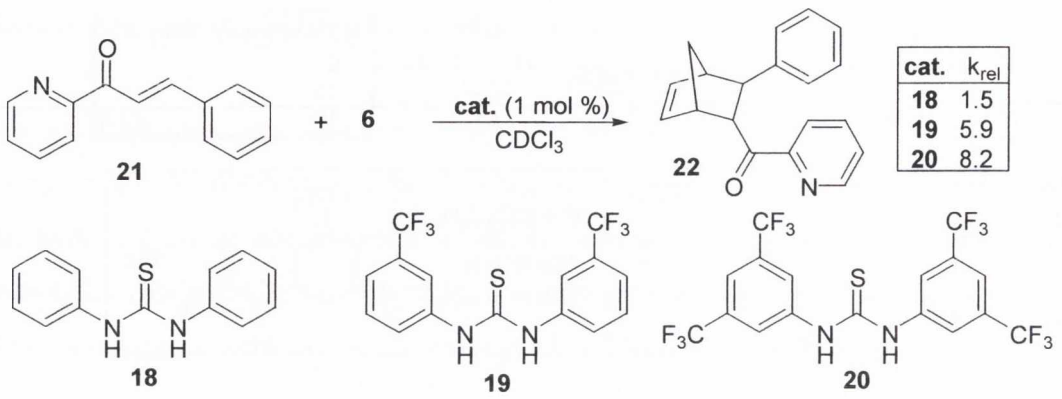


A *N*-methylated analogue of **15a**, **15b** was catalytically inactive. Likewise the benzanilide **15c**, a molecule with only one proton donor, confirmed that both urea protons are involved in catalysis.

More recently, Schreiner employed thiourea derivatives related to **15a** in the catalysis of the Diels-Alder reaction between **6** and α,β-unsaturated carbonyl compounds.[48,49,50,51] Thioureas were preferred over their urea counterparts for a number of reasons including greater solubility in a range of solvents, ease of preparation and the inferiority of the thiocarbonyl group as a hydrogen-bond acceptor (compared to the carbonyl group) thereby reducing the problems of self-association. The hydrogen bond donor capability of the thiourea analogue was expected to be greater than that of the urea, based upon their relative acidity (pK_a thiourea = 21.0; pK_a urea = 26.9).[52]

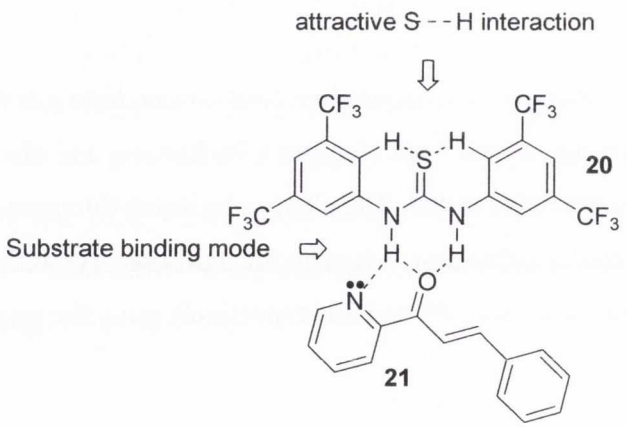
Several symmetrical thioureas were evaluated as catalysts including both aromatic and alkyl derivatives. Aniline derivatives with both electron withdrawing and electron donating groups in various ring positions were also tested. The alkyl-substituted thioureas and diphenylthiourea **18** only gave minimal rate acceleration, whereas the fluorophenyl and most importantly the trifluoromethyl-substituted thioureas **19** and **20** respectively gave the greatest rate acceleration overall (Scheme 1.7).

Scheme 1.7 Schreiner's diarylthiourea catalysis of the Diels-Alder reaction.



The rate acceleration observed using thiourea catalyst **20** can be rationalised in terms of both enthalpic and entropic effects.[49] The electron withdrawing CF_3 groups ($\sigma_m = 0.46$) on the ring act to acidify the N-H urea protons, thereby improving substrate binding. Computational studies[48] suggest that entropy loss upon binding of the substrate is minimised through the rigidity of the catalyst, which is due to an attractive (rigidifying) interaction between the polarised *ortho*-hydrogen atoms and the Lewis basic sulfur atom (Figure 1.5). The "rigidified" lowest energy conformation is *thus* the most catalytically active and through which substrate turnover occurs.[5]

Figure 1.5 Rigidifying effect of *ortho* hydrogen atom in catalyst **20**



1.3.2.1 Summary of *N,N'*-diarylurea catalyst applications.

The pioneering work of Etter, Curran and Schreiner on thiourea catalyst design has demonstrated that the *N,N'*-diarylthiourea template with strategically placed *meta* and *para* aryl substituents are the most effective catalysts in this class.

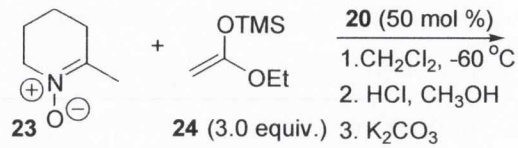
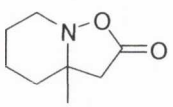
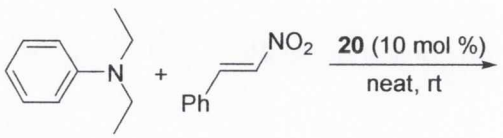
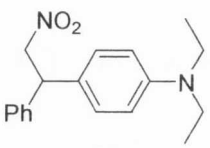
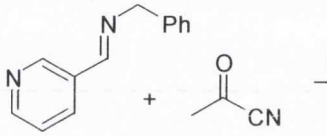
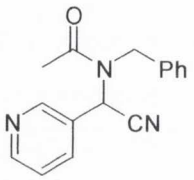
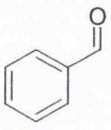
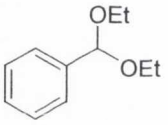
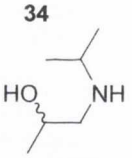
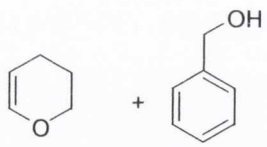
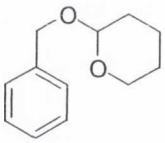
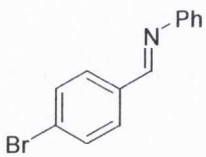
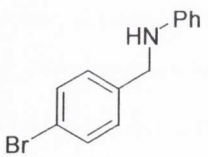
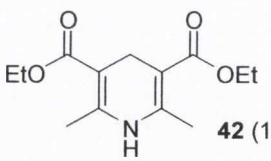
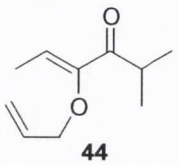
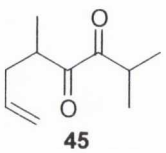
1.3.2.2 Recent advances in C-C bond formation using 20.

To date the *tetra* substituted *N,N'*-diarylthiourea catalyst **20** is the most effective hydrogen bond activating catalyst for many C-C bond forming reactions. Since Schreiner's seminal paper in 2002[49] on the Diels-Alder reaction there has been an array of studies carried out utilising **20**. Scheme 1.8 outlines a timeline of these advancements. **20** Found application as an efficient Lewis acid-like activator of the addition of cyanide ion and silyl ketene acetals to nitrones (Scheme 1.8, Entry 1),[53] and the Friedel-Crafts type alkylation addition reaction of a range of electron-rich aromatic and heteroaromatic systems to nitroolefins, a reaction commonly catalysed by $Y(OTf)_3.3H_2O$,[54] $Sc(OTf)_3$[55] or $Bi(OTf)_3$[56] (Scheme 1.8, Entry 2).[57]

Thiourea **20** was also found to be an effective promoter of the catalytic acylcyanation of both aliphatic and aromatic aldimines (using acetyl cyanide as the cyanide source - Scheme 1.8, Entry 3),[58] acid-free acetalisations (Scheme 1.8, Entry 4),[59] epoxide ring opening reactions with various nucleophiles (Scheme 1.8, Entry 5),[60] and the tetrahydropyranylation protection of alcohols (Scheme 1.8, Entry 6).[61]

Catalyst **20** through hydrogen-bond activation, in conjunction with Hantzsch 1,4-dihydropyridine **39** as the hydrogen source catalyses the transfer hydrogenation of imines (Scheme 1.8, Entry 7)[62] and further studies on Claisen rearrangements have also recently been carried out using **20** (Scheme 1.8, Entry 8).[63]

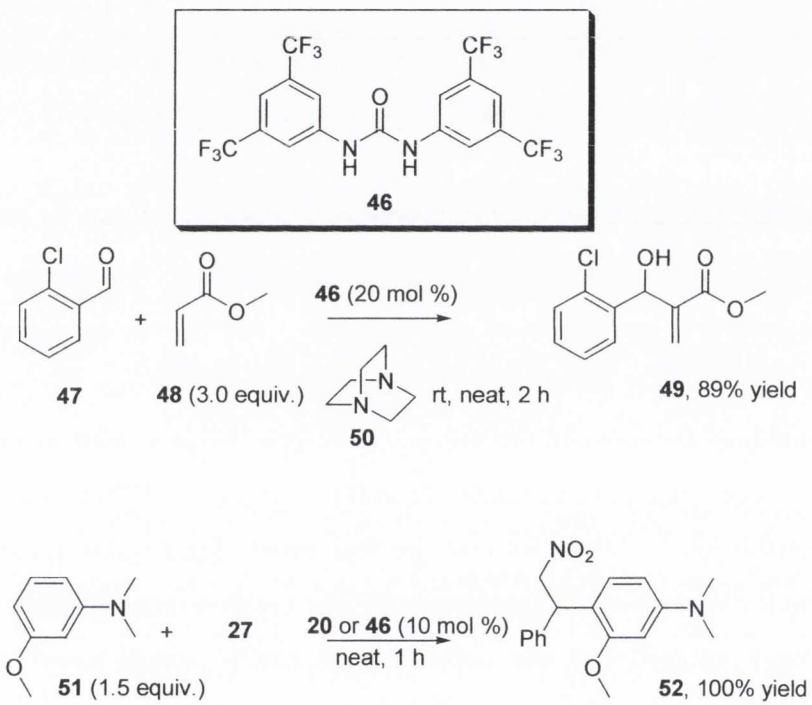
Scheme 1.8 Examples of reactions catalysed by catalyst **20**

Entry	Reactants	Product	Yield	Year
1	 **23** + **24** (3.0 equiv.)	**20** (50 mol %) 1. CH_2Cl_2, -60 °C 2. HCl, CH_3OH 3. K_2CO_3	 **25**	1 h = 88%	2003
2	 **26** (1.5 equiv.) **27**	**20** (10 mol %) neat, rt	 **28**	24 h = 97%	2004
3	 **29** + **30** (1.5 equiv.)	**20** (2 mol %) CH_2Cl_2, 0 °C	 **31**	24 h = 96%	2006
4	 **32** + $HC(OEt)_3$ **33** (2.0 equiv.)	**20** (1 mol %) CH_3CH_2OH, rt	 **34**	8 h = 86%	2006
5	 **35** + **36**	**20** (10 mol %) H_2O, rt ultrasonication	 **37**	21 h = 64%	2006
6	 **38** (2.0 equiv.) + **39**	**20** (0.001 mol %) neat, rt vigorous stirring	 **40**	48 h = 98%	2007
7	 **41**	**20** (1 mol %) CH_2Cl_2, rt	 **43**  **42** (1.1 equiv.)	15 h = 93%	2007
8	 **44**	**20** (100mol %) $CHCl_3$, 45 °C sealed tube	 **45**	24 h = 41%	2007

1.3.2.3 3,5-*Bis* trifluoromethylurea 46 catalyst applications

The less acidic urea counterpart **46** (pK_a thiourea = 21.0; pK_a urea = 26.9)[52] is also a valuable hydrogen bond activator, of particular interest is its use as a promoter in the bifunctional catalysis (in conjunction with a tertiary base) of the Baylis Hillman reaction (Scheme 1.9) [64] and interestingly in the Friedel-Crafts addition reaction[57] where the urea catalyst **46** exhibited similar activity to the thiourea analogue **20** in the addition of the electron-rich *m*-Ome-*N*, *N*'-dimethylaniline derivative **51**, both additions were complete after just one hour.

Scheme 1.9 Recent examples of C-C bond forming reactions catalysed by catalyst **46**.



Catalytic amounts (20-40 mol %) of **46** greatly accelerate the DABCO-promoted Baylis–Hillman reaction between a range of aromatic aldehydes and methyl acrylate. The reactions were performed neat and urea's such as **46** were found to be better mole-per-mole promoters than more protic hydrogen-bond activators such as water and methanol.[28]

1.3.2.4 *N,N'*-diaryurea development: conclusions

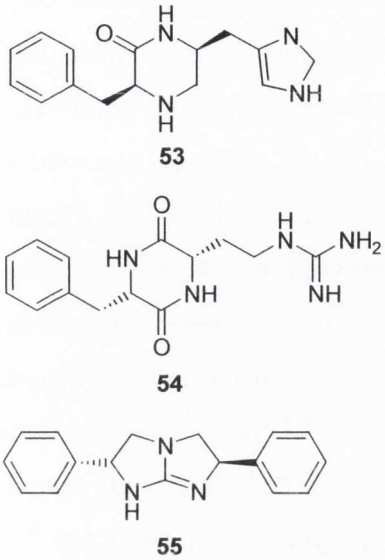
The *N,N'*-diaryl(thio)urea based catalysts have distinctly advantageous features which facilitate further catalyst design, these include tunability (using aromatic substituents and the choice of urea/thiourea), robustness (stability), easy accessibility (from iso(thio)cyanates). The presence of two co-planar hydrogen atoms are well placed to donate two hydrogen bonds to stabilise developing negative charge in the transition states of a number of synthetically useful addition reactions.

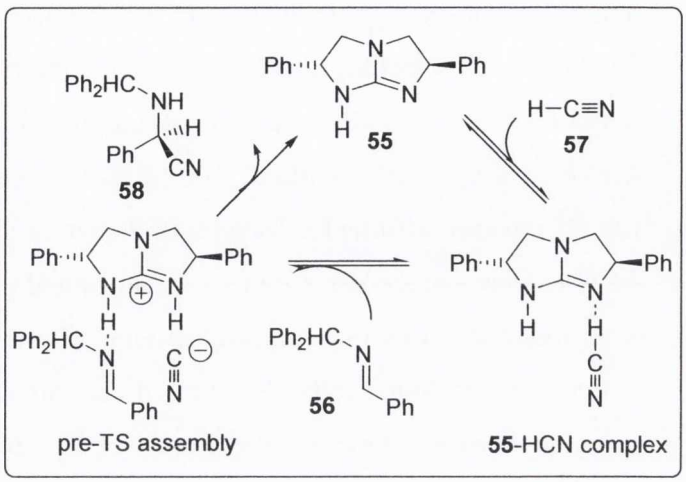
1.3.3 Chiral (thio)ureas as catalysts

Due to the advantages outlined previously regarding the use of the *N,N'*-diaryl(thio)urea template, the design of chiral (thio)urea catalysts was the next obvious objective because of the ready availability of chiral amines from the chiral pool. The emergence of versatile and tuneable chiral (thio)urea catalysts as small enzyme mimics has been swift.

Early studies on the hydrocyanation of carbonyl compounds catalysed by cinchona alkaloids such as quinine[65] gave modest enantiomeric excesses.[66] The introduction of small cyclic peptides incorporating a guanidine motif (Scheme 1.10) led to an improvement in the enantiomeric excesses of the products.[66-68] This result indicated that the guanine motif was effective at promoting asymmetric induction. Since this result similar guanidine containing compounds have been used as chiral catalysts in the addition of HCN to aldehydes[68] (**53**) and two Schiff bases (**54**, **55**).[31,66] 20 years after the first report of the hydrocyanation of aldehydes by **53**, a clear understanding of the mechanism of the catalyst remains elusive, yet it remains an important early example of the capability of small peptide-based catalysts for the promotion of asymmetric transformations.[69] The results reported by Inoue and his group[68] on the hydrocyanation of imines using catalyst **54** have been disputed as proton transfer and the subsequent addition of cyanide can occur in the absence of the catalyst.

Scheme 1.10 Examples of chiral additives for the enantioselective addition of HCN to aldehydes and Schiff bases and mode of action of **55**.





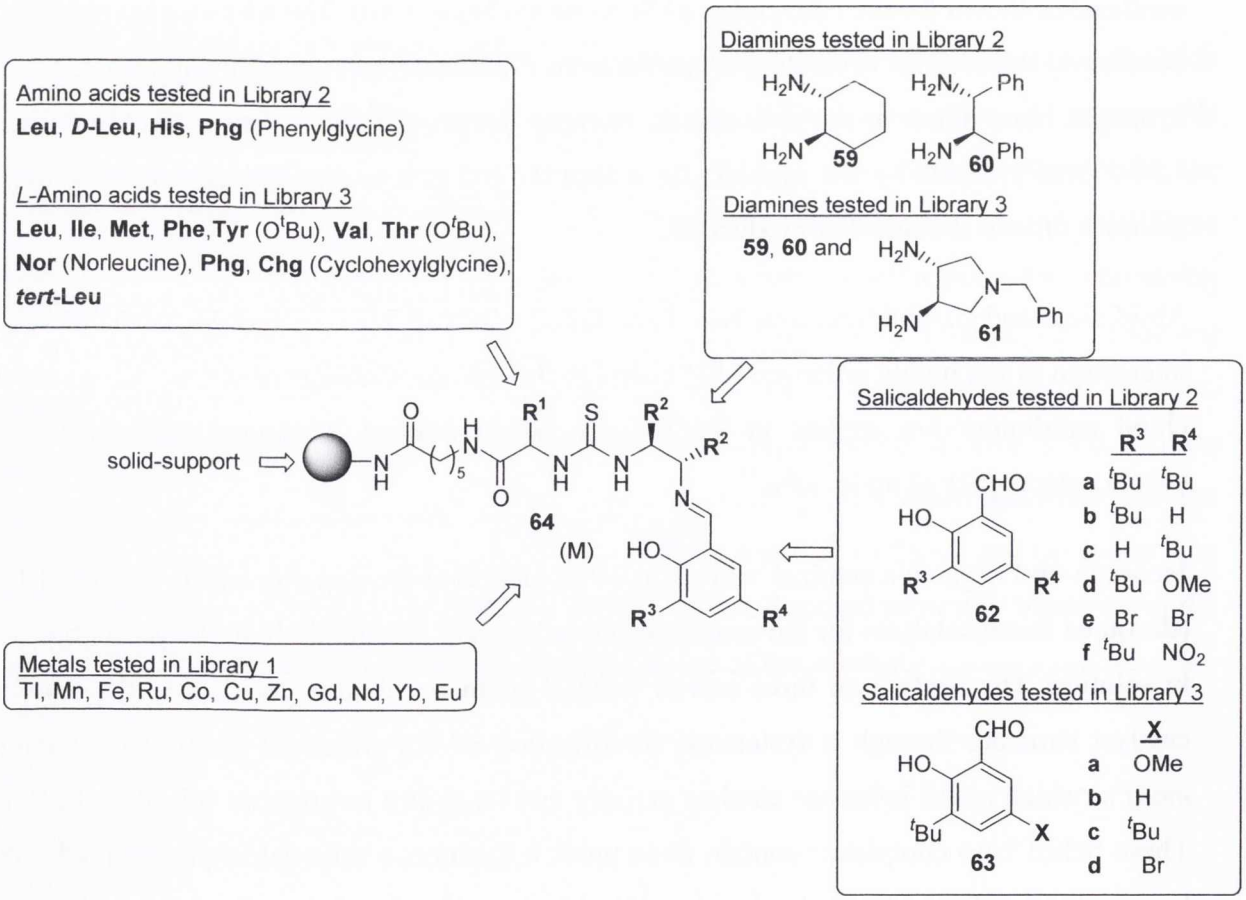
The catalytic action of the bifunctional catalysts **54** and **55** can be explained through the mechanism shown for the conversion of **56** to **58** (Scheme 1.10). The first step involves HCN bonding to the catalyst generating a guanidinium cyanide complex, which can also serve as a hydrogen bond donor to the aldimine **56** forming the pre-transition state assembly (Scheme 1.10). Finally, attack by the cyanide ion within the ion pair on the hydrogen-bond-activated aldimine affords the Strecker product **58**.[31]

Amidinium and guanidinium ions have been found to be capable catalysts due to the increased interaction of the highly polarised N-H bonds in the cations. Gobel *et al.* found that an axially chiral amidinium ion applied in the reaction of unsaturated diketones with dienes gave enantioselectivities of up to 50%.[32]

Jacobsen and Sigman's seminal work[70] in 1998 identified the superior utility of Schiff base (thio)urea based catalysts for the enantioselective Strecker reaction in both the solid phase and in solution. The study used three sets of parallel synthetic libraries to identify the optimum catalyst structure through a systematic modification of key tridentate Schiff base complex *motif's*, which could influence catalyst activity and its ability to promote selective reactions. These Schiff base complexes contain three units, a diamine, a salicylaldehyde-derived Schiff base and a metal ion, the study aimed to identify the optimum catalyst through modifications

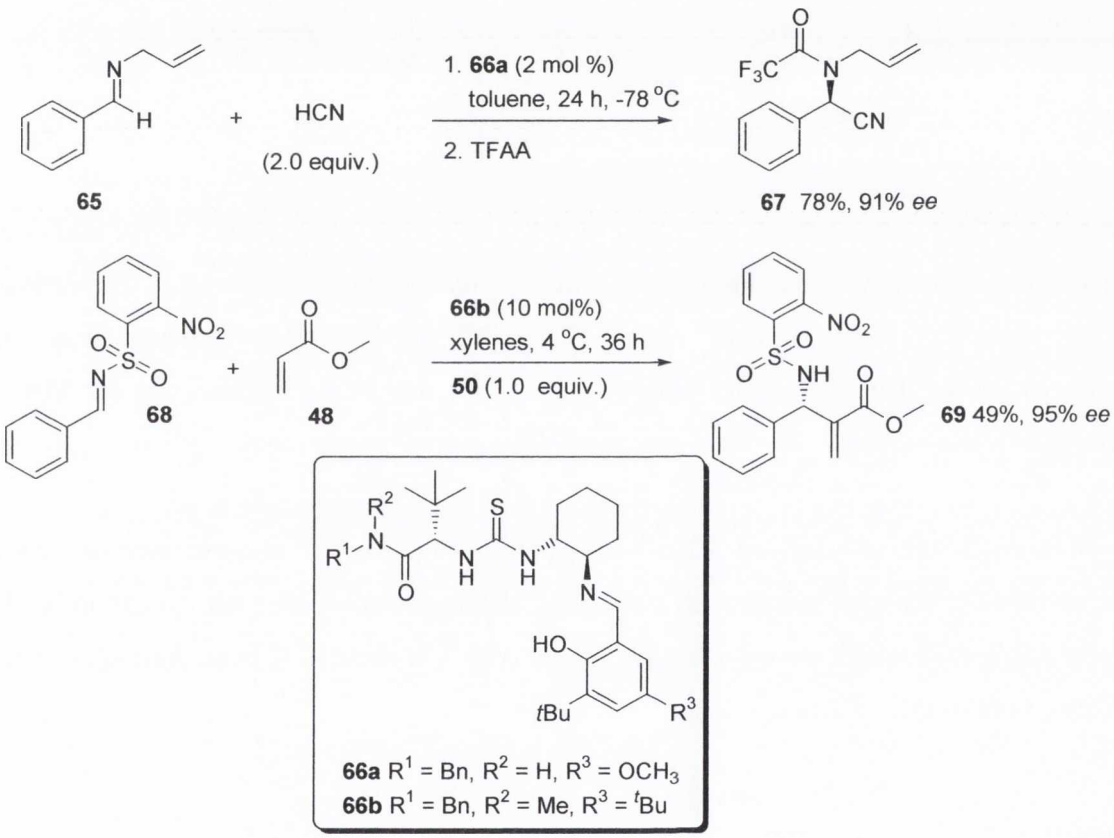
of these elements. An additional amino acid was incorporated as a diversity element between the diamine and the polymer support (see Figure 1.6).[70] Library one confirmed previous study findings[66] that the organic ligands (in the absence of any metal ion) were the optimal catalysts for the enantioselective Strecker reaction. Library three identified the optimum amino acid component as a *tert*-leucine-derived group (Figure 1.6, R^1 group) and that the relative stereochemistry was important. The (*R,R*)-1,2-diaminocyclohexane-derived catalysts (Figure 1.6, R^2 groups) afforded substantially higher *ee*'s when coupled with the *L-tert*-leucine than the *D*-leucine enantiomer. Library two confirmed the superiority of the thiourea (relative to the urea) *motif* in terms of enantioselectivity. The optimum substituent on the salicylaldehyde component was found to be 3-*tert*-butyl derivatives (Figure 1.6, R^3/R^4 groups). Library three was comprised of a large parallel library of 132 thiourea derivatives; the bulkiest amino acids (*tert*-Leucine, cyclcohexylglycine and isoleucine) afforded the highest *ee*'s (Scheme 1.11).[70,71]

Figure 1.6 Libraries tested on the catalyst template **64** by Jacobsen *et al.*



The optimal catalyst identified was the *tert*-Leucine-derived thiourea **66a** which was tested in the Strecker reaction with HCN and *N*-allylbenzaldimine, affording the corresponding adduct in 78% yield and 91% enantioselectivity at –78 °C.[70] *N*-Nosyl protected imines[72] were also later identified as excellent substrates for the enantioselective aza-Baylis Hillman reaction with methyl acrylate in the presence of DABCO (**50**) as a nucleophilic co-catalyst. In the presence of thiourea catalyst **66b** the synthetically useful adduct **69** could be isolated in moderate yield of 49% and an excellent 95% *ee* (Scheme 1.11).

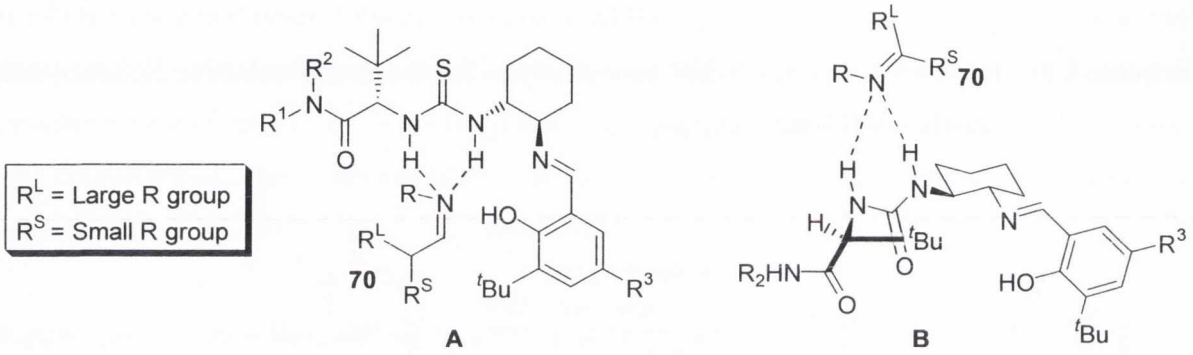
Scheme 1.11 Jacobsen's thiourea Schiff base catalysts for the enantioselective Strecker and aza-Baylis-Hillman reaction.



Using spectral experiments and binding studies it was suggested that the *Z*-isomer of the imines preferentially bind to the two thiourea hydrogens of the catalyst *via* the imine lone-pair in a mode which minimises steric interactions between the catalyst and the imine substituents[73] (Figure 1.7, Diagram A). Takemoto's 'bridging' binding mode[74] using a urea derivative illustrates the preference of the largest substituent (R^L of the incoming imine) into a

position that minimises steric hindrance with the catalyst (Figure 1.7, Diagram B). It was also determined through these studies that the thiourea-catalysed Strecker reactions display Michaelis-Menten kinetic behaviour, which implies reversible substrate binding to the catalyst.[5]

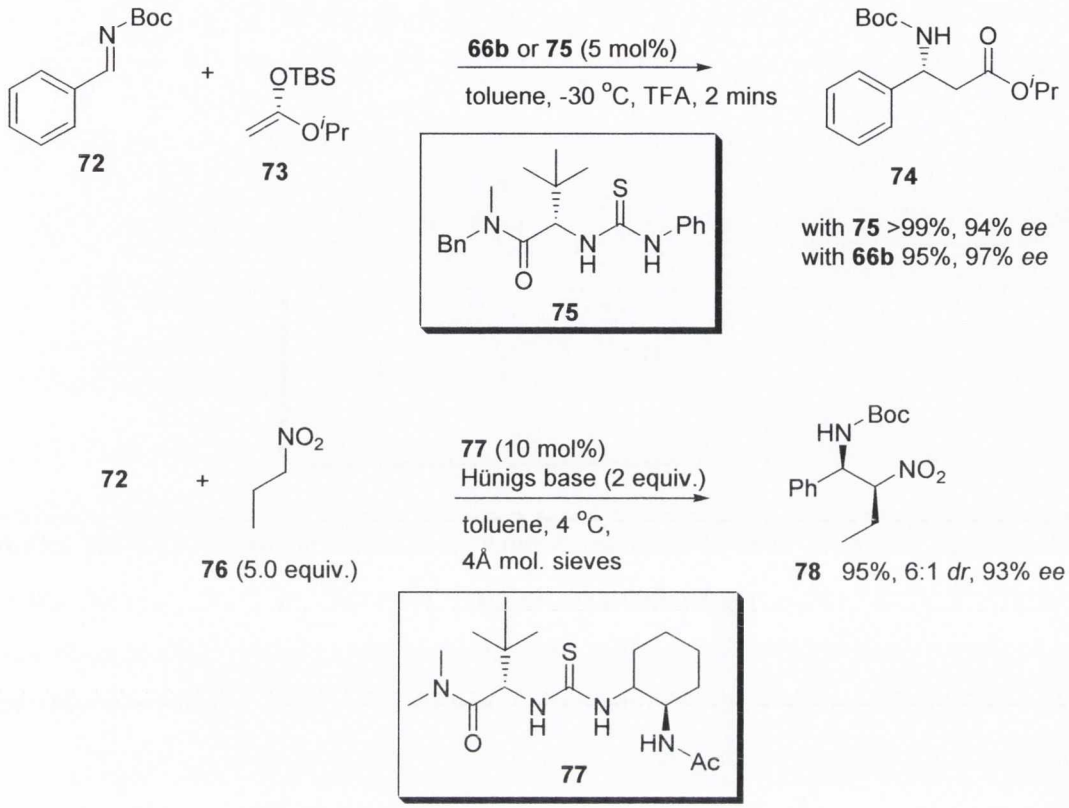
Figure 1.7 Proposed binding mode of imines with the Jacobsen template.



Jacobsen's Schiff base catalysts were also found to be effective promoters of the addition of silyl ketene acetals to *N*-Boc-aldimines (the Mannich reaction) to form *N-tert*-butoxycarbonyl-(*N*-Boc) protected β-amino acids. The absolute configurations of the products from these reactions signified that a different mechanism was operating in the Strecker and the Mannich reactions.

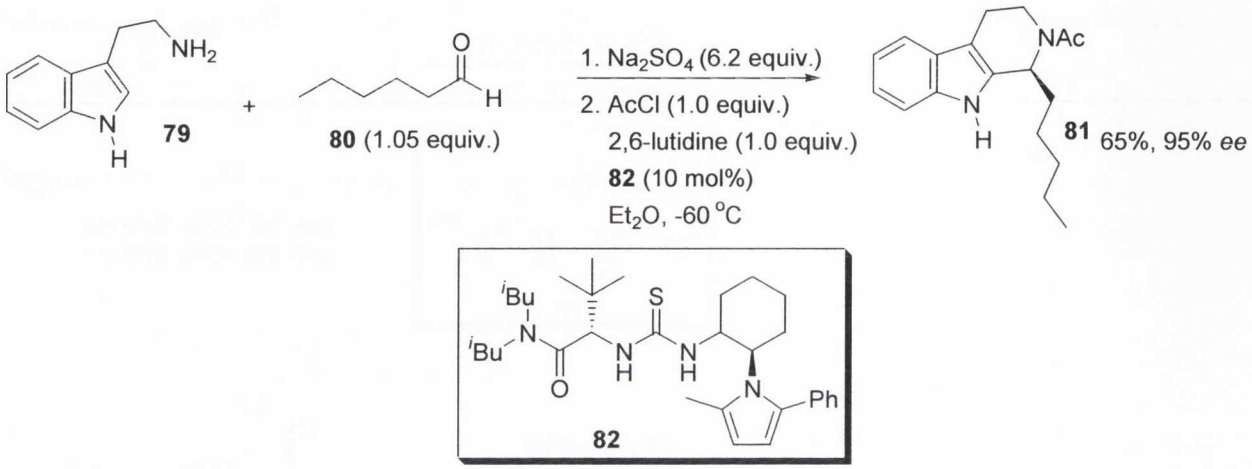
The diaminocyclohexane-derived Schiff base portion of the catalyst was not necessary for the enantioselective Mannich reaction. Replacement of this moiety with a phenyl group led to a simpler catalyst **75** which possessed improved activity[75] in these C-C bond forming reactions of *N*-protected imines (Scheme 1.12).

Scheme 1.12 Thiourea catalysed C-C bond forming reactions of *N*-Boc imines.



N-Boc imines participate in nitro-Mannich reactions in the presence of thiourea **77** which bears an acetamidocyclohexane substituent,[76,77] the function of which is not fully understood but it has been suggested to have a hydrogen-bonding role in binding one of the substrates, the other being bound by the thiourea moiety. Of all the imines covered thus far none are as reactive as the *N*-acyliminium ions which have a diminished Lewis basicity and H-bond activation scope due to their cationic nature. Jacobsen *et al.* demonstrated the first use of a H-bond activating catalyst **82** in the promotion of the acyl-Pictet-Splenger reaction using *N*-acyliminium ions in the novel heterocycle forming reaction (Scheme 1.13).[78] Catalyst **82** is also an efficient promoter of the Mannich reaction of acylisoquinolinium ions producing enantioenriched dihydroisoquinoline products.[79]

Scheme 1.13 Thiourea catalysed enantioselective acyl-Pictet-Spengler reaction

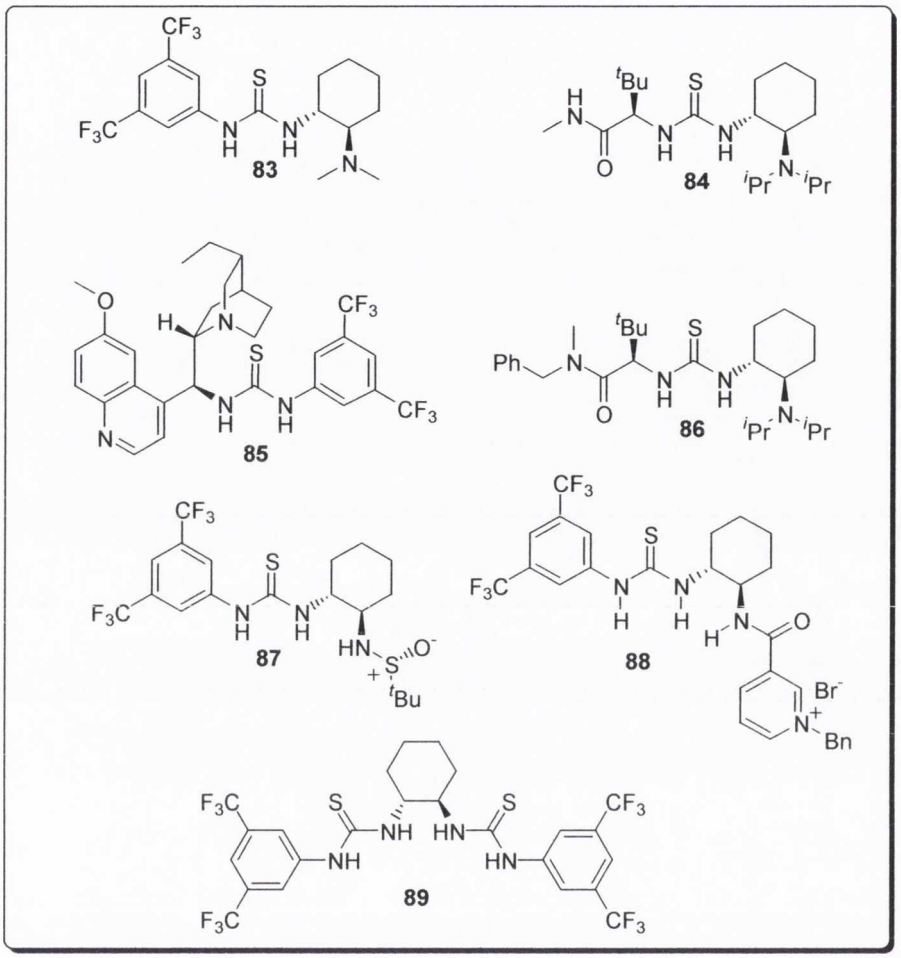


The *ee* values of both the acyl-Mannich and acyl-Pictet-Spengler reaction exhibit a dependence upon the substitution pattern of the pyrrole moiety of catalyst **82**. A solid-state crystal structure of catalyst **82** depicts the orientation of the 2-methyl-5-phenylpyrrole *motif* and places the bulkier phenyl group in the correct position to interact closely with any species that takes part in hydrogen-bonding with the catalyst thiourea protons.[79]

The choice of a urea or a thiourea (degree of H-bond activation of the electrophile) component and the modification of the amide substituents allow the fine-tuning of the catalyst to suit the needs of the reaction of choice. The attachment of additional acidic or basic functional groups to the primary catalyst structure has seen an easy transition into the field of bifunctional catalysis (facilitated by the high functional group tolerance of the isothiocyanate coupling reaction).

The advantages of bifunctional catalysis include the ability to activate both the electrophilic and nucleophilic reaction components (mimicking natural enzymatic systems) and subsequent control over their encounter in a chiral environment. An added advantage of this includes significantly improved catalytic activity. The vast majority of bifunctional catalyst systems are based upon a hybrid catalyst design strategy involving the design principles set out by Curran, Jacobsen and Schreiner (earlier). The strategy involves the combination of readily tuneable aromatic functionality at one (thio)urea nitrogen atom, and chiral functionality (often Lewis basic) at the other. Representative bifunctional catalyst designs are illustrated in Figure 1.8.

Figure 1.8 Representative bifunctional catalyst designs



Bifunctional catalyst designs based on Jacobsen's original template[70] have found application in a vast range of enantioselective reactions including Michael addition reactions,[80,81] nitro-Mannich reactions,[82] dynamic kinetic resolutions,[83-85] the Baylis-Hillman reaction,[86] stereoselective additions to nitroalkenes,[87] the silylcyanation of ketones,[88] the addition of allylindium reagents to acylhydrazones[89] and the reduction of 1,2-diketones (see Scheme 1.14).[90]

Scheme 1.14 Bifunctional catalyst applications

Entry	Reactants	Product	Yield	Year
1	**27** + H_3CO_2C CO_2CH_3 **90** (2.0 equiv.) — **83** (10 mol %), toluene, rt	H_3CO_2C CO_2CH_3, Ph, NO_2 **91**	36h = 82%, 93% *ee*	2003
2	CHO **92** + O **93** (2.0 equiv.) — **89** (0.4 equiv.), DMAP (0.4 equiv.), neat, -5 °C	OH, O **94**	72h = 55%, 86% *ee*	2004
3	Cl, O, Ph **95** + H_3CNO_2 **96** (5.0 equiv.) — **85** (10 mol %), toluene, rt	O_2N, O, Ph **97**	122h = 94%, 95% *ee*	2005
4	S, N, O **98** — **84** (5 mol%), TMSCN(2.2 equiv.), CF_3CH_2OH (1.0 equiv.), CH_2Cl_2, -78 °C	TMSO, CN, CH_3, S, N **99**	48h = 87%, 97% *ee*	2005
5	^{i}Bu, O, N, O, Ph **100** (rac) + HO **101** (1.5 equiv.) — **86** (5 mol %), toluene, rt	Ph, H, N, O, O, ^{i}Bu **102**	48h =77%, 91% *ee*	2005
6	NO_2, Br **103** — 1. $CHCl(CO_2Me)_2$ (1.05 equiv.), **85** (2 mol%), CH_2Cl_2(0.5M), -30 °C, 25h; 2. filter; 3. HMPA (0.1 M), DBU (1.05 equiv.), rt, 24h	MeO_2C, CO_2Me, NO_2, Br **104**	49h = 67%, >98% *de*, 47% *ee*	2006
7	O, Ph, NHBz, N, Ph **105** + Br **106** (2.63 equiv.) — **76** (10mol %), In (1.75 equiv.), toluene, -20 °C	O, Ph, NH, HN, Ph **107**	15h = 87%, 92% *ee*	2007
8	O, O, Ph, Ph **108** — (*R*,*R*)-**88** (20 mol%), $Na_2S_2O_4$ (2.5 equiv.), $NaCO_3$ (2.0 equiv.), 2.5:1 (H_2O/Et_2O)	O, OH, Ph, Ph **109**	15h = 29%, 25% *ee*	2007

1.4 Binaphtyl based catalyst systems

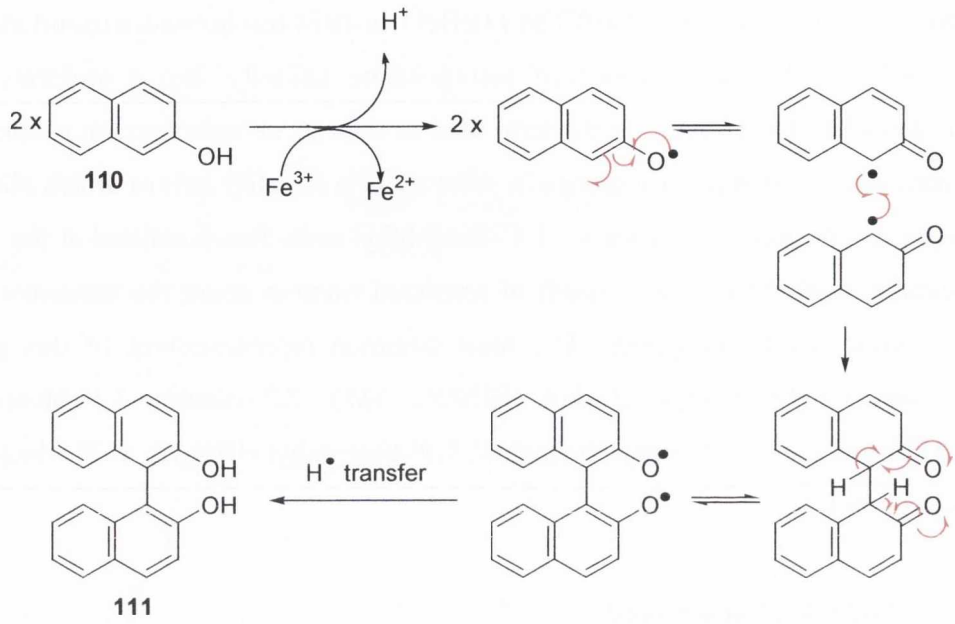
Axial chirality[91] predicted by van't Hoff[92] and LeBel[93] in 1874 has become a useful alternative to the tetrahedral carbon as a means of incorporating chirality into a molecule. 'Axial chirality' is described by IUPAC[94] as the term used to refer to stereoisomerism resulting from the non-planar arrangement of four groups in pairs about a chirality axis of which allenes and biaryls are the most common examples. 1,1'-Binaphthyl units functionalised at the 2 and 2' positions exhibit axial chirality as a result of restricted rotation about the transannular bond and are C_2 symmetrical compounds. The most common representatives of this group of compounds are 1,1'-binaphthyl-2,2'-diol (BINOL, **111**), 2,2'-diamino-1,1'-binaphthalene (BINAM, **112**) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, **113**) which will be covered in Section 1.4.3.

1.4.1 BINOL : background

The C_2 symmetrical **111** is one of the best-known representatives of axially chiral molecules and was first prepared in the form of a racemate in 1873 by von Richter[95] and subsequently as an optically active compound whose absolute configuration was not determined until some years later.[96] Racemic BINOL can be synthesised using an excess of a mild oxidising agent such as Cu(II),[97] Fe(III),[98] Mn(III)[99]or Ti(IV)[100] complexes as coupling agents in both high-yield and efficiency (Scheme 1.15).

Other methods of racemic BINOL synthesis include the catalytic ultrasonic irradiation of 2-naphthol with $FeCl_3.6H_2O$ at 50 °C[101-103] and the use of either $VO(acac)_2$,[104] methyltrioxo rhenium,[105] an alumina-supported copper(II) sulfate catalyst under aerobic conditions,[106-108] or vanadyl phosphate (VOPC)[109] and mesoporous molecular sieves.[110] BINOL can be prepared as the enantiopure (*R*) or (*S*) enantiomer through two different routes, **a)** enzymatic[111] or chemical resolution[112,113] of racemic BINOL or **b)** a direct stoichiometric/catalytic oxidative coupling synthesis.[114,115]

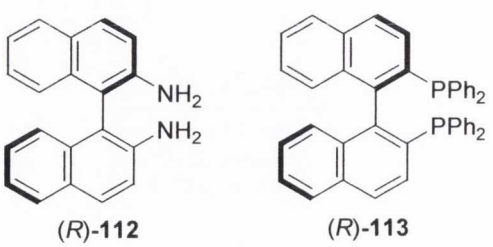
Scheme 1.15 $FeCl_3$ catalysed synthesis of BINOL



1.4.2 BINAM and BINAP background

Structurally related to **111** are the compounds 2,2'-Diamino-1,1'-binaphthalene (BINAM, **112**) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP, **113**) both of which can be synthesised from using similar oxidising agents to that of **111**.[116] Both **112** and **113** possess the feature of atropisomery and are easily incorporated into catalyst structures (Figure 1.9). The binaphthyl template has been found to be an excellent ligand for the transfer of chemical information in many metal-ion based catalysts and more recently in organocatalysts. Examples of asymmetric reactions catalysed by these binaphthyl-derived catalysts will be covered in section 1.4.3.

Figure 1.9 Ligands **112** and **113**

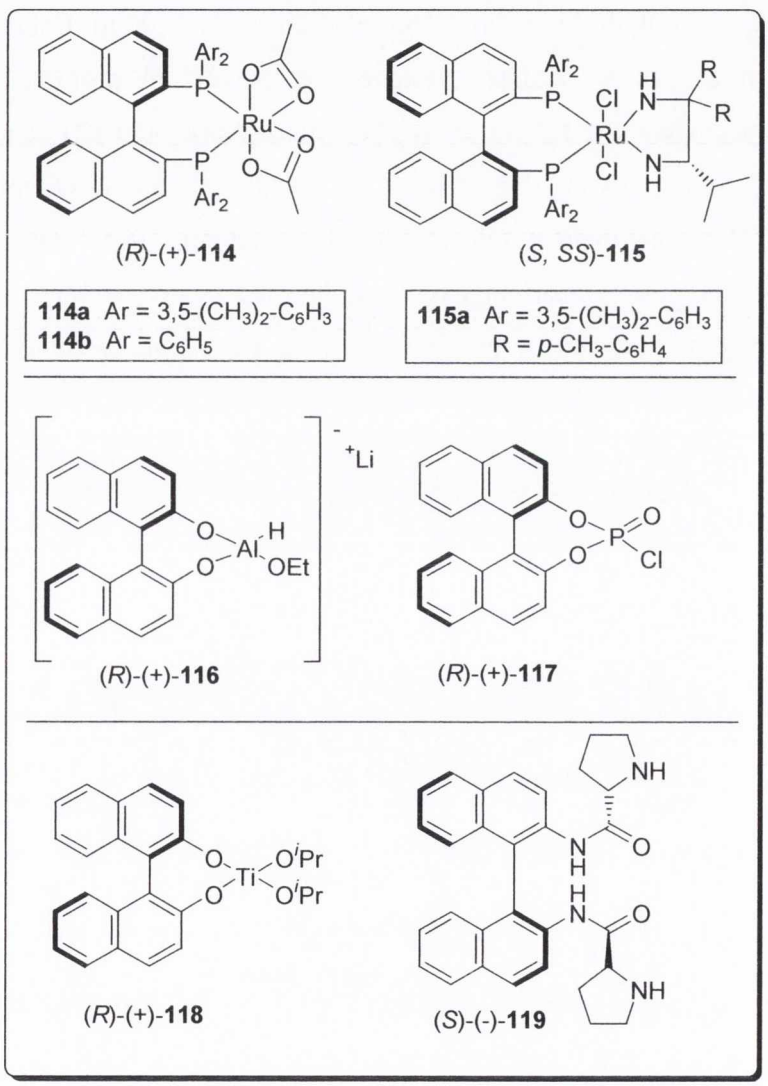


(*R*)-**112** (*R*)-**113**

1.4.3 Asymmetric catalysis by BINAP-, BINOL- and BINAM-based catalysts

The area of binaphthyl-based metal-ion catalysts for the field of asymmetric synthesis is vast, for this reason these topics will only briefly be covered in order to display the utility of the binaphthyl motif for the catalysis of enantioselective reactions. Figure 1.10 shown includes some of the catalysts derived from the binaphthyl template.

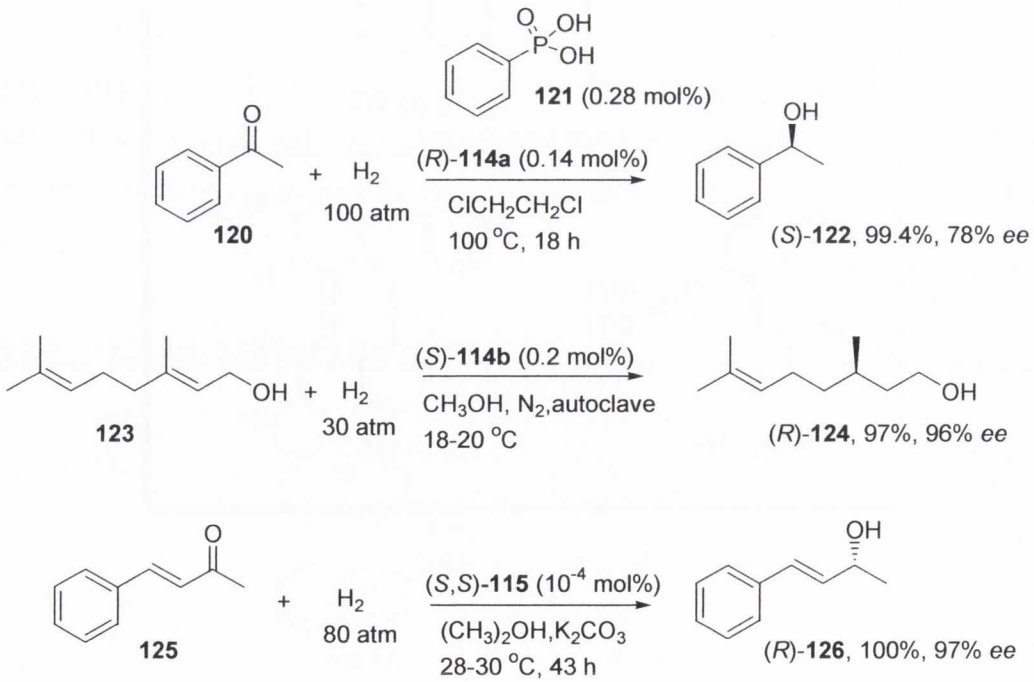
Figure 1.10 **111, 112** and **113**-derived catalysts for use in asymmetric synthesis



1.4.3.1 BINAP-derived catalysts in asymmetric synthesis

Since Noyori's synthesis of **113** from **111** in 1980[117] it has been one of the most influential commercially available catalyst ligands widely used to achieve asymmetric catalysis under a variety of conditions. Few examples dealt with the enantioselective hydrogenation of ketones when Noyori *et al.* developed some of his early ruthenium catalysts for this purpose. An understanding that both the ketone carbonyl group and the hydride (for transfer to the carbonyl) needed to be bound closely at or near the central metal-ion centre was essential. Bulky ligands often with hydrogen-bonding functionalities were often used to facilitate preferential attack of the hydride to the π face of the carbonyl group. Catalyst **114a** (Figure 1.10) was one of the early catalysts designed by Noyori to promote the asymmetric hydrogenation of acetophenone **120** aided by phenylphosphoric acid **121** as additive (Scheme 1.16) **121** appeared to activate the chiral diphosphane-ruthenium complex through the formation of a RuH-phosphonate complex in which the anionic ligand has an additional OH group which interacts with the carbonyl oxygen. The (*S*)-1-phenylethanol product **122** was obtained in 99.4% yield and a moderate 78% *ee* using a substrate-to-catalyst ratio of 700/1. (Scheme 1.16)[118]

Scheme 1.16 Asymmetric hydrogenation by **113**-derived catalysts



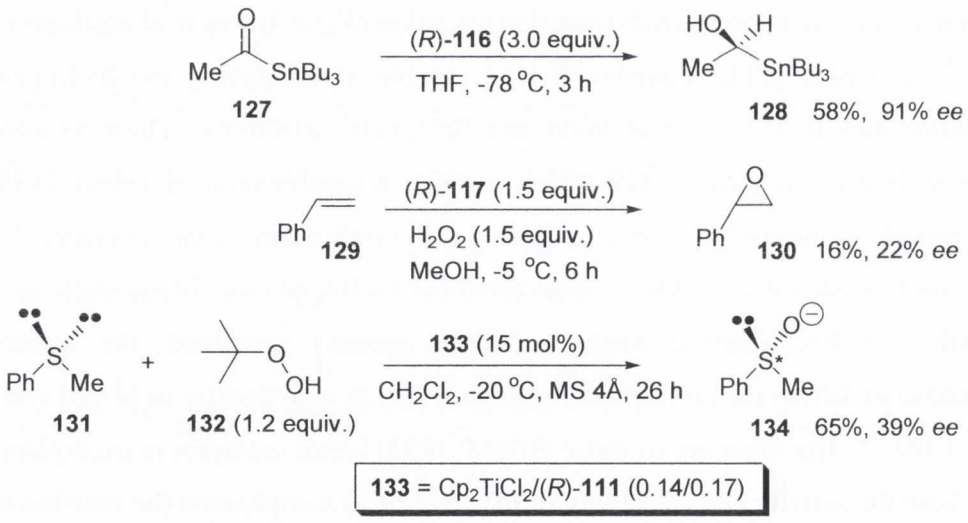
In 1987 Noyori[119] described the potential of the modified Ru(II) dicarboxylate complex **114b** for the enantioselective hydrogenation of allylic and homoallylic alcohols which had previously been reduced by cationic Rh[120] and Ir[121] phosphines complexes. Diastereoselective hydrogenation of chiral allylic and homoallylic alcohols was the literature precedent whereby the pre-existing chirality of the sp^3-hybridised carbon induced the asymmetry on the neighbouring carbon (through coordination of the hydroxyl group to the Rh/Ir metal centre). The example shown in Scheme 1.16 illustrates the industrially useful enantioselective hydrogenation of racemic geraniol **123** (used in perfumery, flavouring and as a biopesticide) to the (*R*)-citronellol product **124** (used in perfumery and as a biopesticide) in excellent yield and enantioselectivity.[119] The stereochemical outcome of these reactions suggests that the catalyst **114b** is capable of differentiating between the C(2) enantiofaces of the substrate during the course of the reaction. Both the *R* and *S* enantiomers are accessible through a variation of the allylic olefin geometry or by variation of the enantiomer of the catalyst.[119]

The stereoselective hydrogenation of alkenyl ketones held some selectivity challenges such as the presence of two types of unsaturated functional groups C=O and C=C, (the latter having more reactivity in conventional hydrogenation procedures) and low optical and keto selectivity profiles.[118] A known Ir/**113** complex[122] was capable of catalysing the hydrogenation of benzalacetone **125** in 65% optical yield and 97% keto selectivity. These problems were overcome somewhat by catalyst **115** which contains a combination of xylene/**113**/DAIPEN (1,1-di-4-anisyl-2-isopropyl-1,2-ethylendiamine) and a ruthenium metal ion centre.[118] Catalyst **115** in combination with K_2CO_3 (conventional hydrogenation bases such as KOH or $(CH_3)_3COK$ are too reactive towards simple enones) permitted the stereoselective hydrogenation of **125** to the corresponding alcohol **126** in quantitative yield and with 97% *ee* (Scheme 1.16).[123] The diversity of these BINAP (**113**) based catalysis is exemplified by the ability to tune the activity and selectivity of the catalyst to complement the reaction substrates by *e.g.* the addition of a diamine moiety (DAIPEN) to catalyst **114b** (see previous-for the enantioselective hydrogenation of alkenes) to make catalyst **115**, which selectively hydrogenates the carbonyl moiety in alkenyl ketones in excellent yields and enantioselectivities.

1.4.3.2 BINOL-derived catalysts in asymmetric synthesis

Noyori *et al.* demonstrated the efficiency of BINOL as a superb chiral ligand in the reduction of ketones with stoichiometric amounts of $LiAlH_4$ giving the corresponding alcohols in up to 99% *ee*.[124-127] Necessary for significant enantiomeric excess is the replacement of one hydride of the $LiAlH_4$-BINOL complex (*R*)-(+)-**116** by an ethoxy group that binds the lithium counter-ion (through the lone-pair on the oxygen atom), which promotes subsequent Lewis-acid activation of the carbonyl substrate (which is concomitantly bound to the Al-hydride centre). Replacement of one of the hydrides on the central Al-ion in effect defines the single remaining proton as the only hydride source available, thus predisposing hydride transfer to occur through a single transition state of lowest energy.[128] A range of prochiral ketones and imines[129] can be reduced using variable equivalents of (*R*)-(+)-**117** at low temperatures to give the corresponding adducts in high enantiomeric excesses (Scheme 1.17).

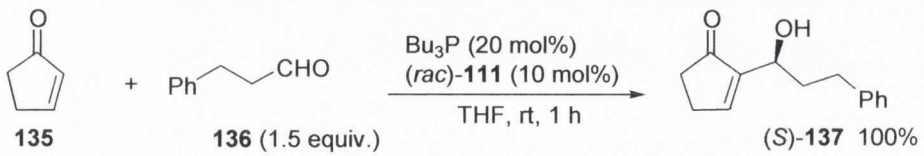
Scheme 1.17 Reactions promoted by binaphthyl-based catalysts shown in Figure 1.10



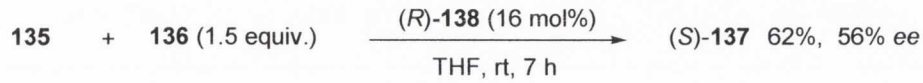
Both phosphoric acid derivatives of **111** *e.g* **117** and titanium metal based derivatives *e.g* **110, 118** have recently been found to be promoters of oxidation reactions, amongst them the epoxidation of olefins[130-134] and the oxidation of sulfides[135] with excellent yields and enantioselectivities. An example of each is illustrated in Scheme 1.17. Ikegami *et al.* described the first example of an optically active calcium catalyst incorporating a binaphthyl motif for

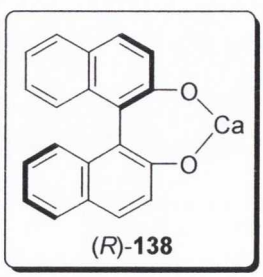
the asymmetric Baylis-Hillman reaction of aliphatic aldehydes with α,β-unsaturated ketones. Previous findings by Hatakeyama *et al.*[136] reported the excellent asymmetric Baylis-Hillman reaction catalysed by an amine possessing a phenolic hydroxy group (derived from a *cinchona* alkaloid), which binds to the aldol-type intermediate of the reaction and facilitated enantioselective addition reactions. Initial findings by Ikegami identified co-operative catalysis between tributylphosphine (a mild Lewis base) and (*R*)-**111** (a mild Bronsted acid) which may serve to promote the conjugate addition step and remain hydrogen-bonded to the resulting enolate. The (*R*)-**111**/PBu_3 catalysed reaction of 2-cyclopenten-1-one **135** and 3-phenyl-1-propanol **136** yielded the desired product **137** with significantly enhanced reaction rate and quantitative yield, but with <10% *ee*. Encouraged by this result, the group subsequently synthesised the calcium-ion based binaphthyl catalyst (*R*)-**138** from the strong base $Ca(O\text{-}^{i}Pr)_2$ and (*R*)-**111** in THF. Subsequent evaluation of catalyst **138** in the Baylis Hillman reaction of **135** and **136** yielded the highly functionalised adduct **137** in 62% yield and 56% *ee* (Scheme 1.18)[137] Subsequent to this work bifunctional organocatalysts based on the binaphthyl-motif,[138] and catalysts based on the co-operative coupling of the binaphthyl and phosphine Lewis base have been developed[139] for similar addition reactions.

Scheme 1.18 Binaphthyl-based organocatalysed Baylis-Hillman reaction



135 + **136** (1.5 equiv.) → (*S*)-**137** 100%

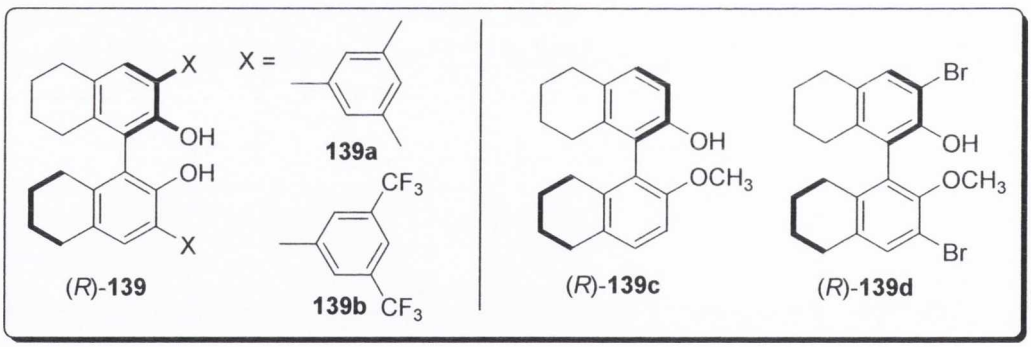




In a similar study, the Morita-Baylis-Hillman (MBH) reaction (using cyclohexenone **93** as the α,β-unsaturated alkene) was found to be promoted by a range of chiral **111**-derived Brønsted

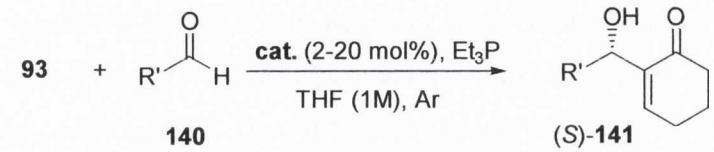
acids in co-operation with triethylphosphine as the nucleophilic promoter. The MBH reaction of **93** with **136** using triethylphosphine (0.5 equiv.) in THF yielded the corresponding adduct **142** in 5% yield at 0 °C after 48 hours. However, with the addition of only 2 mol% (*R*)-**111** to an otherwise identical reaction the product **142** was obtained in 74% yield with 32% *ee* after a reduced reaction time (36 hours).[140] From this result the group undertook the evaluation of a series of **111**-derived Brønsted acids; two modifications were of particular interest, those modified at the 3,3'-positions and those characterised by variation of the degree of saturation of the binaphthyl backbone. The highest levels of enantioselectivity in the MBH reaction of **93** with **136** using 2 mol% catalyst and 50 mol% triethylphosphine at 0 °C for 36 hours were recorded using the (*R*)-3,3'-(3,5-dimethylphenyl)-H_8-BINOL catalyst **139a** (70% yield and 88% *ee*), whilst the greatest levels of conversion were obtained using the 3,3'-(3,5-bis(trifluoromethyl)phenyl)-catalyst **139b** (84% yield, 86% *ee*). (Figure 1.11 and Table 1.1) Suggesting the necessity for two Brønsted-acidic units for both high activity and enantioselectivity is the diminished activity and complete loss of enantioselectivity using catalysts **139c** and **139d** in this reaction (Figure 1.11, Table 1.1, entries 4 and 5)

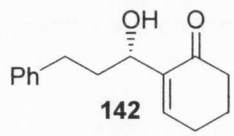
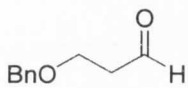
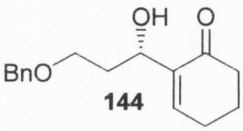
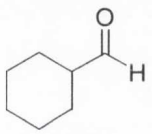
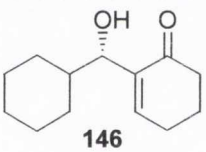
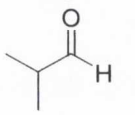
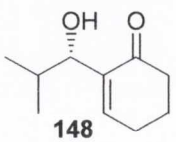
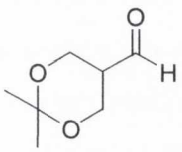
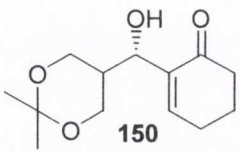
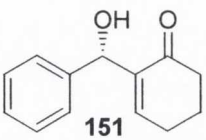
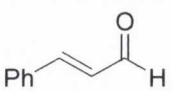
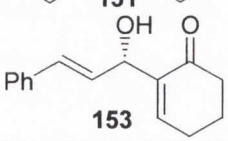
Figure 1.11 Asymmetric Morita-Baylis-Hillman catalysts 139a-d



Optimal results were obtained using catalyst **139b** and unhindered aliphatic aldehydes (Table 1.1, entries 6 and 7), whilst the best catalyst for the addition of more hindered aldehydes was catalyst **139a** (entries 8-10). Less successful in terms of both yield and enantioselectivity was the MBH addition reaction of conjugated aldehydes (entries 11 and 12). Overall, catalysts **139a** and **139b** marked a significant improvement on the literature benchmark for organocatalysed asymmetric reactions using the binaphthyl motif.

Table 1.1 139a-d catalysed asymmetric Morita-Baylis-Hillman reactions



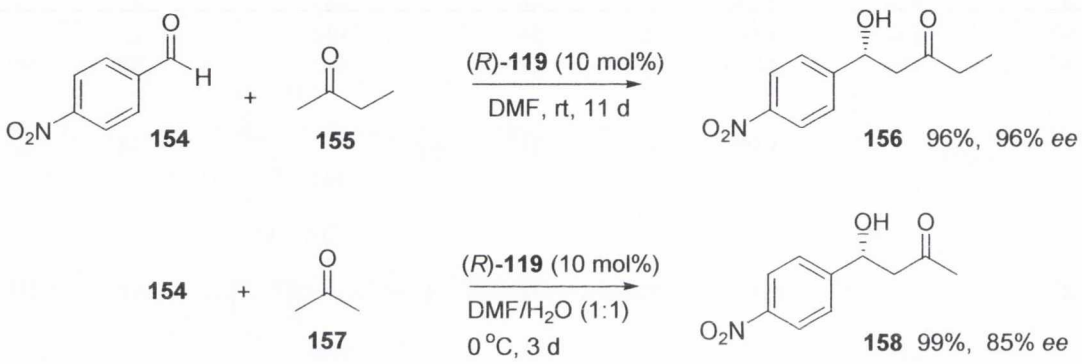
entry	aldehyde	cat.	mol %	Time (h)	product	Yield[c]	*ee*[d] (%)
1[a]	**136**	-	-	48	 **142**	5	-
2[a]	**136**	**139a**	2	36	**142**	70	88
3[a]	**136**	**139b**	2	36	**142**	84	86
4[a]	**136**	**139c**	2	36	**142**	43	3
5[a]	**136**	**139d**	2	36	**142**	15	3
6[b]	**136**	**139b**	10	48	**142**	88	90
7[b]	 **143**	**139b**	10	48	 **144**	74	82
8[b]	 **145**	**139a**	10	48	 **146**	71	96
9[b]	 **147**	**139a**	10	48	 **148**	82	95
10[b]	 **149**	**139a**	20	48	 **150**	70	92
11[b]	**32**	**139b**	10	48	 **151**	40	67
12[b]	 **152**	**139a**	10	48	 **153**	39	81

[a] Reactions were performed using 1 mmol of **136**, 1 mmol of **93**, 0.5 mmol of PEt_3 at 0 °C. [b]Reactions were performed using 1 mmol of aldehyde, 2 mmol of **93** and 2 mmol of PEt_3 at –10 °C. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

1.4.3.3 Asymmetric synthesis using BINAM

An approach taken by the Najera group involved the design of a catalyst incorporating the broad substrate scope of proline (a known catalyst with specificity analogous to the aldolase enzymes for the aldol reaction) with a binaphthyl moiety for the direct aldol reaction. Using the binaphthyl motif to restrict rotation around the biaryl axis and the known activity of the proline template allowed Najera *et al.*[141] to develop catalyst **119** (*S*,-BINAM-*L*-Pro) for the enantioselective aldol reaction, two examples of which are shown in Scheme 1.19.

Scheme 1.19 Enantioselective aldol reactions catalysed by the BINAM-derivative **119**



The reaction of *para*-nitrobenzaldehyde **154** with 2-butanone **155** afforded the aldol product **156** in 96% yield with an *ee* of 96% (also yielded 4% of the *syn* product in 31% *ee).* With acetone **157** the best enantioselectivities (up to 95%) were achieved when *ortho*-substituted aromatic aldehydes were used, the example shown in Scheme 1.19 shows the coupling of acetone (**157**) with **154** yielding the synthetically useful aldol adduct **158** in excellent yield of 99 % and enantioselectivity of 85%. In general these examples demonstrtate the utility and ability to promote enantioselective reactions (shown *via* the challenging aldol reaction) of **112**-derived catalysts for the asymmetric synthesis of densely functionalised adducts from cheap and readily available starting materials.

1.4.4 Asymmetric synthesis by binaphthyl based catalysts: conclusions

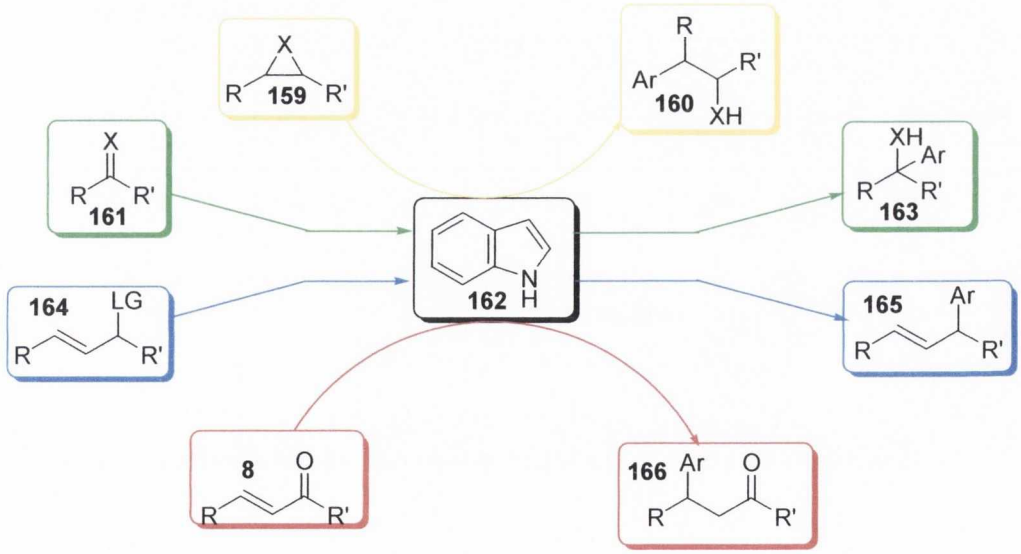
The previous section firmly establishes the binaphthyl moiety as a proven and efficient template upon which the design of highly active catalysts (including organocatalysts) for the

promotion of enantioselective reactions can be constructed. Whether the point of attachment of the binaphthyl component is oxygen (as in **111**), phosphorus (as in **112**) or nitrogen (as in **113**), the binaphthyl component maintains its ability to promote preferential nucleophilic attack from one face of a prochiral substrate in the transition state thereby promoting an enantioselective reaction.

1.5 Friedel-Crafts type reaction: the asymmetric addition of indoles to nitroolefins

Over the last decade, there has been an unprecedented interest into the development of more efficient, reliable and environmentally benign catalysts for Friedel-Crafts type reactions.[142-144] Functionalisation of indoles for use in the materials science, agrochemical and pharmaceutical sectors[145-147] necessitated the development of multiple routes for the ring-alkylation of indolyl compounds, depending on the nature of the electrophile used (Figure 1.12). There are many ways of alkylating indoles, among them the 1,2-addition of arenes to carbonyl compounds, Michael-type reaction between arenes and electron-deficient C=C bonds, ring-opening of strained heterosubstituted cycles (epoxides, aziridines) and transition-metal catalysed allylic substitution (Tsuji-Trost reaction).[146]

Figure 1.12 Different Approaches to functionalised indoles *via* Friedel-Crafts alkylation.[146]

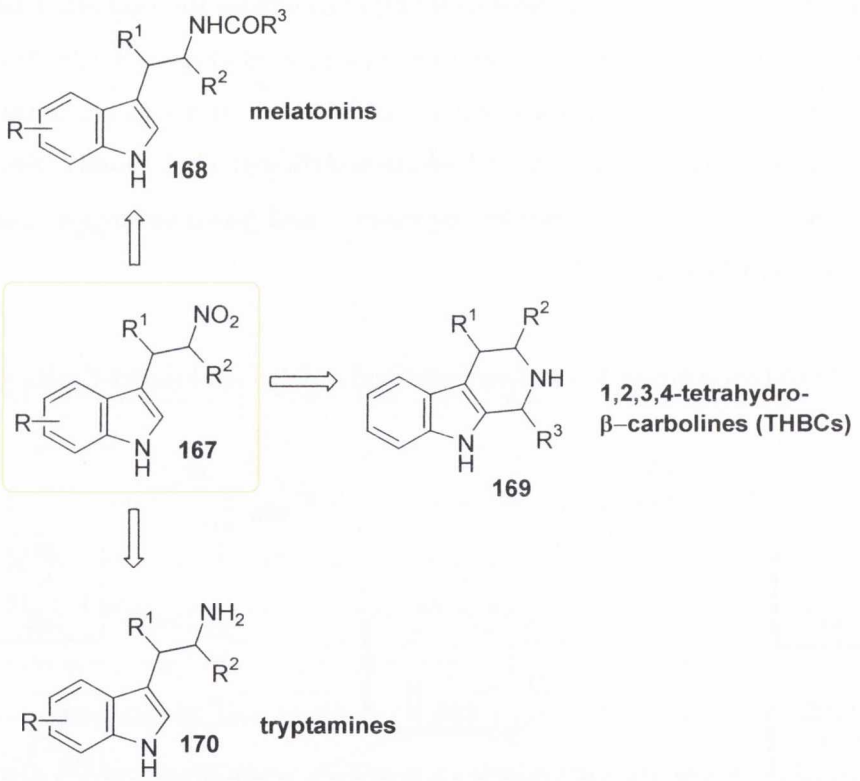


X: O, NR''; LG: leaving group; Ar: Indole

1.5.1 Biological relevance of the asymmetric Friedel-Crafts (FC) reaction

The indole framework has been identified as a central structural *motif* with representation in over 3000 natural product isolates[148] and 40 medicinal agents of diverse therapeutic action.[149] The products of the FC alkylation of indoles are important precursors to many compounds of biological relevance including the tryptamines, melatonins and 1,2,3,4-tetrahydro-β-carbolines (THBC's). The nitro group of the nitroalkene products from the FC addition of indoles to nitroolefins are particularly amenable to further functionalisation.[150] Figure 1.13 contains some of the biologically active compounds accessible *via* nitroalkene as precursors.

Figure 1.13 Biologically active compounds from the indole/nitroalkene FC adduct.[146]

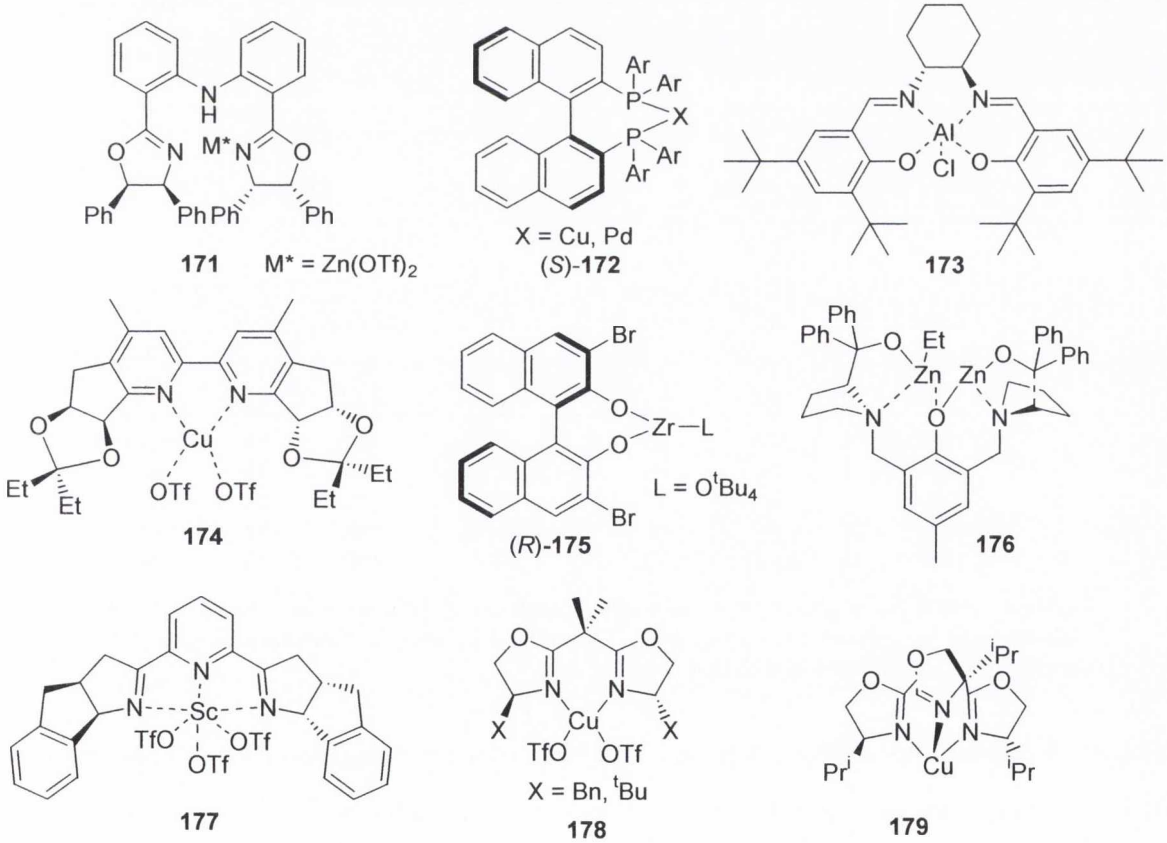


1.5.2 Metal-based catalysts for the asymmetric Friedel-Crafts reaction

The past seven years has witnessed the re-emergence of transition metal-based catalysts[151] as promoters of the stereoselective alkylation of indoles with a range of activated α,β-unsaturated compounds including the arylidene pyruvates,[152-154] ethane di- or tri-carboxylates,[155-161] α,β-

unsaturated acyl phosphonates,[162-164] enones,[165,166] and imines.[167] Alkylation using nitroolefins[150] has been used by the groups of Xu,[168] Zhou[169] and Singh.[170] Preliminary work in the area focused primarily on reactions with unsubstituted indole but later on its derivatives[169,171] including *N*-methyl indole.[162-164,168] The most common barriers to stereoselectivity and enantioselectivity in the indoles are the poor N-1 versus C-3 regioselectivity and poisoning of the catalyst by the strong coordinating behaviour of indoles.[146] Figure 1.14 lists some of the commonly used ligands in metal-ion centre catalyst design for the asymmetric FC alkylation of indoles and pyrroles. Thus far, the design rationale for the asymmetric FC alkylation has been based on a Lewis acid and a chiral ligand, among which Cu^{II}/bis(oxazoline) complexes are currently preferable (**178, 179**),[152,153,155-160,169,170,172] whereas Zn^{II}/*bis*-ProPhenol (**171**, **176**),[173] salen, (**173**)[174] C_2-symmetric binaphthyl (**172**, **175**)[159,166,175] and pyridine based complexes (**174**, **177**) are increasingly used.[161-164,176,177]

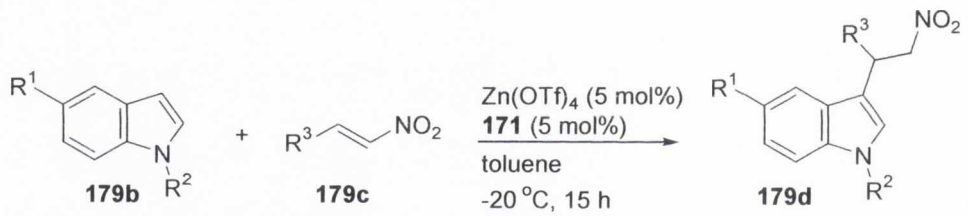
Figure 1.14 Metal-ion based catalysts for the alkylation of indoles



1.5.2.1 Bis(oxazoline)-Zn(OTf)$_2$ catalysed addition of indoles to nitrostyrenes

Relevant to this work is the bifunctional tridentate *bis*(oxazoline)-Zn(OTf)$_2$ catalyst **171** which was developed for the asymmetric FC alkylation of substituted indoles with nitroalkenes (Table 1.2).[168] In a series of experiments designed to evaluate the optimum transition metal for use with this ligand, Zn^{2+} was found to be the optimum ion for high stereoinduction. Ni^{2+} was the only other ion capable of generating a complex which promoted the reaction with significant enantioselectivity. The tridentate *bis*(oxazoline) catalyst **171** was found to be compatible with both substituted indole and nitrostyrene compounds to yield the nitroalkylated indoles in excellent yields (up to 99%) and enantioselectivities (up to 98% *ee*). The model Michael addition reaction of indole **162** with nitrostyrene gave an impressive result of 99% yield and 94% *ee* (Table 1.2, entry 1)

Table 1.2 Friedel-Crafts Alkylation of indoles with nitroalkenes catalysed by catalyst **171**



Entry	indole	R^1	R^2	substrate	R^3	product	yield[b]	*ee*[c] (%)
1	**162**	H	H	**27**	Ph	**180**	99	94 (*R*)[d]
2	**181**	H	Me	**27**	Ph	**182**	93	90 (*R*)[d]
3	**162**	H	H	**183**	$CH_3(CH_2)_2$	**184**	91	92
4	**185**	Cl	H	**27**	Ph	**186**	88	81
5	**162**	H	H	**187**	cyclohexyl	**188**	92	84
6	**189**	H	MeO	**27**	Ph	**190**	96	98

[a]Reaction conditions: indole (0.50 mmol) with nitroalkene (0.50 mmol) in 2 mL of toluene. [b]Isolated yield by column chromatography. [c]Determined by HPLC.[d] Determined to be *R* by comparison of optical rotation with that in ref. [178]

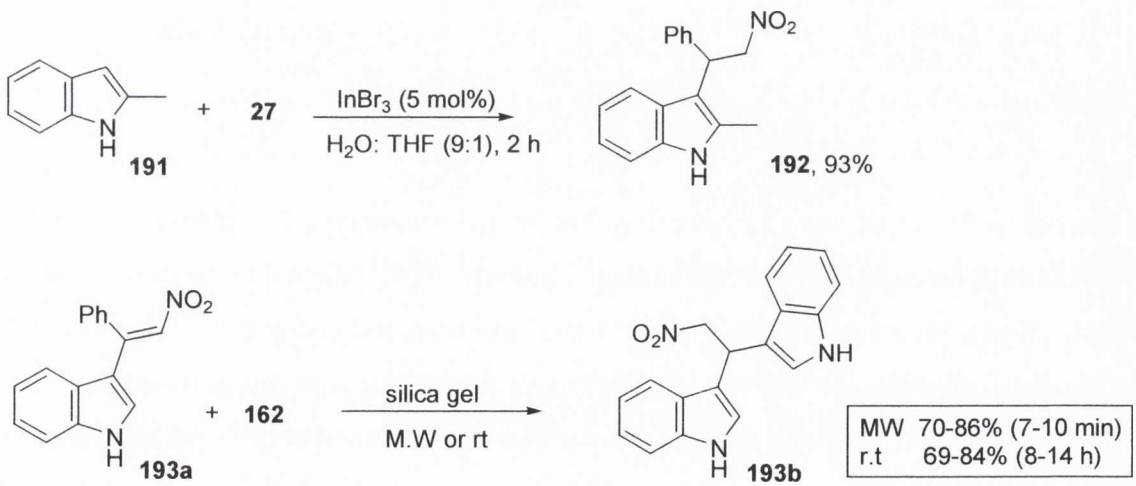
When an electron-withdrawing group such as chlorine in the 5-position of the indole ring in **185** there was a small decrease in the yield and enantioselectivity (Table 1.2, entry 4), yet when electron-rich 5-methoxyindole **189** was used both yield and enantioselectivity improved with an *ee* value of 98% (Table 1.2, entry 6). *N*-methylindole **181** also proved to be a

compatible substrate for addition to nitrostyrene **27** giving 93% yield and 90% *ee*, a significant improvement on the literature benchmark for these two substrates.

1.5.2.2 $InBr_3$ catalysed Michael addition of indoles to nitroalkenes

A more environmentally friendly method of catalysing the Michael addition of nitroolefins to indoles is through the replacement of whole or part of the volatile organic solvent media and recycling of the catalyst. Work carried out by the group of Umani-Ronchi, on the $InBr_3$ catalysed addition of indoles to enones[179] in various reaction media, encouraged the workers to attempt the indium-catalysed 1,4-addition of indole **191** to **27** in a solvent mixture of 9:1 H_2O:THF, the desired β-indolylnitro compound **192** was isolated in 93% yield in just 2 hours (Scheme 1.20).[180] Further work revealed that both electron-rich and electron-poor indoles quickly reacted with α,β-unsaturated nitroolefins giving complete conversions (up to 99%) in short reaction times (up to 16 h). $InBr_3$ catalyst proved to be incredibly recyclable in a series of runs carried out using indole **191** and nitrostyrene **27** (using 10mol % **cat**. rt, H_2O:THF, 9:1) catalyst activity did not decrease and the corresponding 1, 4-adduct **192** was isolated in almost quantitative yields.

Scheme 1.20 $InBr_3$-catalysed indole alkylation in aqueous media



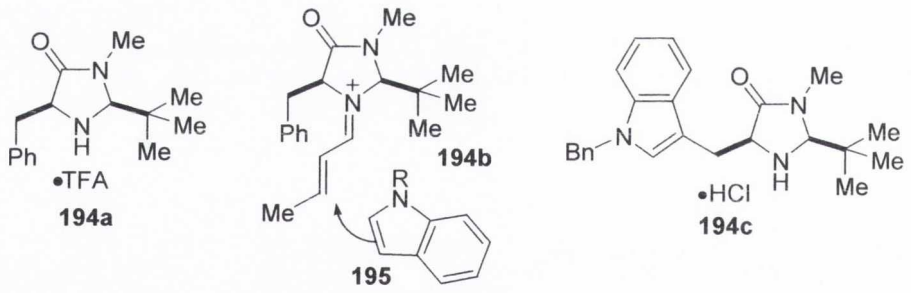
Chakrabarty *et al.* went a step further in developing the acid catalysed addition of indoles to 3-(2'-nitrovinyl)indole **193a** in the presence of TLC-grade silica gel and microwave irradiation

to afford the 2,2-bis(indolyl)nitroethanes **193b** which are precursors to the synthesis of an important class of natural compounds- the bis(indolyl)ethylamines (BIEA's). The effect of microwave irradiation is the shortening of the reaction time to minutes from hours at room temperature (see Scheme 1.20).

1.5.3 Organocatalysts for the asymmetric Friedel-Crafts reaction

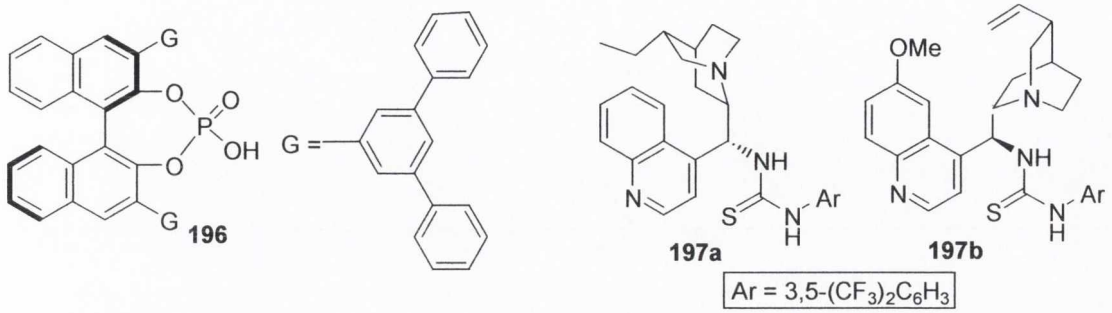
McMillan *et al.* [174,181] were the first to demonstrate the utility of organocatalytic methods in the promotion of the enantioselective FC alkylation reactions using chiral imidazolidinone salts **194a** (Figure 1.15) catalyse the alkylation of pyrroles,[174] and indoles,[181] with α,β-unsaturated aldehydes using iminium ion catalysis (intermediate shown as **194b** in Figure 1.15). More recently McMillan *et al.* described the first enantioselective organocatalytic conjugate addition of trifluoro(organo)borates to α,β-unsaturated aldehydes using catalyst **194c** also through iminium ion catalysis.[182]

Figure 1.15 McMillans Chiral Iminium ion catalysts



Subsequent to this work many organocatalyst promoted asymmetric FC addition reactions of α,β-unsaturated ketones,[183,184] enecarbamates,[185] imines,[25,186,187] (*e.g.* using the BINOL derived monophosphoric acid catalyst **196**, Figure 1.16) and carbonyl compounds,[188,189] to indoles have emerged. Recently the addition of naphthols to nitrostyrenes (promoted by catalysts **197a** and **197b**, Figure 1.16) has also been developed[190] but more importantly in the context of this work the development of the organocatalytic asymmetric FC alkylation of indoles with nitrostyrenes has also been achieved.

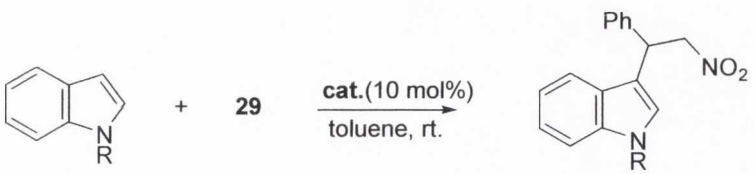
Figure 1.16 Organocatalysts for the FC alkylation of indoles



1.5.4 Organocatalytic asymmetric addition of indoles to nitroolefins

The presence of two Lewis-basic oxygen atoms potentially allow for the activation of an olefin by the acceptance of two hydrogen bonds from a suitably designed catalyst.[191] Previously in Section 1.3 the *bis* 3,5-trifluoromethylthio(urea) catalyst family members **20** and **46** were shown to be excellent promoters of this reaction through hydrogen bond activation of the electrophile. Ricci *et al.* found that *bis*-arylthioureas,[57] **20** and **46** were efficient promoters of the FC alkylation reaction of π-heteroaromatic compounds with a range of nitroolefins (Scheme 1.21).

Scheme 1.21 Friedel-Crafts type reactions promoted by urea and thioureas

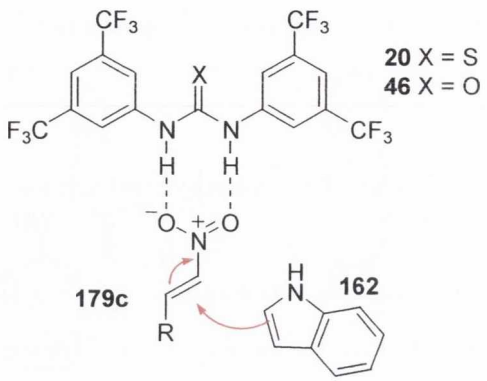


162 R = H
181 R = CH_3

180 R = H
182 R = CH_3

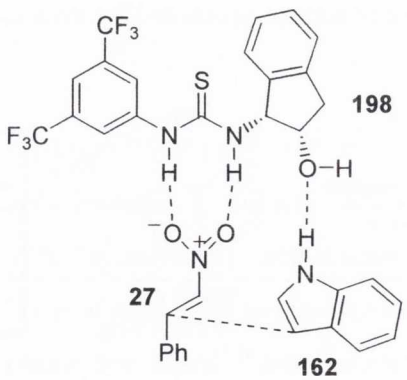
cat.	product	t (h)	yield(%)
20	**180**	72	85
20	**182**	4	93
46	**180**	72	58
46	**182**	4	77

Figure 1.17 Chiral thiourea catalysts for FC Alkylations



The mode of substrate activation by catalysts **20** and **46** is depicted in Figure 1.17, coordination of the nitroolefin to the (thio)urea protons results in activation of the substrate, facilitating subsequent nucleophilic attack by the indole nucleophile. Encouraged by these results Ricci *et al.* demonstrated that the bifunctional catalyst **198** was a highly efficient promoter of the addition reaction of substituted indoles with nitrostyrenes yielding high levels of stereoinduction (up to 89% *ee*).[192] The bifunctional catalyst **198** retained the thio(urea) *motif* but contained an additional hydroxyl group which could activate the incoming nucleophile *via* weak hydrogen bonding (Figure 1.18).

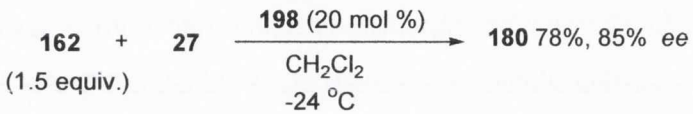
Figure 1.18 Proposed bifunctional mode of action associated with catalyst **198**

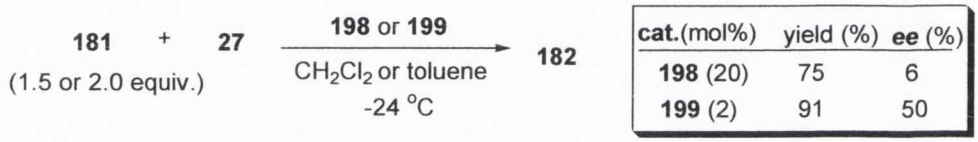


The addition reaction of **27** to **162** was carried out using 20 mol% of catalyst **198** at –24 °C to afford the indole product **180** after 72 h in good yield (78%) and enantioselectivity (85% *ee*). Both heteroaromatic and alkyl nitroolefins were tolerated by the catalyst yielding substituted

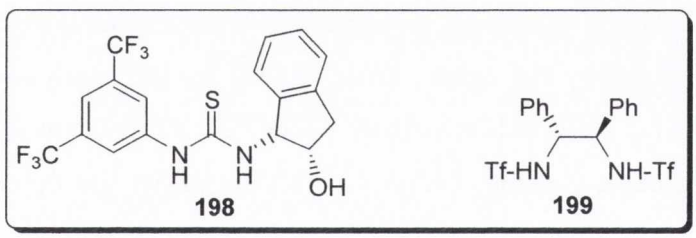
indoles in similar yields although with slightly reduced enantioselectivity compared to the reaction in which **27** is the substrate. However, thiourea catalyst **198** promoted *N*-methylindole (**181**) addition reactions to nitrostyrenes were not selective; **182** was isolated in 75% yield and 6% *ee* (Scheme 1.22).[192] The poor performances of both *O*-protected and deoxygenated variants of catalyst **198** confirmed the bifunctional mode of activation in addition to activating the nitroalkene by hydrogen bonding; it was also envisaged that the hydroxyl OH group (of the amino indanol component) engages the indole proton *via* a weak hydrogen bond which acts to direct the indole to the *si* face of the nitroolefin as is shown in Figure 1.18.

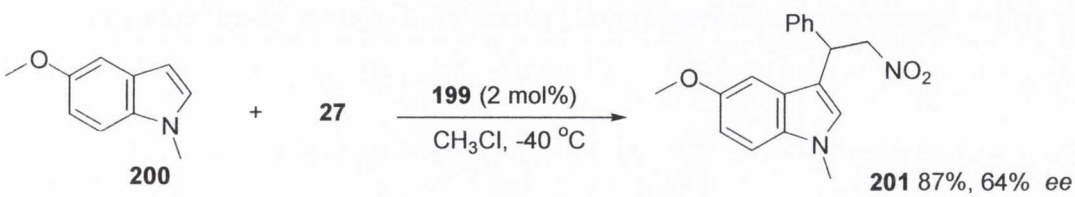
Scheme 1.22 Asymmetric Friedel-Crafts type reactions catalysed by **198/199**





cat.(mol%)	yield (%)	ee (%)
198 (20)	75	6
199 (2)	91	50



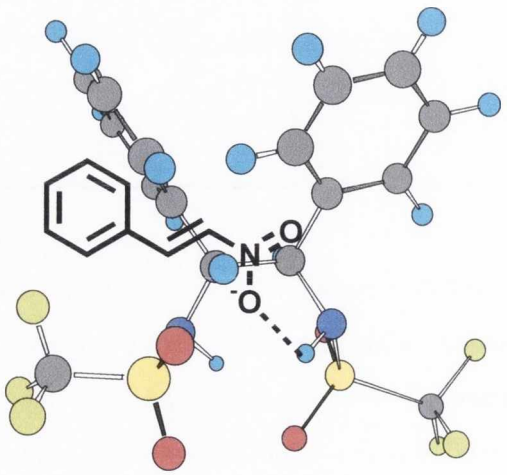


Further studies by the Jørgensen group[178] described the development of the highly acidic and active *bis*-sulfonamide catalyst **199**, capable of promoting the FC alkyaltion of *N*-methylindole (**181**) to a range of nitrostyrenes with improved enantioselectivity of 50% *ee* using only 2 mol% catalyst loading (Scheme 1.22). Unlike catalyst **198**, catalyst **199** is monofunctional in nature relying upon hydrogen bond activation of the substrate *via* the highly acidic NH protons

alone. Changing from substrate **181** to indole **162**, the high yields were maintained yet the enantioselectivities decreased. Bulky substituents on the nitrogen atom of the indole did not improve either the enantiomeric excess or yield. Reducing the temperature to –40 °C and using *N*-methyl-5-methoxy-indole **200** with **27** yielded the densely functionalised addition product **201** in 87% yield and 64% *ee*, a significant improvement on the Ricci bifunctional catalyst[192] results mentioned earlier (see Scheme 1.22)

In an attempt to explain the degree of stereoinduction in the above reaction Jørgensen and co-workers[178] proposed an intermediate for the reaction whereby the nitrostyrene interacts with one of the amino hydrogen atoms in the *bis*-sulfonamide catalyst **199** (Figure 1.19). In the model proposed (simply a nitrostyrene drawing super-imposed onto a crystal structure of catalyst **199**) the *re* face of the alkene is shielded by the phenyl substituents of the chiral catalyst, leaving the *si* face open for attack by the indole. The relatively large N-C-C-N dihedral angles of 64.2° of the catalyst **199**, the amino hydrogen atoms appear diastereotopic. In comparison the dihedral angle of the *tert*-butyl derivative (which gave racemic products) has a N-C-C-N dihedral angle of 19.4 °C making the amino hydrogen atoms less enantiotopic. The smaller dihedral angle leads to an intermediate where the catalysts substituent's (*e.g.* the *tert*-butyl groups) shield the *re* face of the substrate to a lesser extent allowing more random angles of nucleophilic attack by the indole. Later studies by Jørgensen *et al.* included the promotion of the Mukaiyama-aldol, hetero Diels-Alder reaction and the FC reaction of α-carbonyl compounds to indoles[193] using similar *bis*-sulfonamide type catalysts as **199**.

Figure 1.19 Jørgensen model (redrawn) of **199** and **27** to explain enantioinduction



Most recently, organocatalysts not incorporating the urea *motif* have emerged which promote the FC alkylation reaction. Sulfamic acid-catalysed Michael addition of indoles and pyrroles to electron-deficient nitroolefins under solvent-free conditions have appeared in the last year (2007).[194] Albeit an achiral promoter, the rapid alkylation of the indole shows how catalyst acidity can play a key role in determining the degree of activation of the nitroolefin substrate by the catalyst. The sulfamic acid catalysed process facilitates a straightforward approach to the synthesis of racemic 3-substituted indole and 2-substituted pyrrole adducts with nitroolefins.[194]

1.5.5 Friedel-Crafts additions to nitroolefins: conclusions

Notwithstanding the plethora of catalyst systems that efficiently promote the Friedel-Crafts addition of nitroolefins to indoles, no system can be successfully applied to both cyclic and acyclic nitrostyrenes. Moreover, only one organocatalyst (**199**) is capable of promoting the enantioselective reaction of nitrostyrenes to *N*-methyl indole (**181**) in reasonable *ee,* however this process requires sub-ambient temperatures. To date the alkylation of **181** by nitroalkenes using a metal-ion catalyst has only been tackled by the Xu group.[168] Thus, the development of a relatively inexpensive class of organocatalyst (available in both antipodal forms), showing broad substrate scope (with respect to both nucleophilic and electrophilic reacting partners) and capable of excellent enantioinduction at room temperature is an important challenge.

1.6 Friedel-Crafts reaction: addition of indoles to epoxides

Synthetically useful for the synthesis of tryptophol derivatives is indole addition to epoxides (*e.g.* the synthesis of antibiotics such as indolmycin[195]). Methods of catalysing the addition of epoxides to indoles include the use of high-pressure[196] (which necessitates specialised equipment), high-pressure-promoted silica gel techniques,[197] and the use of metal-ion catalysts and organocatalysts (which will be covered in depth in the proceeding sections).

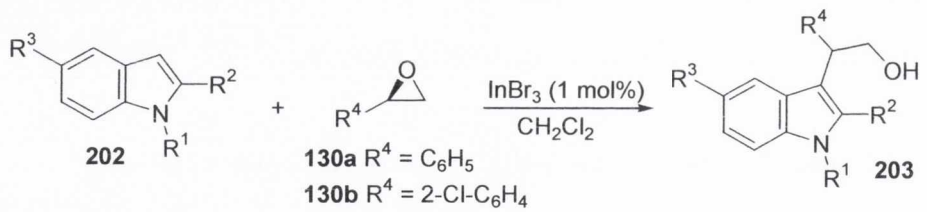
1.6.1 Metal(ion)-based catalysts for Friedel-Crafts additions of indoles to epoxides

Due to the low heterophilicity exhibited by indium compounds, they are invaluable Lewis acid catalysts for addition reactions over a range of strongly co-ordinating substrates. The simplest

metal-based catalyst for the FC addition of indoles to epoxides is $InBr_3$. The Umani-Ronchi group[198] have tested a series of Lewis acids (under strictly anhydrous conditions) in the addition reaction of indoles (**202**) to epoxides (**130**). $InBr_3$ was identified as the optimum catalyst in terms of functional group tolerance, regio/stereoselectivity and activity, while $Sc(OTf)_3$ and $BF_3.OEt_2$ were also very active Lewis acids in this reaction. $InBr_3$ was also evaluated as a Lewis acid catalyst in the addition of a range of indoles to (*R*)-(+)-styrene oxide **130a** with excellent yields and enantioselectivities (Table 1.3), chemoselectively furnishing the alcohol derived from attack at the α position of the epoxide.

As Table 1.3 illustrates, indoles with electron donating substituents were found to yield indolyl products in moderate to good yields (up to 79%) with excellent enantioselectivities of 99% (Table 1.3, entries 3 and 4 respectively). Indoles with electron withdrawing groups furnished products after longer reaction times and with lower yields (41%) and enantioselectivities (Table 1.3, entry 2). $InBr_3$ was also tolerant of substituted epoxides catalysing the addition to indoles **162** and **191** in excellent yields and enantioselectivities (Table 1.3, entries 6 and 7).

Table 1.3 $InBr_3$ promoted addition of indoles to epoxides



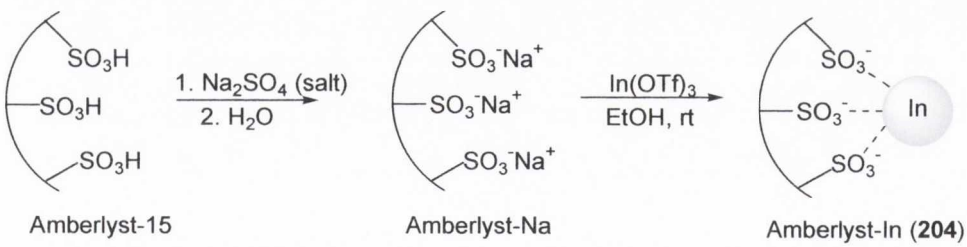
entry[a]	indole	R^1	R^2	R^3	epoxide	R^4	product	yield[b]	*ee*[c] (%)
1	**162**	H	H	H	**130a**	Ph	**203a**	70	99
2	**202a**	H	H	CN	**130a**	Ph	**203b**	41[d]	70
3	**202b**	H	H	OCH_3	**130a**	Ph	**203c**	54	99
4	**191**	H	CH_3	H	**130a**	Ph	**203d**	79	99
5	**181**	CH_3	H	H	**130a**	Ph	**203e**	68	99
6	**162**	H	H	H	**130b**	2-Cl-ClC_6H_4	**203f**	65	99
7	**191**	H	CH_3	H	**130b**	2-Cl-ClC_6H_4	**203g**	82	99

[a]Reaction conditions: indole (1.00 mmol) with epoxide (1.50 mmol) in anhydrous CH_2Cl_2 (3 ml) for 8-16 h. [b]Isolated yield after column chromatography. [c]Determined by HPLC (Chiralcel OD column). [d]The reaction was performed using 10 mol% of $InBr_3$ at room temperature for 16 h.

Of particular interest (due to few examples), is entry 5, the $InBr_3$ catalysed addition of **130a** to indole **181** with excellent enantioselectivity of 99%. It was found that aliphatic epoxides were not suitable substrates, the reaction of **162** with (*S*)-(-)-propylene oxide **35** using 10 mol% $InBr_3$ yielded two regioisomers in 1:1 ratio and an overall yield of 35%.[198] A similar study using $InCl_3$ as the Lewis acid catalyst at room temperature did not prove satisfactory results due to inferior regioselectivity of the catalysis in comparison to the $InBr_3$ study.[199]

Encouraged by the numerous chemoselective organic reactions promoted by indium salts and the development by other groups of organic polymer-supported $AlCl_3$[200] and the advancements in metal based Lewis acid catalysis[201-204] the group synthesised a polymer-supported indium (III) Lewis acid. Amberlyst-In (Amb-In) polymer catalyst **204** was formed by the mixing of amberlyst-Na (2 g) and $In(OTf)_3$ (2 mmol), shaking at room temperature for 16 h, followed by filtration and vacuum drying (Scheme 1.23).

Scheme 1.23 Resin-supported indium Lewis acid synthesis[205]



The resin-supported Indium (III) catalyst **204**[205] did not require the anhydrous conditions necessary with the $InBr_3$ catalyst. All of the indoles tested in the **204** promoted ring-opening reaction furnished the alcohol chemoselectively, from attack at the benzylic carbon (α position) in moderate to good yields (up to 62% yield, Table 1.4, Entry 3) and excellent enantioselectivities (*ee* >98%). Overall, the resin-supported indium catalyst was found to be a regio- and stereoselective, recyclable environmentally benign catalyst (admittedly this is open to debate, metal based systems often have associated human toxicity issues) and usable under very mild conditions.[205]

Table 1.4 The addition of indoles to epoxides catalysed by **204**

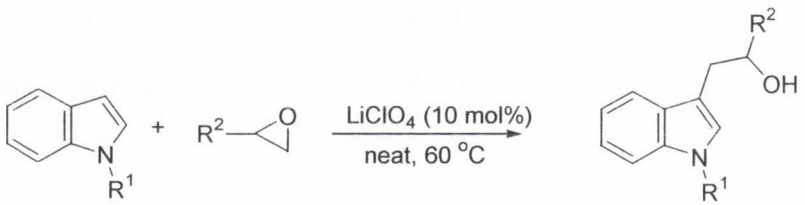


entry[a]	indole	R^1	R^2	R^3	epoxide	R^4	product	yield[b]	*ee*[c] (%)
1	**162**	H	H	H	**130a**	C_6H_5	**203a**	54	90
2	**202b**	H	H	OCH_3	**130a**	C_6H_5	**203c**	54	97
3	**191**	H	CH_3	H	**130a**	C_6H_5	**203d**	62	>98
4	**162**	H	H	H	**130b**	2-ClC_6H_4	**203f**	57	>98
5	**191**	H	CH_3	H	**130b**	2-ClC_6H_4	**203g**	58	>98

[a]Reaction conditions: indole (1.00 mmol) with epoxide (1.50 mmol) in wet Et_2O (2 mL) for 24 h. [b]Isolated yield by column chromatography. [c]Determined by HPLC (Chiralcel OD column).

Recently, a nanocrystalline titanium (IV) oxide catalyst for the racemic FC alkylation of indoles with aromatic epoxides was disclosed by Sreedhar *et al.*[206] The study involved the use of nanocrystalline titanium oxide metal to act as a Lewis acid in catalysing the addition of substituted indoles to aromatic epoxides at room temperature (the times taken for conversion ranged from 10-62 h with yields of 21-72%).[206]

Table 1.5 Lithium perchlorate catalysed FC type addition reactions to epoxides.



162 R^1 = H
181 R^1 = CH_3

130c R^2 = $OCH(CH_3)$
130d R^2 = c-C_6H_{11}

205a R^1 = H, R^2 = $OCH(CH_3)_2$
205b R^1 = CH_3, R^2 = $OCH(CH_3)_2$
205c R^1 = H, R^2 = c-C_6H_{11}
205d R^1 = CH_3, R^2 = c-C_6H_{11}

entry[a]	indole	epoxide	product	time (h)	yield (%)[b]
1	**162**	**130c**	**205a**	2	66
2	**181**	**130c**	**205b**	1	78
3	**162**	**130d**	**205c**	3	45
4	**181**	**130d**	**205d**	3	62

[a]In a mixture of **162/181** (4 mmol) and epoxide (4 mmol) anhydrous lithium perchlorate (0.1 mmol) was added and stirred at 60 °C for 1-4 h. TLC or GC was used to indicate completeness of the reaction.[b] Isolated yield.

The use of aliphatic epoxides in the FC addition reaction to indoles had not been reported until Saidi *et al.*[207] demonstrated the use of lithium perchlorate as an inexpensive and efficient catalyst for the ring opening of epoxides by indole (**162**) and *N*-methylindole (**181**). Complete regioselectivity in favour of nucleophilic benzylic attack on the aromatic epoxides was reported, with aliphatic unsymmetrical alkene oxides undergoing selective attack at the sterically less-hindered carbon atom (*e.g.* the addition of **181** to glycidyl isopropyl ether **130c** to furnish the aliphatic addition product **205b** in 78 % yield after just one hour (Table 1.5, entry 2).

1.6.1.1 Metal-based catalysts for epoxide additions to indoles: conclusions

Overall the metal-based catalysts for the addition of indoles to epoxides have relied upon the use of Lewis acids to activate the indole for attack on the epoxide. Regio- and enantioselective addition of epoxides to indoles has only been achieved by the $InBr_3$ catalyst of the Umani-Ronchi group.[146] The $InBr_3$ catalyst is yet to be tested in the addition of other heteronuclear-based nucleophiles to epoxides or in the addition of a broad range of substituted indole species to epoxides. The metal-based methodologies suffer from one or more disadvantages such as long reaction times, elevated temperatures, moderate yields, air and/or moisture sensitivity[208] and an applicability confined to aromatic substrates. This is an area that is devoid of a mild catalyst for the enantioselective addition of a broad range of nucleophiles to epoxides.

1.6.2 Organocatalytic Friedel-Crafts addition of indoles to epoxides

There are currently no organocatalysts for the FC addition of indoles to epoxides, with the only non-metal based example being the neutral alkylations of indoles and pyrroles with vinyl epoxides under high-pressure conditions. This method requires elevated temperatures in the range of 42-62 °C, yielding regioselective products in low to moderate yields.[196]

1.6.3 The Friedel-Crafts addition of carbon based nucleophiles to epoxides: conclusion

This area has been dominated by the use of metal-based catalysts which exhibit high substrate specificity and possess potential toxicity. The epoxide component has required sufficient activation (from highly Lewis acidic (metal-ion) centres) in order to undergo nucleophilic attack by an indole component. The design of an organocatalytic system for the promotion of

carbon based nucleophilic addition to epoxides remains a significant challenge from both a synthetic and an environmental point of view.

1.6.4 Metal-based catalysts for Friedel-Crafts additions of non carbon-based nucleophiles to epoxides

For the purpose of synthesising more diverse tryptophol based products, oxygen, nitrogen and sulfur based nucleophiles have found application in addition reactions to epoxides.

1.6.4.1 Metal catalysed additions of *N*-based nucleophiles to epoxides

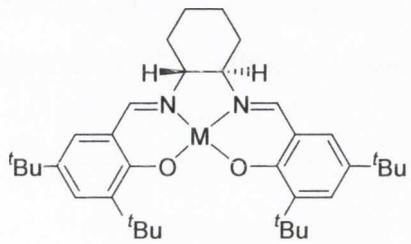
The ring opening of epoxides using amines and azides is one of the most powerful methods of synthesising β-amino alcohol derivatives for the synthesis of many natural products, synthetic amino acids and chiral auxiliaries for asymmetric synthesis. The easiest methods of synthesising these products include the use of an excess of the nucleophile at elevated temperatures.

Seminal studies by the Jacobsen group on the asymmetric epoxidation of olefins[209] using a Mn(salen) catalyst led the group to hypothesise that a similar complex would be capable of promoting the asymmetric ring-opening of *meso* epoxides through Lewis acid activation of the epoxide. Knowledge that the Mn(salen) catalyst did not coordinate irreversibly with epoxides and subsequent evaluation studies proved the Mn(salen) complex to be inefficient at promoting the ring opening of *meso* epoxides. However the Cr(salen) complex Cr-Cl **206b** proved to be a highly efficient catalyst with respect to both reactivity and enantioselectivity.[210-212] Catalyst **206b** was found to be recyclable- retaining full activity after eleven cycles. As many of the common azido silyl ether products are liquids the reactions could be performed neat, as such the process is described to be "atom economical".[213] It was ascertained through experimental evidence that a catalytic amount of water is essential for full conversion to the azido products **211**. The catalyst was found to form a **206b**-N_3 intermediate which functions as both a Lewis-acid for epoxide activation and as an azide-delivery agent.

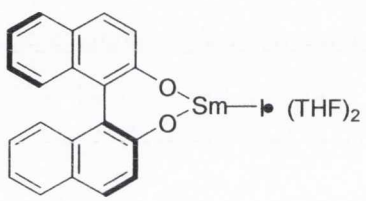
The mechanism requires two molecules of the catalyst in the rate-determining step of the reaction. As one catalyst molecule binds the epoxide another delivers the metal-bound azide to form an azido alkoxide complex. Rapid protonolysis of the intermediate by water affords the product azido silyl ether products and the **206b**-N_3 complex. This mechanistic rationale

necessitates epoxide dissociation from the metal complex in the transition state (from the resting state of the catalyst which is (salen)Cr(N_3)-(epoxide)) yielding the **206b**-N_3 complex which is more nucleophilic than the six-membered Cr(III) complex.[213] This second order dependence on the catalyst prompted the subsequent development of bimetallic catalysts (*via* ester linkages of metal-complexes) to reinforce cooperative catalysis. Dimeric catalysts were found to display reactivity 1-2 orders of magnitude greater than monomeric catalysts **206**, and trimeric catalysts were 2-3 times more reactive than the dimeric counterparts whilst maintaining the same levels of enantioselectivity.

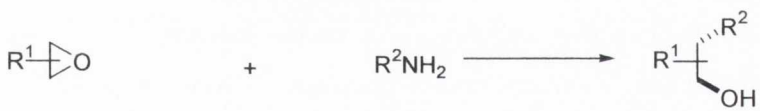
Table 1.6 Asymmetric ring opening of epoxides using azides and amines



(*R*,*R*)-**206a**: M = H
(*R*,*R*)-**206b**: M = CrCl
(*R*,*R*)-**206c**: M = CoI



207



208a R^1 = c-C_5H_4
208b R^1 = $CH(OEt)_2$
208c R^1 = CH_2CN
208d R^1 = cyclobut-3-ene

209 R^2 = C_6H_5
210 R^2 = 2-OMe-C_6H_4

211a R^1 = c-C_5H_4, R^2 = N_3
211b R^1 = CH_3, R^2 = N_3
211c R^1 = $CH(OEt)_2$, R^2 = N_3
211d R^1 = CH_2CN, R^2 = N_3
211e R^1 = c-C_6H_{11}, R^2 = $C_6H_5NH_2$
211f R^1 = cyclobut-3-ene, R^2 = 2-OMe-$C_6H_4NH_2$

Entry	nucleophile	epoxide	product	yield[e] (%)	*ee*[f] (%)
1[a]	**$TMSN_3$**	**208a**	**211a**	80	94
2[b]	**$TMSN_3$**	**35**	**211b**	98	97
3[c]	**$TMSN_3$**	**208b**	**211c**	96	89
4[c]	**$TMSN_3$**	**208c**	**211d**	80	92
5[d]	**209**	**130d**	**211e**	79	91
6[d]	**210**	**208d**	**211f**	75	92

[a]Reaction performed using (*R*,*R*)-**206b** (2.0 mol%) in Et_2O after 28 h. [b] Reaction carried out using 1.0 mol% catalyst. [c] Reaction carried out using 2.0 mol% catalyst. [d]Reactions carried out using 10 mol% catalyst for 18 h at –40 °C. [e]Yield of isolated product. [f]Determined by HPLC.

Broadening the scope of catalyst **206b**-N_3, the simultaneous enantioselective synthesis of chiral terminal epoxides and optically active 1,2-amino alcohols was possible through hydrolytic kinetic resolution (HKR) of a range of terminal epoxides. Kinetic resolution of terminal epoxides using **206b**-N_3 and TMSCN was found to be a general and effective method for the synthesis of 1-azido 2-alcohol derivatives **211** (Table 1.6, entries 1-4). The asymmetric ring-opening of *meso*-epoxides is an elegant route to synthetically useful compounds in optically active form of biologically interesting compounds.[214,215]

However, a more attractive nucleophile (as $TMSN_3$ is expensive and heat sensitive) was considered more applicable for future industrial use, therefore the use of carboxylic acids with the Co(salen) complex **206c** was found to be an alternative for epoxide resolution.[216] The HKR using the Co(salen) catalyst **206c** is a highly applicable method as every terminal epoxide (including aliphatic and electron-deficient epoxides) tested to date has undergone clean and highly selective resolution.[213]

The asymmetric addition of amines to *meso*-epoxides promoted by metal-based catalysts for the direct synthesis of chiral β-amino alcohol units.[217] The addition of amines to epoxides has benefited from the use of promoters: metal triflates,[218-220] metal halides,[208,221-223] metal amides,[224,225] alkali metal perchlorates,[226] silica under pressure,[197] ionic liquids[227] and clay[207,228] have all been used.[222] Chiral metal-based catalysts used in the enantioselective addition of amines to epoxides have included the use of Ti,[229] Sc,[230] Sm,[231] Yb,[232,233] Cu,[234]and Niobium[235] based catalyst systems. An interesting recent example of Lewis-acid activation and simultaneous stereoinduction is the lanthanide iodo binaphtholate **207** promoted addition of aromatic amines to *meso*-epoxides. The synthesis of enantioenriched β amino alcohols (up to 93% *ee*) was achieved using 10 mol% catalyst **207** at an optimum temperature of –40 °C. Reactions of **209**, *o*-anisidine **210** with five or six membered ring epoxides were carried out to prepare the β-amino alcohols in moderate yields and excellent enantioselectivities (Table 1.6, entries 5-6). These examples illustrate the utility of the Lewis acid metal-ion centre and the cooperative binding potential between it and its associated chiral ligands for the promotion of enantioselective reactions.

1.6.4.2 Metal catalysed additions of *S*-based nucleophiles to epoxides

The thiolysis reaction of epoxides is one of the most widely used methods for the synthesis of β-hydroxy sulfides which are versatile intermediates for the synthesis of cyclic sulfides,[236] allylic alcohols,[237] benzoxathiepines,[238] benzothiazepines,[239] and thioketones.[240] Readily accessible also from these materials are the β-hydroxy sulfoxides which are useful in the preparation of naturally occurring compounds such as leukotrienes.[241] Current methods of promoting thiolysis reactions of epoxides include the use of Lewis acids,[205,242-245] microwave irradiation,[246] ionic liquids[247] and the use of PBu_3.[248]

Metal triflates have found tremendous application in the promoted addition of a range of thiols to epoxides. Gallium (III) triflate is one such catalyst for the addition of thiols to epoxides to afford β-hydroxy sulfides with high regioselectivity and chemoselectivity in high yields (84-97%) under solvent free conditions.[249] The selective nucleophilic attack occurs predominantly on the α-carbon atom of the epoxide ring except in the case of **130a** which underwent preferential attack at the β carbon atom of the epoxide. Regioselectivity and overall yields were both superior in the presence of the gallium (III) triflate catalyst relative to those associated with the uncatalysed reaction. The presence of electron withdrawing and electron donating substituents on the epoxides did not alter the observed selectivity. The reactions were found to be chemoselective even in the presence of other nucleophilic functional groups such as amino and hydroxyl. The subsequent synthesis of β-hydroxy sulfoxides in water (no β-hydroxy sulfones detected) is also achievable in excellent yields (81-94%) using a gallium triflate-water complex. These catalysts are readily recoverable and re-useable if somewhat environmentally unfriendly.[249]

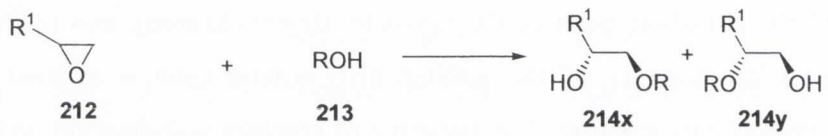
1.6.4.3 Metal-catalysed additions of *O*-based nucleophiles to epoxides

Similar to the cases of metal-catalysed additions of both the *N*- and *S*- based nucleophiles a range of metal complexes have been utilised for the hydrolysis and addition of alcohols to both *meso* and terminal epoxides. The asymmetric addition of nucleophiles to terminal (as opposed to 1,2-disubstituted) epoxides has proven a greater challenge yet the alcohol products are of more synthetic value. Metal triflates,[250,251] metal halides,[252] metal bipy complexes,[230]

metal-salen complexes,[253,254] metal salts,[255] and nanoparticles,[256] have all been used as catalysts for the addition of *O*-based nucleophiles to epoxides.

The enantioselective addition of both aromatic and aliphatic alcohols to aliphatic terminal epoxides using the Co(salen) complex **206c** were reported in 1999 allowing the synthesis of α-aryloxy alcohols in both high yields and *ee*'s through kinetic resolution of terminal epoxides (Table 1.7, entries 1-3).[253] The mechanistic rationale involves a dual role of the catalyst as a Lewis acid activator of the epoxide and counterion for nucleophile delivery. The complex is thought to form a (salen)Co(aryloxide) intermediate analogous to previous findings in the addition of azides to epoxides.[213] The use of an oligosalen version of **206c** facilitated the addition of the alcohols **101** and phenol (**213a**) to **212** and **130a** in good yield and excellent enantioselectivities (Table 1.7, entries 4-6).[254]

Table 1.7 Catalysed alcohol additions to epoxides



212 **213** **214x** **214y**

212a $R^1 = CH_2Cl$
212b $R^1 = C_4H_9$

213a $R = C_6H_5$
213b $R = 3\text{-}CH_3\text{-}(C_6H_4)$
213c $R = 4\text{-}OCH_3\text{-}(C_6H_4)$
213d $R = C(CH_3)_3$

214a/b $R = C_6H_5$, $R^1 = CH_2Cl$
215a/b $R = 3\text{-}CH_3\text{-}(C_6H_4)$, $R^1 = C_4H_9$
216a/b $R = 4\text{-}OCH_3\text{-}(C_6H_4)$, $R^1 = C_4H_9$
217a/b $R = OCH_2(C_2H_3)$, $R^1 = C_4H_9$
218a/b $R = C_6H_5$, $R_1 = C_6H_5$
219a/b $R = C(CH_3)_3$, $R^1 = C_6H_5$
220a/b $R = CH_2\text{-}C_6H_5$, $R^1 = C_6H_{10}$

entry	alcohol	epoxide	product	temp. (°C)	time (h)	yield[a] (%)	*ee*[b] (%)
1[c]	**213a**	**212a**	**214**	-15	12	97	99
2[c]	**213b**	**212a**	**215**	25	16	99	99
3[d]	**213c**	**212a**	**216**	4	18	75	99
4[d]	**101**	**212b**	**217**	4	18	87	97
5[d]	**213a**	**212b**	**214**	4	4	96/99	99
6[d]	**213a**	**130a**	**218**	4	8	60	97
7[e]	**213d**	**130a**	**219**	rt	12	87	-
8[e]	**39**	**130d**	**220**	rt	2	95	-

[a] Isolated yields based on the phenol. [b] Determined by HPLC or GC analysis. [c] To the alcohol (1.00 equiv.) and epoxide (2.20 equiv.) was added 100/200 µl of TBME and the resulting solution was stirred at the temperature and time indicated. [d] To the alcohol (2.25 mmol) and the epoxide (5.0 mmol) was added CH_3CN (0.2 mL) and stirred for the temperature and time indicated. [e] Copper(II)tetrafluoroborate (0.25 mmol) in 20 mL of CH_2Cl_2 were added to 100 mmol (4 equiv.) of the alcohol and 2.5 mmol of epoxide at rt.

Commercially available copper(II)tetrafluoroborate is found to be an excellent Lewis-acidic promoter of the regioselective addition of both aromatic and aliphatic alcohols to aliphatic *meso*- and aromatic terminal epoxides (Table 1.7, entries 7-8).

1.6.5 Organocatalysis of the addition of *S*-, *N*-, and *O*-based nucleophiles to epoxides

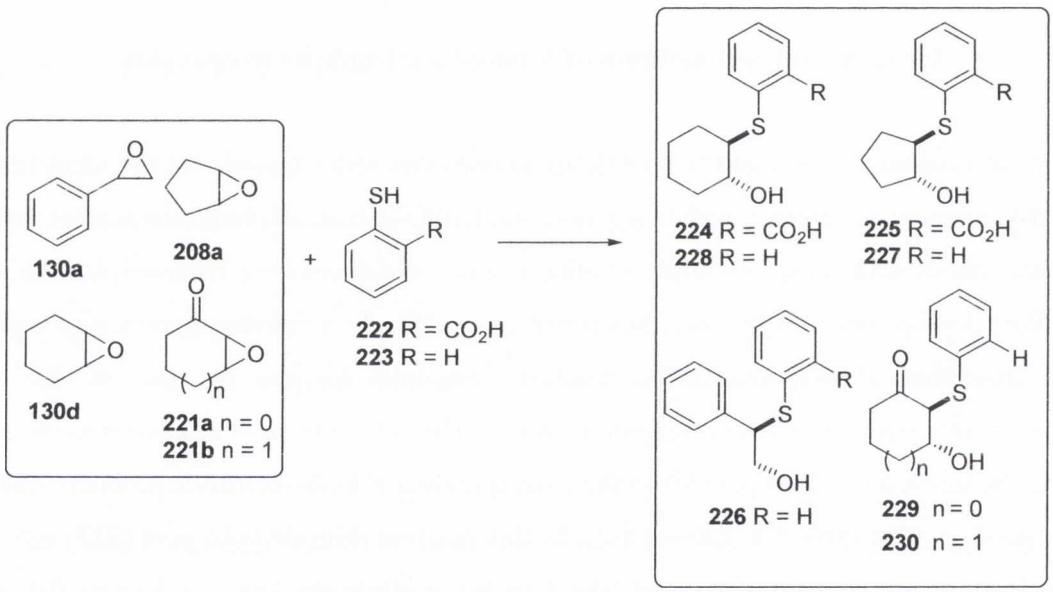
The high synthetic utility of the densely functionalised products of the FC type addition reaction of heteroatom based nucleophiles to epoxides have stimulated great interest in the development of more benign methods of catalysis of these types of reaction. The synthesis and use of complex metal-based catalysts and the toxicity issues associated with them has led to the development of organocatalysed methods for promoting these reactions.

1.6.5.1 Organocatalysed addition of *S*-based nucleophiles to epoxides

The area of organocatalysed addition of thiols to epoxides relies heavily on the identification of suitable reaction conditions. Thiols are more nucleophilic than alcohols and amines towards soft electrophiles such as sp^3 carbons, alkaline reaction conditions are commonplace in order to facilitate deprotonation of the thiol functional group, thereby rendering it more nucleophilic. Recent examples of organocatalysed thiolysis reactions involve the use of the more environmentally friendly reaction medium of water. Thiosalicyclic acid **222** has been found to promote the thiolysis of 1,2-epoxides to the corresponding β-hydroxysulfide products **224-225** in very good yields (Table 1.8, Entries 1-2). In this reaction thiosalicyclic acid (**222**) acts both as a nucleophile and as a Brønsted acid. The β-hydroxysulfide products can be transformed in both a regio- and diastereoselective manner to the corresponding 1,4-oxathiepin-5-ones in a one-pot procedure under solvent free conditions and satisfactory yields.[257] The thiolysis of 1,2-epoxides with thiophenol **223** did not occur, even under solvent-free conditions, either Brønsted or Lewis acid catalysis were necessary in this case despite the fact that the thiol group of thiosalicyclic acid (**222**) is expected to be less nucleophilic than that of thiophenol (**223**). The self-promoted thiolysis reaction is thought to be due to the activation of the electrophile through formation of a hydrogen bond between the epoxide and **222**.

Tributylphosphine (TBP) has been used as a promoter of nucleophilic addition reactions of alcohols, amines and thiols to epoxides in moderate to excellent yields in water.[248] In contrast with some metal-based catalyst systems[219] the reaction conditions were found to be tolerant of both aromatic and aliphatic nucleophiles, and TBP was found to promote nucleophilic attack onto the least hindered epoxide carbon, in its absence the regiochemistry of the addition reaction was reversed (Table 1.8, entries 3-5). The NaOH-catalysed thiolysis of α,β-epoxyketones in water (30 °C, pH 6 or 9) proceeds with complete C-α-regioselectivity and *anti*-stereoselectivity for the corresponding *anti*-β-carbonyl-β-hydroxysulfides **229-230** in excellent yields (Table 1.8, Entries 6-7).[258]

Table 1.8 Representative examples of organocatalysed epoxide thiolysis reactions



entry	NuH	epoxide	product	time (h)	yield[a] (%)
1[b]	**222**	**130d**	**224**	6	94
2[c]	**222**	**208**	**225**	8	94
3[d]	**223**	**130a**	**226**	12	88
4[d]	**223**	**208**	**227**	12	78
5[d]	**223**	**130d**	**228**	12	72
6[e]	**223**	**221a**	**229**	0.5	95
7[e]	**223**	**221b**	**230**	0.3	96

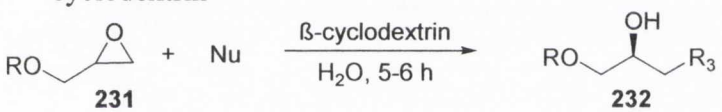
[a]Yield of isolated products. [b]Reaction carried out at 50 °C under neat conditions using 1.05 equiv. of thiol. [c]Reaction carried out at 30 °C under neat conditions using 1.05 equiv. of thiol. [d]Reactions were carried out using 1.1 equiv. of thiol in 2 mL of water at rt. [e]Reactions were carried out in water at 30 °C using 1.05 equiv. of thiol.

In conclusion, the use of strong acids and bases can afford racemic thiol-addition products in moderate to good yields. Aliphatic substrates have not been shown to be useful substrates and no other nucleophiles were demonstrated to be suitable in these studies.

1.6.5.2 Organocatalysed addition of *N*-based nucleophiles to epoxides

Very few widely applicable examples have been reported of organocatalysed additions of nitrogen containing nucleophiles to epoxides. Water at high temperatures,[259] and strongly basic conditions[248,260] have all been utilised to synthesise diverse β-amino alcohol derivatives of clinically important use from the addition of amines to epoxides.[261] The enantioselective ring opening of epoxides with $TMSN_3$ and **36** has been accomplished in the presence of β-cyclodextrin under mild aqueous conditions affording the azido alcohol and subsequent amino alcohol products as the (*S*)-isomers (Table 1.9).[262]

Table 1.9 Ring opening of racemic epoxides with $TMSN_3$ and **36** in the presence of β-cyclodextrin



231

231a R = 2-OCH_3-C_6H_4
231b R = 1-naphthyl
231c R = C_6H_5

232

232a R = 2-OCH_3)C_6H_4, R_3 = N_3
232b R = 1-naphthyl, R^3 = N_3
232c R = C_6H_5, R_3 = $CH(CH_3)_2NH$

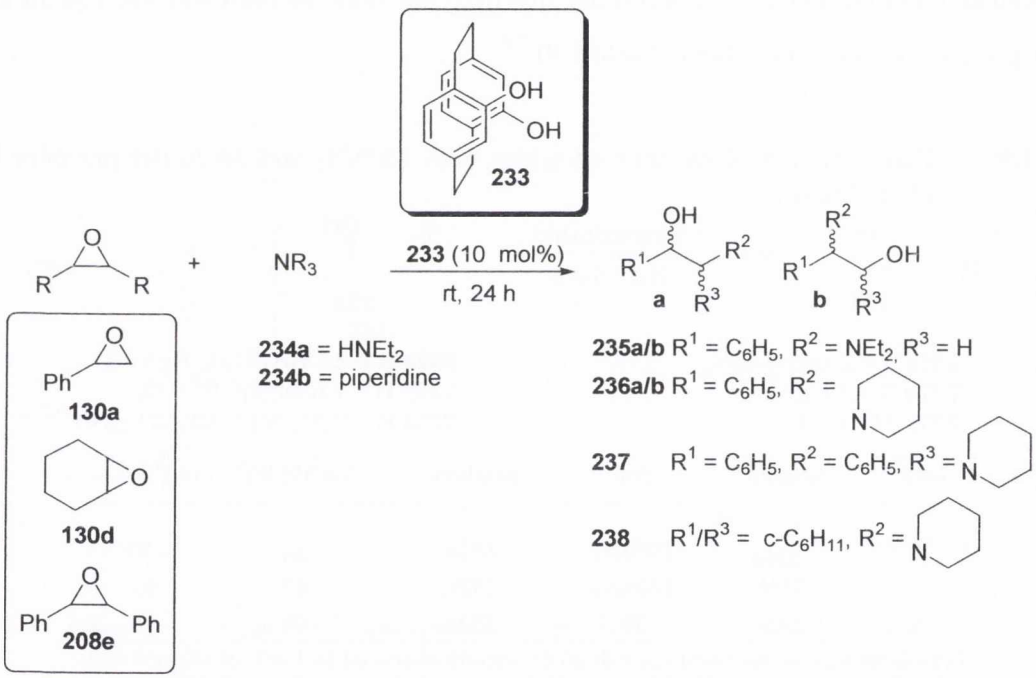
entry	epoxide	Nu	product[a]	Yield (%)[b]	ee (%)[c]
1	**231a**	**$TMSN_3$**	**232a**	40	>99
2	**231b**	**$TMSN_3$**	**232b**	47	95
3	**231c**	**36**	**232c**	46	90

[a]Typical procedure involved epoxide (0.66 mmol) dissolved in 1 mL of ethanol and to this β-cyclodextrin (1.13g in 20 mL H_2O) was added. After stirring for 30 min. at rt the nucleophile was added (0.86 mmol) and incubated at 37 °C in an orbital shaker for 5-6 h.[b]Isolated yield [c] Determined by HPLC.

The method was found to be applicable to a range of epoxides with varying aryl substituents affording β-azido alcohols in up to 99% *ee* using $TMSN_3$ and up to 92% *ee* with **36**. No aliphatic epoxides were evaluated as substrates in this study and the maximum yield of the azido and amino alcohols was 48% in both studies. While the mode of catalysis by the cyclodextrin is unknown, the 4,12-dihydroxy[2.2]paracyclophanediol (PHANOL, **233**)

catalysed addition of amines to epoxides is known to occur through double hydrogen bond activation through the two lone pairs of the epoxide. In a test reaction using **130a** and diethylamine in the presence of 10 mol% **233**, at rt for 24 h yielded a conversion of 50% and the desired ring-opened products **235a** and **235b** in a 3:1 ratio.[263] A series of amines and epoxides were then evaluated as substrates, the results of which appear in Table 1.10. A library of substituted PHANOLs were tested in the addition of amines to epoxides, however **233** was found to be the optimal. The attachment of electron-withdrawing groups to the PHANOL backbone led to an increase in acidity, however these species are subsequently easier to be deprotonated by the substrate amines leading to reduced catalytic activity.

Table 1.10 PHANOL promoted addition of amines to epoxides

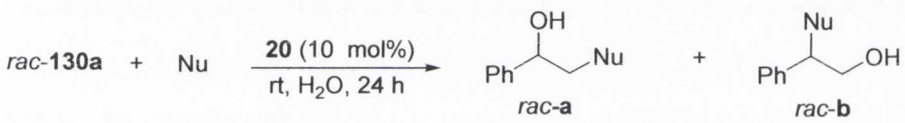


entry[a]	epoxide	amine	product	time (h)	yield (%)[d]
1	**130a**	**234a**	**235**	24	50 (3.4:1)
2	**130a**	**234b**	**236**	19[b]	>95 (4:1)
3	**208e**	**234b**	**237**	7d[c]	36
4	**130d**	**234b**	**238**	32	50

[a]All reactions were carried out using a 1.5:1 ratio of amine:epoxide.[b]Control reaction gave 49% conversion. [c] Control reaction gave 14 % conversion.[d] % conversion as determined by ^{1}H NMR spectroscopy. The figures in parenthesis give the ratio of "terminus" to "internal" attack, respectively.

Inspection of the results in Table 1.10 suggests that terminal epoxides are more reactive towards ring-opening by amines than 1,2-disubstituted *meso*-epoxides. Diethylamine and piperidine **234b** sufficiently attack the **130a** (entries 1 and 2) whilst **234b** attacks both *cis*-stilbene oxide **208e** (entry 3) and **130d** (entry 4). Morpholine (**239**) did not show any nucleophilic activity towards these epoxides. This result suggests the order of nucleophilicity is piperidine>diethylamine>morpholine. In order to test the enantioselecetivity of the PHANOL catalyst a test reaction was carried out using cyclohexene oxide with piperidine (no background reaction in the absence of catalyst was detected) and 10 mol% (*R*)-**233**, HPLC analysis confirmed a racemic mixture of products. An interesting feature of the **233** catalysed addition reactions to **130a** is that attack preferentially occurs at the terminus of the epoxide, analogous to the activation carried out by a mild Lewis acid where there is little carbocationic nature in the transition state.

Table 1.11 (Thio)urea promoted addition of amines to racemic epoxides



240a Nu = *t*-$BuNH_2$ **241a** Nu = *t*-$BuNH_2$ **241b** Nu = *t*-$BuNH_2$
240b Nu = *n*-$BuNH_2$ **242a** Nu = *n*-$BuNH_2$ **242b** Nu = *n*-$BuNH_2$
240c Nu = *n*-Bu_2NH **243a** Nu = *n*-Bu_2NH **243b** Nu = *n*-Bu_2NH
239 Nu = Morpholine **244a** Nu = C_4H_9NO **244b** Nu = C_4H_9NO
240d Nu = $(CH_2CH_2CH_3)_2NH$ **245a** Nu = $(CH_2CH_2CH_3)_2NH$ **245b** Nu = $(CH_2CH_2CH_3)_2NH$

entry	Nu[a]	product	H_2O no cat.	H_2O cat	Ratio a:b
1	**240a**	**241**	61	71	1:2
2	**240b**	**242**	-	96	3:17
3	**240c**	**243**	-	80	1:1
4	**239**	**244**	-	85	1:1
5	**240d**	**245**	-	92	1:1

[a]Epoxide (1 mmol) was dissolved in 2 mL of dist. H_2O and cooled to 0 °C. Catalyst was added and the reaction mixture was homogenised. Amine (1 mmol) was added in one portion and the reaction mixture allowed to warm to room temp. The resulting emulsion was vigorously stirred for 24 h.

In a more recent study Schreiner *et al.*[60] demonstrated the use of the (thio)urea catalyst **20** for the addition of amines to racemic epoxides in aqueous conditions. Schreiner found that the addition reactions carried out in water as opposed to CH_2Cl_2 had relative accelerations as large as 200-fold, this was taken as proof-of-principle that hydrogen-bonding catalysis and the use

of water as a solvent are not mutually exclusive. The results shown in Table 1.11 demonstrate the ability of water to accelerate the reaction (entry 1) however this methodology still suffers from low regioselectivity in comparison with the reaction catalysed by PHANOL derivatives dealt with earlier.

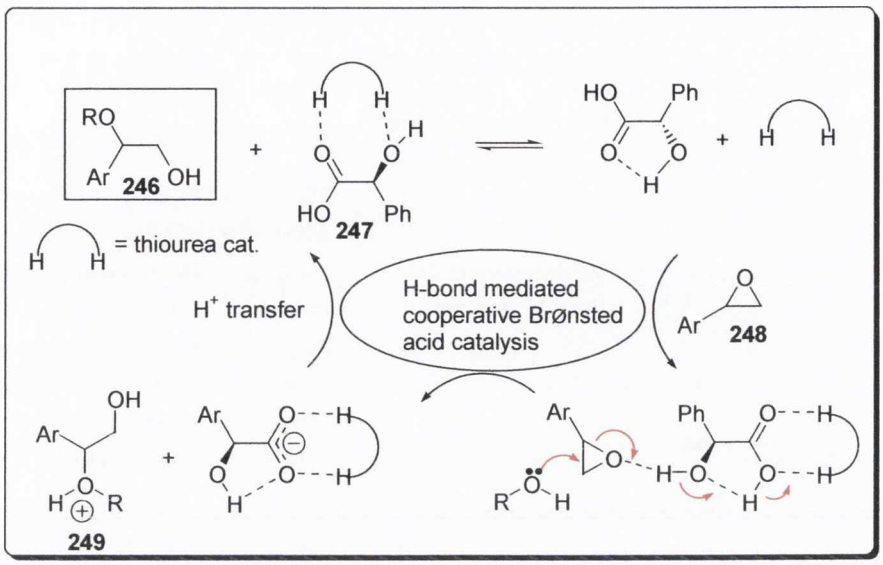
The acceleratory effect of water is due to the ability of water to stabilise developing negative charge in the transition states of these reactions and more significantly also due to a hydrophobic effect where water insoluble substrates are brought together artificially through the minimisation of the solute's volume ("like attracting like"). The term "hydrophobic amplification" effectively describes this phenomenon. This methodology however does not show applicability with a wide range of epoxides: **35**, **130a** and **130d** were the only epoxides tested and insignificant hydrophobic amplification was reported in some cases.

1.6.5.3 Organocatalysed addition of *O*-based nucleophiles to epoxides

The most frequently documented addition of *O*-based nucleophiles to epoxides is the promoted addition of a water molecule (hydrolysis). Organocatalytic methods which have been used successfully have included the use of tributylphosphine in water,[248] tetrabutylammonium bisulfate[264] and hot water alone.[259] Recently, epoxide hydrolases[265] have been shown to be cheap and practical bio-catalysts for the promotion of highly regioselective hydrolysis reactions affording (*R*)-diols from racemic epoxides in up to 99% *ee* and 69% overall yield (after recrystallisation).[265]

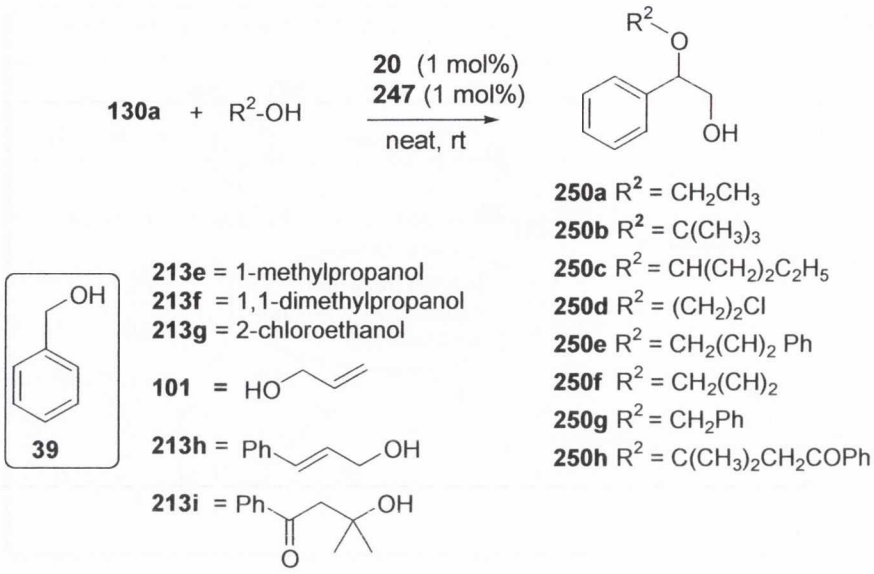
As recently as this year (2008-subsequent to our work) Schreiner *et al.* have described a mild and efficient method for the completely regioselective alcoholysis of a range of epoxides utilizing a Brønsted acid-type organocatalytic system comprised of 1 mol% mandelic acid **247** and 1 mol% (thio)urea catalyst **20**.[51] This approach relies upon the cooperation of two hydrogen-donating catalysts (Scheme 1.24).

Scheme 1.24 Catalytic cycle for epoxide alcoholysis by co-operative H-bond catalysis



Experimental findings suggest that catalyst **20** coordinates to the acid present through double H-bonding to stabilise the acid in the *cis*-hydroxy conformation, hence acidifying the α-OH proton *via* an intramolecular H-bond. This proton activates the epoxide through a single interaction and facilitates nucleophilic attack singularly onto the benzylic position of the epoxide (Scheme 1.24). The initial oxonium ion reprotonates the mandelate and yields the β-alkoxy alcohol product. A range of styrene oxides can be readily transformed into the corresponding β-alkoxy alcohols in good to excellent yields at full conversions. Sterically demanding and aliphatic (Table 1.12, entries 1-5), unsaturated (entries 6 and 7) and acid-sensitive alcohols (entries 8 and 9) were suitable substrates for this reaction.

Table 1.12 (Thio)urea catalysed addition of alcohols to epoxides



entry[a]	alcohol (R^2-OH)	product	time (h)	Yield (%)[c]
1	EtOH	**250a**	22	86
2[b]	*t*-BuOH	**250b**	15	74
3	**213e**	**250c**	21	94
4	**213f**	**250d**	20	73
5	**213g**	**250e**	23	89
6	**101**	**250f**	18	80
7	**39**	**250g**	23	78
8	**213h**	**250h**	16	65
9[b]	**213i**	**250i**	18	58

[a]Reaction conditions: 1 equiv. of epoxide, 12 equiv. of alcohol and 1 mol% of **20** and **247** respectively at rt. All catalysed reactions were accompanied by parallel reference experiments. without **20** as well as experiments. with **20** and without **247** under identical conditions. Reactions were monitored by GC/MS. [b]At 50 °C. [c]Yield of isolated product.

Schreiner's co-operative system is a significant improvement on the previous literature benchmark work carried out using metal catalysts[252] and the previous work of Schreiner[60] using catalyst **20** for hydrophobic amplification of epoxide addition reactions. Overall the co-operativity shown by **247** and catalyst **20** renders it an excellent system for the regioselective alcoholysis of epoxides compatible with a broad range of alcohols and substituted epoxides which affords high product yields at convenient rates.

1.6.6 The Friedel-Crafts addition of non-carbon-based based nucleophiles to epoxides: conclusions

The metal-based Jacobsen catalysts are the current benchmark for the enantioselective addition of both amines and azides to epoxides. No organocatalyst synthesised is capable of bringing about similar yields and selectivities. While the β-cyclodextrin study is impressive, the exact mechanism of catalysis is still unknown. The best promoters for thiol and alcohol addition to epoxides remains the metal-based catalysts in terms of both yield and enantioselectivity, however in both the metal and organocatalysed case achieving control over the regioselectivity of epoxide opening remains quite a challenge.

1.7 The Johnson-Corey-Chaykovsky reaction

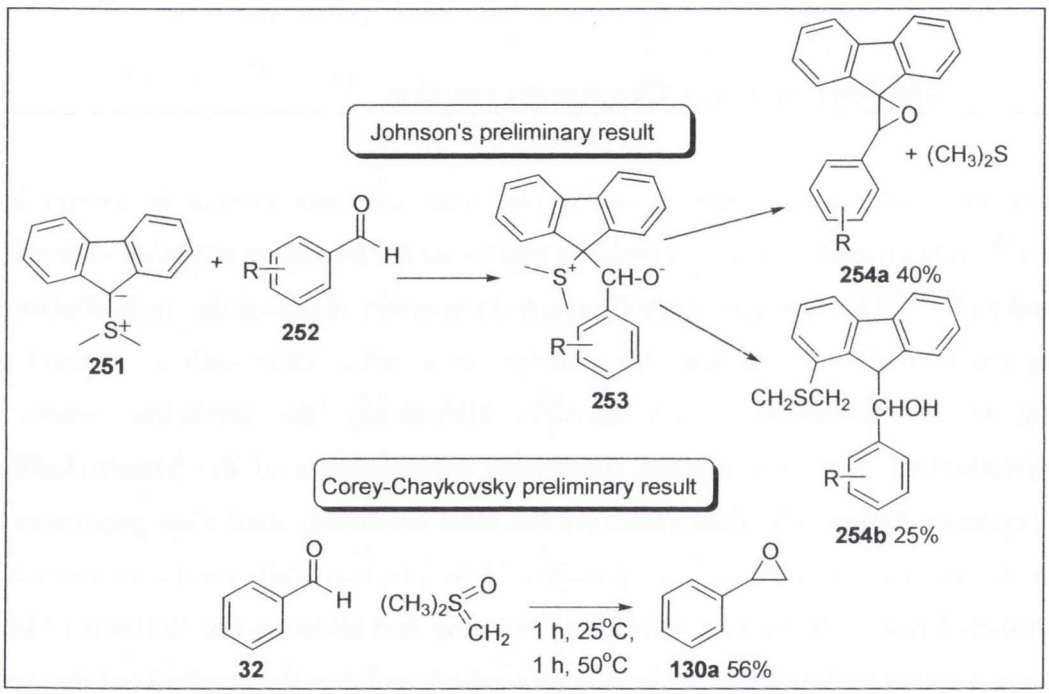
Epoxides are small, highly strained carbocyclic ring structures present in several natural products[266] and play a pivotal role as building blocks for the formation of C-C, C-X bonds (X= N, O and S).[267,268] The Johnson-Corey-Chaykovsky reaction is one of the most effective ring forming reactions possible through the reaction of a sulfur ylide with a carbonyl group resulting in the formation of an epoxide. Historically the methylene source was dimethylsulfonium methylide derived from base deprotonation of the trimethylsulfonium iodide precursor. Chiral sulfonium ylides are the most commonly used ylide precursors to be used in the asymmetric synthesis of epoxides. There are two main routes for carrying out ylide-mediated epoxidations; one involves preforming and isolating the sulfonium ylide for addition to a carbonyl electrophile. The second method, which is the emphasis of this section, is the formation of the sulfonium ylide in situ with immediate reaction taking place with an aldehyde. After methylene transfer the reaction returns the starting material sulfide which can therefore be used in substoichiometric amounts.[269]

1.7.1 Historical Perspective

Johnson *et al.*[270] were the first to report (more than 40 years ago) that sulfur ylides were capable of forming epoxides upon reaction with aldehydes and ketones. In an attempt to witness the Wittig reaction between 9-dimethylsulfonium fluorenylide **251**, and benzaldehydes **252** to form 9-benzalfluorenes, the formation of benzalfluorene oxides **254a** and phenyl-9-

fluorenylcarbinols **254b** was observed instead (Scheme 1.25). The sulfonium ylide was found to react specifically to yield the epoxides even in the presence of α,β-unsaturated carbonyl systems. Two years later Corey and Chaykovsky reported a preliminary results paper[271] citing the formation of dimethylsulfoxonium methylide (from the trimethylsulfoxonium halide precursor) and its reactivity towards ketones and aldehydes in forming epoxides in moderate-to-excellent yields (56-95%) (Scheme 1.25).

Scheme 1.25 Seminal epoxidation results



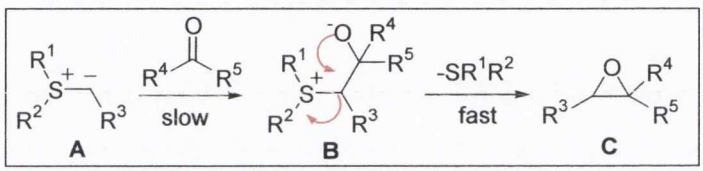
These reactions are widely applicable yet they exhibit discrete preferences *re* stereochemistry in certain reactions *e.g* in the carbonyl addition reaction of cyclohexanones variances exist depending on the ylide; the sulfoxonium ylide preferentially reacts by equatorial addition (*i.e* of methylene) while the sulfonium ylide reacts by axial addition.[272]

1.7.2 The mechanism of the Johnson-Corey-Chaykovsky (JCC) reaction

From the earliest work of Johnson the mechanism of the sulfur ylide catalysed epoxidation reaction was postulated to occur in an analogous fashion to the Wittig reaction involving

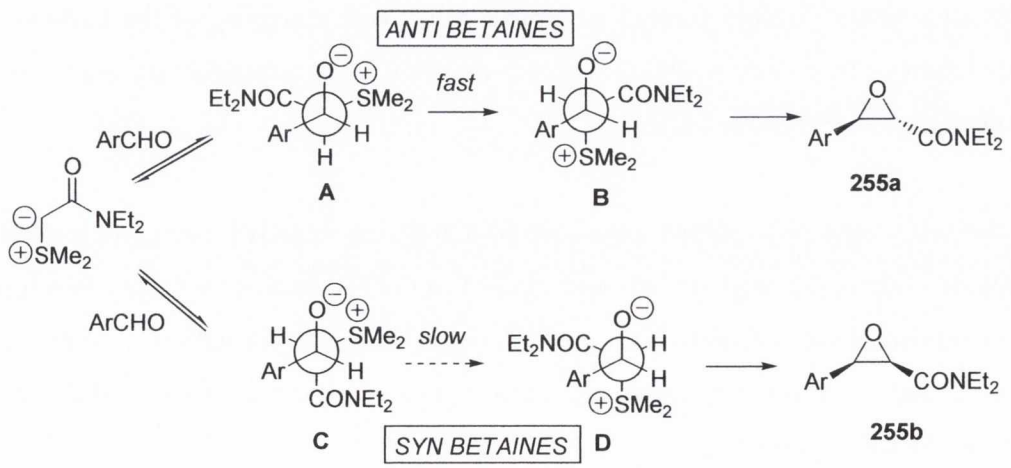
phosphorus ylides. Base-mediated deprotonation of the trimethylsulfonium salt to afford the ylide **A** (Scheme 1.26) is the first step of the reaction (often phase transfer conditions *e.g.* CH_2Cl_2/base (aq) conditions are used). The second step of the JCC involves attack of the sulfonium ylide on the carbonyl electrophile to produce an oxyanion tetrahedral intermediate **B** (Scheme 1.26), which undergoes ring closure to afford the epoxide **C** (Scheme 1.26). The nature of the sulfonium ylide (stabilised, semi-stabilised or non-stabilised) and the reaction conditions are key variables to controlling the selectivity of the JCC epoxidation reaction. To understand the origins of enantio- and diastereoselectivity in the sulfonium ylide epoxidation reaction, a detailed study of the ylides involved is necessary.

Scheme 1.26 Mechanism of the Johnson-Corey-Chaykovsky reaction



The first class are known as stabilised ylides, which as the name suggests bear an anion-stabilising group at the carbon α-to the sulfur heteroatom (Scheme 1.27). Sulfonium ylides stabilised by esters do not react with aldehydes while the less stabilised amide analogues do react sufficiently with aldehydes.

Scheme 1.27 Origin of high *trans*-selectivity in the stabilised ylides



There are three distinct steps in the mechanism, the first is betaine formation with charges adjacent to each other, followed by bond rotation to the *anti*-conformation, and finally ring closure.[273]

Both *syn* and *anti*-betaines may form, yet experimentally it has been found that the C-C bond rotation in the *syn*-betaine has a much higher activation barrier as two large groups must pass each other as the charges separate (Scheme 1.27). This results in the barrier for torsional rotation of the *syn*-betaine being larger than in the *anti*-betaine case, and the barrier for reversal to starting materials. In the *anti*-betaine case it is also possible for the large substituents to pass over a small substituent during bond rotation.[274] The consequence of this is the C-C bond rotation-ring closure is faster for the *anti*-betaine case, thus *trans*-epoxides predominate.[273]

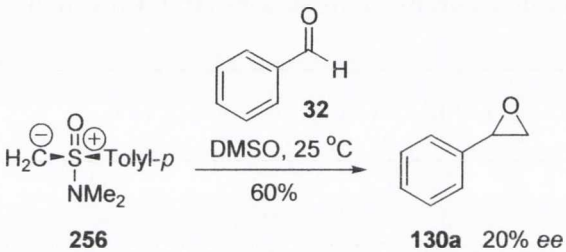
Often two diasteromeric *anti*-betaines may be formed which may lead to two enantiomeric epoxides, the enantiomeric outcome of the reaction will depend on the equilibrium ratio of the betaines and the relative rates of C-C bond rotation leading to the epoxide. High enantioselectivity indicates a significant energy difference between the betaines formed.[274]

Semi-stabilised ylides bear weakly anion-stabilising groups such as benzyl or allyl groups. The major difference in comparison to the stabilised ylide case is that the characteristic *anti*-betaine is formed irreversibly while the *syn*-betaine is formed reversibly, leading to high *trans*-selectivity of benzyl-stabilised ylides using aromatic aldehydes. Diastereoselectivity tends to be low if *syn*-betaine formation is non-reversible or only partially reversible and four characteristics of the betaine formed determine this. High reactivity of the carbonyl group, reduced stability of the ylide, reduced steric hindrance of the ylide/aldehyde and the degree of solvation of the charges of the betaine.[274]

Non-stabilised ylides bear groups incapable of stabilising negative charge (*e.g* alkyl or H). This type of ylide is the least utilised and studied as the representative ylides do not promote highly enantioselective reactions due to non-reversible betaine formation. In these cases the origin of enantioselectivity arises solely from control over which face of the aldehyde is attacked by the sulfonium ylide.

Chiral aminosulfoxonium ylides[275,276] promote enantioselective epoxidation reactions for terminal epoxide synthesis; the formation of the intermediate diastereomeric betaines is reversible (Scheme 1.28). This implies that the origin of enantioselectivity is due to either a low equilibrium ratio of the diastereomeric betaines or similar rates of C-C bond rotation and ring closure of both betaines (Scheme 1.27). A recent experimental study using cross-over experiments concluded that betaine intermediates can be subject to base catalysed isomerisation leading to increases in diastereoselectivity (in favour of the prefereed isomer) but decreases in enantioselectivity.[277]

Scheme 1.28 Aminosulfoxonium ylide promoted epoxidation reaction



256 **130a** 20% *ee*

1.7.2.1 The effect of reaction conditions on rate and selectivity in the JCC reaction

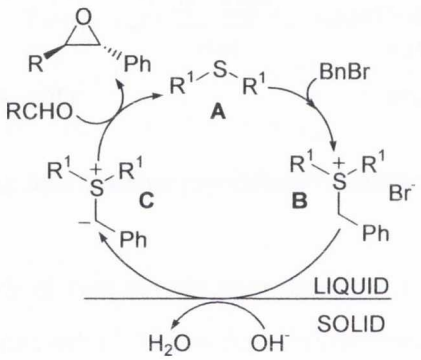
The earliest evidence that reaction conditions play a part in the success of the JCC addition reaction was in the seminal paper by Johnson *et al.*[270] who carried out solvent screening tests in the reaction depicted in Scheme 1.25. It was found that the more acidic solvents favoured formation of the epoxide while more basic solvents facilitated the formation of the ring-opened alcohol product. Johnson proposed that it is possible that basic media facilitate the proton exchange of the intermediate to the addition intermediate thereby facilitating alcohol formation. Unexpectedly, (and unexplained by Johnson) it was found that the use of neutral solvents facilitated the formation of the epoxide **254a** and alcohol **254b** product in a 2:1 ratio. Ethanol and chloroform were found to give the best yields and rates of conversion, while the solvents diethylamine, ethyl ether, acetonitrile and methyl sulfoxide, the alcohol product predominated. Aggarwal *et al.*[278] in 1998 tested the effect solvent had on both the enantioselectivity and yield of enantioselective epoxidation reactions between sulfide catalysts and copper tetra methylheptanedionate as a metal catalyst. It was found that the use of protic solvents or lithium cations improved enantioselectivity in the epoxidation of benzaldehyde (**32**) as the reaction becomes less reversible from the point of betaine formation.[273,279] If low

diastereoselectivity is occurring the use of an aprotic solvent and avoidance of species capable of solvating an alkoxide was found to increase diastereoselectivity as such conditions increase the barrier to bond rotation of the intermediate betaine, thereby making the reaction more reversible.[274]

1.7.3 Chiral sulfonium ylides for enantioselective alkylidene transfer

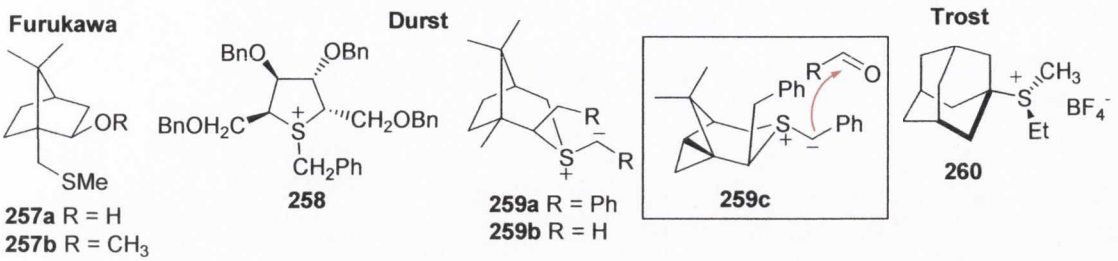
The first successful application of a chiral sulfonium ylide for asymmetric epoxidation was by Furukawa *et al.*[280] using chiral sulfides **257a** and **257b** (Figure 1.21) derived from (+)-10-camphorsulfonic acid in a catalytic process (Scheme 1.29). The use of substoichiometric quantities of sulfide under phase-transfer conditions (PTC) was demonstrated.

Scheme 1.29 Catalytic cycle of sulfonium ylide epoxidation.



The sulfide (Scheme 1.29, part **A**) mediates the alkylation reaction (through sulfonium ylide formation **C**) of an aldehyde and an alkyl halide (*e.g* benzyl bromide) in the presence of a base. In the epoxidation of **32**, Furukawa found CH_3CN to be the optimal solvent due to increased solubility of KOH in solution. The level of enantiomeric excess varied from 7% (with 4-chlorobenzaldehyde, **261b**) to 47% *ee* using benzaldehyde as a substrate (Table 1.13). The sign of optical rotation was found to depend on the presence of either a hydroxyl or a methoxy group on the sulfonium ylide: **257b** gave the opposite enantiomer of stilbene oxide to that obtained using **257a** (Table 1.13, Entry 1). The low levels of enantioselectivity could be due to the possible formation of a diastereomeric mixture of sulfonium ylides which would react preferentially with opposite enantiomers of the aldehyde.

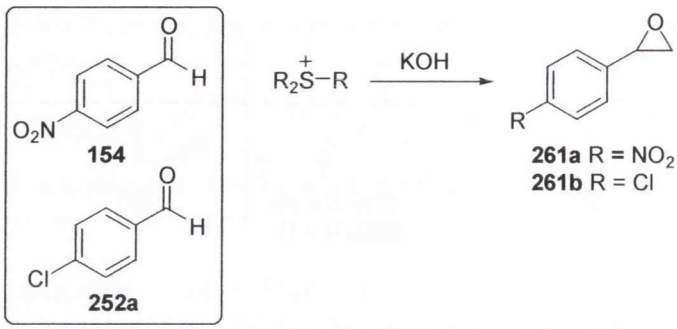
Figure 1.21 Chiral sulfonium ylides for alkylidene transfer published in the literature



Durst *et al.*[281,282] with the design rationale of reducing the number of possible competing, diastereomeric transition states designed a range of C_2-symmetric sulfide ligands such as **258** for the asymmetric epoxidation of aldehydes. The sulfonium ylide was formed from treating **258** with benzylbromide followed by addition of $AgClO_4$. The greatest enantioselectivity was obtained in the reaction of **32** with the sulfur ylide derived from **258** (the substituents at the C-2 and C-5 positions close to the reaction centre of the ylide are important). Whilst no mechanistic rationale was outlined, the optimal catalyst was found to be **258,** yielding the epoxide product in a modest 41% yield and an excellent 83% *ee* (Table 1.13, Entry 2). Subsequent work by the group identified a library of non-C_2-symmetric sulfide ligands derived from (1*R*, 3*S*)-(+)-camphoric acid.

The benzylidene transfer ylide **259a** yields the greatest enantioselectivity (up to 96% *ee*) whilst the methylene equivalent **259b** only afforded 4% *ee*, which is consistent with the lack of enantioselectivity reported by Trost[283] using sulfonium ylide **260** (Table 1.13, entries 3 and 4). Epoxidation of **32** using **259a** was found to proceed to the *trans*-epoxide (38% yield) with 8% yield of the *meso*-epoxide and 22% of β-elimination product (Table 1.13, Entry 3). The reactions were found to proceed using stoichiometric sulfide quantities under phase transfer conditions initially at 0 °C then at room temperature for three hours, both *cis* and *trans* epoxides were formed and a degree of β-elimination was observed. A rationale to explain the asymmetric induction was postulated: preferential attack by the aldehyde onto the *si*-face of the ylide occurs while the ylide is in the conformation depicted above (**259c**, Figure 1.21).

Table 1.13 Chiral sulfonium ylide catalysed asymmetric epoxidation

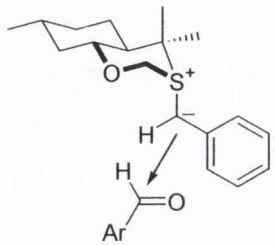


entry	sulfide	aldehyde	product	solvent	yield (%)	*ee* (%)	config.
1	**257a**[a]	**32**	**130a**	CH_3CN	100[b]	47[c]	*R, R*
2	**258**[d]	**154**	**261a**	PTC	41	83[e]	*R, R*
3	**259a**[d]	**32**	**130a**	PTC	38	96[f]	*S, S*[e]
4	**259b**[d]	**252a**	**261b**	PTC	46	4[f]	*S, S*[e]
5	**262**[g]	**32**	**130a**	PTC	80	72[h]	*R, R*

[a] Equimolar amount of aldehyde and BnBr used in the presence of 50 mol% of the sulfide under PTC using KOH as base after 36 h. [b] Yield calculated based on the sulfide. [c] Determined by chiral HPLC (Chiralpak OT(+)) [d] 50 mol% NaOH/cat. $BnEt_3NHCl/CH_2Cl_2$ –0 °C [e] Based on $[\alpha]_D$ measurements. [f] Determined by $Eu(hfc)_3$-shifts in ^1H NMR 300 MHz machine. [g]Reaction conditions. $PhCH_2OH/Tf_2O^iPy/NaH/CH_2Cl_2$.[h] Determined using a chiralcel OD Column.

The oxothiane **262b** designed by Solladié-Cavallo (Figure 1.23) was obtained from (+)-*R*-pulegone and is easily transformed to its sulfonium salt using benzylbromide with subsequent treatment with $AgClO_4$ forming one diastereomer.[284] Initial experiments of the sulfonium salt **262b** with benzaldehyde (**32**) under PTC afforded the corresponding epoxide **130a** in good yields (up to 80%) and excellent enantiomeric excess (up to 72%) (Table 1.13, Entry 5). The switch to NaH and EtP_2 [$EtN{=}P(NMe_2)_2{-}N{=}P(NMe_2)_3$] as base allowed the synthesis of a broader range of epoxides in near enantiomeric purity including the difficult to synthesise 2 and 3- pyridyl and 2-furyl epoxides.[285] X-ray cryatal structure analysis of the salt confirms the position of the benzyl group in the axial position forming a six-membered sulfonium ion (Figure 1.22).[286]

Figure 1.22 Solladié-Cavallo salt **262a** illustrating the axial position of the benzyl group



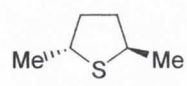
262a solladie-cavallo

The 1,3-anomeric effect effectively determines the positioning as the overlap of the equatorial lone pair with the σ* of the axial C-O bond which makes the lone pair less nucleophilic than the axial lone pair.[287] Aggarwal *et al.* have also utilised similar oxothiane ligands for asymmetric epoxidation (see section 1.7.3.1).[278,288-290] The groups of Metzner,[291,292] Dai,[293,294] Shimizu,[295] Goodman[296] and Saito[297] have also developed alternative chiral sulfides (Figure 1.23) for use under similar reaction conditions. The C_2 symmetrical sulfides developed by Metzner and Goodman gave the highest enantioselectivities. The higher enantioselectivity (but lower yields) associated with the Goodman sulfide is thought to be due to its increased steric hindrance.[298] Metzner's system involving low catalyst loadings of **263** was achievable using substoichiometric loadings of Bu_3NI, which promotes the slow alkylation step of the mechanism. However, under the Simmons-Smith methylene transfer conditions used by Aggarwal afforded epoxide **130a** in only 12 % *ee*.[299,300]

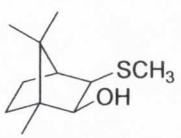
Figure 1.23 Chiral sulfides for alkylidene transfer reactions



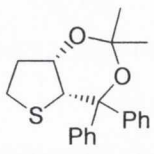
262b Solladie-Cavallo



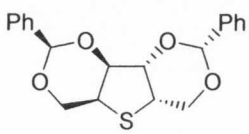
263 Metzner



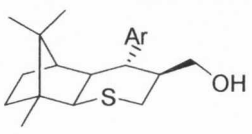
264 Dai



265 Shimizu



266 Goodman



267 Saito

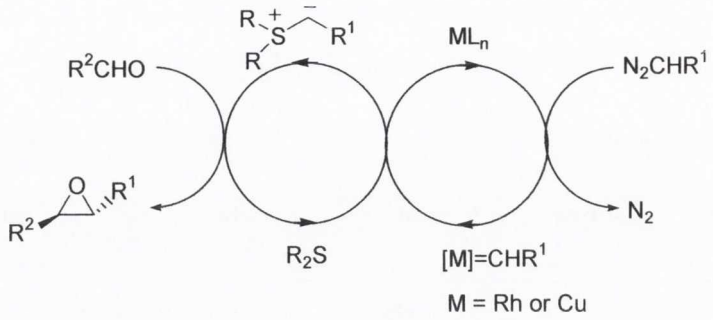
The use of an alkyl halide (*e.g.* benzyl bromide, 4-substituted benzyl and allyl[301]) and a base in these reactions has procluded the use of enolizable aldehydes whilst the use of aliphatic aldehydes as electrophiles has also proven problematic. Aromatic and heteroaromatic aldehydes have predominantly been employed with moderate to excellent levels of enantio- and diastereoselectivity.[280,291-293,295-297]

1.7.3.1 Chiral sulfonium ylide generation in the presence of metal carbenes

Aggarwal and co-workers took an alternative approach to the formation of the sulfonium ylide in these reactions. An alternative method used for the generation of the sulfur ylide was described through the reaction of a sulfide with a diazo compound in the presence of a metal catalyst. One of the advantages of this reaction is that it is conducted under neutral conditions, thereby facilitating the use of a broader range of substrates including aromatic,[302] aliphatic and base-sensitive aldehydes.[303] The intermediate metal carbenes are less reactive than the alkyl halides used previously for ylide generation, therefore milder reaction conditions are possible. A catalytic cycle was developed which involved decomposition of the diazo compound in the presence of a metal complex to yield the metallocarbene. The metallocarbene is then transferred to the sulfide to make the sulfur ylide which is then capable of reacting with an aldehyde to form the epoxide. The sulfide is then regenerated and is available for further turnovers (Scheme 1.30).[298] It was found that maintaining a low diazo compound concentration and the use of a narrow range of the nucleophilicity of the sulfide used were key factors in minimising side-product formation.[304] Attempts to use dimethyl sulfide (Me_2S) as the sulfide source failed, resulting in reduced yields of epoxides together with stilbenes and homologated products.[304]

In the development of chiral sulfides Aggarwal took the design principle of devising a C_2 symmetric sulfide ligand to guarantee the formation of one diasteromer upon alkylation. The other idea involved incorporating the sulfide into a rigid structure in which only one of the lone pairs is significantly more reactive.

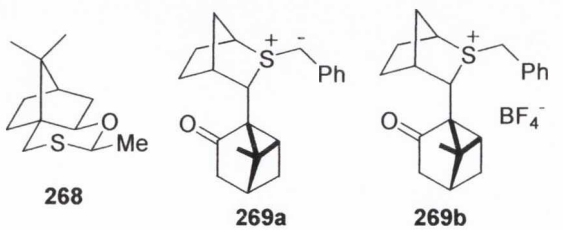
Scheme 1.30 Catalytic cycle of ylide epoxidation-use of metal carbenes



The ready availability of both enantiomeric forms of the catalyst was also a priority. The 2-step synthesis of sulfide **268** (Figure 1.24) and the ability to modify its electronic and steric characteristics (through careful choice of the carbonyl group to form the thioacetal in the synthesis) made **268** a suitable candidate as an initial proof-of concept catalyst. A series of sulfides of general type **268** were synthesised, however **268** itself was found to be the optimal structure (Figure 1.24). Catalyst loadings of 20mol% ensured epoxides were formed in good yields and high enantioselectivities.[278,290] Where the acetal substituent was considerably bulky or contained an electron-withdrawing group the yields were diminished considerably. This observation confirmed the necessity of a sulfide nucleophilic enough to trap the metal carbene in the catalytic cycle to prevent side-reactions.

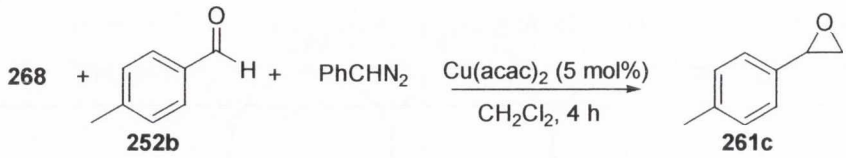
One of the disadvantages of this methodology for the synthesis of epoxides is the addition of the explosive diazo compound. In order to circumvent this an *in situ* generation of diazo compound and coupling this to the epoxidation reaction was developed. This tactic was found to be much more efficient as less diazo compound is needed and better yields and *trans* selectivities were recorded. A range of aryl hydrazone compounds were tested in racemic test reactions of which benzaldehyde tosyl hydrazone sodium salt was the best (Table 1.14).[305]

Figure 1.24 Aggarwal's chiral sulfide **268** and sulfonium salts **269a, b**

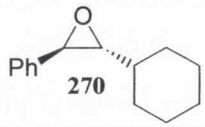


268 **269a** **269b**

Table 1.14 Chiral sulfonium ylide catalysed asymmetric epoxidation



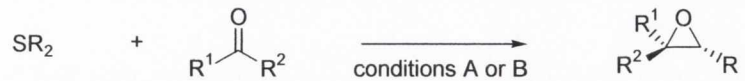
252b **261c**

entry[a]	aldehyde	product	yield (%)	*ee*[b,c] (%)	*trans*/cis
1	**32**	**130a**	73	94 (*R*,*R*)	>98:2
2	**252b**	**261c**	64	92 (*R*,*R*)	>98:2
3	**145**	 **270**	32	90 (*R*,*R*)[d]	70:30

[a]Reaction conditions: 0.2 equiv. of sulfide, $Cu(acac)_2$ (0.05 mol%) and aldehyde (1 mmol) in CH_2Cl_2, under nitrogen was added a solution. of phenyldiazomethane (1.5 mmol in 0.5 ml of CH_2Cl_2) at rt over a period of 3 h. [b]Determined using chiral HPLC (Chiralcel OD Column) [c]Absolute configurations were determined by comparison of $[\alpha]_D$ [d] By analogy it was assumed that the same configuration was obtained.

However sulfide **268** did not tolerate the reaction conditions of these reactions. As a result a series of more stable mono and bicyclic sulfides were designed and sulfide **269a** was found to be a highly applicable ylide precursor for the generation of epoxides. Sulfonium ylide **269a** was found to promote efficient reactions of aromatic, heteroaromatic, and α,β-unsaturated aldehydes and aliphatic substrates (Table 1.15, Entries 1-3).[279] Aldehydes with basic groups and α,β-unsaturated hydrazones were poor substrates in these reactions. To overcome this the chiral sulfonium salt **269b** was prepared by alkylation with either an alkyl bromide in the presence of $AgBF_4$ or the corresponding alcohol in the presence of HBF_4. Phosphazene (EtP_2) which could be used at low temperatures,[285] was used as the base to form the sulfonium ylide that was subsequently tested in the addition of the aldehydes (pyridyl carboxaldehydes) and ketones.[306] Reactions were carried out at –78 °C and afforded high yields, high diastereoselectivities and enantioselectivities (Table 1.15, entries 4-6). This methodology has subsequently found application in the synthesis of the anti-inflammatory agent CDP-840 in enantiomerically pure form.[306]

Table 1.15 Chiral sulfonium ylide catalysed asymmetric epoxidation



32 R^1 = Ph, R^2 = H
152 R^1 = CH=CHPh, R^2 = H
271 R^1 = $(CH_2)_3CH_3$, R^2 = H
274 R^1 = H, R^2 = 2-pyridyl
276 R^1 = H, R^2 = prop-2-enyl

130a R = H, R^1 =Ph , R^2 = H
272 R = Ph, R^1 = CH=CHPh, R^2 = H
273 R = Ph, R^1 = H, R^2 =H
275 R = Ph, R^1 = H, R^2 = 2-pyridyl
277 R = Ph, R^1 = H, R^2 = prop-2-enyl

entry	sulfide	aldehyde	product	time (h)	yield[d] (%)	*trans/cis*	*ee*[e] (%)
1[a]	**269a**	**32**	**130a**	48	82	>98:2	94
2[a,b]	**269a**	**271**	**272**	48	46	75:25	89
3[a]	**269a**	**152**	**273**	48	70[f]	>98:2	87
4[c]	**269b**	**274**	**275**	1	88	98:2	99
5[c]	**269b**	**271**	**292**	1	64	92:8	97
6[c]	**269b**	**276**	**277**	1	52	>99:1	99

[a] Conditions **A**: To a 5 mL rbf under N_2, sulfide **269a**, dry MeCN (0.8 mL) $Rh_2(OAc)_4$ (0.01 mmol), $BnEt_3NCl$ (0.05 mmol), aldehyde (1.0 mmol) and hydrazone salt (1.0 mmol) were stirred at 40 °C for 48 hrs.[b] 20 mol% catalyst used. [c]Conditions **B**: To a solution of **269b** (0.23 mmol) in dry CH_2Cl_2 (0.8 mL) was added the EtP_2 (0.23 mmol) at –78 °C. After stirring for 10-15 min the aldehyde was added dropwise and stirred for 1hr at –78 °C. [d]Isolated yield. [e]Determined by chiral HPLC. [f]Crude yield determined by ^{1}H NMR spectroscopy with internal standard.

In conclusion, two catalytic asymmetric sulfur-ylide mediated epoxidation methods have been developed by Aggarwal *et al.* The first method involves the use of a chiral sulfide **268** which could be transformed to the corresponding ylide through an alkylation step (by an alkyl halide) and subsequent deprotonation by a base in the presence of an aldehyde to afford the corresponding epoxide. However, this methodology is somewhat restricted to the synthesis of styrene oxide derivatives due to the presence of the very reactive alkyl halide (promotes side reactions). On the other hand, the development of sulfide **269a** facilitated the use of a broader range of aldehydes (aromatic, heteroaromatic (excluding pyridyl), aliphatic and unsaturated) with both aliphatic and aromatic diazo precursors. The increased electrophilicity of the metal carbene, neutral reaction conditions and regiospecifc formation of the ylide contributed greatly to the broadened substrate scope. A stoichiometric version involving sulfide **269b** using a phosphazene base facilitated the use of heteroaromatic aldehydes incorporating basic groups and unsaturated aldehydes.

1.7.3.2 Conclusions for Section 1.7.3

In conclusion, the area of asymmetric ylide epoxidation *via* alkylidene transfer has benefited from extensive research since the early experiments of Johnson *et al.* Several new sulfide ligands, reaction conditions and catalytic processes have been developed to broaden the scope and utility of the JCC reaction. At present the benchmark sulfide and process available of highest applicability is the methodology of Aggarwal *et al.* However, issues regarding the use of heavy metals to generate ylide intermediates (toxicity), the use of diazo compounds (safety), requirement for sub-ambient temperatures for certain substrates (issues for industrial scale-up) and the inability to modify the present sulfide ligands for asymmetric methylene transfer highlight the potential for a completely organocatalytic process for this reaction.

1.7.4 The asymmetric JCC reaction: methylene transfer

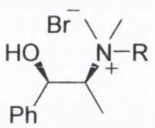
Seminal work by Trost *et al.*[283] demonstrated the configurational stability of sulfur ylides and their ability to retain optical purity under conditions that could potentially facilitate racemisation whilst promoting the epoxidation of aldehydes. Using the adamantyl-derived sulfonium salt catalyst **260** (Figure 1.21) three test reactions were performed including carbonyl addition, conjugate addition and a [2,3]-sigmatropic rearrangement.[283] Even though asymmetric epoxidation was not successful in this work it was later postulated that if sulfonium benzylides instead of sulfonium methylides had been used by Trost, the asymmetric epoxidation using sulfur ylides would have progressed at an earlier stage.[307] Since this result, methylene transfer from sulfonium ylides has been successfully promoted by ionic liquids[268] and under solid-state conditions[308] in racemic studies, whilst asymmetric methylene transfer to aldehydes remains a considerable challenge (*vide supra*).

1.7.4.1 Chiral sulfonium ylides for enantioselective methylene transfer

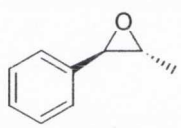
Early findings by the Hiyama[309] and Zhang[310] group initiated the interest in the asymmetric synthesis of epoxides *via* methylene transfer from trimethylsulfonium iodide under liquid-liquid, CH_2Cl_2/NaOH(aq) conditions. Hiyama found that the optically active ephedrine-derived salt **278a** (Figure 1.24) was evaluated as an asymmetric catalyst affording **120a** in moderate yields and excellent enantioselectivity. The enantioselectivity of the reaction was

found to improve with increased catalyst loading. Later studies[311] confirmed that the increase in 'enantioselectivity' was due to ring-closure of the ephedrine salt to epoxide **279** (Figure 1.25). In a similar study by Zhang using the lipophilic catalysts, the enantioselectivity of the epoxidation reaction was found to improve with increased temperature and reaction time. Similarly the reason for which was determined to be due to catalyst decomposition to the epoxide **279**. The reliance of both studies on optical rotation data and the unfortunate coincidence that epoxide **279** and **120a** are difficult to separate and observe in lowfield NMR instrumentation, led to the incorrect communication that compounds **278a**, **278b** and **278c** (Figure 1.25) were catalysts for the JCC reaction.[311,312]

Figure 1.25 Hiyama[309] and Zhangs[310] ephedrine-derived compounds and **279**



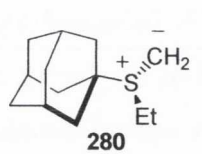
278a R = C_2H_5
278b R = *n*-$C_{12}H_{25}$
278c R = *n*-$C_{16}H_{33}$



279

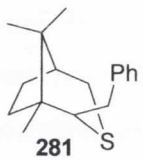
Figure 1.26 includes the chiral catalysts employed to date for the asymmetric epoxidation of aldehydes *via* methylene transfer. Durst *et al.*[281] with a design rationale based on the formation of a single diastereomeric sulfonium salt designed the C_2-symmetric sulfide ligand **281** for the asymmetric epoxidation of aldehydes. The reactions were carried out under phase-transfer conditions at 0 °C initially and then at room temperature for three hours. In the transfer of methylene from the ylide derived from sulfide **281** to 4-chlorobenzaldehyde **252a** only the *trans*-epoxide was formed in 46% yield with 5% of the β-elimination product. This is in contrast to the analogous benzylidene ligands of type **281** which resulted in epoxides with *ee*'s approaching enantiomeric purity. Durst suggested that chiral induction is due to facial selectivity at the ylide rather than at the carbonyl carbon in the benzylidene ylides, a feature which is absent in the methylene ylides.[281]

Figure 1.26 Chiral sulfonium ylide catalysts used in the epoxidation of aldehydes *via* methylene transfer.



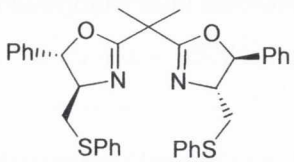
280

Trost (1973)



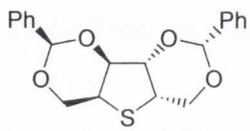
281

Durst (1991)



Aggarwal (2002)

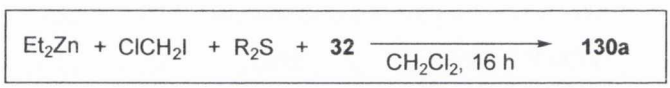
282

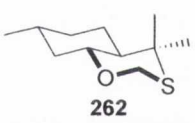


Goodman (2004)

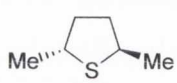
283

Table 1.16 Chiral sulfonium ylide catalysed asymmetric epoxidation

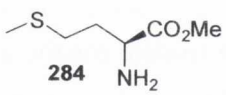




262



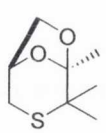
263



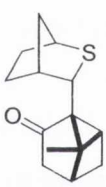
284



(*R*)-285



286



287a

entry	sulfide	yield[a] (%)	*ee*[b] (%)
1[c]	**262**	95	12 (*R*)
2[d]	**284**	<5	0
3[e]	**263**	<5	0
4[e]	**285**	86	4 (*R*)
5[c]	**286**	72	11 (*R*)
6[c]	**287a**	93	16 (*S*)
7[e]	**282**	54	47

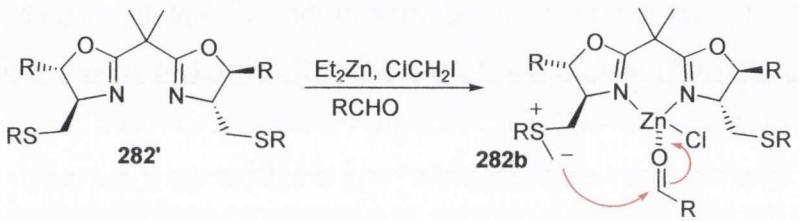
[a]Determined by GC. [b]Determined by GC (α-cyclodextrin column) [c] $R_2S/Et_2Zn/ClCH_2I$/**32** (3:2:2:1)[d]$R_2S/Et_2Zn/ClCH_2I$/**32**(1:1:1:1)[e] $R_2S/Et_2Zn/ClCH_2I$/**32** (2:2:2:1).

Aggarwal's application of Simmons-Smith organozinc reagents for the generation of sulfonium ylides[313] led to the development of a new class of sulfide ligands for methylene transfer. Chiral ligands capable of chelation to zinc were evaluated in the epoxidation reaction (Table 1.16) with low enantioselectivities (up to 16%). However, the linking of a sulfide to a

ligand (which is capable of chelating to a zinc-ion) resulted in the development of the *bis*(oxazoline) based sulfide ligands[314] *e.g.* **282** which could afford *ee* values up to 47% in the epoxidation reaction of **32** (Table 1.16, Entry 6). Although up to 200 mol% of sulfide **282** is required in this reaction this result is 1% lower in *ee* than the benchmark enantioselectivity for asymmetric epoxidation of aldehydes *via* methylene transfer.[300]

The measurable improvement in *ee* observed with **282** suggests that the zinc ion is associated with the ylide prior to reaction and remains in close contact during the course of the reaction.

Figure 1.27 Proposed reaction pathway



Simultaneous binding of the aldehyde substrate also sets-up a *pseudo*-intramolecular reaction pathway which results in enhanced reaction rates and enantioselectivities. (Figure 1.27). The same system was subsequently applied to the asymmetric preparation of terminal aziridines from imines with marginal success.[300]

The most recent attempt at enantioselective methylene transfer was from the Goodman group[315] using sulfide **283** (Figure 1.26). Using Simmons-Smith conditions to directly form the sulfur ylide from the sulfide *via* a carbene addition reaction the epoxidation of **32** was achieved affording 61% yield and 48% *ee*. More sterically demanding aldehydes such as 2,4-dichlorobenzaldehyde **288** were more reactive, yielding epoxides after one day stirring at room temperature in near quantitative yield (96%) and enantioselectivities of up to 76%.[315] Reducing the temperature to 0 °C had a minimal effect on *ee* however these reactions commonly suffered from prolonged reaction times and subsequently poor recovery yields of the sulfides. The major disadvantage of this methodology was found to be the necessity for 100-200 mol% of **283** and the unpredictable reactivity of the zinc active species (formed from diethylzinc). An advancement came in the form of a *bis*(chloromethyl)zinc:bipyridine complex which is a direct methylene transfer agent for sulfonium ylide formation of **283**. For the

reaction involving **32**, 56% yield and an *ee* of 57% was obtained after 20 hours stirring at room temperature. Only one equivalent of sulfide is required for sufficient conversion in comparison to the previous method. However two equivalents of the alkylating agent are required for complete ylide formation, the reasons for which are at present unclear. [315]

1.7.5 Conclusions for Section 1.7.4

High catalyst loadings (100-200 mol%) and low enantioselectivity (max. 48%) are the major drawbacks associated with methylene transfer reactions for epoxide formation. A wide variety of sulfonium ylides have been tried and tested yet the enantioselectivity in general remains low due to insufficient control of the addition of the nucleophilic sulfonium ylide to one face of the aldehyde electrophile. Ineffective binding of the aldehyde in a enantio-discriminating conformation leads to non-selective addition reactions. An organocatalyst that is capable of binding the aldehyde in a selective fashion and simultaneously delivering the ylide from one face of the aldehyde (in either a bifunctional catalyst or through the directing effect of chiral ligands) would be a considerable advancement in the enantioselective promotion of this reaction.

1.8 Cyclopropanation *via* Trimethylsulfoxonium iodide reactions

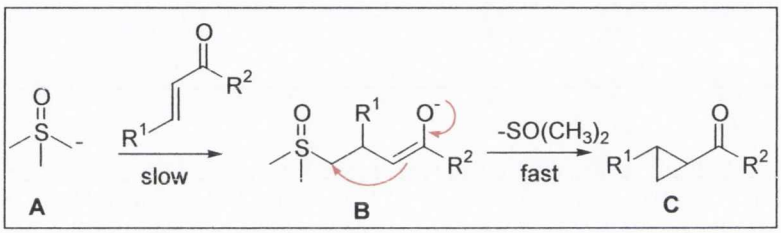
The Corey-Chaykovsky cyclopropanation reaction[272] is one of the most efficient Michael-initiated ring-closure reactions involving methylene transfer from a sulfoxonium ylide (Corey's reagent $Me_2S(O)=CH_2$)[316] with α,β-unsaturated ketones. The cyclopropyl ketone products are synthetically useful,[317-319] with the rigid cyclopropane ring structure having use to restrict possible conformations of biologically active compounds and to improve their activity.[320]

1.8.1 The mechanism of the cyclopropantation reaction using trimethylsulfoxonium iodide

Base-mediated deprotonation of the trimethylsulfoxonium salt to afford the ylide is the first step of the reaction. The second step of the reaction involves ylide addition to the alkene followed by ring closure and regeneration of the sulfide (Scheme 1.31). Standard conditions

employed for the Corey-Chaykovsky cyclopropanation involve preforming the Corey reagent by treatment of trimethylsulfoxonium iodide (TMSOI) with NaH in dimethyl sulfoxide (DMSO) for 20 min-2 hours (depending on the reaction temperature) followed by addition of the enone and heating the reaction to 50 °C for 2 hours.[272,321] Modifications have been made including the use of phase-transfer[322] and solid-state[308] reaction conditions, ionic liquids,[268] organic bases and metal catalysts[323] and the use of chiral sulfonium ylides to induce asymmetric cycloproanation reactions.

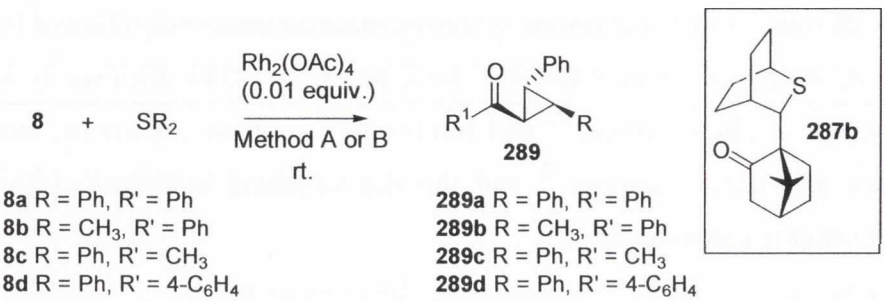
Scheme 1.31 Mechanism of the Corey cyclopropanation reaction



1.8.2 Promoters of the cyclopropanation reaction: recent developments

Sulfonium ylides are the most efficient promoters of the cyclopropanation of enones to date. Aggarwal *et al.* are the most prolific group in this area utilising the catalytic process for recycling chiral sulfides (which was efficient in the JCC epoxidation reaction-*vide supra*) yielding products in excellent yields and enantioselectivity. Both methodologies (using diazo compounds) were evaluated in the cyclopropanation reaction. The *in situ* generation of the diazo compound, method A[324] and the manual addition of the diazo compound, method B[325,326] were both evaluated by Aggarwal *et al.* and proved to be efficient and selective methods for the cyclopropanation of enones (Table 1.17, entries 1-5). The in situ generation of the diazo compound method achieved slightly higher *ee* values and a broader substrate scope than method B.

Table 1.17 Chiral sulfide promoted cyclopropanation reaction



8a R = Ph, R' = Ph
8b R = CH_3, R' = Ph
8c R = Ph, R' = CH_3
8d R = Ph, R' = 4-C_6H_4

289a R = Ph, R' = Ph
289b R = CH_3, R' = Ph
289c R = Ph, R' = CH_3
289d R = Ph, R' = 4-C_6H_4

entry[a]	enone	product	sulfide	method	yield (%)[b]	d.r. *trans:cis*[c]	*ee* (%)[d]	abs. Config.
1	**8a**	**289a**	**287b**	A	73	4:1[c]	91	*R, R*
2	**8b**	**289b**	**287b**	A	50	4:1[c]	90	*R, R*
3[e]	**8c**	**289c**	**268**	B	55	4:1	>98	*R, R*
4[f]	**8c**	**289c**	**268**	B	14	4:1	>98	*R, R*
5[e]	**8d**	**289d**	**268**	B	35	4:1	>98	*R, R*

[a]Method A: Tosylhydrazone salt (1.5 equiv.), alkene (1.0 equiv.), sulfide (0.2 equiv.), PTC (0.2 equiv.), $Rh_2(OAc)_4$ (0.01 equiv.), in dioxane (0.13M) at 40 °C. Method B: Phenyldiazomethane (1.5 equiv.) added over 12 h to mixture of enone (1 equiv.), sulfide (0.2 or 1.0 equiv.), $Rh_2(OAc)_4$ (0.01 equiv.) in toluene (1M in enone). [b]Combined yield of all isomers. [c]Ratio of *trans:cis* isomers was determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC using a Chiralcel OD Column. [e]1.0 equiv. of sulfide. [f]0.2 equiv. of sulfide.

In conclusion, the sulfide catalysed cyclopropanation reaction has not attracted as much attention as the epoxidation reaction probably due to the abundance of methods for synthesising enantioenriched cyclopropanes. The best process to date is Aggarwal's catalytic cycle involving *in situ* generation of the diazo compound, yet this method still has its disadvantages. The toxicity of the rhodium heavy metal, the diazo compound and the 1,4-dioxane solvent of the process pose serious health risks. Overall there is great scope for the design of a clean, efficient, safe organocatalytic process for the promotion of the cyclopropanation reaction. A highly active organocatalyst capable of promoting enantioselective reactions at ambient temperatures and with broad substrate scope is required.

2.1 Catalysis of the asymmetric Friedel-Crafts reaction

Previous studies in the Connon laboratory have demonstrated the ability of the thio(urea) catalysts of general type **20** and **46** to promote the Baylis-Hillman reaction.[64] Ricci *et al.* also demonstrated that catalysts **20**, **46** and **198** were efficient promoters of the addition of π-excessive aromatic compounds to nitroolefins.[57,192] Ricci *et al.* also expanded the scope of the

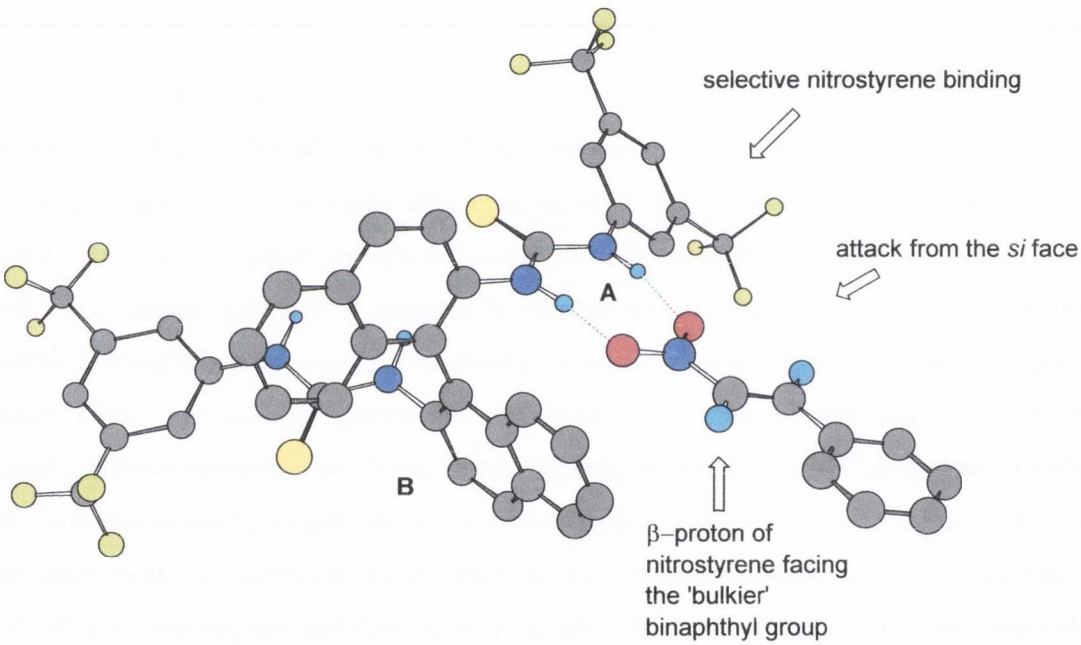
organocatalysed Friedel-Crafts addition reaction the most by reacting *N,N*-dialkylanilines with substituted nitrostyrenes and substituted indoles, with moderate enantioselectivity using simple urea-based systems.[57] The Ricci[57,192] and Jørgensen[178] (**199**) catalysts (*vide supra*) are incapable of catalysing the Friedel-Crafts addition reaction of *N*-methylindole (**181**) to (*E*)-β-nitrostyrene (**27**) with comparable levels of moderate enantioselectivity to that obtained using indole derivatives (*i.e.* **162**). The absence of an indole NH proton in the substrate precludes the possibility of bifunctional catalysis, thereby making the design of an organocatalyst for the asymmetric addition of *N*-alkyl indoles to nitroolefins a considerable challenge. Thus, we set out a plan for the achievemant of this goal.

2.1.1 Axially chiral (thio)urea catalysts: design rationale

There were three goals to be realised in the design of a successful catalyst for this reaction; a) the catalyst must be able to activate the electrophilic nitroolefin substrate by H-bonding to both Lewis-basic oxygen atoms of the nitro-group, b) the catalyst must be able to bind to the oxygen atoms in a single orientation with respect to the styrene's large substituent ('left-right selectivity') c) the catalyst must then be capable of completely blocking access to one face of the bound nitroolefin ('top-bottom selectivity').With this in mind we designed a library of catalysts which incorporate an axially chiral 1,1,*bis*-naphthyl-2,2-diamine (**112**) backbone coupled to a powerful H-bond donating (thio) urea structural unit. Seminal work by Schreiner *et al.*[48] and previous findings in the Connon laboratory on the Baylis-Hillman reaction[64] found that thiourea catalysts without aromatic substituents were exceptionally poor catalysts in challenging reactions. More importantly, Ricci *et al.* found that the presence of the *N*, *N*'-diaryl motif was a *sine qua non* for high catalyst activity in the (thio)urea-catalysed addition of π-excessive nucleophiles to nitroalkenes.[57] We therefore postulated that a thio(urea) catalyst incorporating both an aromatic chiral and aromatic achiral component was an ideal design template to begin probing the influence of both steric and electronic characteristics of a catalyst. At the outset it was decided that a central thio(urea) *motif* flanked on one side with tuneable aryl-substituents (to enhance the acidity of the urea protons and steric requirements) and on the other side by a tuneable chiral group was a good starting point based on the literature evidence mentioned previously. The critical (thio)urea design features established by Schreiner *et al.* in Section 1.3 were retained and a catalyst for the asymmetric Friedel-Crafts reaction of substituted indoles to nitroolefins was envisaged.

The proposed binding mode/mode of action of these catalysts is shown in Figure 2.1. We envisaged that the nitroolefin would accept two hydrogen bonds from the (thio)urea (Figure 2.1, **A**) in such a way as to minimise steric interactions with the catalyst, *i.e.*, the nitrostyrenes large styrenyl substituent would be oriented out into the solvent while the smaller β-hydrogen atom would be directed towards the catalyst ('left-right selectivity). Thus the electrophile is bound in a (hopefully) selective manner, in which it is clear that its *si*-face is selectively blocked by the axially-chiral catalyst substituent ((*S*)-configuration shown) catalyst substituent (Figure 2.1, **B**).

Figure 2.1 Proposed mode of action of the binaphthyl thiourea catalysts

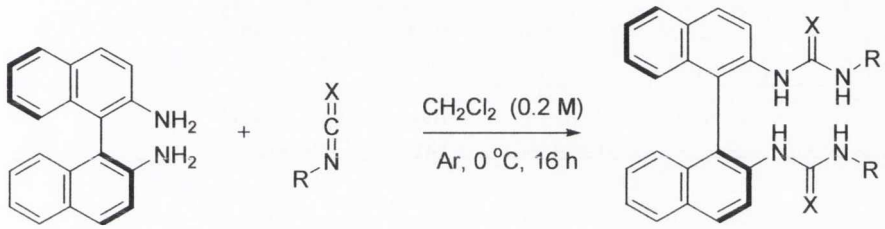


We chose novel chiral (thio)-urea derivatives of general type (*S*)-**291** as a basis for catalyst design. The key potential advantages of such systems are that the axially chiral unit is aromatic in nature-thereby the use of aliphatic "tetrahedrally"-chiral substituents (which reduce catalyst activity) can be avoided. They incorporate an achiral aromatic substituent-the steric and electronic character of which can be controlled to a considerable degree. Their preparation from commercially available enantiopure (*S*)-1,1, *bis*-naphthyl-2,2-diamine (**112**) and a variety of iso(thio)cyanates was also envisaged to be straightforward.

2.1.1.1 Preparation of the binaphthyl *bis*-(thio)urea catalysts

We prepared a series of catalysts that were both economical and practical from a synthetic point of view. Thus, the coupling of commercially available (*S*)-1,1-binaphthyl-2,2-diamine (**112**) and iso(thio)cyanates (**290a-h**) were obvious choices (Scheme 2.1). Purification by flash chromatography afforded the (thio)ureas **291** in moderate to excellent yields (Scheme 2.1).

Scheme 2.1 General synthesis of binaphthyl (thio)urea catalysts



(*S*)-**112**

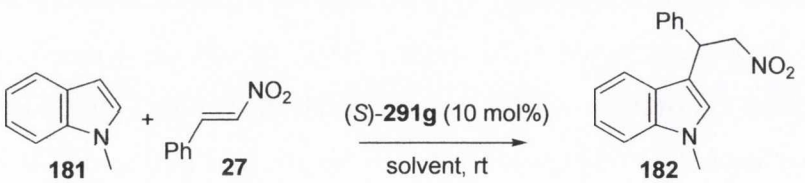
290a X = O, R = Ts
290b X = O, R = *c*-C_5H_{11}
290c X = O, R = C_6H_5
290d X = O, R = 2,6-$(CH_3)_2$-C_6H_4
290e X = O, R = 4-OCH_3-C_6H_4
290f X = O, R = 3,5-$(CF_3)_2$-C_6H_3
290g X = S, R = 3,5-$(CF_3)_2$-C_6H_3
290h X = O, R = C_6F_5

(*S*)-**291a** X = O, R = Ts (90%)
(*S*)-**291b** X = O, R = *c*-C_5H_{11}(55%)
(*S*)-**291c** X = O, R = C_6H_5 (90%)
(*S*)-**291d** X = O, R = 2,6-$(CH_3)_2$-C_6H_4 (89%)
(*S*)-**291e** X = O, R = 4-OCH_3-C_6H_4 (83%)
(*S*)-**291f** X = O, R = 3,5-$(CF_3)_2$-C_6H_3 (91%)
(*S*)-**291g** X = S, R = 3,5-$(CF_3)_2$-C_6H_3 (91%)
(*S*)-**291h** X = O, R = C_6F_5 (83%)

2.1.2 Optimisation of reaction conditions for the asymmetric Friedel-Crafts reaction.

In order to maximise any catalytic effect, which the binaphthyl catalysts may exhibit, determining the optimum reaction conditions was essential, therefore using the test reaction of **181** with **27** at room temperature (Scheme 2.2), the variables of solvent identity and concentration, catalyst and substrate loading were evaluated.

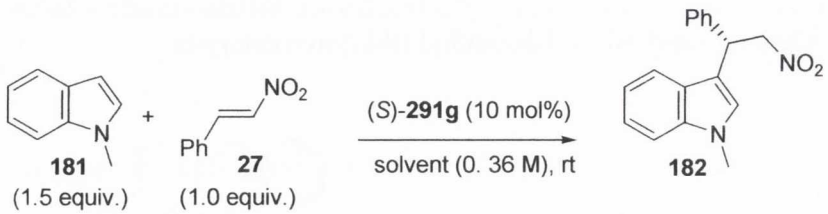
Scheme 2.2 Optimisation of reaction conditions for the addition of **181** to **27**



Solvent screening studies

Initial testing of catalyst (*S*)-**291g** was performed in toluene at 0.36 M concentration using 10 mol% of the catalyst at room temperature. As can be seen from Table 2.1, 16 hours reaction time was necessary to achieve 30% conversion of the nitrostyrene (entry 1).

Table 2.1 Solvent screening study



entry	solvent.	loading. (mol %)	time (h)	conversion[a] (%)
1	toluene	10	16	30
2[b]	toluene	10	25	49
3	$CHCl_3$	10	42	52
4	$CDCl_3$	0	20	0
5	$CDCl_3$	10	20	53
6	CH_2Cl_2	30	91	58
7	THF	30	91	0
8	CCl_4	30	19(91)[c]	33(76)[c]
9	Et_2O	30	91	0
10	^{i}PrOH	30	91	0

[a]Conversion of **27** determined by ^{1}H NMR spectroscopy [b]Reaction carried out using 2.0 equiv. of **181**.[c]Figures in parenthesis correspond to later reaction time and associated conversion at that time.

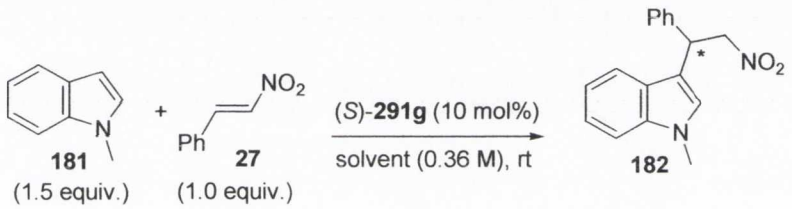
To find better reaction conditions a solvent screening study was carried out on a range of solvents using an increased catalyst loading of 30 mol% (Table 2.1, entries 6-10), CCl_4 yielded the fastest conversions however due to toxicity concerns this solvent was not selected for further studies. The next best solvent was chloroform which promoted significant catalysis in 42 hours at room temperature (entry 3). As ethanol is a natural contaminant of chloroform and deuterated chloroform would yield simpler NMR spectra we decided to use deuterated chloroform instead. Gratifyingly $CDCl_3$, had an acceleratory effect on the catalysed reaction relative to the undeuterated form (possibly due to the presence of trace EtOH in the latter) and no reaction was observed at comparable times in the uncatalysed reaction (entries 4 and 5). As $CDCl_3$ afforded improved reaction times (compared to the undeuterated form) the catalyst loading could be reduced to just 10 mol%. Dichloromethane, tetrahydrofuran, ethanol and

isopropanol yielded no FC products whatsoever. Clearly, from this study deuterated chloroform was the optimal solvent and was used for all further studies into the FC addition of indoles to nitrostyrenes.

The effect of substrate-loading and catalyst-loading on reaction efficiency.

Increasing the catalyst loading from 10 to 20% did have a beneficial effect in the tests in toluene (Table 2.2, entries 2 and 3), however we felt the level of catalysis present using $CDCl_3$ was efficient enough to maintain the 10 mol% loading (Table 2.2, entry 6). Increasing the loading of **181** from 1.5 to 2.0 equivalents (compare entries 5 and 7) facilitated the uncatalysed reaction to a considerable extent. For this reason it was decided that the optimum ratio of indole substrate to nitrostyrene was 1.5:1 in these initial catalyst studies.

Table 2.2 Optimisation of reaction conditions for the addition of **181** to **27**



entry	solvent.	loading. (mol %)	time (h)	conversion[a] (%)
1	toluene	10	20	29
2	toluene	10	2	0
3	toluene	20	2	20
4	toluene	10	25	49[b]
5	$CDCl_3$	0	20	0
6	$CDCl_3$	10	20	66[b]
7	$CDCl_3$	0	5	5[b]

[a]Conversion of **27**determinedby ^{1}H NMR spectroscopy [b]Reaction carried out using 2.0 equiv. of **181**.

Both the indole loading and reaction concentration was increased in later experiments due to extended reaction times at sub-ambient temperatures (see Section 2.1.5).

Overall, the optimised reaction conditions were concluded to be a 0.36 M reaction in $CDCl_3$ using 10 mol% of the catalyst and 1.5 equivalents of the indole to 1.0 equivalent of the nitrostyrene at room temperature.

2.1.3 Evaluation of catalysts employed in the asymmetric Friedel-Crafts reaction.

The catalysts selected for testing in the Friedel-Crafts addition reaction of *N*-methylindole (**181**) and (*E*)-β-nitrostyrene (**27**) are shown in Figure 2.2. Diols **292** and **293** were available commercially, while the rest were synthesised from the general procedure outlined in Scheme 2.1. The results of the preliminary experiments are tabulated in Table 2.3.

Figure 2.2 Catalysts screened in the Friedel-Crafts alkylation of indoles reaction

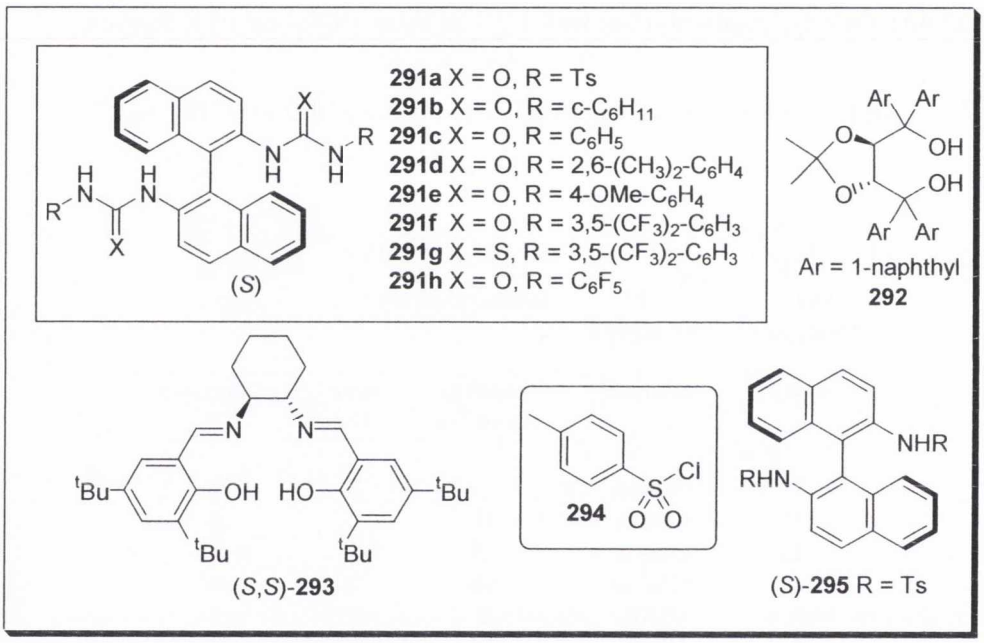
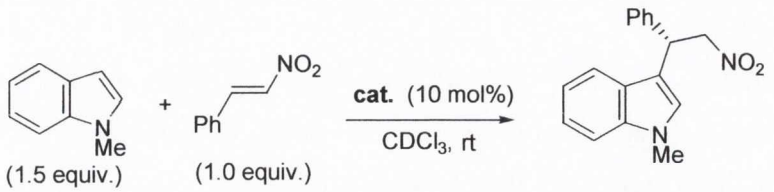


Table 2.3 Catalysis of the addition of **27** to **181** by (*S*,*S*)-**293** and (*S*)-**291-295**



(1.5 equiv.) **181** (1.0 equiv.) **27** **182**

entry	cat.	conc. (M)	temp (°C)	time (h)	conversion[a] (%)	*ee*[b] (%)
1	-	0.36	rt	72	<2	-
2	(*S*)-**295**	0.36	rt	72	<2	-
3	**292**	0.36	rt	72	<2	-
4	**293**	0.36	rt	72	<2	-
5	(*S*)-**291a**	0.36	rt	20	80(100)[c]	0
6	(*S*)-**291b**	0.36	rt	113	2	7
7	(*S*)-**291c**	0.36	rt	113	2	4.5
8	(*S*)-**291d**	0.36	rt	113	14	10
9	(*S*)-**291e**	0.36	rt	113	4	8
10	(*S*)-**291f**	0.36	rt	113	100	11
11	(*S*)-**291g**	0.36	rt	20	66(100)[d]	12
12	(*S*)-**291g**	0.36	-30	64	**88**	30
13	(*S*)-**291h**	0.36	rt	113	55(93)[c]	15
14	(*S*)-**291h**	0.36	-20	167	42	34
15	(*S*)-**291h**	0.72	-20	70	80	28

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by HPLC using a Chiralpak AD-H column (250 x 4.6 mm). [c]Conversion after 166 h in parenthesis. [d]Conversion after 160 h.

In the absence of catalyst, only trace amounts of the FC adduct **182** were observed after 3 days reaction time (Table 2.3, entry 1). The catalytic importance of the thiourea moiety is clear from the superiority of (*S*)-**291a** to (*S*)-*bis*-*N*-tosyl-BINAM-derivative (*S*)-**295** (Table 2.3, entries 2 and 5). The catalytic inferiority of the diols **292** and **293** is also evident (entries 3 and 4 respectively). Disappointingly, catalysis with tosyl-urea (*S*)-**291a** was completely unselective. *Bis*-*N*-arylthiourea-based catalysts incorporating either aliphatic- or electron-rich/sterically hindered aromatic substituents ((*S*)-**291b-e**, entries 6-9) did furnish **182** with low levels of enantioselectivity, if however these catalysts were extremely inefficient promoters of the reaction. More efficient in terms of activity were the analogues bearing electron-deficient aromatic substituents ((*S*)-**291f-h**), which proved more active and marginally more selective catalysts (Table 2.3, entries 10-15).

While at room temperature, urea (*S*)-**291f** and thiourea (*S*)-**291g** afforded similar levels of stereoinduction, when at –30 °C the significantly more active (*S*)-**291g** gave a greater

improvement in levels of enantioselectivity. Of interest is the catalytic activity of the decafluoro-catalyst (*S*)-**291h** relative to (*S*)-**291f** and (*S*)-**291g**, as the *N*-pentafluorophenyl substituent had never been used in *N*-aryl urea-based catalysts before. Unfortunately this substituent hindered catalyst activity at sub-ambient temperatures rendering (*S*)-**291h** convenient to use than catalyst (*S*)-**291g** (entries 8-15).

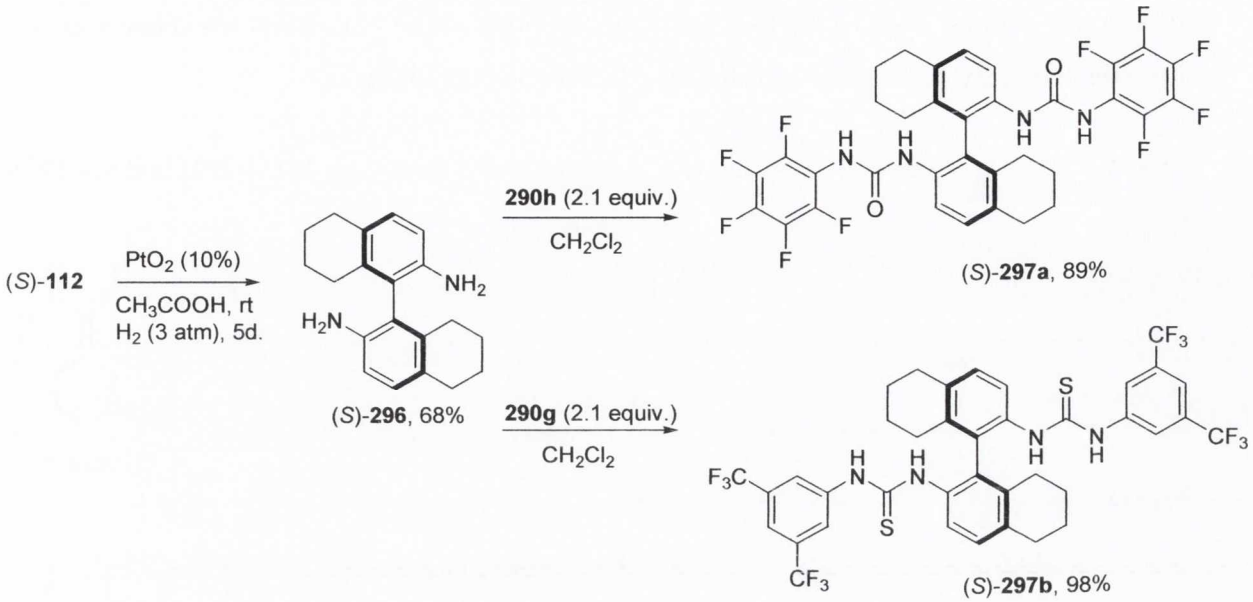
2.1.4 Design of second generation catalysts

We speculated that increased bulk on the chiral backbone could further increase catalyst selectivity as modifications made to the achiral aryl side of the catalyst were found to have a marginal influence on selectivity. Encouraged by recent literature precedents indicating that increased steric bulk of the axially chiral substituent in similar Brønsted acidic organocatalyst systems can considerably improve the stereochemical influence of same,[140] we prepared partially saturated and brominated analogues of benchmark catalyst (*S*)-**291g** and (*S*)-**291h** (Scheme 2.3-2.5 second generation catalysts). See the general experimental Section 5.1 for further details.

2.1.4.1 Preparation of the second generation catalysts

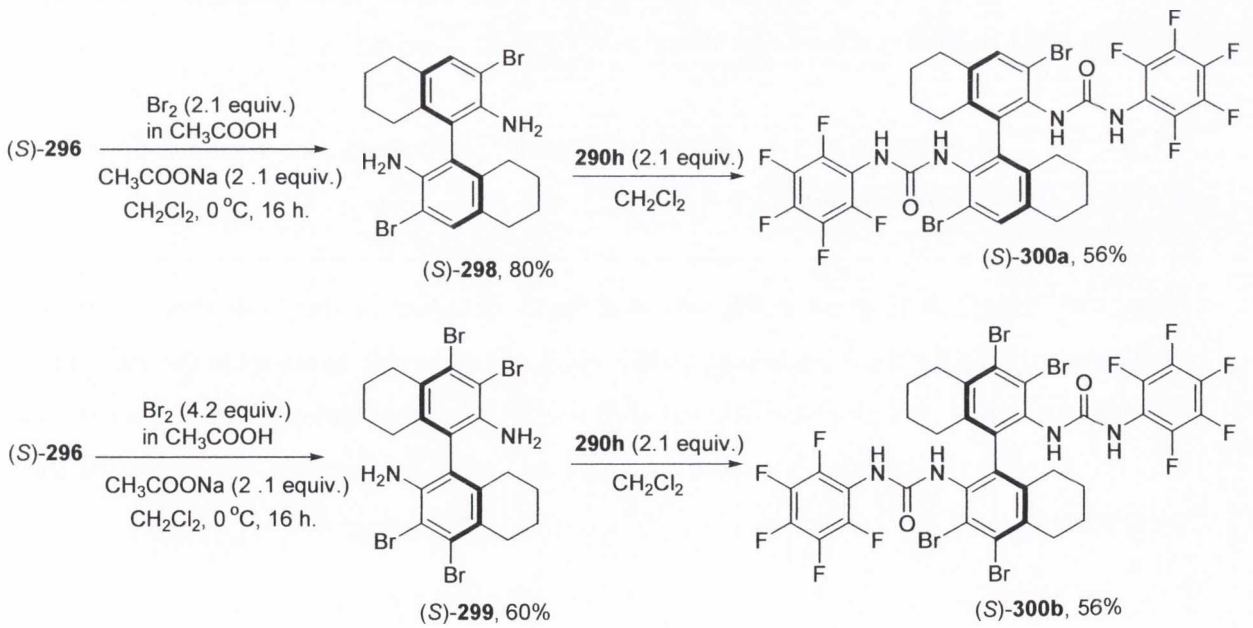
Initial catalyst screening identified the *N*-pentafluorophenyl- and 3,5 *bis* trifluoromethylphenyl groups as the best, in terms of catalyst activity and enantioselectivity. Therefore, these aryl substituents were maintained as the non chiral components as modifications were made to the chiral component of the catalyst.

Scheme 2.3 Preparation of octahydro-analogues of (*S*)-**291f** and (*S*)-**291h**



The synthesis of the saturated binaphthyl backbone analogues ((*S*)-**297a** and (*S*)-**297b**) was to probe the effect of the bulkier non-aromatic substituent in this position and the influence this would have on the degree of enantiomeric excess in the products.

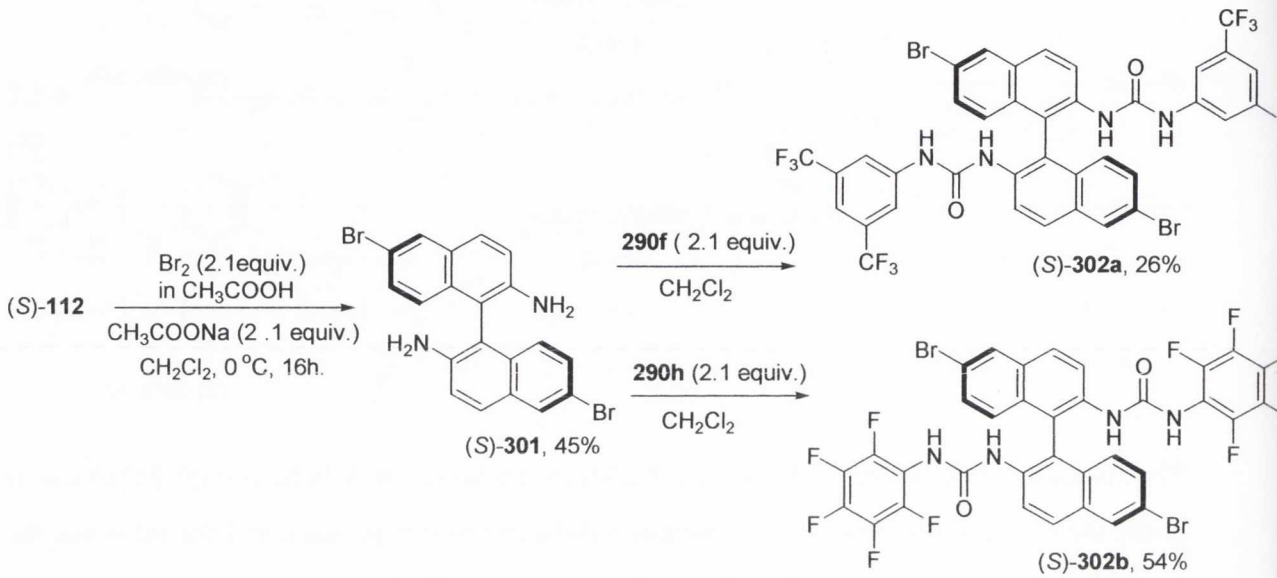
Scheme 2.4 Preparation of brominated analogues of (*S*)-**297a**



The large bromine atom was also incorporated in many different positions (catalysts. (*S*)-**300a**,**b** and (*S*)-**302a**,**b**) to potentially influence the direction of nucleophilic attack of the

indole and to determine the effect on enantiodiscrimination in the products. The incorporation of a large bromine atom at the C-6 and C-6' positions of the binaphthyl backbone was also investigated in the preparation of catalysts (*S*)-**302a** and (*S*)-**302b**.

Scheme 2.5 Preparation of C-6 and C-6' bromominated analogues of (*S*)-**291f** and (*S*)-**291h**

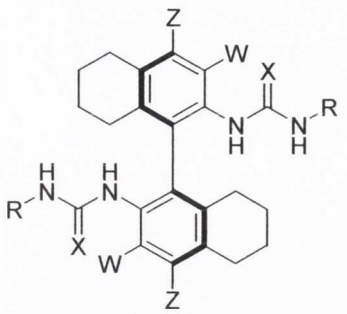


In order to fully explore the effect of the aryl substituents both the 3,5-bistrifluoromethylphenyl and *N*-pentafluorophenyl groups were used, giving rise to catalysts (*S*)-**302a** and (*S*)-**302b** respectively (Scheme 2.5).

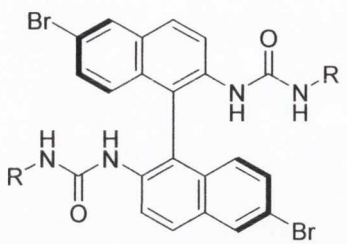
2.1.4.2 Evaluation of the second generation catalysts in the asymmetric Friedel-Crafts reaction

Using the optimised reaction conditions that were identified in the evaluation of the first catalysts designed for the FC addition of **181** to **27**, we were able to compare the influence of the steric and electronic characteristics of both chiral and achiral catalyst components on both catalyst activity and product enantiomeric excess. Table 2.4 outlines the results of these experiments.

Table 2.4 Results of second generation catalyst testing.



(*S*)-**297a** X = O, W = H, Z = H, R = C_6F_5
(*S*)-**297b** X = S, W = H, Z = H, R = 3,5-$(CF_3)_2$-C_6H_3
(*S*)-**300a** X = O, W = Br, Z = H, R = C_6F_5
(*S*)-**300b** X = O, W = Br, Z = Br, R = C_6F_5



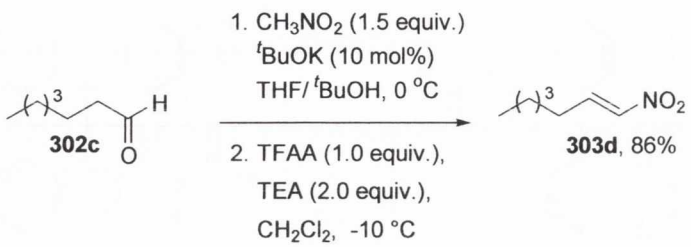
(*S*)-**302a** R = 3,5-$(CF_3)_2$-C_6H_3
(*S*)-**302b** R = C_6F_5

Entry	cat.	conc.	temp. (°C)	time (h)	conversion[a] (%)	*ee*[b] (%)
1	(*S*)-**297a**	0.36	rt	65	23	20
2	(*S*)-**300a**	0.36	rt	113	29	0
3	(*S*)-**300b**	0.36	rt	113	46	0
4	(*S*)-**297b**	0.36	-30	113	15	28
5	(*S*)-**302a**	0.36	rt	22	100	5
6	(*S*)-**302a**	0.36	-20	70	100	8
7	(*S*)-**302b**	0.36	rt	167	93	16
8	(*S*)-**302b**	0.72	-30	167	38	23

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by HPLC using Chiralcel AD-H column (250 x 4.6 mm).

The alteration of the chiral *bis*-naphthyl moiety did not provide the expected results, instead single modifications led to appreciable improvements in either activity or selectivity but not both concurrently. Octahydro-analogues of (*S*)-**291g** and (*S*)-**291h** ((*S*)-**297b** and (*S*)-**297a** respectively) were significantly less efficient (yet reasonably selective) catalysts. The mono and di-brominated derivatives of (*S*)-**297a** ((*S*)-**300a** and (*S*)-**300b** respectively) gave racemic products (Table 2.4, entries 2 and 3). It was interesting to find that the activity of the urea-based catalyst (*S*)-**291f** could be substantially improved *via* insertion of bromo substituents at the C-6 and C-6' positions (catalyst (*S*)-**302a**, Table 2.4, entries 5 and 6). Overall, the results of these trials identified catalyst (*S*)-**291g** as the optimum catalyst as it possesses the best balance of properties in terms of both catalytic activity and stereoinductive ability. Attention now turned to the question of substrate scope. The majority of the nitroalkenes used in this study had previously been synthesised by Dr. Seamus McCooey. The two-step Henry reaction-trifluoroacetic anhydride (TFAA) elimination procedure developed by Denmark *et al.*[327] was used to synthesise the remaining nitroalkene **303d** (Scheme 2.6).

Scheme 2.6 Synthesis of nitroalkene substrates

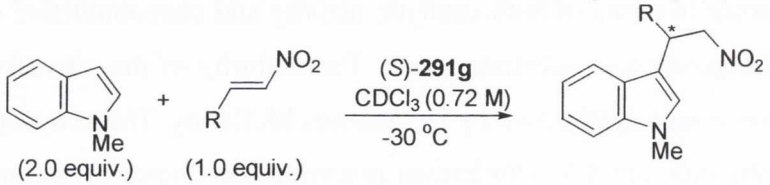


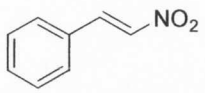
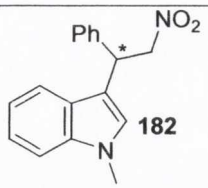
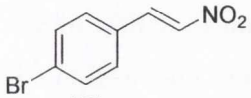
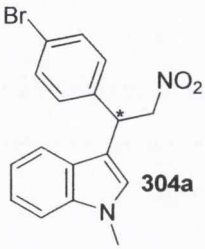
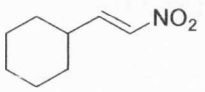
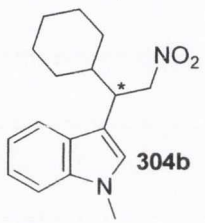
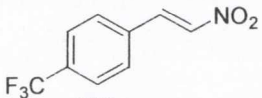
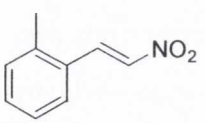
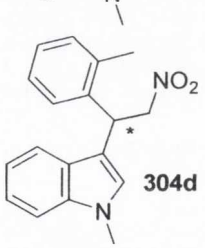
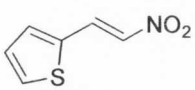
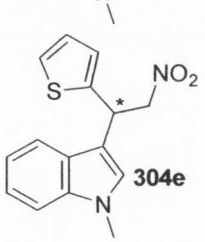
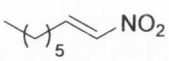
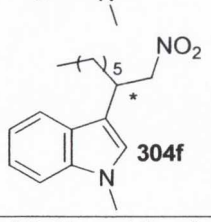
2.1.5 Broadening the substrate scope of the (*S*)-291g catalysed asymmetric Friedel-Crafts addition reaction

To probe the compatibility of the catalyst with substrates with a variety of steric and electronic characteristics we investigated the addition of **181** to both aromatic and aliphatic nitroalkenes catalysed by **291g** at low temperature (Table 2.5). Aromatic nitroalkenes bearing electron-withdrawing functionality (Table 2.5, entries 2 and 4) and sterically hindered *ortho*-substituted nitrostyrenes (Table 2.5, entry 5) afforded FC adducts with similar enantioselectivities to the parent nitrostyrene **27**. However the electron-rich nitroalkene **303c** did not furnish the corresponding FC adduct at sub-ambient temperature but at room temperature only (Table 2.5, entry 6). In contrast to the findings of Jørgensen *et al.*[178] nitroalkenes with aliphatic substituents (which are more difficult substrates in asymmetric organocatalytic Michael reactions)[178,328] underwent FC addition reactions with improved enantioselectivity relative to the aromatic counterparts (Table 2.5, entries 3 and 7).

Surprisingly, the FC addition reaction of indole (**162**) to **27** catalysed by (*S*)-**291g** proceeded slowly resulting in the FC adduct in enantioselectivity of 24% *ee* before chromatography and a diminished 10% *ee* after chromatography (Scheme 2.7).

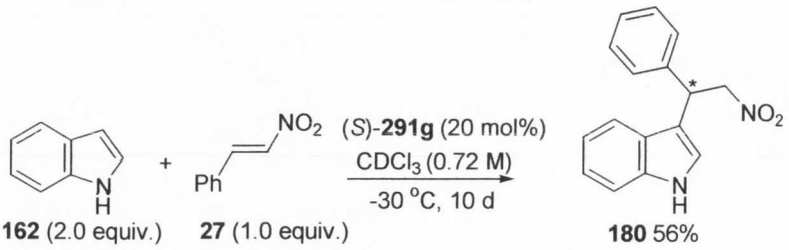
Table 2.5 Asymmetric addition of **181** to nitroalkenes catalysed by (*S*)-**291g**



entry	substrate	Loading (mol %)	product	time (h)	yield (%)[a]	*ee* (%)[b]
1[b]	 **27**	10	 **182**	117	98	30
2[b]	 **103**	20	 **304a**	287	54	28
3[c]	 **187**	20	 **304b**	120	65	43
4[d]	 **303a**	10	 **304c**	140[c]	89	36
5	 **303b**	10	 **304d**	115	78	28
6	 **303c**	10	 **304e**	140[d]	60[e]	12
7	 **187**	20	 **304f**	69	76	50

[a]Isolated yield. [b]Determined by HPLC-Chiaralpak AD-H or AS column (250 x 4.6 mm).[c]Reaction concentration 0.36 M. [d]At room temperature. [e]Refers to conversion.

Scheme 2.7 Asymmetric addition of indole to **27**



The low enantioselectivity can in part be explained by the known ability of silica to catalyse FC addition reactions.[178] This factor can be a problem in the purification of FC reactions where conversion is not complete.

2.1.6 Examination of the catalytic effect of catalyst (*S*)-291g

In an attempt to understand the catalyst mode of action and the origins of selectivity in these reactions we determined the X-ray crystal structure of (*S*)-**291b**, (*S*)-**291d** and (*S*)-**291g**. Unexpectedly the crystal structures of both (*S*)-**291d** and (*S*)-**291g** indicated that the *s-trans, cis* conformation (Figure 2.3) was preferred over the expected *s-cis, cis* isomer which the cyclohexyl analogue (*S*)-**291b** exhibits (Figure 2.4). The X-ray crystal structure of cyclohexyl-substituted urea-based catalyst (*S*)-**291b** displayed a H_a to H_b distance of ca. 2.12 Å which is a close-fit to the O-O bond distance of the nitro group of 2.15Å. This evidence supports a catalytic binding mode whereby the catalyst is capable of donating two hydrogen bonds to the nitro-group of the nitrostyrene substrate directly or to the nitrostyrene in the transition state.

Figure 2.3 The *s-cis, cis* conformation catalyst (*S*)-**291b**

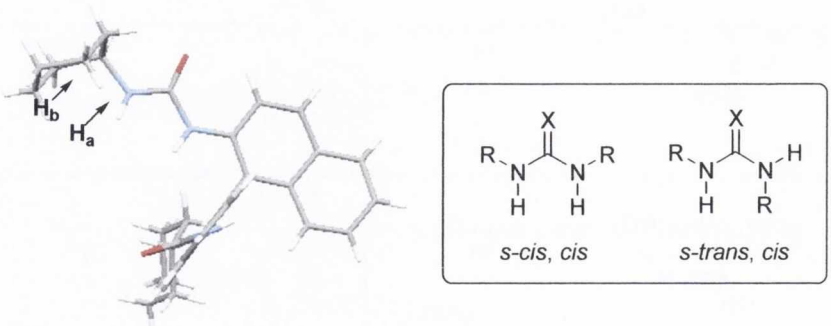
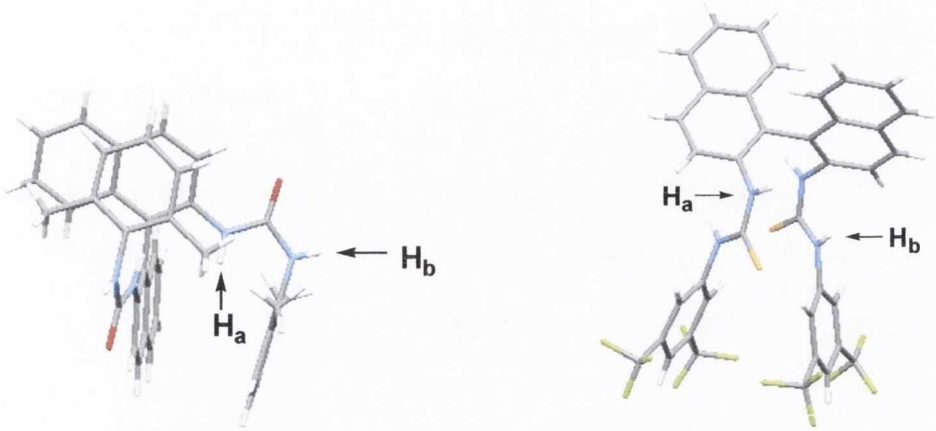


Figure 2.4 X-ray crystal structure of (*S*)-**291d** (left) and (*S*)-**291g** (right) showing *s-trans, cis* conformations



The unusual thiourea *s-trans, cis* structure prevents a substrate binding scenario in which the nitrostyrene (and the transition state of the rate determining step) accepts two hydrogen bonds from a single thiourea moiety. Binding of the electrophile nitro functionality between thiourea moieties is also unlikely as the most suitably oriented hydrogen atoms (*i.e.*, H_a and H_b, Figure 2.5) are separated by 3.53Å while the O-O distance in the nitrostyrene is considerably shorter (*ca.* 2.15 Å). These crystal structures therefore support the possibility that the catalytic activity of catalyst (*S*)-**291g** is due to binding of the substrate/transition state nitro group to a single thiourea hydrogen atom.

2.1.6.1 Explanation of the origins of enantioselectivity of catalyst (*S*)-291g

An examination of models, crystal structures and Chemdraw 3D representations indicate that Figure 2.5 is a reasonable representation of the catalyst (*S*)-**291g** binding with (*E*)-β-nitrostyrene (**130a**) in which each thiourea NH proton donates one hydrogen bond to each O of the nitrostyrene (marked **A**), a bond distance of approximately 1.7 Å. The thiourea selectively binds the nitrostyrene in place in an orientation which avoids steric interactions with both the binaphthyl backbone (**B**) and the 3,5-*bis*trifluoromethyl group of the catalyst (**C**). The *si* face of the nitrostyrene is blocked to a certain extent by the binaphthyl group of the opposite strand (**B**). Thus, *N*-methylindole (**181**) is predicted to attack from the *re* face of the electrophile, leading to the formation of the observed (*R*)-**182** enantiomer.

Figure 2.5 Side view (as drawn) of (*E*)-β-nitrostyrene binding to catalyst (*S*)-**291g**

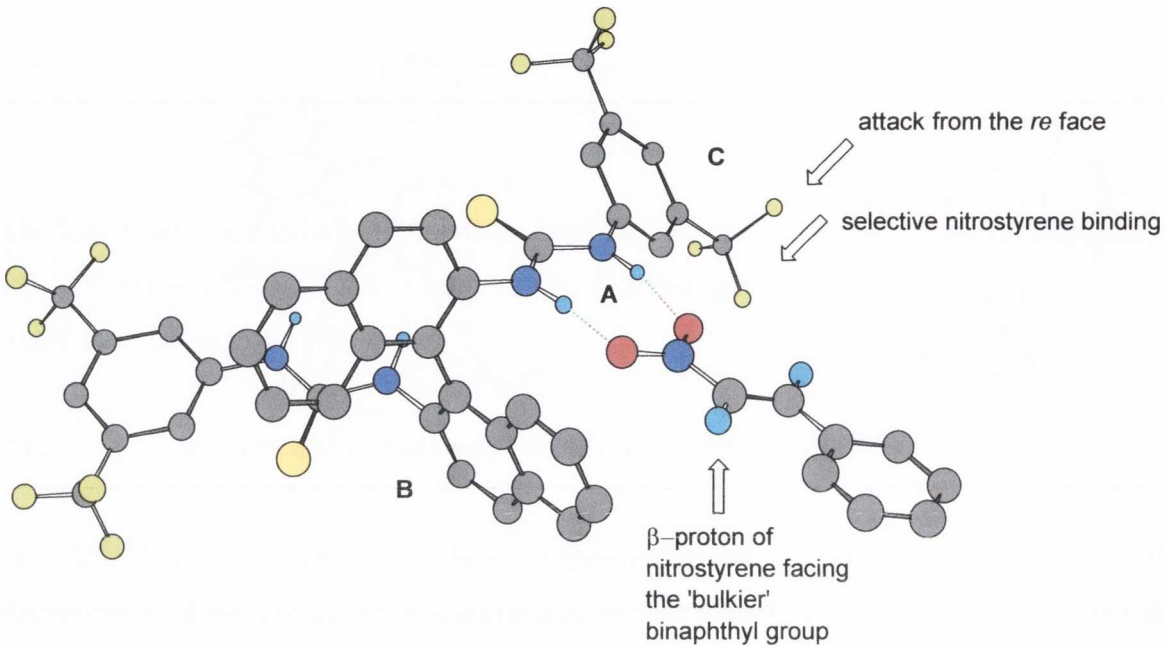


Figure 2.6 shown, is a crystal structure of catalyst (*S*)-**291g** in the solid state. In this scenario it is possible to observe the possibility of single thiourea NH binding to the nitrostyrene, however in the picture shown in Figure 2.6 it is difficult to predict a selective binding mode which wcould ensure enantioselectivity in the product formed.

Figure 2.6 Top view of the solid state crystal structure of (*S*)-**291g**

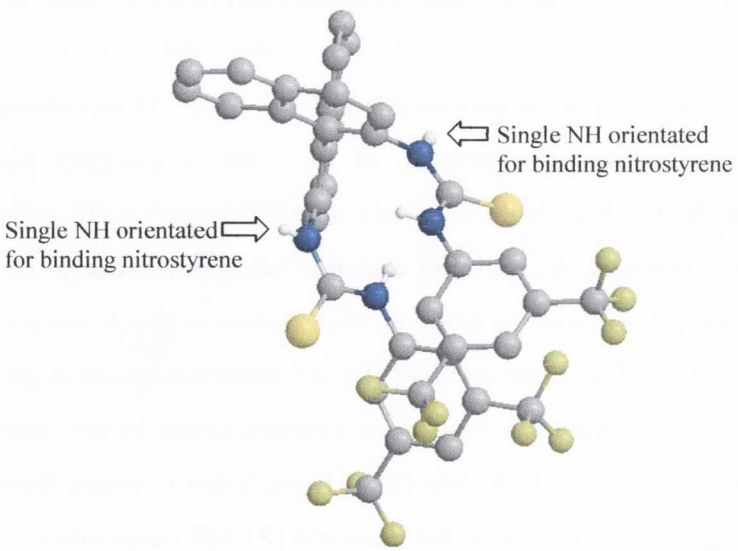
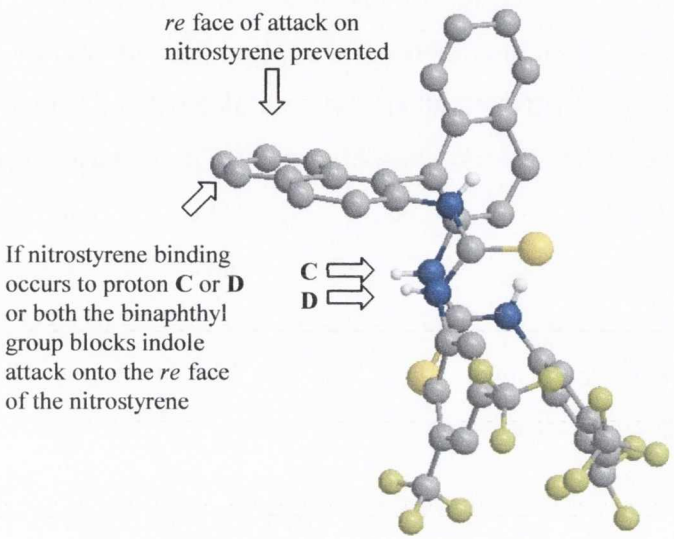


Figure 2.7 shown represents a possible explanation whereby the *re* face of the nitrostyrene is blocked by the binaphthyl group which is positioned above the plane of the thiourea binding motif as shown in the crystal structure.

Figure 2.7 Side view of the solid state crystal structure of (*S*)-**291g**



It is difficult to propose a definitive binding mode to explain the precise origin of enantioselectivity based on these crystal structures as the representations shown may be the optimal lowest energy structure conducive to crystal packing in the solid-state. As a result these structure representations may not be a true reflection of the catalyst structure in solution.

2.1.7 Conclusions for Section 2.1

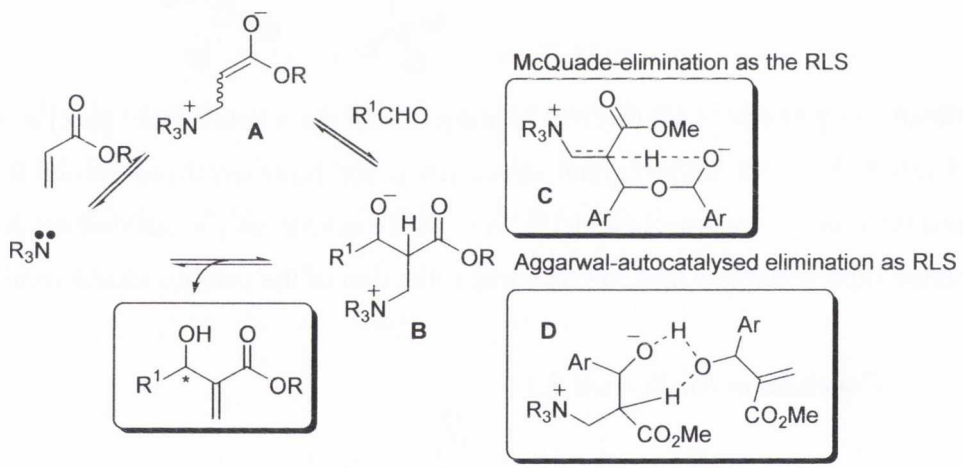
In summary, a broad library of novel thiourea-based axially chiral organocatalysts for the asymmetric addition of *N*-methylindole (**181**) to nitroolefins has been prepared and evaluated. The easily synthesised and simple catalyst (*S*)-**291g** was identified early on as a good structure for further catalyst design. While catalyst (*S*)-**291g** is less active than Jørgensens catalyst **199**,[178] it is nonetheless an efficient promoter of the addition of **181** to nitrostyrenes in good yields with comparable levels of enantioselectivity. Catalyst (*S*)-**291g** has advantages over the literature benchmark catalysts[57,178,192] including its compatibility with challenging nitroolefin substrates incorporating aliphatic substituents, which undergo FC addition with **181** in the presence of thiourea (*S*)-**291g** with considerably higher enantioselectivities than previously reported in the literature. We have been pleased to discover that catalyst (*S*)-**291g** has since

been synthesised by other groups and used as a promoter in the Morita-Baylis-Hillman reaction,[329] the Henry reaction[330] and carbonyl-ene reactions.[331]

2.2 Catalysis of the Morita-Baylis-Hillman reaction

The Morita-Baylis Hillman (MBH) reaction is an organocatalytic process that generates aldol-type adducts *via* reaction at the α-carbon of an unsaturated carbonyl moiety.[332] The reaction involves the coupling of an activated alkene with an aldehyde or ketone and is catalysed by tertiary amines (*e.g.* DABCO, **50**) and phosphines.[333,334] On the basis of pressure dependence, rate, and kinetic isotope effects, Hill and Isaacs[335] suggested a mechanism akin to that depicted in Scheme 2.8.

Scheme 2.8 Hill and Isaacs mechanism for the Morita Baylis Hillman reaction and subsequent modifications



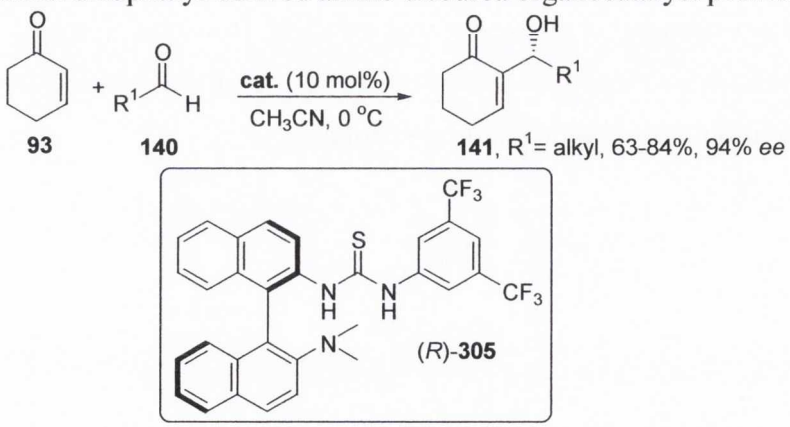
The mechanism involves reversible addition of the tertiary amine to the acrylate (for example) to form an enolate **A** (Scheme 2.8), which subsequently nucleophilically adds to an aldehyde in an aldol-type process to form zwitterionic intermediate **B** (Scheme 2.8). This Zwitterionic intermediate subsequently undergoes a proton transfer-driven elimination of the amine catalyst to afford the product. Using kinetic studies the aldol-type addition step was determined to be rate-limiting, with the reaction displaying third order kinetics or *pseudo* second order kinetics overall if the relative concentration of the amine is considered to remain constant. Recently however, two groups have independently proposed modifications to the accepted mechanistic rationale.

McQuade *et al.*[336,337] reported that deprotonation of the α-position is the rate-determining step and that it occurs through a cyclic transition state, with proton transfer to a hemiacetal alkoxide formed by addition of a second aldehyde molecule to the intermediate alkoxide (Scheme 2.8, **C**). This mechanism explained the observed second order kinetics with respect to aldehyde concentration in the absence of protic solvents. Aggarwal *et al.*[338,339] later demonstrated the elimination step as being rate-determining initially (at low concentrations) but significant autocatalysis of the elimination step during the later stages of the reaction as becoming dominant and leading to a rate-limiting aldol-type step in aprotic solvents (Scheme 2.8, Part D). Leitner *et al.* have since verified Aggarwal's rate determining step assumption in an *aza*-Baylis-Hillman system, however no autocatalysis was observed.[340]

2.2.1 Selected advancement in the asymmetric Morita-Baylis-Hillman reaction: a brief overview

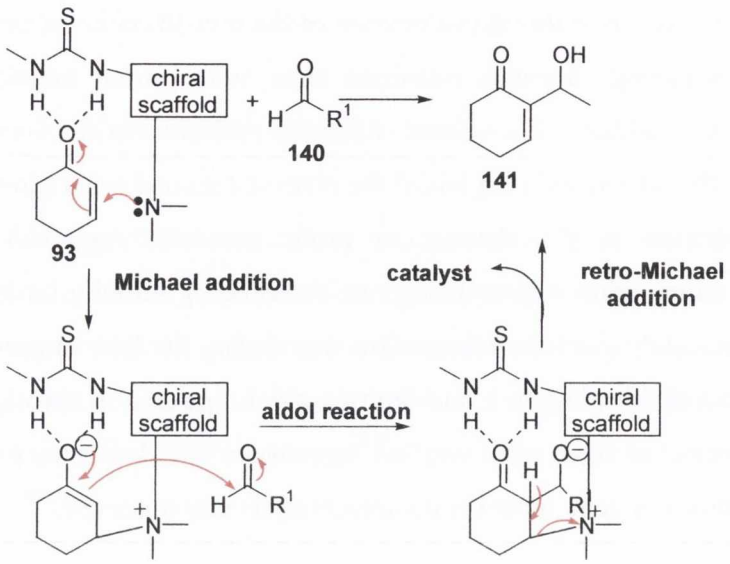
The emergence of a new bifunctional organocatalyst based on both the binaphthyl and thiourea motifs (by Wang *et al.*) for the enantioselective synthesis of allylic alcohol building blocks in high yields and high enantioselectivities (using the Morita-Baylis-Hillman reaction) coupled with previous work carried out by the Connon group (see Section 1.3.2) prompted us to design a modified version of the Wang organocatalyst (Figure 2.8).[341]

Figure 2.8 Chiral binaphthyl-derived amine-thiourea organocatalyst promoted MBH.[341]



The proposed organocatalytic cycle for this process involves the bifunctional thiourea catalyst serving as a carbonyl-activating group, which can simultaneously facilitate the Michael addition of the tertiary amine to the β-position of the substrate (Scheme 2.9).

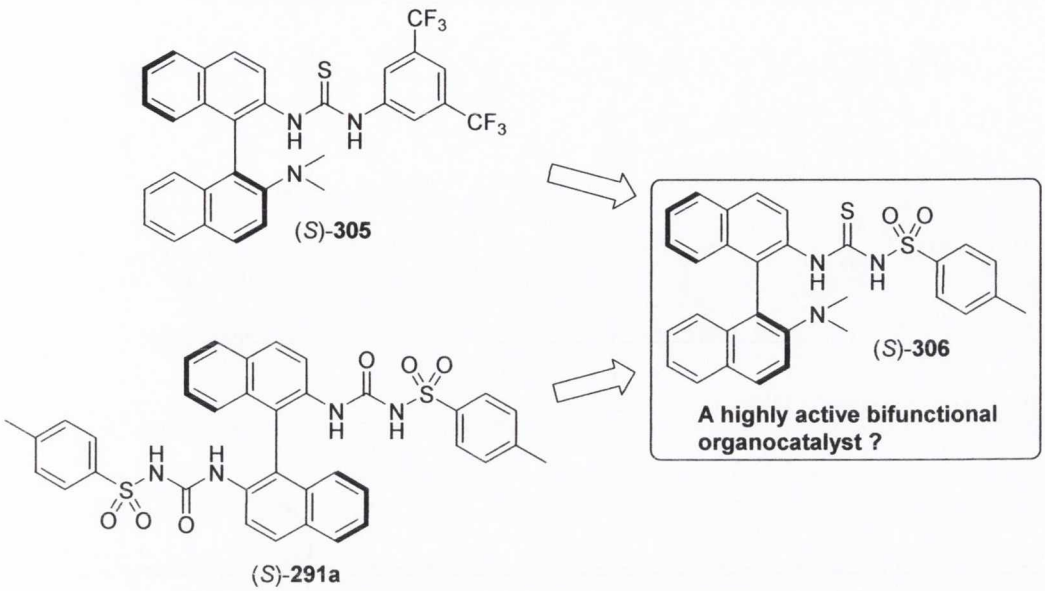
Scheme 2.9 Catalytic cycle for amine-thiourea promoted MBH reaction



2.3 Development of binaphthyl (thiourea) bifunctional organocatalysts

The extensive optimisation studies carried out by Wang *et al.*[341] using catalyst (*S*)-**305** and the remarkable activity of the tosyl-derived catalyst (*S*)-**291a** in our Friedel-Crafts study (Section 2.1) inspired us to merge the best features of both catalyst genres and create a new bifunctional thiourea catalyst (Figure 2.9) for the MBH reaction. Ordinarily speaking, one would not consider the use of a tosyl-thiourea in conjunction with a tertiary amine catalyst due to self-quenching concerns (*i.e.* internal proton transfer). However, in this instance the amino unit is a less basic aniline and thus we felt that the use of the acidic *N*-tosyl thiourea held promise as an electrophile-activating hydrogen donor.

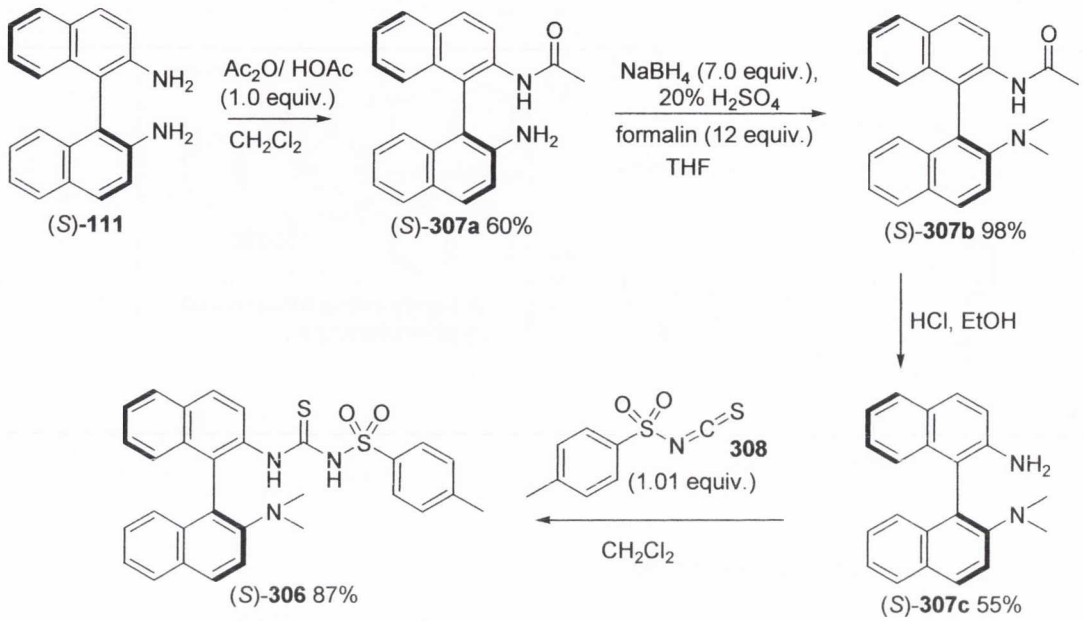
Figure 2.9 Bifunctional thiourea catalyst rationale



2.3.1 Synthesis of catalyst (*S*)-306

The synthesis of (*S*)-**306** is given in Scheme 2.9. Reaction of (*S*)-**111** with acetic anhydride in acetic acid afforded the protected amine derivative (*S*)-**307a**. Reductiveand amination with formaldehyde in the next step afforded (*S*)-**307b**, subsequent deprotection of the acetyl protecting group resulted in the amine (*S*)-**307c** which could be easily modified to the corresponding urea compound *via* the addition of *p*-toluenesulfonylisocyanate (**308**). The resultant white solid was purified *via* column chromatography to afford (*S*)-**306** in 87% yield. The route outlined in Scheme 2.10 is modular, allowing for straightforward alteration of the chiral amine or nonchiral components.

Scheme 2.10 Synthesis of the bifunctional catalyst (*S*)-**306**

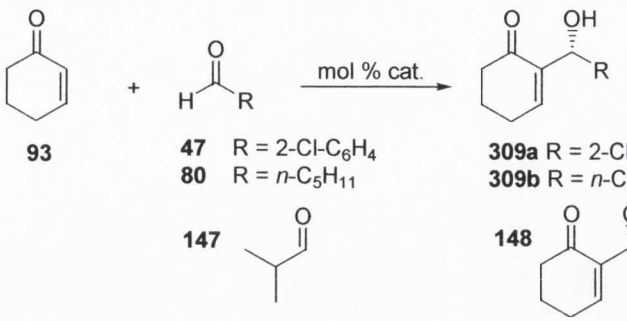


2.3.2 Initial evaluation of (*S*)-305 and (*S*)-306 as catalysts in the MBH reaction

The objective of these preliminary experiments was to determine whether the modified, (predicted to be more acidic) catalyst (*S*)-**306** was capable of improving upon the benchmark Wang catalyst (*S*)-**305** in terms of both reaction rates and enantioselectivity.

The optimal reaction conditions reported by Wang were used using 10 mol% of each catalyst at room temperature. Unfortunately, no conversion was observed using either the Wang catalyst (*S*)-**305** (which was synthesised using the literature procedure[341,342] or the tosyl-derived catalyst (*S*)-**306** (Table 2.6).

Table 2.6 Evaluation of catalysts (*S*)-**305** and (*S*)-**306** in the MBH reaction



entry	cat.	conc. M	substrate	product	time (h)	conversion[a] (%)
1[b]	(*S*)-**305**	0.36	**47**	**309a**	74	0
2[c]	(*S*)-**305**	neat	**47**	**309a**	115	0
3[c]	(*S*)-**306**	neat	**47**	**309a**	115	0
4[c]	(*S*)-**305**	neat	**80**	**309b**	138	0
5[c]	(*S*)-**306**	neat	**80**	**309b**	138	0
6[d]	(*S*)-**305**	0.72	**80**	**309b**	62	0
7[d]	(*S*)-**306**	0.72	**80**	**309b**	62	0
6[e]	(*S*)-**305**	0.18	**140**	**141**	84	0
7[e]	(*S*)-**306**	0.18	**140**	**141**	84	0

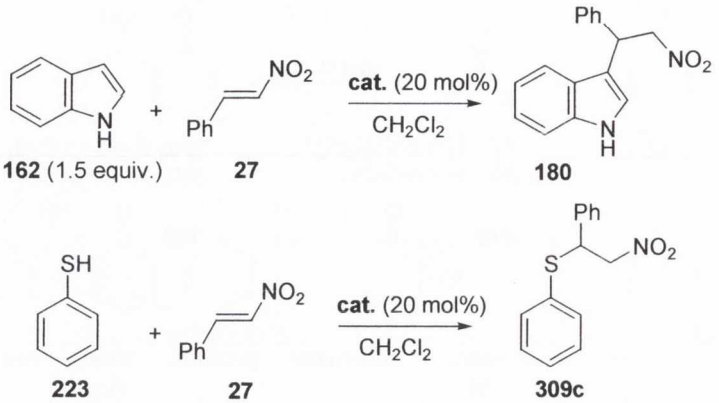
[a]Conversion determined by ^{1}H NMR spectroscopy. [b]Reaction using 1.0 equiv. of aldehyde and 1.0 equiv. of **93** using 10 mol% catalyst. [c]Reaction using 1.0 equiv. of aldehyde and 4.0 equiv. of **93** using 20 mol% catalyst. [d]Reaction using 1.0 equiv. of aldehyde and 2.0 equiv. of **93** and 10 mol% catalyst. [e]Reaction using 1.0 equiv. of aldehyde and 2.0 equiv. of **93** using 5 mol% catalyst.

Several attempts were made to promote the reaction using more reactive substrates and modified reaction conditions yet no catalytic activity was found using either (*S*)-**305** or (*S*)-**306**.

2.3.3 Catalysis of addition reactions using catalyst (*S*)-306

Following the poor performances of the bifunctional catalysts (*S*)-**305** and (*S*)-**306** in the MBH reaction. Ensuring no background reaction (Table 2.7, entries 1,4 and 6), we initiated an evaluation of catalyts (*S*)-**305** and (*S*)-**306** in addition reactions of indole (**162**) and thiophenol (**223**) to (*E*)-β-nitrostyrene (**27**)(Table 2.7).

Table 2.7 Results of bifunctional catalysis of the addition reactions



entry	cat.	conc. (M)	product	temp (°C)	time (h)	conversion[a]	*ee* (%)[b]
1	-	0.67	**180**	rt	266	0	-
2	(*S*)-**305**	0.67	**180**	rt	266	0	-
3	(*S*)-**306**	0.67	**180**	rt	266	45	4
4	-	0.43	**309c**	-30	24	38	-
5	(*S*)-**306**	0.43	**309c**	-30	24	66	nd
6	-	0.11	**309c**	-30	71	0	-
7	(*S*)-**306**	0.11	**309c**	-30	71	45	0

[a]Conversion determined by ^{1}H NMR spectroscopy. [b]Determined by HPLC (AD-Column). nd = not determined

We were pleased to find that the binaphthyl-tosyl(urea)-derived catalyst (*S*)-**306** proved considerably more active than Wangs catalyst (*S*)-**305**, although long reaction times were necessary. Unfortunately, no enantiomeric excess was detected in the reaction product **309c** (Table 2.7, entries 1-3). In order to overcome the necessity of long reaction times we replaced indole (**162**) with a more reactive nucleophile, thiophenol (**223**). At first we observed significant levels of background reaction, this could be controlled through performing the reaction at sub-ambient temperatures and under more dilute conditions (Table 2.7, compare entries 4 and 6). Gratifyingly, the tosyl-containing catalyst (*S*)-**306** displayed significant activity in this reaction promoting 45% conversion of the substrate nitrostyrene after 71 hours. Unfortunately, the product **309c** was isolated as a racemic mixture (Table 2.7, entry 7).

2.3.4 Conclusions for Section 2.3

At this point, the bifunctional catalyst developed by Wang had proved inactive in the asymmetric Morita-Baylis-Hillman reaction in our hands using both aromatic and aliphatic aldehydes and various reaction conditions. However, our binaphthyl-tosyl derived thiourea

catalyst ((*S*)-**306**) was catalytically active in the same sets of reactions. Therefore we had succeessfully developed an active organocatalyst for the promotion of MBH reactions, regrettably the catalyst did not promote enantioselective reactions. Consequently, we decided to design a more active H-bond donating organocatalyst to quantify the collective effectiveness of using a mixture of H-bonding functionalities on catalysis. In these preliminary results, a new approach was taken to design an organocatalyst incorporating multiple hydrogen bond functionalities.

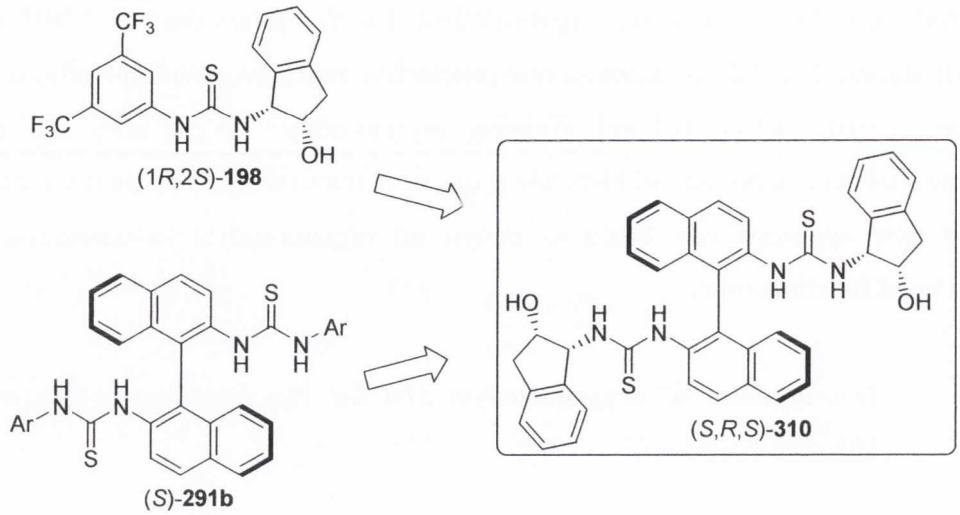
2.4 Development of organocatalyst 310 for the asymmetric Morita-Baylis-Hillman reaction

The impressive results of Ricci *et al.*[192] in the catalysis of the Friedel-Crafts reaction and the knowledge gained from our own work using the binaphthyl backbone of (*S*)-**291b** (Section 2.1) inspired us to merge the best features of both catalysts (Figure 2.10). Previous work carried out in the Connon group[64] using simple (thio)urea catalysts suggested that the Morita-Baylis-Hillman reaction could benefit from the presence of multiple hydrogen bond donors which could stabilise the transition state of the reaction.

2.4.1 Design principles and synthesis of catalyst 310

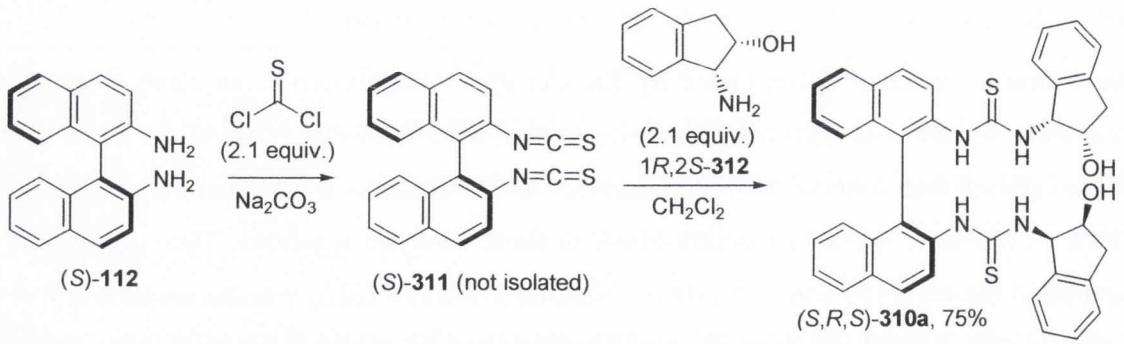
The 1-amino 2-indanol species used by Ricci *et al.*[192] was chosen as an easily incorporated potentially double hydrogen bond donating component. With this in mind we developed an organocatalyst that contains two stereocentres and one chiral axis, which we hoped would afford us a greater degree of stereocontrol in these catalytic reactions. The coupling of the binaphthyl amine (**112**) with (1*S*,2*R*)-*cis*-1-amino-2-indanol (**312**) was accomplished through an iso(thio)cyanate intermediate. Two of the diastereomers were synthesised and evaluated in order to quantify any degree of co-operativity between adjacent stereocentres *i.e* the (*S*,*S*,*R*) or (*S*,*R*,*S*) diastereomeric pair scenario (Scheme 2.11).

Figure 2.10 Binaphthyl(thio)urea **310**:design rationale



The obvious choice of substrates were the (*S*)-1,1'-binaphthyl-2,2'-diamine template (**112**) and 1-amino-2-indanol (**312**-both enantiomers of which were available commercially). Incorporation of the iso(thio)cyanate functionality was carried out using thiophosgene, followed by the addition of (1*R*,2*S*)-*cis*-1-amino-2-indanol **312** to yield (*S*,*R*,*S*)-**310** as a white solid which was purified by column chromatography (ethyl acetate/haxanes (1:1)) in 75% yield (Scheme 2.11).

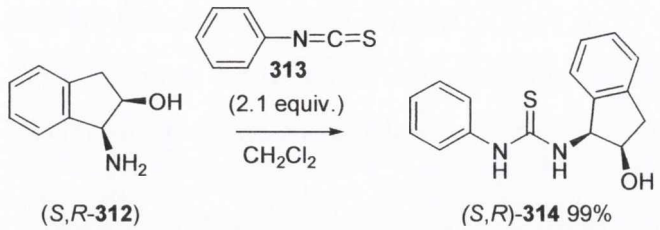
Scheme 2.11 Synthesis of catalyst (*S*,*R*,*S*)-**310**



2.4.1.1 Further catalyst screening in the MBH reaction

In order to determine which catalyst unit is responsible for inducing enantioselectivity in the products, three different catalysts were used (Figure 2.11). Catalyst (*S*,*R*)-**314** with a single (thio)urea moiety and a single indanol-alcohol unit was chosen to determine the degree of influence which the indanol-alcohol group would have on catalyst activity and product enantioselectivity (Scheme 2.12 for analogous synthesis).

Scheme 2.12 Synthesis of catalyst (*S*,*R*)-**314**

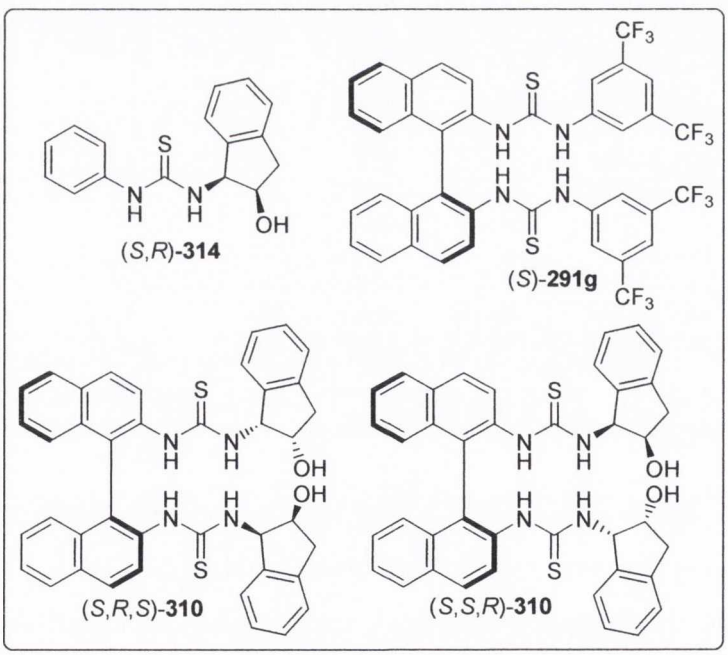


(*S*,*R*-**312**) (*S*,*R*)-**314** 99%

The presence of the single (thio)urea moiety also allowed us to quantify the degree of cooperative binding (if any) is occurring in the binaphthyl (thio)urea catalysts (*S*)-**291g** and **310**.

An evaluation of catalyst (*S*)-**291g** in the asymmetric Morita-Baylis-Hillman reaction allowed us to quantify the degree of (thio)urea activation occuring and whether the absence of the indanol-alcohol unit aids or detracts from either activity or selectivity.

Figure 2.11 Catalysts screened in the MBH reaction

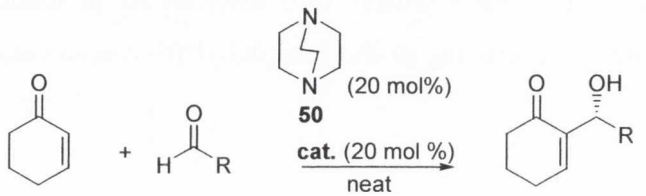


Due to the sluggish nature of these reactions in initial testing (Table 2.6) and the nature of the reactants it was decided to perform the reactions neat at room temperature.

2.4.1.2 Enantiomeric excess of the MBH adducts

As can be seen from Table 2.8 long reaction times were needed for adequate conversion of the substrates to enable isolation of the products for HPLC analysis. Catalyst **314** was used at 40 mol% loading to permit a comparison with the *bis*(thio)urea catalysts (*S*)-**291g** and **310**.

Table 2.8 Results of MBH reaction using catalysts in Figure 2.8



93 **32** R = C_6H_5 **151** R = C_6H_5
47 R = 2-Cl-C_6H_4 **309a** R = 2-Cl-C_6H_4
80 R = *n*-C_5H_{11} **309b** R = *n*-C_5H_{11}

entry[c]	cat.	substrate	product	time (h)	conversion[a] (%)	*ee* (%)[b]
1	-	**47**	**309a**	115	30	-
2	(*S*,*R*)-**314**[d]	**47**	**309a**	115	91	8
3	(*S*)-**291g**	**47**	**309a**	115	99	2
4	(*S*,*S*,*R*)-**310**	**47**	**309a**	115	85	11
5	(*S*,*R*,*S*)-**310**	**47**	**309a**	115	75	6
6	-	**32**	**151**	66	2	-
7	(*S*,*S*,*R*)-**310**	**32**	**151**	66	23	21
8	(*S*,*R*,*S*)-**310**	**32**	**151**	66	23	14
9	-	**80**	**309b**	210	0	-
10	(*S*)-**291g**	**80**	**309b**	210	64	0
11	(*S*,*R*)-**314**[d]	**80**	**309b**	210	13	16
12	(*S*,*S*,*R*)-**310**	**80**	**309b**	210	32	62
13	(*S*,*R*,*S*)-**310**	**80**	**309b**	210	23	36

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using Chiralcel (AS Column)
[c]Using 4.0 equiv. of **93** and 1.0 equiv. of aldehyde.[d]40 mol% of the catalyst was used.

The binaphthyl *bis*-(thio)urea catalyst (*S*)-**291g** exhibited an appreciable degree of activity yet was unselective using both the aromatic and aliphatic aldehydes (Table 2.8, entries 3 and 10). On the other hand the binaphthyl(thio)urea-indanol catalysts (*S*,*S*,*R*)-**310** and (*S*,*R*,*S*)-**310** performed better with the more reactive aromatic substrate than the aliphatic aldehyde. The catalyst with the 'matched' stereocentres (*S*,*S*,*R*)-**310** out-performed the 'mismatched' catalyst ((*S*,*R*,*S*)-**310**) in terms of both activity and enantioselectivity in all the cases (Table 2.8, entries 4 and 5, 7 and 8, and 12 and 13). The (*S*,*S*,*R*)-**310** catalyst was also more soluble in these reactions. The greatest levels of enantiomeric excess was found using the (*S*,*S*,*R*)-**310** catalyst

with aliphatic aldehyde **80**, yielding product **309b** in 32% yield and 62% *ee* (entry 12). The other diastereomer, catalyst (*S*,*R*,*S*)-**310**, was less soluble in these reactions and yielded the product **309b** in 23% and 36% *ee* after extended reaction time (Table 2.8, entry 13). As the rate of catalysis was slow in these cases, promoting the reaction at sub-ambient temperatures (to optimise enantioselectivity in the reaction) was not an option at this stage. Overall, the least reactive aldehydes (where there is no uncatalysed reaction taking place) afforded the greatest levels of enantioselectivity, therefore all product synthesised in these reactions was as a result of catalysis by catalysts **310a** and **310b**.

2.4.2 Conclusions for Section 2.4

Preliminary findings investigating the promotion of the asymmetric Morita-Baylis-Hillman reaction suggest that enantioselectivity can be improved by the use of multiple hydrogen bond donating catalysts. The incorporation of additional chiral centres in this example has also had a beneficial effect on product *ee*.

The results clearly identify the indanol catalyst (*S*,*S*,*R*)-**310** as the best catalyst in terms of both activity and enantioselectivity for all substrates tested. This we suggest may be due to the chiral centre on either side of the thiourea motif of the same rotation and the greater solubility of the (*S*,*S*,*R*)-**310** catalyst over the (*S*,*R*,*S*) catalyst.

The best enantioselectivity result obtained (*i.e.* 62% *ee* using aliphatic aldehyde **80**) was comparable to the literature benchmark results for organocatalysed bifunctional catalysis[341] of the MBH reaction. Subsequent to this work a binaphthyl(thio)urea organocatalyst capable of multiple hydrogen bond donation (similar to (*S*)-**291g**) appeared in the literature,[329] however this catalyst was incompatible with aliphatic aldehydes (unlike catalyst **310**) and long reaction times were necessary for complete substrate conversion.

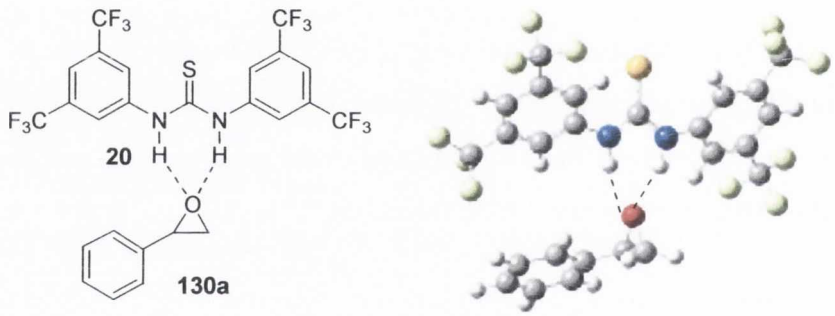
The findings in this chapter served as the inspirational thrust behind the development of a new class of highly acidic urea-based catalysts for Friedel-Crafts-type addition reactions.

3.1 The highly active urea-based catalyst 316

A comprehensive appraisal of both metal and organocatalyst mediated epoxide-ring opening reactions using a variety of different nucleophiles has been given in Section 1.6. The emphasis

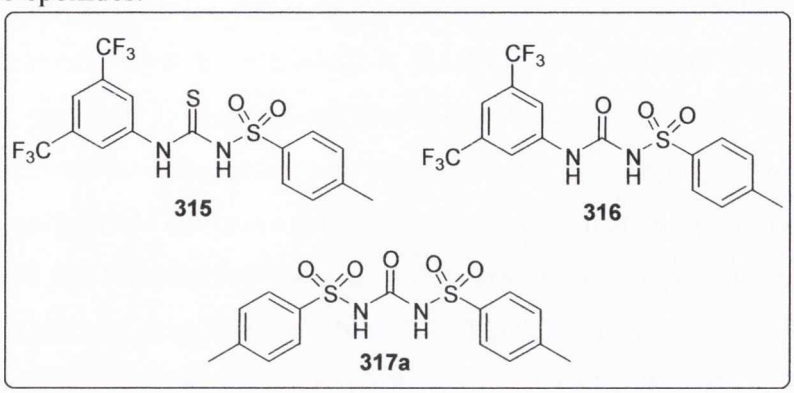
placed on the use of epoxides and the associated addition reactions is due to the biological and industrial relevance of the products produced.[343] The idea of using urea-based organocatalysts for the activation of epoxides is based upon the fact that epoxides are highly-strained compounds which contain an oxygen atom with two lone pairs capable of taking part in hydrogen bond activation by two co-planar NH's of urea group. During nucleophilic addition reactions involving epoxides the electron density on the oxygen atom of the epoxide tends to increase forming an oxyanion during the transition state. We predicted that this oxyanion may be stabilised by a urea-based organocatalyst which may bind to the epoxide and facilitate nucleophilic attack by stabilising this epoxide-species in solution. The minimum energy structure shown in Figure 3.1 (carried out by Dr. Rozas) illustrates such binding *via* two hydrogen bond donating NH's of Schreiner's thiourea catalyst **20** to styrene oxide **130a** (Figure 3.1).

Figure 3.1 Miniumum energy structure of the complex formed between **130a** and **20**



Catalyst screening in the asymmetric Friedel-Crafts reaction uncovered catalysts **291a** and **295** as exceptionally active promoters of the Friedel-Crafts type alkylation reactions with indoles. Encouraged by this we initiated a separate experimental study (supported by computational modelling studies) to probe the potential of catalyst type **315** (Figure 3.2) to promote Friedel-Crafts type addition reactions involving epoxide electrophiles. A small library of catalysts of general type **315** were synthesised by Mr. Cormac Quigley (both the urea **316** and *bis*-tosyl analogues **317a**), however the thiourea **315** was not sufficiently hydrolytically stable to be of use as a general-purpose organocatalyst and often decomposed before complete conversion of the starting materials in a number of test reactions. The *bis*tosylurea compound **317a** was only soluble in DMSO and acetone and was also of insufficient stability on solution therefore no test reactions were carried out with these catalysts (Figure 3.2).

Figure 3.2 Catalysts synthesised for screening in the Friedel-Crafts type addition reaction to epoxides.



3.1.2 Catalyst design rationale and its interaction with the substrate based on computational studies

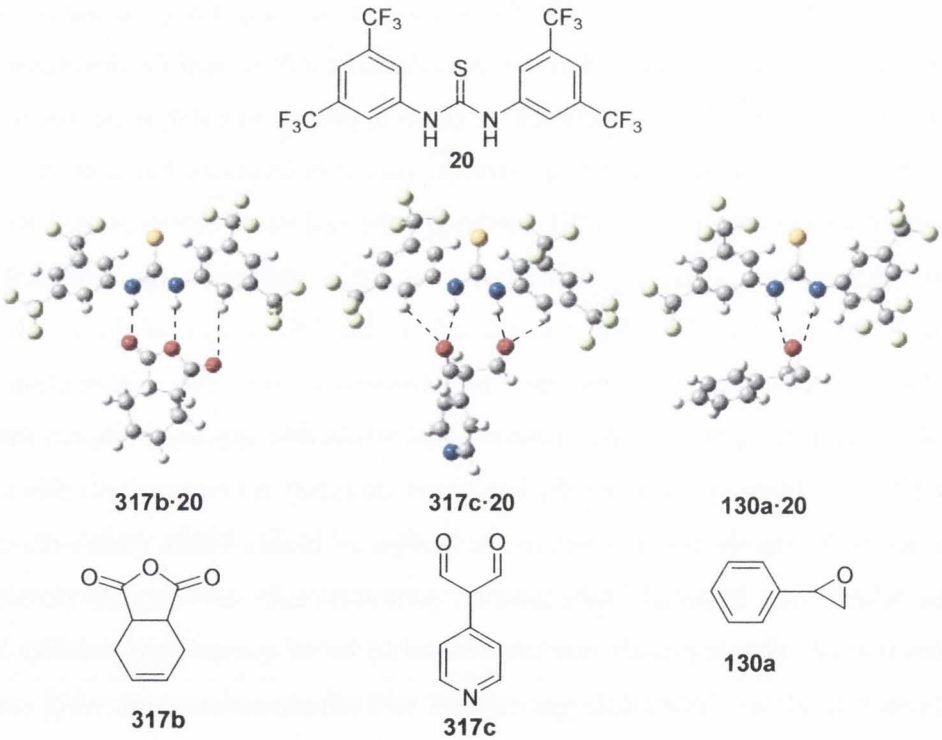
Given the proven activity of catalyst **20** in previous studies, we were interested in pursuing more acidic (thio)urea analogues of **20**. As part of an ongoing program aimed at both the expansion of the scope of (thio)urea derivative-mediated catalysis and the development of new catalyst systems, we undertook an unusual in *silico* approach to catalyst design in which the relative compatibility of a given catalyst-substrate pair is determined based on the stability of the catalyst-substrate complex (*via* DFT methods), the results of which guided the course of subsequent experiments. The key difference in this approach (as opposed to more conventional strategies) is the emphasis placed on the interaction of the catalyst and the electrophilic component, in contrast to emphasis on the interaction between electrophile/nucleophile partners. We reasoned that while this approach ignores the transition state (stabilisation of which is usually the key to the design of a new catalyst) this is less of an advantage in an exergonic process where the design of highly-acidic (thio)urea catalysts is envisioned which will hopefully take part in proton-transfer as early as possible on the reaction coordinate. This approach was envisioned to be of general applicability by the fact that the interaction of the electrophile and catalyst will remain constant allowing compatibility of a wide range of nucleophilic reaction partners.

Computational Methods used in this study:

Density Functional Theory (DFT), this method allows the prediction of catalyst reactivity and substrate recognition/interaction based on the geometries and hydrogen-bond (HB) patterns

exhibited by a range of catalysts and substrates and, additionally evaluates the predictability of the model with subsequent experimental studies. In order to determine the very existence of HBs and their characteristics, the computed electron charge density for each complex was analysed using the Atoms In Molecules (AIM) methodology.[344] A necessary formalism of this method is the establishment of an interaction between two atoms which is the formation of a bond critical point (bcp), which corresponds to a point where the electron density function is a minimum along the bond path and maximum in other directions. Therefore, an interaction between two compounds can be characterised by the properties of the electron density in that point, and thus, an electron density [ρ(bcp)] of approximately 10^{-2} au and a positive Laplacian of the charge density [$\nabla^2\rho$(bcp)] at the bcp correspond to what is defined as closed-shell interaction of the HB type.

Figure 3.3 Minimum energy structure of the complexes formed between **20** and the three classes of compound, anhydride, aldehyde and epoxide



A collaborative computational study with Dr. Isabel Rozas examining the hydrogen bond (HB) patterns exhibited by a series of complexes involving (thio)urea-based organic catalysts with a number of substrates were theoretically studied using DFT. Dr Isabel Rozas carried out all the computational work. The stabilities of hydrogen-bonded complexes between thio(urea) catalyst **20** and three different electrophiles (anhydride, aldehyde and epoxide) incorporating

Lewis-basic oxygen-based functionality were calculated (Figure 3.3 and Table 3.1). This result was somewhat of a surprise as the activity of catalyst **20** has been postulated to arise due to the formation an intramolecular net of HB interactions. Therefore it was expected that the substrate with the largest number of HB acceptors (O atoms) would give the strongest interaction (*i.e* the anhydride **317b**).

Table 3.1 Interaction energies, HB distances, ρ(bcp) and $\nabla^2\rho$(bcp) found for complexes **317b·20**, **317c·20** and **130a·20** computed at B3LYP/6-31+G* level of theory.

entry	complex	E_I (kcalmol^{-1})	HB distance (Å)		ρ(bcp)	$\nabla^2\rho$(bcp)
1	**317b·20**	-10.03	NH···O	2.07	0.0201	0.0640
			NH···O	2.23	0.0135	0.0468
			CH···O	2.91	0.0035	0.0140
2	**317c·20**	-10.66	NH···O	2.05	0.0198	0.0667
			NH···O	2.11	0.0166	0.0595
			CH···O	2.66	0.0056	0.0224
			CH···O	2.81	0.0046	0.0181
3	**130a·20**	-12.79	NH···O	2.02	0.0219	0.0723
			NH···O	2.08	0.0187	0.0640

The anhydride formed three HBs, the aldehyde formed four HB's while the epoxide formed two HB's with the catalyst. Surprisingly it was the epoxide which formed the most stable complex with catalyst **20**, further analysis of the interactions explained the reasoning behind this. It was found that there is a clear correlation between the HB distance and the electron density at the bcp [ρ(bcp)]. Thus the shorter the HB distance the larger the electron density and therefore the stronger the interaction. Accordingly it was found that the interaction between the catalyst and the substrate will be favoured not by the number but by the strength of the HB's in the complex.

The more acidic compound **316** (Figure 3.2) was evaluated next. This catalyst was stable under the reaction conditions chosen and exhibited the best combination of interaction energy, HB distance and electron density (with styrene oxide (**130a**) as substrate) in the computational modelling studies.

Figure 3.4 Minimun energy structure of the complexes found between **316** and **130a** optimised at the B3LYP/6-31+G* level.

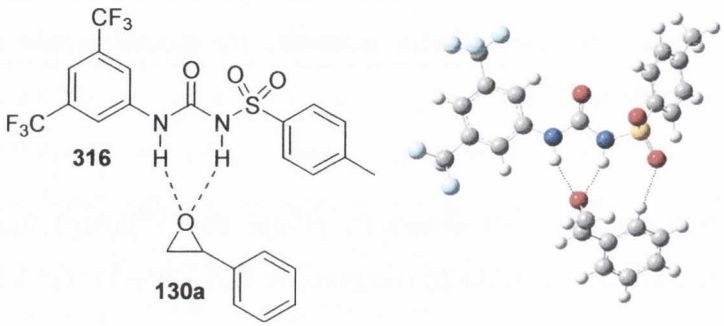


Table 3.2 Interaction energy, HB distance, ρ(bcp) and $\nabla^2\rho$(bcp) found for complex **316·130a**, computed at B3LYP/6-31+G* level of theory.

Complex	E_I (kcalmol^{-1})	HB distance (Å)	ρ(bcp)	$\nabla^2\rho$(bcp)
316·130a	-14.1	NH···O 1.97	0.0240	0.0795
		NH···O 2.09	0.0181	0.0627
		CH···O(S) 2.48	0.0086	0.0307

The complex of **316·130a** (and in all the optimised complexes investigated) is characterised not only by the expected bifurcated interaction between the O atom (from the epoxide) and the two thiourea NH hydrogen atoms formed, but also secondary interactions are observed between one of the sulfonamide O atoms and either the methylene hydrogen atoms of the epoxide or a CH of the substrate phenyl moiety (Figure 3.4). The epoxide oxygen interacts better with the nonsymmetrically substituted **316** than with the symmetrical thiourea catalyst **20**.

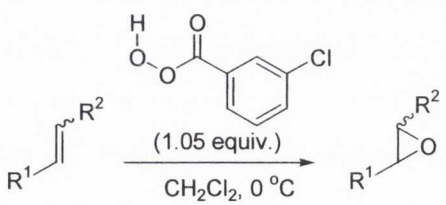
All the interactions established between the host and the guest were identified as hydrogen bonds according to both atoms in molecules (AIM) theory and analysis of the electron density ρ. The data obtained for the **316·130a** complex was the most stable in comparison to the study using the symmetrical thiourea catalyst **20** and the corresponding *N*-tosyl thiourea catalyst **315**. In particular the most stable complex **316·130a** possesses two very strong NH…O HBs

(2.09 & 1.97 Å and ρ (at the bond critical point(bcp)) of 0.02 and 0.18 respectively) and a secondary weak HB formed between one of the O atoms of the sulfonamide and an *ortho*-hydrogen atom of the substrate benzene ring (distance of 2.48 Å, ρ(bcp) of 0.008 (Figure 3.4 and Table 3.1). In terms of interaction energy (calculated as the difference between the total energy of the complex minus the sum of the total energy of the host and guest), the –14.1 kcal mol^{-1} value in Table 3.2 for the complex between **130a** and **316** signifies a very stable favourable interaction between these two species. The value for the thiourea **315·130a** complex was calculated to be 0.06 kcal mol^{-1} less stable at –14.0 kcal mol^{-1}. Therefore catalyst **316** was found to form a most favourable complex with **130a** than the corresponding (thio)urea **315** and Schreiner's thiourea **20**, the complex's minimum energy structure is shown in Figure 3.4.

3.1.2.1 Epoxide substrate synthesis

Only styrene oxide (**130a**) was purchased from a commercial source while the remaining epoxides were synthesised from the corresponding alkenes or aldehydes using one of two possible literature procedures. Procedure **A** involved alkene oxidation by *meta*-chloroperoxybenzoic acid (*m*CPBA). A general synthesis of epoxides utilising this method is shown in Scheme 3.1. The yields of these reactions were generally high yet the recrystallisation process of *m*CPBA was time-consuming and somewhat dangerous.

Scheme 3.1 Preparation of epoxides *via* method **A**



Method **B** involved the epoxidation of readily available aldehydes using the Johnson-Corey-Chaykovsky reaction. Product yield was always high and purification by column chromatography was not always necessary. The syntheses of epoxides by this protocol (method B) are given in Scheme 3.2. Epoxides synthesised by method **A** or **B** are shown in Figure 3.5.

Scheme 3.2 Preparation of epoxides *via* method **B**

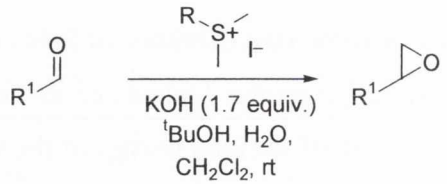
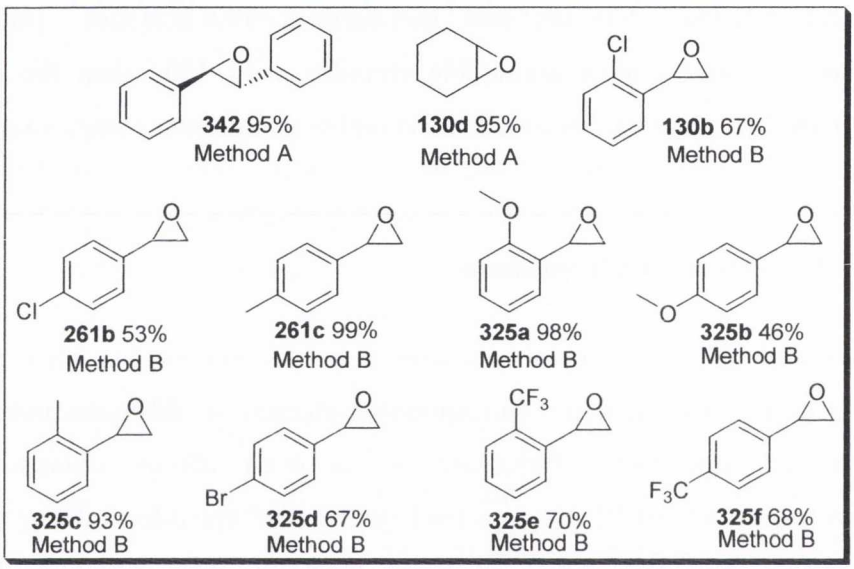


Figure 3.5 Epoxides synthesised by either method **A** or **B**

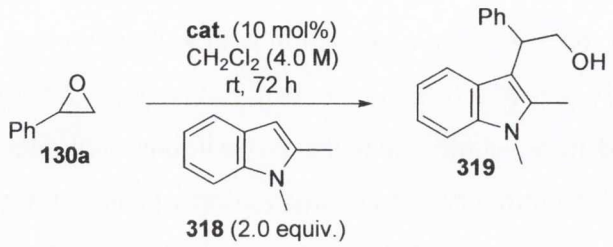


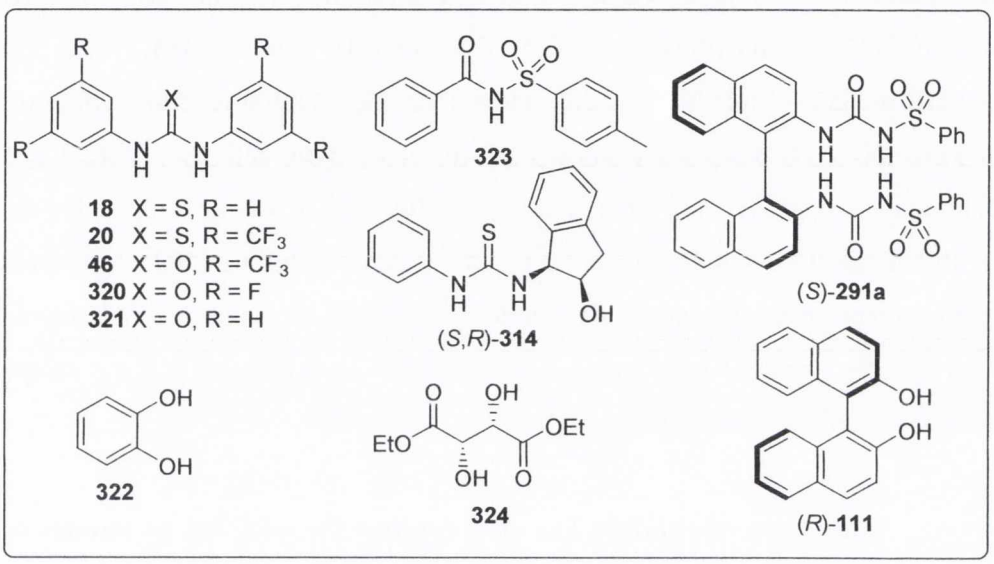
3.2 Preliminary testing of catalyst 316

Next, our attention turned to identifying the nucleophilic reaction component. Schreiner and Kleiner[60] reported the first (thio)urea catalysed addition of aliphatic amines, thiophenol and alcohols to epoxides.[60] Yields were low to moderate in dichloromethane solvent; however, the same reactions (which require ultrasonication before the addition of the nucleophile) under the influence of hydrophobic amplification in water were highly efficient. As a starting point, we selected indole derivatives as the nucleophilic reaction partner as they do not possess basic functionality that could deprotonate the acidic urea **316**. Also, the 3-alkyl indole addition products from such reactions are useful synthetic building blocks for the synthesis of compounds of biological interest. At the outset of this work the previous benchmark for organocatalysis of this reaction involved the use of a silica gel catalyst under elevated temperatures and pressures (10 kbar) to afford moderate to good adduct yields.[197,345] In order to compare catalyst **316** with the previous organocatalysts in the field initial testing of the

reaction of **130a** with 1,2-dimethylindole (**181**) was carried out using a range of known hydrogen-bond activating catalysts, the results of which are summarised in Table 3.3.

Table 3.3 Preliminary catalyst screening results





entry	catalyst	time (h)	yield[a] (%)
1	-	72	0
2	**20**	72	<2
3	**46**	72	0
4	**320**	72	0
5	**18**	72	0
6	**321**	72	0
7	**316**	72	71
8	**323**	72	56
9	(*S*, *R*)-**314**	72	0
10	**322**	72	39
11	**324**	72	0
12	(*R*)-**111**	245	21[b,c]
13	(*S*)-**306**	119	0[d]
14	(*S*)-**291a**	89	10[e]

[a]Refers to isolated yield after chromatography. [b]Conversion, determined by ^{1}H NMR spectroscopy. [c](*R*)-BINOL afforded **319** as a racemate: no kinetic resolution was observed.[d] Using 1.0 equiv. of indole (**162**) instead of **181** and 0.5 equiv. of **130a**. [e]Reaction halted at this conversion as multiple products began to appear in the ^{1}H NMR spectrum therefore the *ee* was not determined.

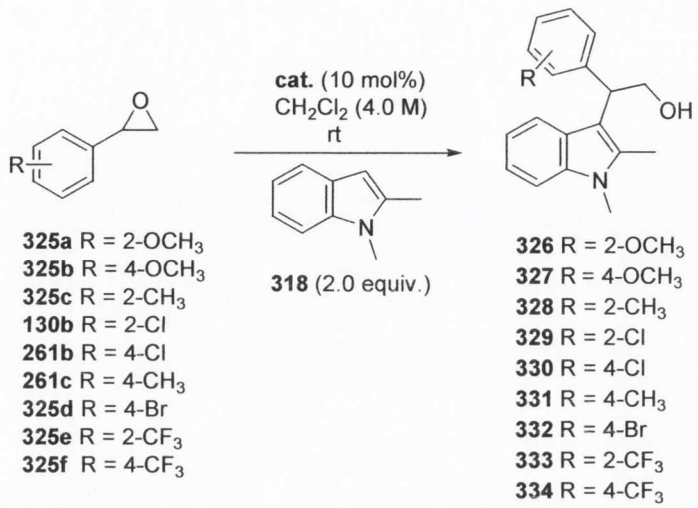
The addition of 1,2-dimethylindole to **130a** in dichloromethane does not proceed at room temperature (Table 3.3, entry 1). The same reaction catalysed by **20** (10 mol%) afforded only trace amounts of **318** (Table 3.3, entry 2), and *N*,*N*-diaryl(thio)ureas **18**, **20**, **46** and **321** were inactive (Table 3.3, entries 3-6). Thankfully, *N*-tosylurea (*S*)-**291a** identified in the in *silico* study as potentially suitable for use in conjunction with **130a** proved to be an effective catalyst capable of providing product **319** in good isolated yields after 72 hours (Table 3.3, entry 7). Catalyst **316** was found to be stable under these conditions unlike its counterparts shown in Figure 3.2). The catalytic significance of the urea moiety of catalyst **316** is demonstrated by its catalytic superiority to compound **323** although it is noteworthy that **323** is a better catalyst than either of the *N*,*N*-diaryl(thio)ureas (Table 3.3, entry 8). Thiourea **314**, which possesses an additional HB donating functionality, did not catalyse the addition reaction, while of the diols **322** and **111,** only **322** exhibited a moderate level of catalytic activity (Table 3.3, entry 10). The bifunctional binaphthyl-tosylurea catalyst (*S*)-**306** which was developed for the Morita-Baylis-Hillman reaction was also inactive in the reaction of indole (**162**) with styrene oxide (**130a**) under these reaction conditions (Table 3.3, entry 13). Catalyst (*S*)-**291a**, which was highly active in the Friedel-Crafts addition of indoles to nitrostyrenes, was a poor promoter of these reactions (Table 3.3, entry 14).

3.2.1 Evaluation of catalyst 316 as a catalyst for addition of indoles to various epoxides

Evaluated next was the compatibility of catalyst **316** with styrene oxides of variable steric and electronic properties (Table 3.3). A broad range of styrene oxides could be converted to the corresponding indole derivatives with ease in good to excellent yields (Table 3.3, entries 1-9).

These results indicate that both *ortho*- and *para*-substitution is well-tolerated by catalyst **316**, and styrene oxides with electron-rich aromatic rings (Table 3.4, entries 1-4) react at considerably faster rates than their more electron deficient counterparts (Table 3.4, entries 5-7).

Table 3.4 Broadening the scope of the catalysed addition reaction



325a R = 2-OCH_3
325b R = 4-OCH_3
325c R = 2-CH_3
130b R = 2-Cl
261b R = 4-Cl
261c R = 4-CH_3
325d R = 4-Br
325e R = 2-CF_3
325f R = 4-CF_3

318 (2.0 equiv.)

326 R = 2-OCH_3
327 R = 4-OCH_3
328 R = 2-CH_3
329 R = 2-Cl
330 R = 4-Cl
331 R = 4-CH_3
332 R = 4-Br
333 R = 2-CF_3
334 R = 4-CF_3

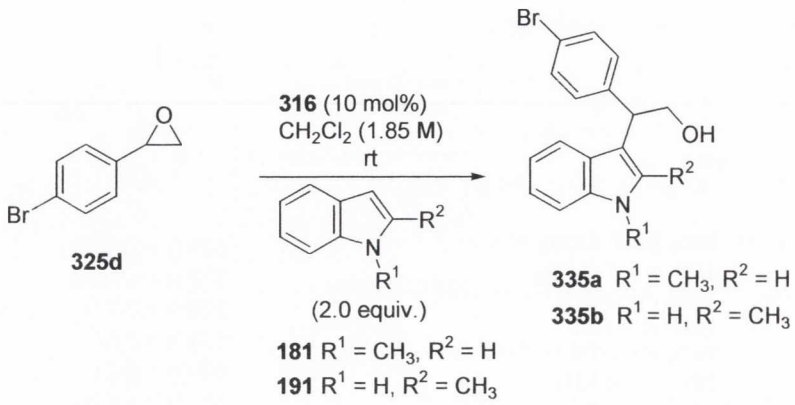
entry	substrate	product	time (h)	yield[a] (%)
1	**325a**	**326**	26	90[b]
2	**325b**	**327**	26	90
3	**325c**	**328**	48	98
4	**261c**	**331**	48	94
5	**130b**	**329**	621	80
6	**261b**	**330**	163	93
7	**325d**	**332**	77	92
8	**325e**	**333**	72	0
9	**325f**	**334**	72	0

[a]Refers to isolated yield after chromatography. [b]An identical reaction without molecular sieves afforded 75% yield.

We were surprised to find that both *ortho* and *para* substituted trifluoromethyl epoxides **325e** and **325f** were unsuitable substrates in this reaction due to insolubility in the highly concentrated reaction media (Table 3.4, entries 8 and 9).

Indoles other than **318** can also be employed as the nucleophilic component: both 1- and 2-methylindole derivatives could be reacted with 4-bromostyrene oxide **325d** to give **335a** and **335b** in good yields (Table 3.5).

Table 3.5 Catalysed addition of 1- and 2-methylindole to 4-bromostyrene oxide



entry	substrate	product	time (d)	yield[a] (%)
1	**181**	**335a**	7.8	98
2	**191**	**335b**	7.2	89

[a]Refers to isolated yield after chromatography.

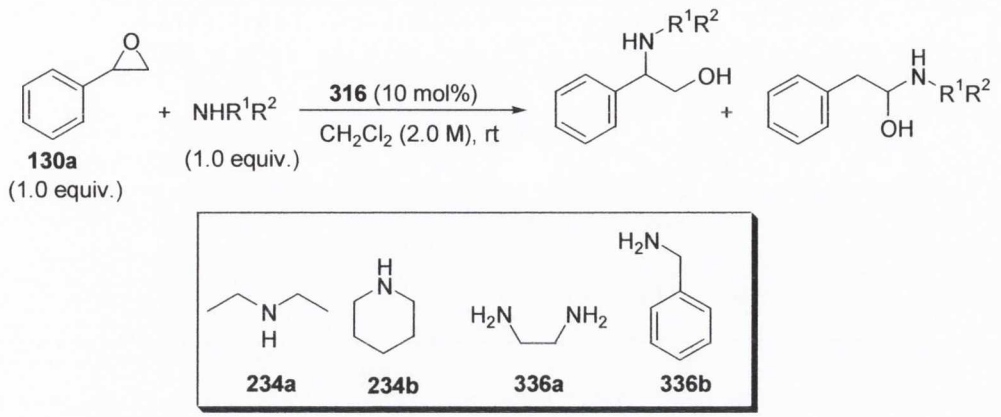
3.3 Examination of nucleophiles other than indole derivatives

The success of these Friedel-Crafts type reactions prompted us to investigate the compatibility of **316** with other nucleophiles. Preliminary studies focused on the use of amines, and then diversified to the use of thiols and alcohols. However under our reaction conditions, sufficient amounts of the amino alcohol products were observed in the absence of the catalyst.

3.3.1 Catalysis of amine additions to epoxides by 316

Preliminary experiments concerning the addition of amines to epoxides began with a screening of a range of both aliphatic and aromatic amines of variable basicity. Reactions involving ethylene diamine **336a** were characterised by poor conversions and the formation of an unidentified white precipitate. Diethylamine (**234a**) was capable of adding to styrene oxide to a significant extent without catalysis and both benzylamine (**336b**) and piperidine (**234b**) participated in poorly regioselective addition reactions (Scheme 3.3).

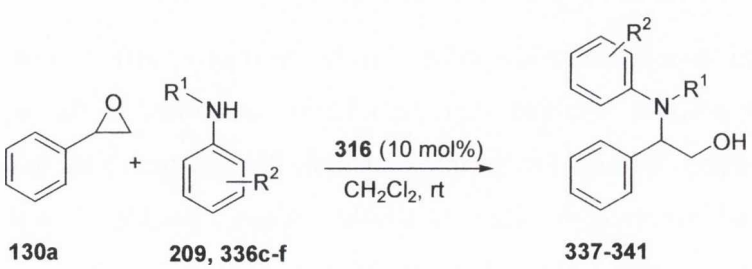
Scheme 3.3 Amines evaluated in the catalysed addition to epoxides by **316**

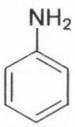
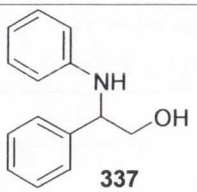
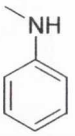
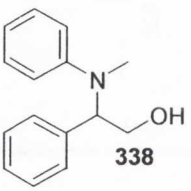
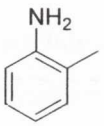
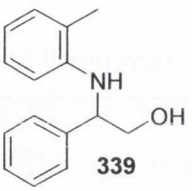
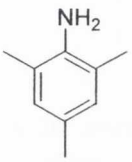
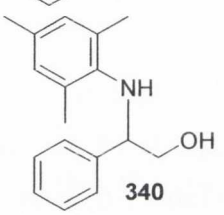
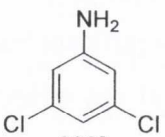
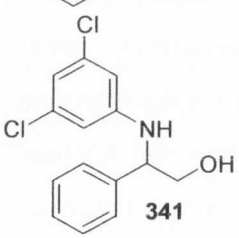


Schreiner and Kleiner[60] had already developed efficient catalytic methodologies for the use of aliphatic amines in aqueous solvent; therefore the application of less reactive aniline derivatives seemed a greater and more rewarding challenge to test the activity and utility of catalyst **316** (Table 3.6).

Catalyst **316** was found to be capable of the promotion of the β-amino alcohol products derived from the addition of **209** (Table 3.6, entry 1), *N*-methyl aniline (**336c**), and both steric and electronically deactivated derivatives thereof (Table 3.6, entries 2-5) to styrene oxide using 10 mol% of catalyst. These results represent a significant improvement on the literature precedent, as the work of Schreiner and Kleiner[60] did not utilise aniline substrates and the work of Saidi *et al.*[207] did not describe a catalytic system compatible with such a broad range of aromatic amines (Section 1.6).

Table 3.6 Results of both 1- and 2-methylindole additions



entry	substrate	product	time (h)	yield (%)[a]
1[b]	 **209**	 **337**	91	86
2[b]	 **336c**	 **338**	91	78[b]
3[c]	 **336d**	 **339**	90	75[e]
4[d]	 **336e**	 **340**	147	92
5	 **336f**	 **341**	71	84

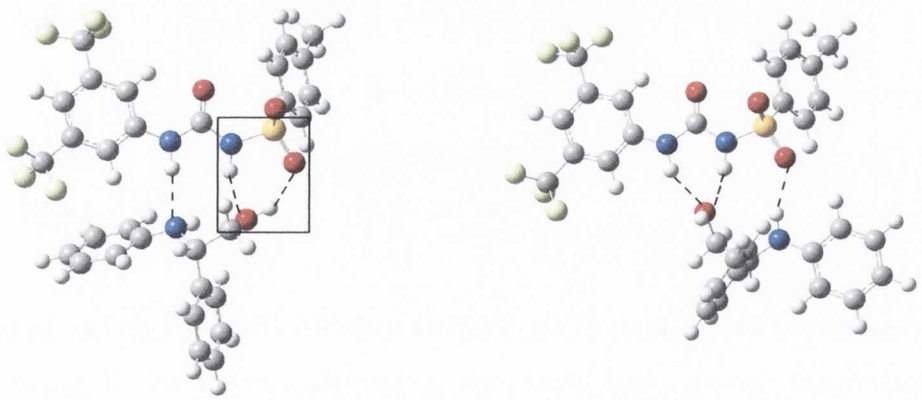
[a]Refers to isolated yield after chromatography. [b]2.0 M concentration. The crude reaction mixture was determined to be 94:6 ratio of regioisomers using ^{1}H NMR spectroscopy. The yield cited corresponds to that of the isomer shown. [c]1.5 M concentration. [d]Using 20 mol% **316**. [e] Crude reaction mixture was determined to be 92:8 ratio of regioisomers using ^{1}H NMR spectroscopy.

Finally we studied from a theoretical point of view, the relative affinities of the catalyst for the substrate and the product obtained after the addition of aniline to the styrene oxide. If the catalyst had a greater affinity for the product than the substrate this would lead to slower reaction times and eventual the catalyst would become inactive. The possible complexes formed between urea catalyst **316** and adduct **337a** were analysed. Initially the conformational space of **337a** was explored, the conformer of minimum energy identified and then used for

the rest of the calculations. The catalyst conformer utilised was that previously determined with the complex of **316·130a** (Section 3.1.2).

Considering the structure of both molecules, all possible approximations were taken into account at the B3LYP/6-31G* level, and 12 complexes of minimum energy were identified. Eight of these involved interactions between the catalyst urea moiety and the O atom of the hydroxyl group of the product. The other four approximations involved dual interactions between the urea and both the O(OH) and the N(H) groups of the product. Those conformers of minimum energy for each approximation were further optimised at the 6-31+G* level, resulting in two different complexes of minimum energy (**337a·316** and **337b·316** (Table 3.7 and Figure 3.6).

Figure 3.6 Structure of minimum energy found for the complexes formed between **337a** and **316**: complexes **337a·316** (left) and **337b·316** (right). The ring of cooperative HBs in complex **337b·316** is framed.



Complex **337a·316** if formed between the catalyst (acting as a HB donor) and **337** with both product amino and the hydroxyl groups acting as HB acceptors (Figure 3.6), and an additional HB is formed between the hydroxylic proton and one of the O atoms of the SO_2 moiety. Complex **337b·316** is characterised by bifurcated HBs between the O atom of the product and the urea protons and two secondary interactions between the product amino and methine protons as HB donors with one of the catalysts sulfonamide O atoms. Analysing the electron

density surface, it was possible to identify four HBs in each complex. In the case of **337a·316** complex, parallel HBs are formed between the urea NH groups and the N(medium HB) and O(very strong HB) atoms of the product, and a very strong HB is established between the hydroxyl group of the product (which acts now as HB donor) and one of the sulfonamide O atoms. Additionally, an intramolecular NH---O(H) HB is found in the product molecule (Table 3.7).

Table 3.7 Interaction energies (kcal/mol), HB distance (Å), ρ(bcp) and $\nabla^2\rho$(bcp) found for complexes **337a·316 and 337b·316** computed at the B3LYP/6-31+G* level of theory.

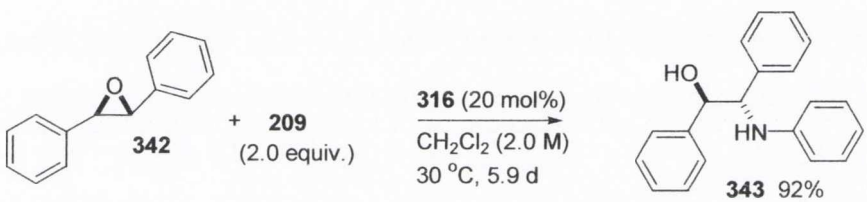
Complex	E_I (kcalmol^{-1})	HB distance (Å)	ρ(bcp)	$\nabla^2\rho$(bcp)
337a·316	-11.5	NH···N 2.26	0.0176	0.0466
		NH···O 1.94	0.0288	0.0852
		OH···O(S) 1.95	0.0253	0.0855
		NH···O 2.23(intra)	0.0168	0.0774
337a·316	-13.0	NH···O 2.20	0.0158	0.0524
		NH···O 1.88	0.0310	0.0990
		NH···O(S) 2.23	0.0133	0.0476
		CH···O(S) 2.55	0.0069	0.0269

The reason behind the strength of the NH---O and OH---O(S) bonds lies in the cooperative effect established between these two HBs formed through the O---H group.[346] Thus, it is possible to identify a ring of HBs connected in a cooperative fashion: (S-)N-H---O-H---O-S(-N). In complex **337b·316**, bifurcated HBs are formed between both urea NH protons and the hydroxyl O atom. Additionally, two weak HBs are established between the NH and one CH group of the product and one of the sulfonamide O atoms. These two complexes, which are the most stable of all the possible complexes found at lower levels of computation, are less stable than complex **316·130a** found between the catalyst and the epoxide derivative (Table 3.7). The significance of this result is that the catalyst will not preferentially bind to the product rather

than the starting material epoxides, *i.e.* product inhibition is not an issue and reactions can be expected to continue to complete conversion using these substrates. However, as the interaction energy of the **337b·316** complex is only 1.1 kcal/mol-[1] less stable than the **316·130a** complex computational methods have been invaluable in analysing the HBs which determine whether catalysis is possible, as the synthesis of substrates which are capable of forming stronger interactions with the catalyst than with the substrate may experience product inhibition issues.

Gratifyingly, we were pleased to find that **316** was capable of promoting the addition of **209** to the more hindered (*E*)-stilbene oxide **342** in high yield at 30 °C (Scheme 3.4).

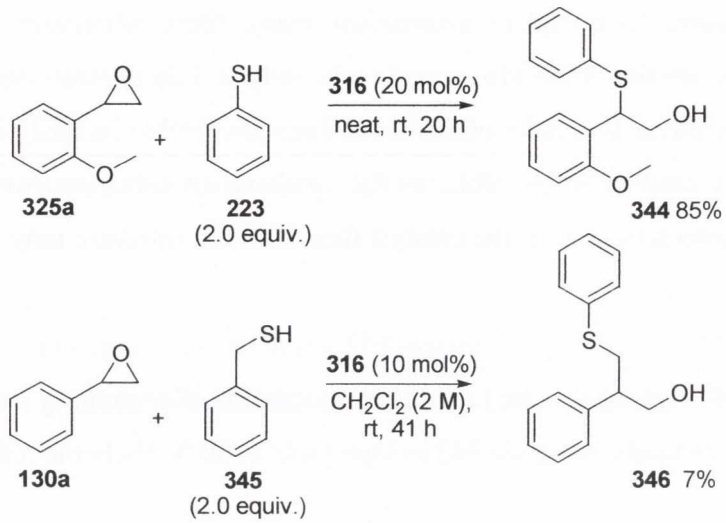
Scheme 3.4 Addition of **209** to (*E*)-Stilbene oxide catalysed by **316**.



3.3.2 The addition of thiols to epoxides catalysed by 316

The scope of these catalysed processes was not restricted to carbon and nitrogen-based nucleophiles. Catalyst **316** was capable of promoting the addition of thiols to **130a** in good yield at room temperature (Scheme 3.5). In the absence of catalyst **316** there was no conversion to product. Benzyl mercaptan proved a poor nucleophile due to a lack of solubility in the concentrated reaction mixtures required, however thiophenol (**223**) afforded high adduct yields under similar conditions aside one days reaction time (Scheme 3.5).

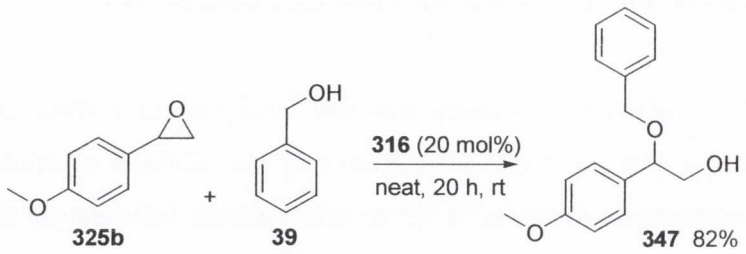
Scheme 3.5 Results of thiol additions to epoxides



3.3.3 The addition of alcohols to epoxides catalysed by 316

The weakly nucleophilic benzyl alcohol (**39**) could also be used in the Friedel-Crafts type addition reaction involving methoxy-substituted styrene oxide **325b** in good yield at room temperature using **316** as the promoter. In the absence of catalyst there was no yield of the products (Scheme 3.6). This reaction is quite significant as alcohols are not ordinarily considered good nucleophiles in epoxide addition reactions.

Scheme 3.6 Alcohol addition to methoxy-substituted styrene oxide catalysed by **316**



3.4 Conclusions for Section 3.1

In summary, we utilised computational DFT methods to evaluate the stabilities of hydrogen-bonded complexes between thio(urea) catalysts and three different electrophiles that incorporate Lewis-basic oxygen-based functionality. These data were then used to select a urea-electrophile pair predicted to be best suited for use in catalytic reactions in conjunction with a generic nucleophile. While this approach ignores the reaction transition state, it is rapidly executed, and the results can potentially be applied to a range of reactions involving a

given electrophile and a diverse array of nucleophiles if discretion is exercised regarding nucleophile compatibility with the catalyst's acidity. The results of these investigations strongly indicated that the previously unknown acidic urea-based catalyst **316** would potentially be able to serve as a more active promoter of addition reactions to epoxide derivatives than benchmark literature catalyst **20**. Synthesis and evaluation of **316** led to the validation of this computational study-guided design strategy: **316** possessed unprecedented activity for a urea catalyst and promoted the addition reactions under conditions that other (thio)urea derivatives (including) **20** could not. The catalyst was robust and of high synthetic utility: various styrene oxides (including non-terminal analogues) and indoles were tolerated, and (demonstrating the general applicability of the methodology) it was found that the catalyst was equally proficient in the promotion of C-N, C-S, and C-O bond formation *via* the addition of weak nucleophiles to epoxides under conditions that do not yield products in the absence of **316**.

4.1 The design of organocatalysts for the Johnson-Corey-Chaykovsky reaction

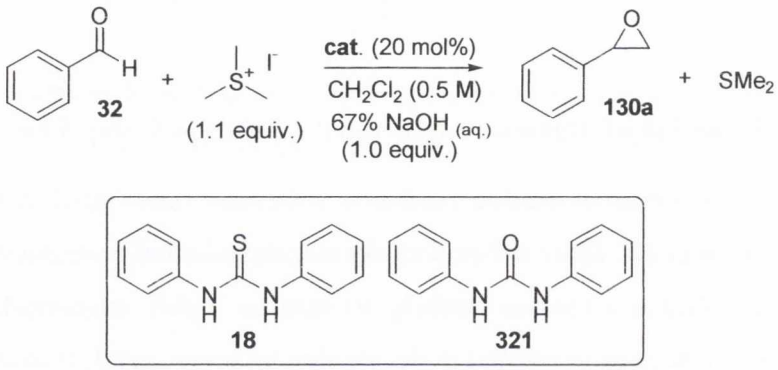
A comprehensive appraisal of sulfide mediated Johnson-Corey-Chaykovsky reactions has been detailed in Section 1.7. Since the previously mentioned most common strategy involving the use of chiral sulfonium ions is unlikely to lead to highly enantioselective methylene transfer reactions, we became interested in developing an organocatalyst strategy based on the use of hydrogen bonding to activate the aldehyde towards nucleophilic attack by the ylide. The overall concept envisaged was one involving the use of an organocatalyst capable of aldehyde activation under conventional JCC reaction conditions. This was prompted by the demonstration in the Connon group that dihydropyridine (thio)urea precatalysts could promote the reduction of diketones under phase transfer conditions similar to those used in JCC processes.[90] It was envisaged that the design of a hydrogen-bond donating catalyst capable of promoting the addition of a sulfonium ylide to an aldehyde in a face-selective manner under these conditions would be possible.

4.1.1 Preliminary catalyst screening in the Johnson-Corey-Chaykovsky reaction

The lack of activity of the commercially available and inexpensive trimethylsulfonium iodide salt at room temperature under liquid-liquid reaction conditions (aq. NaOH-CH_2Cl_2) prompted us to consider the potential of *N,N'*-diaryl(thio)ureas as promoters of the JCC reaction utilising

this salt (Section 1.7). We speculated that the dearth of studies concerning the use of hydrogen-bond donating catalysts in the JCC reaction is due to the alkaline conditions required to form the sulfonium ylide nucleophile, which precludes the use of catalysts of strong-medium acidity. Upon inspection we found that the pK_a (DMSO) of diarylurea **321**, its thiourea analogue **18** and trimethylsulfonium iodide are 19.55, 13.4 and 18.2 respectively.[347] Therefore, we expected urea derivatives to be compatible with the deprotonated sulfonium methylide, to test this hypothesis a group of (thio)urea derivatives were evaluated as promoters in the JCC reaction of benzaldehyde (**32**) under unoptimised reaction conditions (Table 4.1).

Table 4.1 Preliminary (thio)urea catalyst screening in the JCC reaction using unoptimised liquid-liquid reaction conditions



entry	cat.	time (h)	conversion[a] (%)
1	-	24	0
2	-	94	9
3	**18**	24	0
4	**18**	94	0
5	**321**	16	<2
6	**321**	94	12

[a]Determined using ^{1}H NMR spectroscopy.

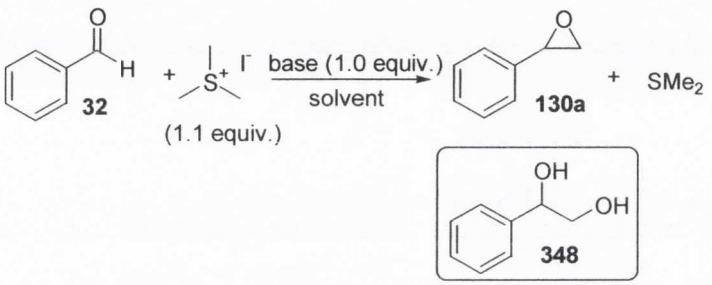
By using only one equivalent of a 67% NaOH aqueous solution and one equivalent of trimethylsulfonium iodide (TMSI) we hoped to establish the determining factors for catalyst turnover under challenging conditions. These experiments clearly established the superiority of the urea catalyst **321** over its thio(urea) analogue **18**, yielding 12% conversion. This superiority of the urea over the thiourea derivatives is unusual,[45,64,348] in this case we would propose that it is related to the high acidity of the thiourea derivatives relative to the sulfonium ion. In order to

optimise the observed catalytic effect of the urea catalyst we set about devising optimum reaction conditions.

4.2 Optimisation of the reaction conditions

We investigated the influence of the solvent, base and the concentration of the electrophile in the organic phase on the efficiency of the process in the absence of catalyst. To determine the effect of the base used to generate the sulfonium ylide, a series of experiments were also carried out to determine whether an organic or inorganic base would be ideal (Table 4.2).

Table 4.2 Determination of the optimal base and solvent components



Entry	base	solvent	Conc. of organic layer (M)	time (h)	conversion[a] (%)
1	K_2CO_3	CH_3CN	1.0	101	0
2	Cs_2CO_3	CH_3CN	1.0	101	8
3	DBU	CH_3CN	1.0	101	0[b]
4	KOH	CH_3CN	0.68	16	62
5	KOH	CH_3CN	0.34	16	52
6	KOH	CH_2Cl_2	0.34	16	37
7	KOH	CH_2Cl_2	0.10	40	0
8	NaOH	CH_2Cl_2	0.34	16	0

[a]Determined using ^{1}H NMR spectroscopy.[b]Epoxide hydrolysis products **348** present in the ^{1}H NMR spectrum.

As can be seen from an examination of the results outlined in Table 4.2 a selection of bases were evaluated under liquid-solid reaction conditions. The inorganic bases K_2CO_3 and Cs_2CO_3 were used to evaluate what strength of base was necessary to deprotonate the sulfonium salt to initiate the JCC reaction. Unfortunately, these reactions were heterogeneous and did not afford any significant epoxide product (Table 4.2, entries 1-2). The organic base, DBU afforded trace amounts of both the epoxide and its hydrolysis product **348** (Table 4.2, entry 3). The stronger bases NaOH and KOH afforded greater quantities of product, this we propose is due to the

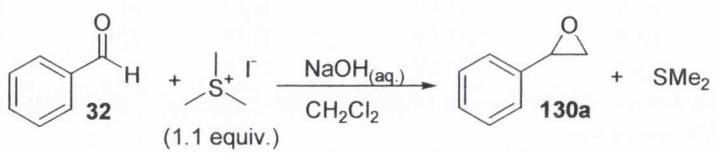
more basic nature of NaOH and KOH which can readily deprotonate the sulfonium salt to the corresponding ylide. Significant quantities of epoxide **130a** were produced using these bases, *e.g* entry 4, after 16 hours there was a 62% conversion of the benzaldehyde **32** to the corresponding epoxide **130a**.

We were pleased to find that the background reaction (*i.e* in the absence of catalyst) could be controlled by dilution of the reaction from 0.68 M to 0.34 M (entry 5) and by changing the solvent to CH_2Cl_2-which warranted liquid-liquid reaction conditions (entries 6 and 7). We were further able to modify the level of background reaction in the NaOH case whilst increasing the concentration of the reaction from 0.1 M to 0.34 M (Table 4.2, entries 7 and 8). We concluded that optimal reaction conditions under which sulfonium-ion deprotonation occurs but no JCC reaction is observed in the absence of catalyst involves the use of NaOH as base, CH_2Cl_2 as solvent in a 0.34 molar reaction.

4.2.1 Base-loading and Base-concentration

In order to fully quantify the efficiency of NaOH in these reactions we facilitated the solubility of the base (and trimethylsulfonium iodide) by the addition of the minimum amount of deionised water.

Table 4.3 Determination of the optimal base loading and reaction concentration.



entry	equiv. base	Stock NaOH soln. (w/v)	conc. of organic layer (M)	time (h)	conversion[a] (%)
1	1	67%	0.1	94	0
2	4	67%	0.1	94	0
3	4	67%	0.5	94	5
4	40	50%	0.1	20	13
5	93	50%	0.34	16	0

[a]Determined using ^{1}H NMR spectroscopy.

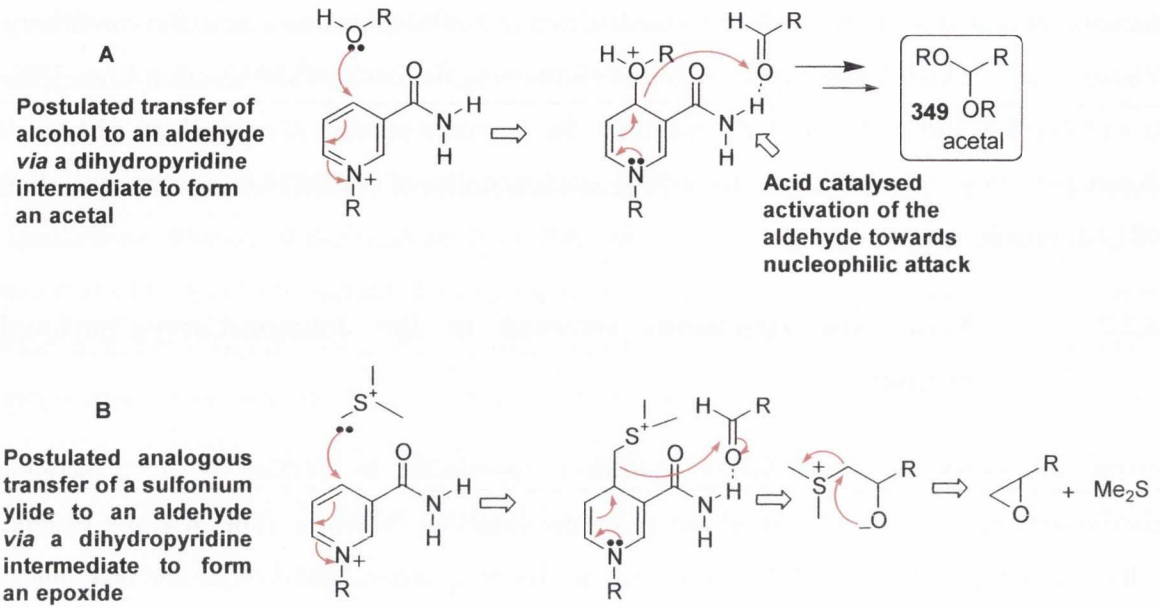
Initial experiments quickly identified the optimum base loadings (Table 4.3, entries 3 and 4) and reaction concentrations (Table 4.3, entries 2 and 3) to conversion. Interestingly, the increase in base loading from 40 to 93 equivalents of NaOH (akin to the reaction conditions of Zhang *et al.*[310]) had the beneficial effect of eliminating the background reaction from 13% to 0% (Table 4.3, entries 4 and 5). At this point, the optimum number of equivalents of base was determined to be 93 equivalents (of a 50% stock solution of $NaOH/H_2O$) under liquid-liquid CH_2Cl_2 conditions.

4.2.2 Ureas and (thio)ureas screened in the Johnson-Corey-Chaykovsky reaction

Using the optimised liquid-liquid conditions mentioned in Section 4.2.1, a series of preliminary reactions were carried out using the catalysts shown in Table 4.4, the results of which also appear in Table 4.4. The known ability of synthetic dihydropyridine analogues of NADH to mediate direct hydrogen transfer reactions[349,350] and previous findings in the Connon group[90] for the reduction of diketones prompted us to evaluate aminopyridine derivatives **350**, **351** and **352** as possible sulfonium ylide transfer reagents (Scheme 4.1, **B**). At the time these studies were carried out it was thought that the pyridine derivative both activated the aldehyde by hydrogen-bonding and facilitated the alcohol transfer reaction to successfully catalyse the acetilisation of aldehydes (Scheme 4.1, **A**).

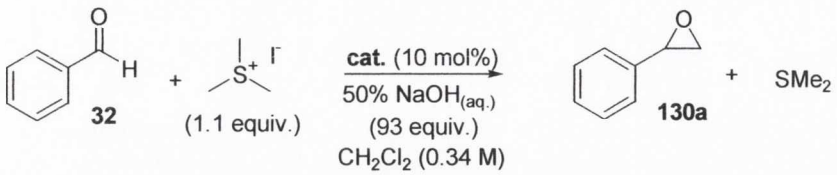
Since this work, it has been found that the α-carbonyl substituent significantly activates the electrophile towards nucleophilic attack hence catalysis is not purely the result of pyridine catalysis (Scheme 4.1, **A**). Therefore, the aminopyridine derivatives in Table 4.4 were evaluated (at the time) as possible sulfonium ylide transfer reagents (Scheme 4.1, **B**). The pyridine derivatives were synthesised by Ms. Barbara Procuranti.

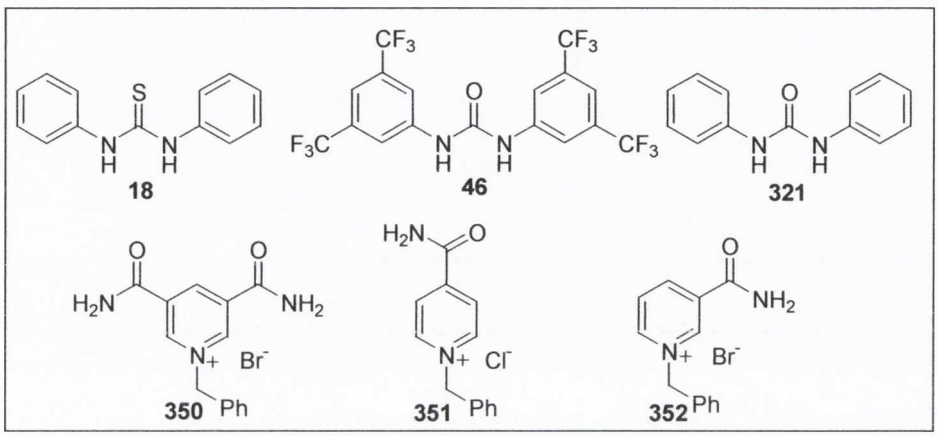
Scheme 4.1 Preliminary evaluation of pyridine derivatives for the JCC reaction



In the absence of catalyst the background reaction exhibits no conversion after 16 h (Table 4.4, entry 1). Gratifyingly, the 3,5-*bis*-trifluoromethyl-urea catalyst **46** and the less acidic phenylurea catalyst **321** were superior promoters of the reaction in comparison to the aminopyridine derivatives (entries 3 and 4). The presence of the pyridine with catalyst **46** appeared to hamper conversion of the aldehyde (compare entries 2 and 6). Considering the low levels of catalysis observed in the pyridine reactions (Table 4.4, entries 5-8) we were satisfied that sulfonium ylide transfer was not a significant process occurring in these reactions. The observed level of catalysis by the pyridines **350**, **351** and **352** we suggest may be due to the primary amide moiety which could activate the aldehyde towards nucleophilic attack in solution (Scheme 4.1).

Table 4.4 Catalysts and additives evaluated for the promotion of the JCC reaction





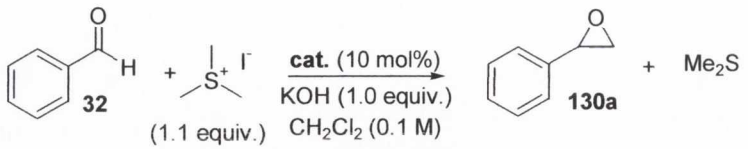
entry[a]	cat.	cat. loading (mol%)	time (h)	conversion (%)[a]
1	-	0	16	0
2	**46**	10	16	43
3	**46**[b]	5	24	97
4	**321**	10	16	23
5	**350**	10	16	8
6	**350 + 46**	10 + 10	16	12
7	**351**	10	16	13
8	**352**	10	16	17

[a] Determined using ^{1}H NMR spectroscopy.[b] Reaction carried out using 60 equivalents of $NaOH_{(aq)}$ 50% solution

Subsequent to these results Ms. Sarah Kavanagh determined that 60 equivalents of NaOH was the most favourable quantity of base to be used under liquid-liquid reaction conditions. Therefore, the 3,5 *bis* trifluoromethyl-urea catalyst **46** was re-evaluated under these reaction conditions. We found that 97% conversion of the benzaldehyde (**32**) was attainable using just 5 mol% of the catalyst (Table 4.4, entry 3).

Use was also made of the liquid-solid reaction conditions mentioned previously (Table 4.2, entry 7) using 1.0 equivalent of KOH in CH_2Cl_2, catalysts **46** and **321** was re-evaluated using these conditions (Table 4.5).

Table 4.5 Liquid-solid reaction conditions using KOH and CH_2Cl_2



entry	cat.	cat. loading (mol %)	time (h)	Conversion (%)[a]
1	-	0	40	0
2	**46**	10	42	50
3	**321**	10	42	54

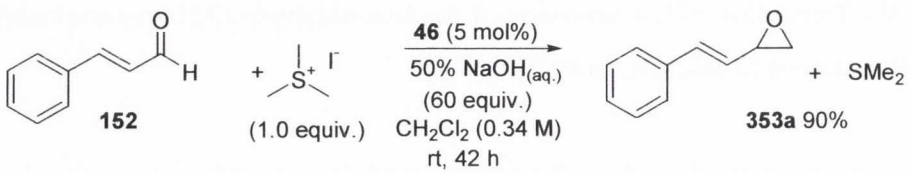
[a]Determined using ^{1}H NMR spectroscopy.

As Table 4.5 demonstrates no product was formed in the absence of catalyst (entry 1). Both catalysts were active but less efficient under these reaction conditions, however the option of performing these epoxidation reactions under an alternative set of reaction conditions demonstrates the versatility of these catalysts and epoxidation reactions.

4.2.3 Evaluation of substrate scope of the urea catalysed Johnson-Corey-Chaykovsky reaction

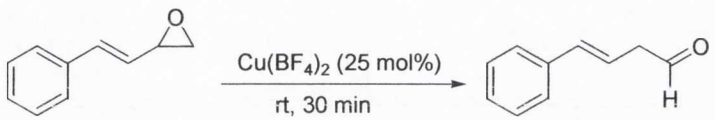
These preliminary findings were the basis upon which epoxides derived from activated, hindered, and electron-rich aromatic aldehydes could be prepared in excellent yield. α,β-Unsaturated and α-substituted aliphatic aldehydes (but not unbranched analogues which underwent competitive aldol reactions) were also amenable to epoxidation under the optimised liquid-liquid conditions using 5 mol% of catalyst **46**.[351] An example of which is shown in Scheme 4.2: *(E)*-Cinnamaldehyde **152** was converted to the corresponding epoxide **353a** in 42 hours.

Scheme 4.2 *(E)*-Cinnamaldehyde epoxidation using 5 mol% of catalyst **46**



The clean catalysis observed in these reactions prompted us to exploit the electrophilicity of the epoxide products through the development of a tandem organocatalytic epoxidation-transition metal catalysed ring opening process. The epoxidation could be combined with a Cu(II) ion-catalysed Meinwald rearrangement[352,353] to give a convenient and potentially useful protocol for the homologation of aldehydes. Organocatalysed epoxidation followed by seperation of the phases and addition of $Cu(BF_4)_2$ (25 mol%, hydrate) to the organic portion resulted in the isolation of the chain-extended aldehydes in good yield (Scheme 4.3).[351]

Scheme 4.3 Epoxidation and Meinwald rearrangement sequence



353a **353b** 60%

4.3 Conclusions for Section 4.1

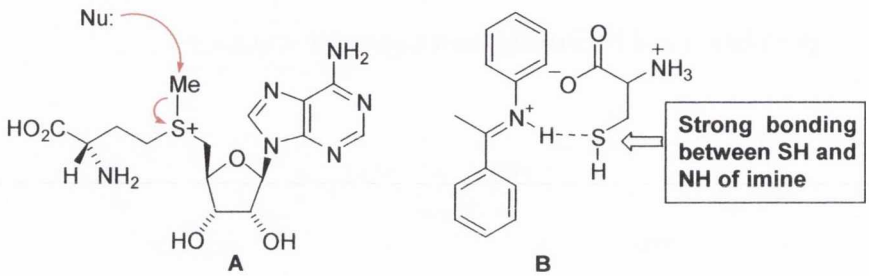
In summary, *N,N'*-Diarylureas were shown to efficiently catalyse the sulfonium ylide-mediated aldehyde epoxidation reaction involving the inexpensive trimethylsulfonium iodide at ambient temperature for the first time. The superiority of the urea catalysts over the thiourea analogues was unusual in this study a fact we propose attributable to the more acidic nature of the thiourea derivatives relative to the sulfonium ion. The catalysed reactions were of wide scope with respect to the aldehyde component and subsequent coupling of the epoxidation to a Meinwald-rearrangement process proves this. The efficient catalysis observed in this study encouraged us to develop an enantioselective variant of this process, which is the subject of the succeeding Section.

4.4 The asymmetric Johnson-Corey-Chaykovsky reaction

Naturally, the remarkable success of the urea derivative promoted JCC reaction prompted us to investigate the possibility of extending this methodology to the synthesis of optically active epoxide products. To address the shortcomings of methylene transfer catalysis detailed in Section 1.7 we attempted to assess the potential of modified amino acids as catalysts in this capacity. The activity and specificity of nature's alkylating agent *S*-adenosyl methionine (formed by the reaction of methionine with Adenosine TriPhosphate (ATP)) provided us with

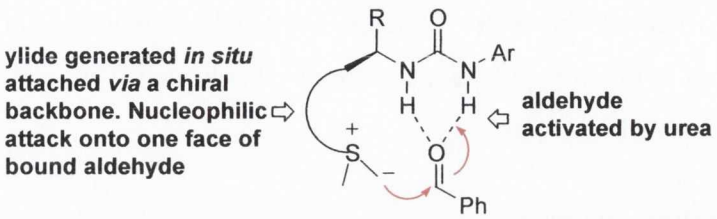
the inspirational thrust for the development of methionine-derived catalysts for the JCC reaction. Figure 4.1, shown depicts the sulfonium salt SAM undergoing nucleophilic attack at the methyl group **A**, there is complete preference for nucleophiles to attack the methyl group rather than the two primary centres of the molecule.

Figure 4.1 Nucleophilic attack on SAM, nature's methylating agent and the asymmetric reduction of imines using α-amino acid salts



Given the success of the achiral JCC studies utilising ureas to activate aldehydes towards sulfonium ylide nucleophilic attack, the design of a urea-based catalyst to activate an aldehyde component whilst delivering the ylide nucleophile in a face selective manner appeared a realistic challenge. It was predicted that the incorporation of a urea motif into a long chain α-amino acid incorporating a sulfur atom could facilitate realisation of this goal. As the sulfide alkylation step would be the rate-determining step of such a process a relatively unhindered sulfide was deemed necessary. As the amino acid methionine in nature readily takes part in alkylation reactions and is also a long-chain amino acid it was chosen as the chiral component around which to develop an organocatalyst for the JCC epoxidation reaction. Figure 4.2 outlines the predicted mode of activation of the aldehyde by the urea and delivery of the methylene source by the long chain amino acid component in a face-selective fashion.

Figure 4.2 Predicted binding-mode of the bifunctional amino acid-derived urea catalyst

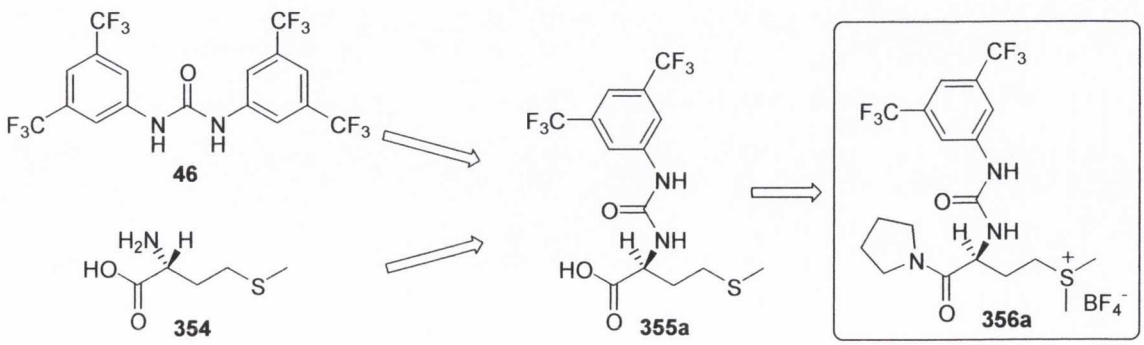


The incorporation of the urea unit into the reaction transition state and the stereoelectronic requirement for the ylide to attack the bound aldehyde at the Bürgi-Dunitz angle necessitates a reasonable long-chain linker connecting the ylide and hydrogen bond donating components. An analysis of models indicated that this requirement could be met by a methionine-derived catalyst system. Enantioselectivity in this reaction was predicted to arise due to the integration of a sterically hindered chiral component and preferential binding of the urea component for one face of the aldehyde which was hoped to occupy the less hindered catalyst hemisphere in the transition state.

4.4.1 Catalyst design rationale

Given the results of the extensive optimisation studies performed on the urea catalysed JCC reactions and encouraged by the potential of the methionine template to act as an efficient template for alkylation, we set about merging the best features of both systems to create a new bifunctional catalyst for appraisal in the asymmetric JCC reaction (Figure 4.3).

Figure 4.3 Amalgamation of design principles for bifunctional catalyst design

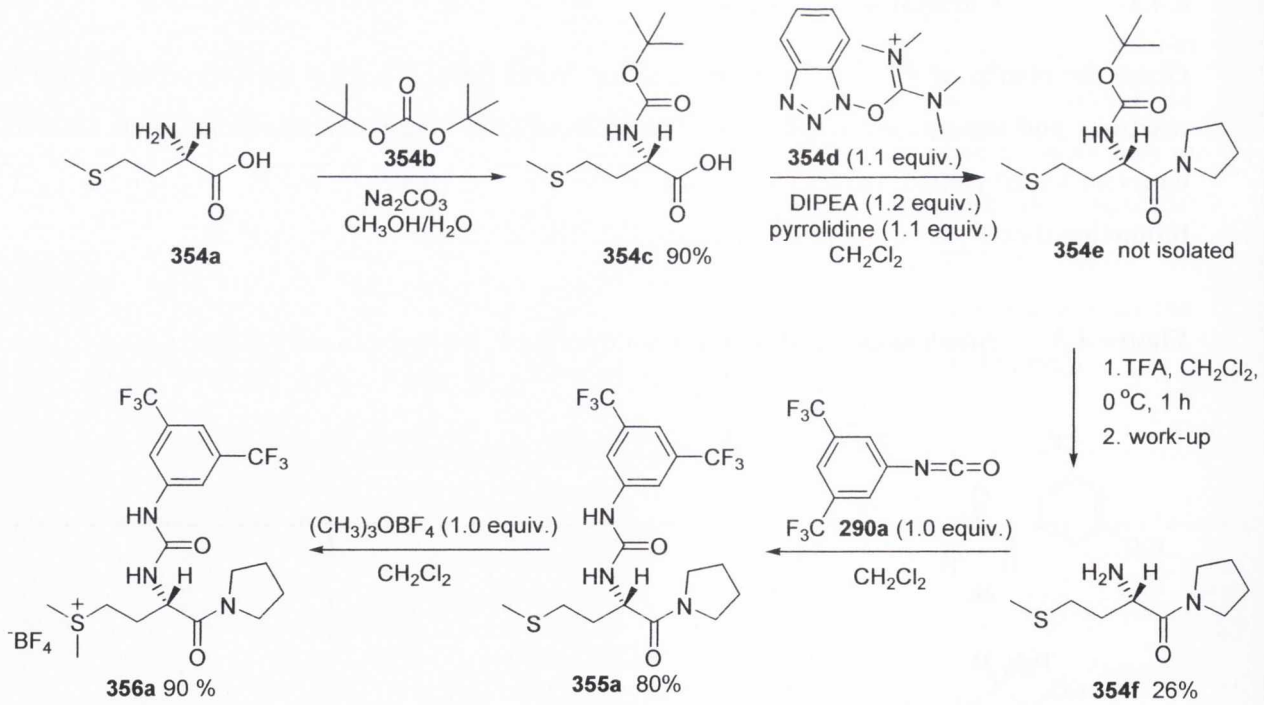


The amino acid carboxylic acid group could be protected as an amide and the methionine sulfur could be transformed to its corresponding alkylated derivative by the use of two possible methods which will be dealt with later. The amino acid amine portion could be easily derivatised as a urea to bind the aldehyde substrate. These modifications led to the design of a methionine derived urea-based catalyst.

4.4.2 Catalyst syntheses

The synthesis of **356a** is given in Scheme 4.4. *N*-Protection of the amine group of the *L*-methionine is achieved using the *t*-butyloxycarbonyl group in the first step, followed by coupling of pyrrolidine to the carboxylic acid group of the amino acid. Subsequent acid-mediated removal of the *t*-butyloxycarbonyl (Boc) group was followed by insertion of the urea functionality *via* an isocyanate coupling reaction. Alkylation of the urea-based catalyst **355a** is easily achieved using Meerwein's salt ($Me_3O^+BF_4^-$) to afford **356a** in excellent yields as a pale-yellow solid (MeI was also used as an alkylating agent however the yields were inferior).

Scheme 4.4 Synthesis of the bifunctional *L*-methionine-derived urea catalysts



The yield of **356a** is moderate, yet the materials are cheap and commercially available. The route outlined in Scheme 4.4 is adjustable allowing for straightforward alteration of both the amide and urea components.

4.4.3 Catalysts employed in the asymmetric Johnson-Corey-Chaykovsky reaction

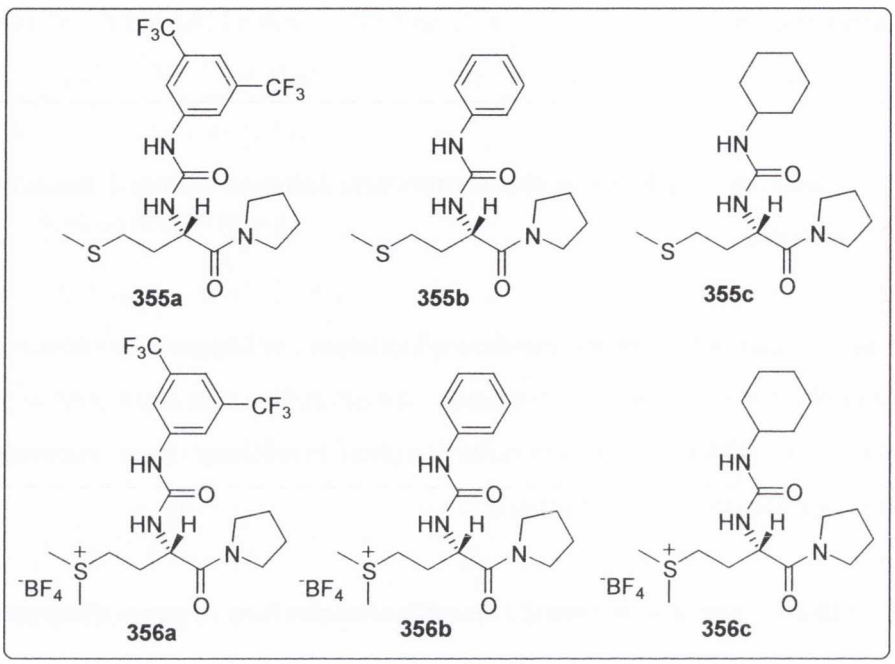
Along with the bifunctional methionine-derived catalysts, a library of monofunctional urea-based catalysts of varying steric and electronic characteristics was evaluated as promoters of the JCC reaction of aldehydes. Alternative reaction conditions were necessary for these catalysts, these will be shown in due course.

4.4.3.1 Mono-, and bifunctional *L*-methionine-derived organocatalysts

We employed both mono- and bifunctional catalysts due to the previous investigation of the use of the ylide component in conjunction with urea-based catalysts in a binary system (Table 4.4). We now wished to evaluate the use of urea derivatives with an adjacent chiral centre and the potential benefits (if any) of locating the ylide-precursor and the aldehyde-activating urea functionality in close proximity with regard to both rate and selectivity. Two sets of reaction conditions were necessary to accommodate these different classes of catalyst (liquid/liquid and liquid/solid).

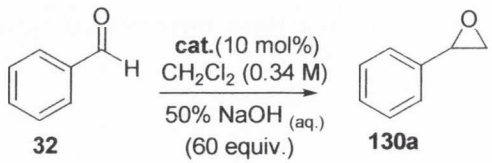
Bifunctional catalysts **356a**, **356b** and **356c** were used as reagents (i.e methylene source) in these reactions where sufficient loading of base maintained the supply of the sulfonium ylide. On the other hand, the monofunctional catalysts **355a**, **355b** and **355c** were used as hydrogen-bond activating catalysts using trimethylsulfonium iodide as the methylene source. The evaluation of monofunctional catalysts in these reactions was to determine the role played by the single aldehyde-binding urea component and the effect this may play (if any) on enantiodiscrimination in the reaction.

Figure 4.4 *L*-Methionine-derived mono-, and bi-functional catalysts



The optimised liquid/solid reaction conditions of the achiral work (Section 4.1) were used in evaluating the catalytic efficiency of these catalysts. The results of which appear in Table 4.6.

Table 4.6 Evaluation of the bifunctional catalysts/reagents **356a** –**356c** in the JCC reaction under liquid-liquid reaction conditions using 60 equivalents of base



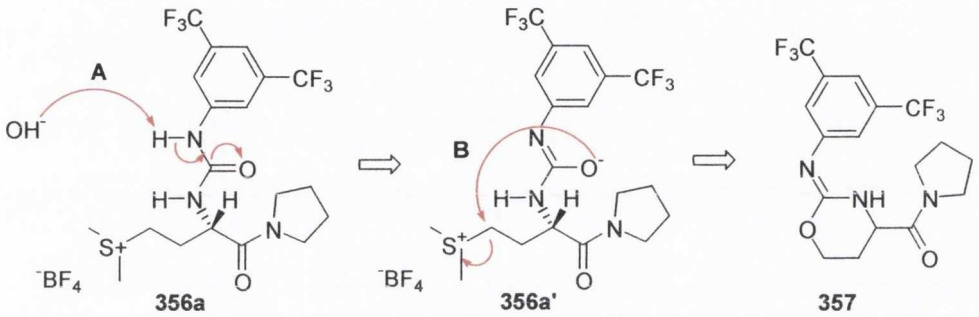
entry[a]	cat.	time (h)	conv. (%)[b]	*ee* (%)[c]
1	**356a**	1	0	-
2	**356b**	1	51	0
3	**356c**	1	39	0

[a]Reaction conditions: methionine-derived salt (1.0 equiv.), NaOH (50 % aq., 60.0 equiv.), CH_2Cl_2 (0.34 M) and (*E*)-stilbene as internal standard (0.5 equiv.), at rt, under Ar. [b]Determined using ^{1}H NMR spectroscopy [c]Determined using chiralcel (OD-H Column).

As Table 4.6 illustrates, catalysis by the least acidic urea catalysts **356b** and **356c** (entries 2 and 3), was the most efficient under these reaction conditions while the most acidic 3,5-*bis*-

trifluoromethyl catalyst **356a** was susceptible to hydroxide deprotonation (Scheme 4.5, **A**). Subsequent ring-closure (Scheme 4.5, **B**) to form compound **357** (confirmed using ^{1}H NMR spectroscopy and mass spectrometry) occurred before any catalysis could commence. The proposed mechanism of which is shown in Scheme 4.4. Unfortunately the epoxide products were formed in a racemic fashion (Table 4.6).

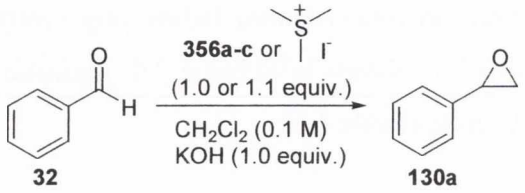
Scheme 4.5 Proposed base-mediated catalyst ring-closure reaction of catalyst **356a**



The liquid/liquid (anhydrous) reaction conditions evaluated in the achiral work were also used to evaluate the catalytic efficiency of these catalysts. The results of which appear in Table 4.7.

As Table 4.7 represents the methionine-derived monofunctional catalysts **355a**, **355b** and **355c** were efficient promoters of the epoxidation reaction with up to 34% conversion after just 16 h (Table 4.7, entries 2-4). Unfortunately, under these conditions the epoxides were formed as racemic mixtures. The use of these conditions for the bifunctional catalysts **356a**, **356b** and **356c** yielded slower reaction rates and a tendency for the more acidic urea catalysts *i.e* the 3, 5-*bis*-trifluoromethyl, and phenyl-urea catalysts (**356a** and **356b** respectively) to be de-alkylated under the basic conditions. Therefore, the cyclohexylurea derivative **356c** was the only bifunctional catalyst to promote sustainable epoxidations to obtain sufficient epoxide for HPLC analysis. The catalysis observed in the bifunctional cyclohexylurea catalyst case demonstrates the bifunctional mode of catalysis we set out to develop albeit without the enantioselectivity we had hoped for (Table 4.7, entry 7). The reaction conditions were postulated to play a role in this. Therefore, modifications to the reaction conditions ensued: using CH_3CN instead of CH_2Cl_2 and varying both the nature, and loading of base unfortunately resulted in the formation of cinnamonitrile **359**.

Table 4.7 Evaluation of the methionine-derived promoters of the JCC reaction under liquid-solid reaction conditions



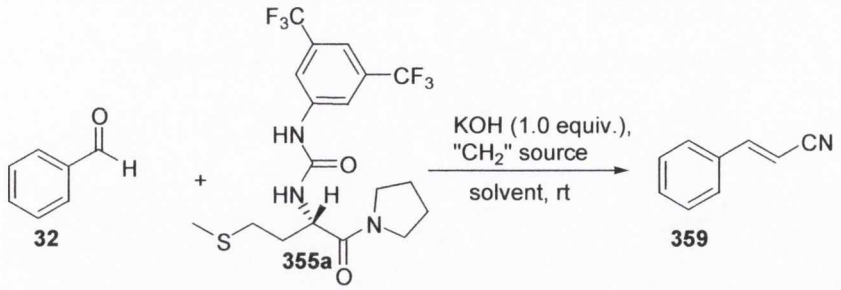
Entry	cat.	Cat loading (mol%)	conditions A or B	time (h)	conv. (%)[b]	*ee* (%)[c]
1	-	0	**A**	16	0	0
2	**355a**	10	**A**	16	30	0
3	**355b**	10	**A**	16	34	1
4	**355c**	10	**A**	16	33	3
5	**356a**	100	**B**	30	0[d]	-
6	**356b**	100	**B**	30	26	n.d[d]
7	**356c**	100	**B**	30	30	6

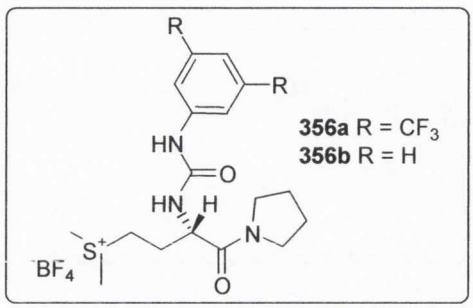
[a]Reaction conditions: **A**-include methionine-derived catalyst (0.1 equiv.), trimethylsulfonium iodide (1.1 equiv.), KOH (1.0 equiv.), CH_2Cl_2 (0.1 M) at rt under Ar. **B**-methionine-derived salt (1.0 equiv.), KOH (1.0 equiv.), CH_2Cl_2 (0.1 M) and *(E)*-stilbene as internal standard (0.5 equiv.), at rt and under Ar. [b]Determined using ^1H NMR spectroscopy. [c]Determined using chiralcel (OD-H Column).[d]Cyclisation of the catalysts occurred before epoxidation began, preventing conversion. n.d. = not determined

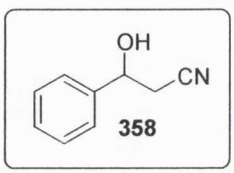
Preferential deprotonation of acetonitrile (rather than the sulfonium ion) by hydroxide in solution and nucleophilic addition of $CNCH_2^-$ to the aldehyde, followed by dehydration afforded cinnamonitrile **359** in all reactions (Table 4.8). Alteration of the "methylene" source did not prevent deprotonation of the solvent (Table 4.8, entries 1, 4 and 7).

Performing the reaction in CH_2Cl_2 proved unsuccessful due to the insolubility of the reagents in CH_2Cl_2 (entry 3). The use of Metzner's conditions[291] *i.e* a solvent mixture of CH_3CN:H_2O (9:1) prevented cinnamonitrile production (entry 8), but was incompatible with catalyst **356b** (entry 9).

Table 4.8 Attempts to modify the reaction conditions to improve activity







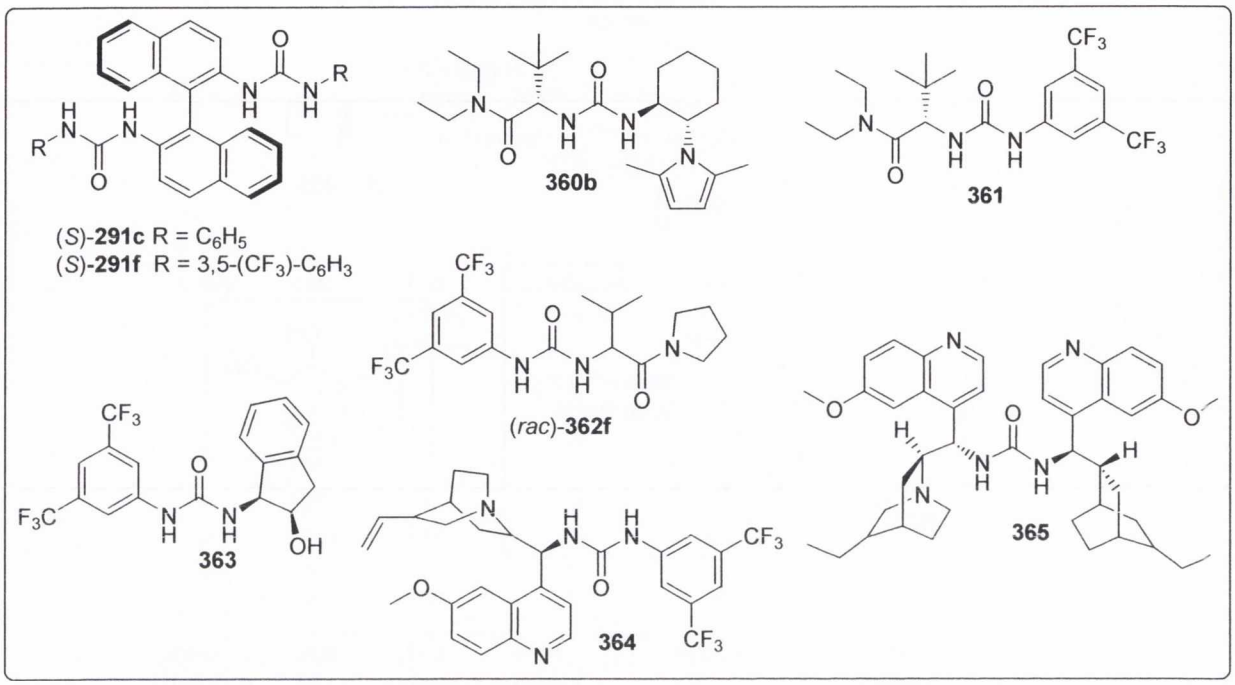
entry	cat. loading	solvent	base (equiv.)	CH_2 source	time (h)	conv. (%)[a]
1	1.0	CH_3CN	2.0	MeI	45	18
2	0.2	CH_3CN	2.0	MeI	45	9
3	0.2	CH_2Cl_2	2.0	MeI	16	0[b]
4	0.2	CH_3CN	2.0	**356a**[c]	70	100
5	0	CH_3CN	2.0	MeI	16	45
6	0.2	CH_3CN	2.0[d]	MeI	112	42[e]
7	0.2	CH_3CN	2.0	TMSI	112	12.5[f]
8	0	$CH_3CN:H_2O$ (9:1)	1.0	TMSI	47	0
9	1.0	$CH_3CN:H_2O$ (9:1)	1.0	**356b**[c]	47	0

[a]Determined by ^1H NMR spectroscopy. [b]Reagents were insoluble.[c]Bifunctional catalyst used as the methylene source. [d]NaOH used intead of KOH. [e]Presence of the cinnamonitrile β-hydroxy intermediate **358** at 16 h. [f]Cinnamonitrile:epoxide ratio of 1:7 at 112 h.

4.4.3.2 Monofunctional catalyst evaluation requiring a 'methylene' source

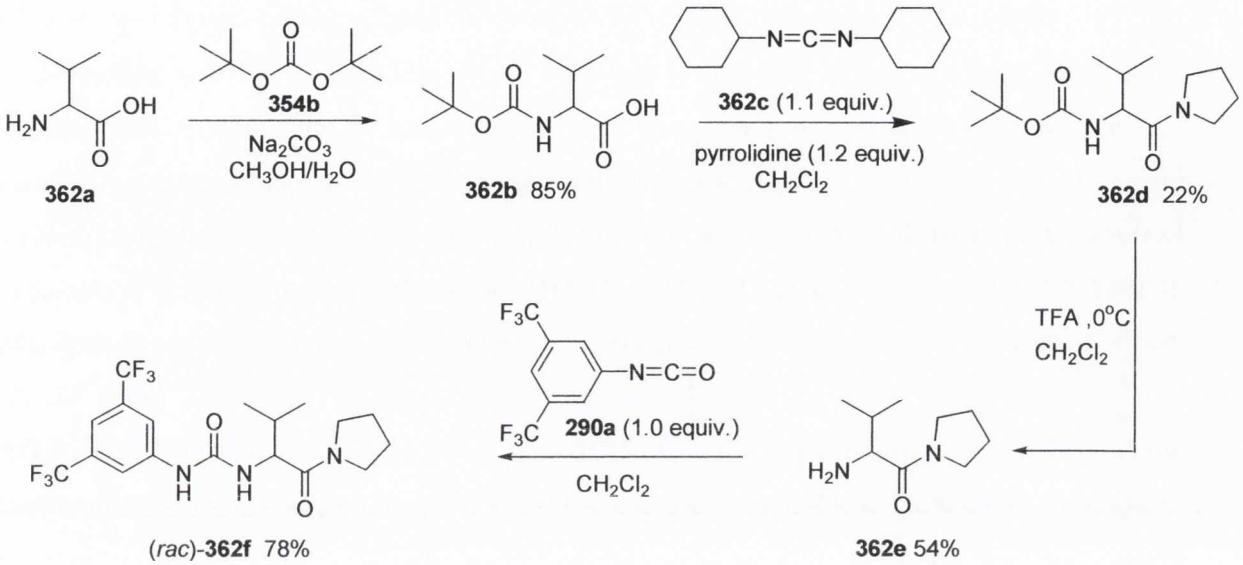
An evaluation of a variety of monofunctional catalysts (Figure 4.5) capable of hydrogen bond activation of the aldehyde was carried out using both the liquid-liquid and liquid-solid reaction conditions mentioned previously. The results of the evaluation of these catalysts in the optimised liquid-liquid reaction conditions are tabulated in Table 4.9. Jacobsen's *tert*-leucine derived catalysts **360** and **361** were evaluated as alternative monofunctional amino acid derived catalysts which are proven enantioselective catalysts for many reactions including the Strecker reaction[73] and the transfer hydrogenation of nitroolefins.[354]

Figure 4.5 Monofunctional urea-based catalysts screened in the JCC reaction



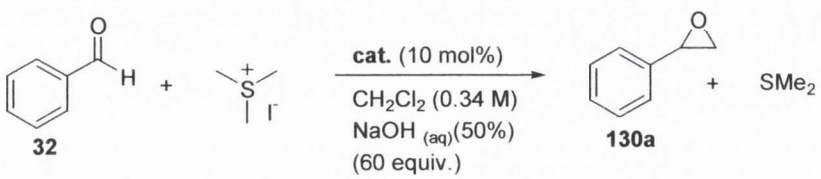
To decipher the relevance of the amino acid component of these catalysts we also synthesised a less-sterically hindered valine-derived urea catalyst **362f**, the synthesis of which is outlined in Scheme 4.6. *N*-Protection of the amine group of *L*-valine is achieved using the *t*-butyloxycarbonyl group as the first step, followed by DCC-mediated (**362c**) coupling of pyrrolidine to the amino acid carboxylic acid group to afford **362d**. Subsequent deporotection of the amino group followed by reaction with isocyanate **290a** afforded catalyst **362f** as a racemate in 78% yield.

Scheme 4.6 Synthesis of valine-derived urea catalyst **362f**



Jacobsen's catalyst **360** was synthesised using the literature procedure of Jacobsen[78] and List,[354]while catalyst **361** was prepared in analogy to the reported synthesis by List,[354] while catalysts **9-*epi* DHQU (364)** and catalyst **C_2-*epi* QU (365)** were readily available in the laboratory.

Table 4.9 Evaluation of the monofunctional urea-based catalysts for the JCC reaction under the optimised liquid-liquid reaction conditions

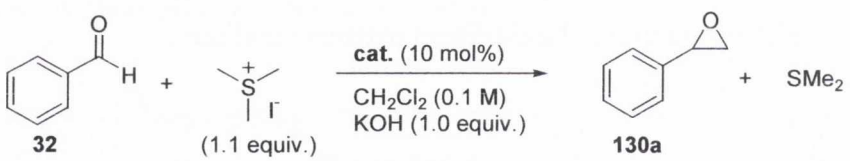


entry	cat.	time (h)	conv. (%)[a]	*ee* (%)[b]
1	-	24	0	-
2	(*S*)-**291c**	24	74	0
3	**360**	24	36	0
4	**362f**	24	65	0
5	**361**	24	100	0
6	**365**	24	45	0
7	**364**	24	85	0

[a]Determined using ^{1}H NMR spectroscopy [b]Determined using chiralcel (OD-H Column).

In the absence of catalyst the control reaction exhibits no conversion (entry 1, Table 4.9). Gratifyingly, all of the urea-based catalysts were efficient promoters of the JCC epoxidation reaction. Jacobsen's catalyst **361** (entry 5) showed distinct catalytic superiority over its structurally similar catalyst **360** (entry 3) which was much less active. The difference in activity we propose is due to the more Lewis-acidic nature of the 3,5-*bis*-trifluoromethyl phenylurea substituents of catalyst **361**. The importance of the amino acid derivative is shown in the superiority of the *L-tert* leucine derived catalyst **361** over the *L*-valine-derived catalyst **362f** (Table 4.9, entries 4 and 5). The **9-*epi*-DHQU** catalyst **364** was an excellent promoter of the reaction (entry 5, Table 4.9) as expected its structurally related, much more sterically hindered C_2-symmetrical version **365** was an inferior catalyst (Table 4.9, entry 6). As anticipated the binaphthylurea catalyst (*S*)-**291c** was also a highly efficient promoter of this reaction, its high catalytic activity most likely being due to the presence of two urea functional groups. Disappointingly, none of the organocatalysts evaluated under these conditions induced significant enantioselectivity in the epoxide products. To determine the effect of reaction conditions on this process, the liquid-solid reaction conditions were used to evaluate catalyst efficiency also, the results of which appear in Table 4.10.

Table 4.10 Evaluation of the monofunctional urea-based catalysts for the JCC reaction under the liquid-solid KOH reaction conditions



32 (1.1 equiv.) **130a**

entry	cat.	time (h)	conv. (%)[a]	*ee* (%)[b]
1	-	40	0	-
2	(*S*)-**291c**	40	51	0
3	(*S*)-**291f**	30	36	1
4	**361**	30	52	5
5	**360**	30	29	2
6	**363**	30	45	1

[a]Determined using ^{1}H NMR spectroscopy [b]Determined using chiralcel (OD-H Column).

As Table 4.10 represents the liquid-solid reaction conditions are less compatible with these catalysts than the liquid-liquid conditions necessitating extended reaction times. However, under these conditions the binaphthylphenyl urea catalyst (*S*)-**291c** exhibits activity equal to

that of the Jacobsen catalyst **361** (Table 4.10, entry 4) which demonstrated far superior catalysis under the liquid/liquid reaction conditions. The binaphthylurea catalysts (*S*)-**291c** and (*S*)-**291f** demonstrated comparable rates of catalysis under these conditions (Table 4.10, entries 2 and 3). The bifunctional catalyst **363** was as expected to be more active than the aliphatic catalyst **360** due to its increased acidity but also due to the presence of an additional hydroxy functionality capable of hydrogen-bond activating ability (Table 4.10, entries 5 and 6). To our disappointment, the epoxide products were isolated as racemic mixtures in all these examples.

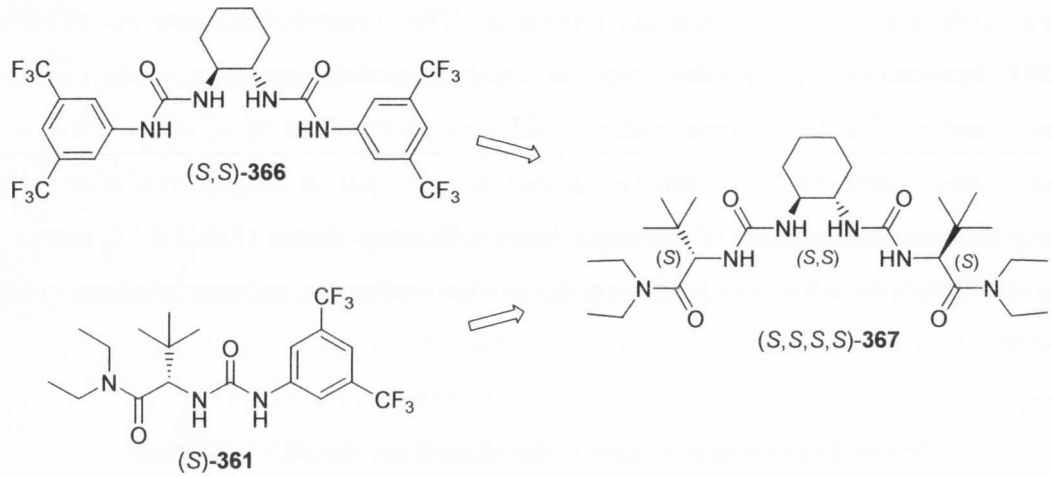
4.4.4 Second generation catalysts developed for the JCC reaction

Encouraged by the excellent activity of the chiral *bis*-urea catalysts screened in the JCC reaction, we postulated that a more sterically hindered *bis*-urea catalyst could be a more efficient catalyst for enantioselective JCC reactions. Nagasawa's catalyst **366** (Scheme 4.7)[86] was found to be an extremely insoluble material under our reaction conditions (both liquid-liquid and liquid-solid). Therefore, we took on the challenge of designing a more soluble new *bis*-urea catalyst for the enantioselective JCC reaction.

4.4.4.1 Catalyst 367: design rationale and synthesis

To improve the solubility of the Nagasawa catalyst **366** and to further increase the steric demands of the catalyst (with a view to improving enantioselectivity) we chose to incorporate an amino acid backbone into the catalyst. Previous catalyst evaluation of amino acid derived catalysts (*vide supra*) in the JCC reaction (*e.g.* **360** and **361**) identified the *tert*-leucine moiety of the Jacobsen catalyst **361** as a good motif to incorporate greater solubility into the design of a new *bis*urea organocatalyst (Scheme 4.7). The *tert*-leucine group was chosen because its hydrophobic nature was envisaged to maximise solubility and with its steric bulk at the stereocentre it was hoped could improve our chances of achieving face-selective addition to a bound aldehyde in a selective manner.

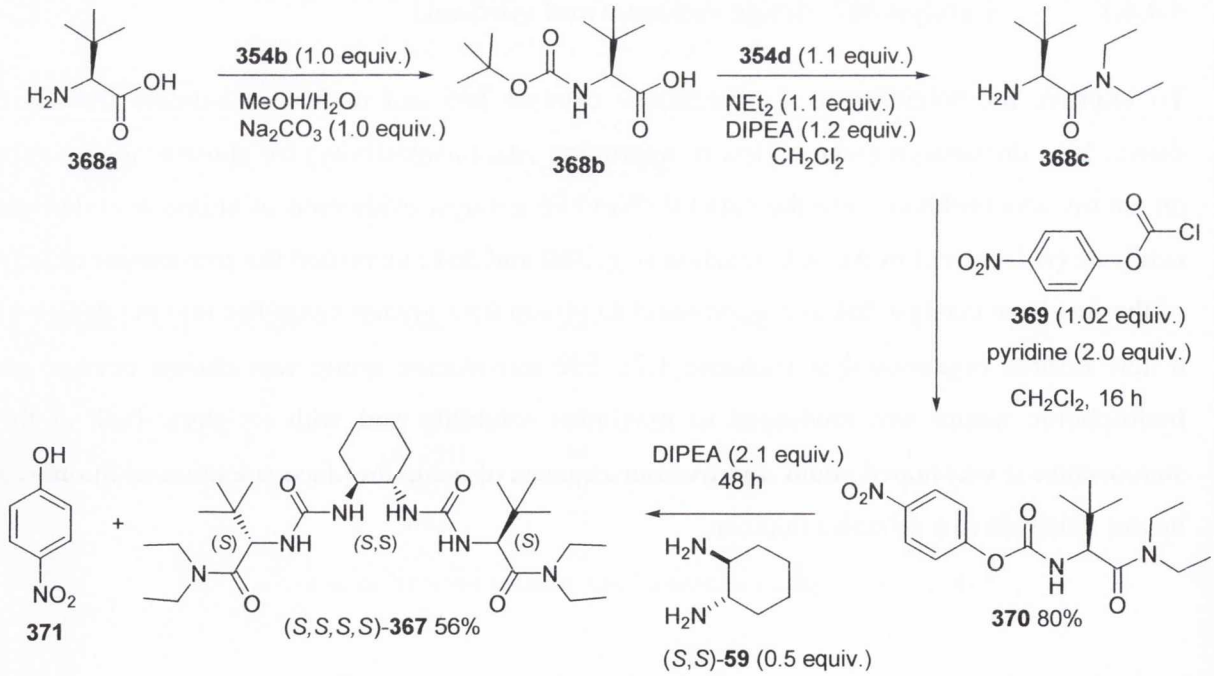
Scheme 4.7 Catalyst (*S,S,S,S*)-**367** design rationale



4.4.4.2 Synthesis of catalyst (*S,S,S,S*)-367

The synthesis of catalyst **367** is shown in Scheme 4.8. The reaction of **368c** and *p*-nitrophenyl chloroformate **369** was performed in the presence of pyridine to generate the carbamate **370** which was isolated and purified *via* flash chromatography (95:5 CH_2Cl_2:EtOAc) in an overall yield of 80%.

Scheme 4.8 Synthesis of catalyst (*S,S,S,S*)-**367**

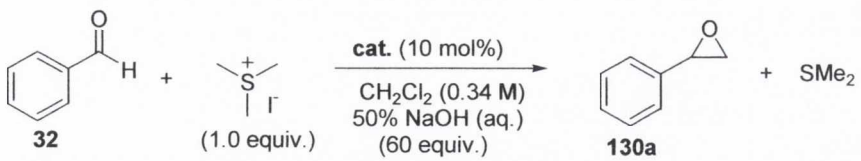


To a solution of **370** in CH_2Cl_2 was added the (*S*,*S*)-1,2-diaminocyclohexane **59** which was allowed to stir for 30 min followed by addition of DIPEA. The reaction was allowed to stir for 2 days after which time catalyst (*S*,*S*,*S*,*S*)-**367** was isolated and purified *via* column chromatography (90:10 EtOAc:MeOH) as a yellow solid in an overall yield of 56%.

4.4.4.3 Evaluation of catalyst 367 under liquid/solid, and liquid/liquid reaction conditions

In order to determine the effect (if any) that the chiral centres may have on the enantioselectivity of the catalysts the (*R*,*R*)-cyclohexane 1,2-diamine was also incorporated into an analogous catalyst synthesis to afford (*S*,*R*,*R*,*S*)-**367**. Both catalysts were found to be soluble under both liquid-solid and liquid-liquid sets of reaction conditions, the (*R*,*R*)-1,2-diaminocyclohexane **59** derivative exhibiting better solubility overall. Both catalysts were subsequently evaluated under liquid/solid and liquid/liquid reaction conditions, the results of which appear in Tables 4.11 and 4.12 respectively.

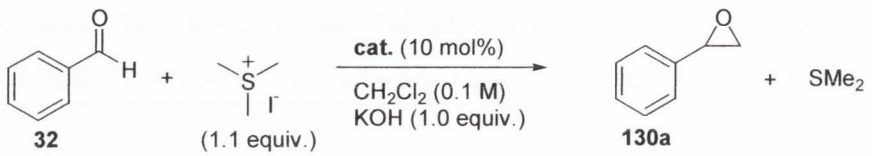
Table 4.11 Evaluation of catalyst **367** in the JCC reaction under liquid-liquid reaction conditions



entry	cat.	time (h)	conv. (%)[a]	*ee* (%)[b]
1	(*S*,*R*,*R*,*S*)-**367**	9	80	0
2	(*S*,*S*,*S*,*S*)-**367**	9	44	0

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using a chiracel OD-H Column.

Table 4.12 Evaluation of catalyst **367** in the JCC reaction under liquid/solid reaction conditions



32 (1.1 equiv.) **130a**

entry	cat.	time (h)	conv. (%)[a]	*ee* (%)[b]
1	(*S,R,R,S*)-**367**	72	31	0
2	(*S,S,S,S*)-**367**	72	20	0

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using chiralcel OD-H Column.

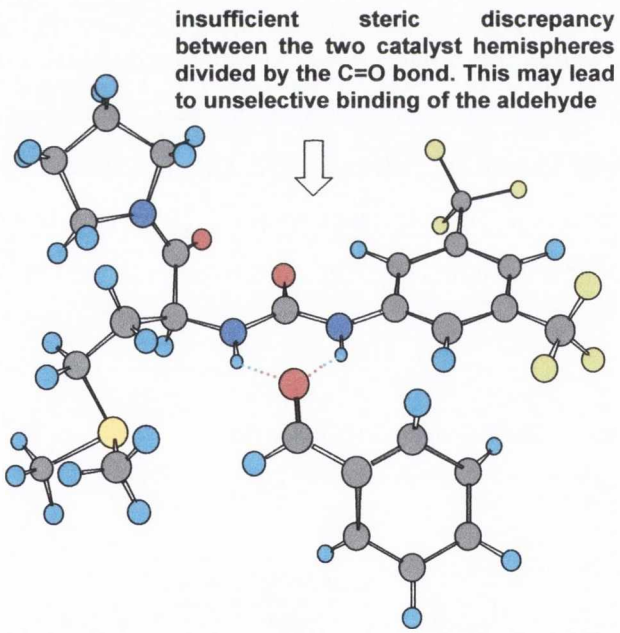
The catalysts were found to exhibit optimal activity in the liquid-liquid reaction conditions (containing 60 equivalents of NaOH), with the more soluble (*S,R,R,S*)-**367** catalyst affording 80% conversion after just 9 h (Table 4.11, entry 1). The less soluble (*S,S,S,S*)-**367** catalyst yielded 44% conversion to the epoxide **130a** after just 9 h. Both of these results represent the most active catalysts evaluated in the JCC reaction thus far. The liquid-solid reactions containing 1.0 equivalent of KOH on the other hand were not conducive to fast reaction times, yet catalysis did occur, the (*R,R,R,S*)-**367** catalyst was superior as previous studies had indicated. However, the epoxide **130a** was isolated as a racemic mixture from both sets of experimental reactions.

4.5 Conclusions for Section 4.4

In summary, it was demonstrated for the first time that chiral urea-based catalysts are highly active catalysts of the JCC reaction of benzaldehyde (**32**). It has been shown for the first time that methionine-derived urea-based catalysts **355-356**, both monofunctional (H-bond donating) and bifunctional (H-bond donating and as 'methylene' sources) are active catalysts for the epoxidation of benzaldehyde (**32**). These results demonstrate the ability of methionine-derived catalysts to form a sulfonium ylide *in-situ* whilst incorporating a H-bond donating functionality (*i.e.* urea) on the same catalyst. The *bis*-urea catalysts (*S,R,R,S*)-**367** and (*S,S,S,S*)-**367** proved exceptionally active promoters of the JCC reaction. These catalysts, which act merely through their H-bond donation capabilities we anticipate will have wide-application as catalysts in future C-C bond transformtions. It is envisaged that these catalysts

could hold great promise in reactions where sterically hindered urea-containing catalysts have found application previously. Using chemdraw 3D models we anticipate that the carbon chain-length of the methionine catalysts may play a significant role in the intramolecular 'face' selective methylene transfer to the urea-bound aldehyde (Figure 4.6). In retrospect an analysis of models indicates that unselective binding of the aldehyde may be the issue while it is likely that the amino acid-derived stereocentre could exert control over the addition of the sulfonium ylide to the aldehyde. The model (Figure 4.6) does not seem to indicate that aldehyde binding would be entirely selective i.e. one would assume that the aldehyde's (in this case) phenyl moiety would occupy the same catalyst hemisphere as the catalysts bulky aromatic substituents. However, given the small steric requirement of the methionine-based alkyl chain this may not be exclusively the case. If binding is unselective then more than one aldehyde face could be presented to the ylide, leading to racemic or near racemic products.

Figure 4.6 Chemdraw 3-D representation of catalyst **356a** binding with benzaldehyde (**32**) rationale for the lack of enantioselectivity found in the epoxide products



The synthesis of a monofunctional catalyst, which is more sterically hindered on one side may improve the selectivity, as attack of the sulfonium ylide onto one face of the bound aldehyde may be favoured (by sterically hindering any other possible route of attack by the sulfonium

ylide). The design of a sulfonium ylide more sterically demanding in a fashion analogous to the benzylidene transfer reagent methodology, which has attained excellent enantioselectivities in the JCC reaction, may hold promise in the future (Section 1.7).

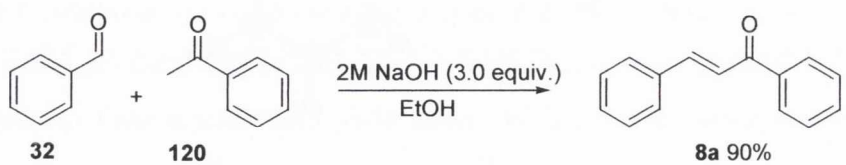
4.6 Application of urea catalysts to the promotion of the cyclopropanation reaction using trimethylsulfoxonium iodide

Persisting with ureas as useful H-bond donors, the scope of urea-based catalysts was probed further in the cyclopropanation of enones using sulfoxonium ylide as the methylene source. Initial evaluation of the achiral ureas as catalysts in the cyclopropanation reaction was swiftly followed by the appraisal of chiral catalysts. The optimised reaction conditions of the JCC epoxidation study were utilised for the cyclopropanation reaction and subsequently fine-tuned.

4.6.1 Preliminary evaluation of the urea catalysed cyclopropanation reaction of chalcone

Chalcone **8a**, was chosen as the model enone to demonstrate any catalytic effect that these catalysts may have on the cyclopropanation reaction. **8a** Could be easily synthesised in high yield from the method shown in Scheme 4.9. The reaction of benzaldehyde (**32**) and acetophenone (**120**) afforded benzalacetophenone (1,3-diphenylprop-2-en-1-one) **8a** as a yellow solid. Recyrstallistaion from 100 % ethanol (using hexane) afforded **8a** as a crystalline solid in 90% yield.

Scheme 4.9 Synthesis of the substrate chalcone **8a**

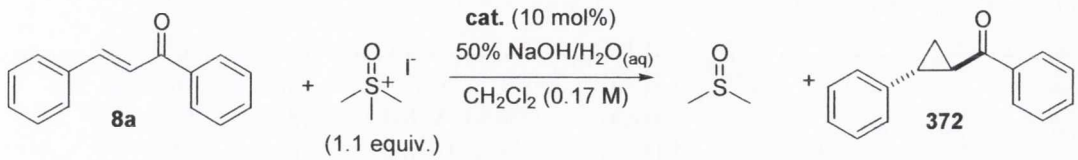


32 **120** **8a** 90%

Preliminary studies to determine the most favourable reaction conditions began with halving the concentration of the reactions (from the 0.34 M used in the JCC epoxidation reactions to 0.17 M) to determine the pace of any uncatalysed product formation due to the abundance of

substrates as the collisions of reactive substrates may promote product formation. We chose catalyst **46** as our standard urea-based catalyst due to its superiority in the JCC study (*vide supra*), to investigate the catalysed cyclopropanation reaction.

Table 4.13 Evaluation of liquid-liquid reaction conditions in the cyclopropanation reaction of **8a**



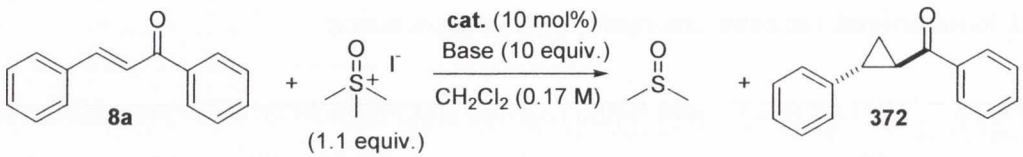
entry	cat.	base (equiv.)	time (h)	conv. (%)[a]
1	-	120	22	57
2	**46**	120	22	100
3	-	60	20	46
4	-	30	20	28
5	-	10	18	0
6	**46**	10	18	36
7	-	1.0	18	0
8	**46**	1.0	18	0

[a]Determined using ^{1}H NMR spectroscopy.

The optimum base loading in this reaction was determined first, starting with 120 equivalents of NaOH (Table 4.13, entry 1 and 2) and decreasing gradually (entries 3 to 6), the minimum requirement of base was found to be between 10 and 1.0 equivalents of the NaOH/H_2O solution (entry 6 and 8). Using less equivalents of base enabled us to maximise the extent of the catalysed reaction relevant to the background reaction. This also facilitated the option of carrying out the reactions under liquid-solid rather than liquid-liquid reaction conditions.

The effect of changing the base counterion was also examined, changing from Na^+ to K^+ resulted in a 50% increase in the background reaction under liquid-liquid reaction conditions (Table 4.14, entries 1 and 3). Altering the reaction solvent to acetonitrile also had a dramatic effect, leading to a 64% increase in the background reaction which would be highly unfavourable in an asymmetric study (Table 4.14, entries 1-2 and 5-6).

Table 4.14 Evaluation of the counter-ion in the cyclopropanation reaction

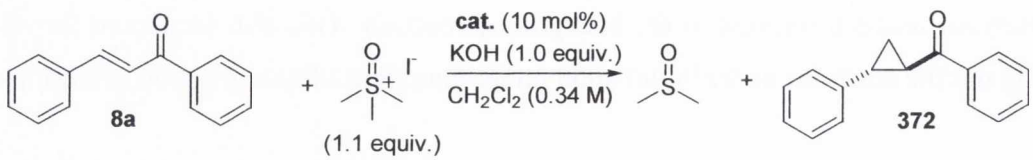


entry	cat.	solvent	base	time (h)	conv. (%)[a]
1	-	CH_2Cl_2	50% $NaOH/H_2O$	18	0
2	**46**	CH_2Cl_2	50% $NaOH/H_2O$	18	36
3	-	CH_2Cl_2	50% KOH/H_2O	18	50
4	**46**	CH_2Cl_2	50% KOH/H_2O	18	54
5	-	CH_3CN	50% $NaOH/H_2O$	18	64
6	**46**	CH_3CN	50% $NaOH/H_2O$	18	78

[a]Determined using ^{1}H NMR spectroscopy.

The results of the base-loading experiments (Table 4.13) *i.e* that ten equivalents of base was sufficient for catalytic turnover encouraged us to evaluate other bases in the reaction. Using just one equivalent of KOH (instead of the best $NaOH_{(aq)}$ conditions-Table 4.13) we identified superior reaction conditions (to Table 4.13, entries 7 and 8) for the cyclopropanation reaction (Table 4.15). The catalysed reaction using urea **46** was improved to 54% conversion whilst maintaining no conversion in the background reaction under liquid-solid reaction conditions (Table 4.15, entries 1 and 3). It should be noted that clean conversion to **372** was observed in the catalysed reaction. No side products were observed.

Table 4.15 Evaluation of the base in the cyclopropanation reaction



entry	cat.	time (h)	conv. (%)[a]
1	-	16	0
2	**321**[b]	16	0
3	**46**	16	54

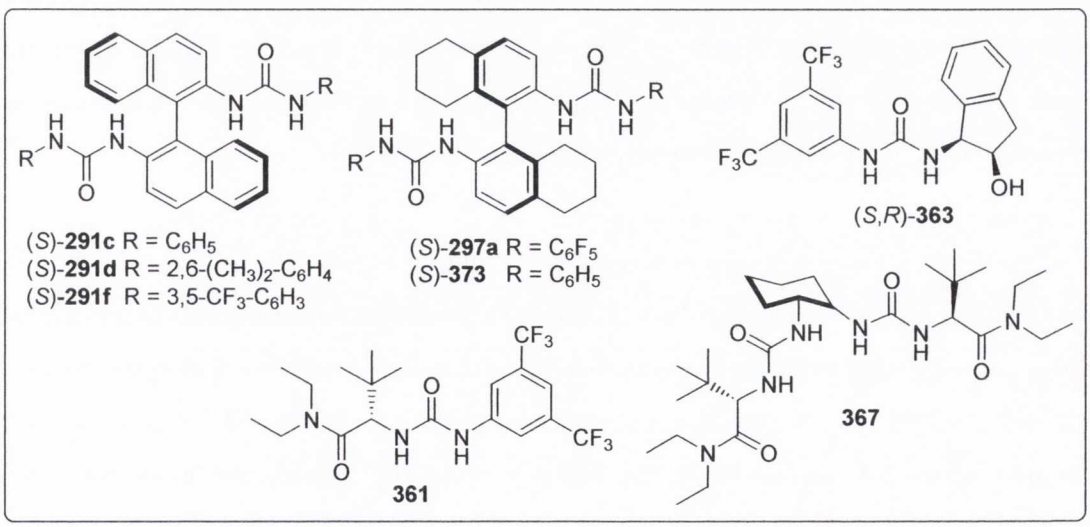
[a]Determined using ^{1}H NMR spectroscopy.
[b] Catalyst insoluble.

Unfortunately the less acidic catalyst *bis*phenyl-urea catalyst **321** was insoluble in these reaction conditions, yet catalyst **46** was a far superior catalyst. In summary, the liquid-solid reaction conditions were found to be optimal for the cyclopropanation reaction evaluated. 1.0 Equivalent of KOH and a 0.17 M CH_2Cl_2 solution was found to be the most useful conditions for further catalyst evaluation studies.

4.6.2 Chiral catalysts evaluated in the cyclopropanation reaction using TMSOI

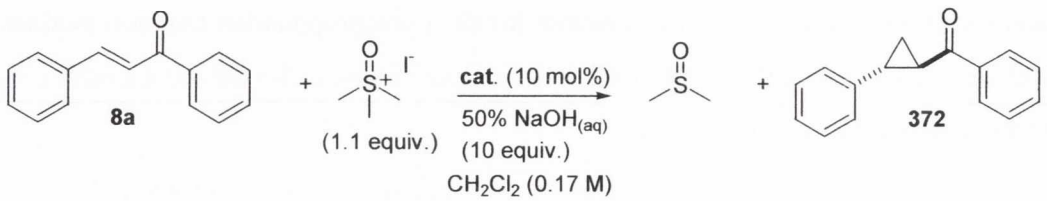
Figure 4.7 depicts the chiral catalysts evaluated in the cyclopropanation reaction of chalcone **8a**. The results of which appear in Tables 4.16 to 4.18. Both the aliphatic (**367**) and the aromatic *bis*-urea motifs (**291**) were evaluated along with both aliphatic and aromatic single urea-containing catalysts (**361**) and (*S*,*R*)-**363**.

Figure 4.7 Catalysts screened in the cyclopropanation reaction of **8a**



Initial catalyst screening was carried out using the optimised JCC liquid-liquid reaction conditions, the results of which are described in Table 4.16.

Table 4.16 Evaluation of binaphthyl-catalysts under liquid-liquid reaction conditions used in the JCC reaction



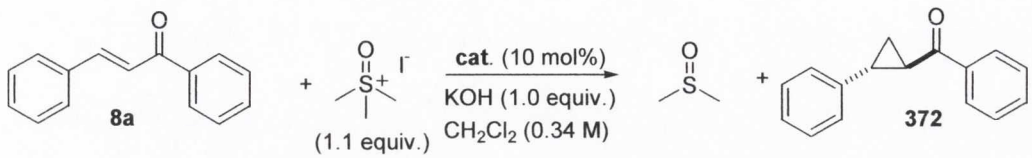
entry	cat.	time (h)	conv. (%)[a]	*ee* (%)[b]
1	-	18	0	-
2	(*S*)-**291c**	18	8	6
3	(*S*)-**291f**	18	24	7

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using chiracel AS Column.

In the absence of catalyst the control reaction exhibited no conversion (Table 4.16, entry 1). Similar to the JCC reaction, the more Lewis acidic catalyst (*S*)-**291f** was a superior promoter to the less Lewis acidic catalyst (*S*)-**291c**. Cyclopropane **372** was isolated from both reactions in 6 and 7% *ee* (Table 4.16). Considering the good activity associated with binaphthyl-catalysts of type **291** in the JCC reaction, the poor activity exhibited by these catalysts under the liquid-liquid reaction conditions in the cyclopropanation reaction (Table 4.16) was unexpected. In view of this, attention shifted to using the optimised liquid-solid reaction conditions described in the earlier optimisation studies (Table 4.15).

Using the liquid-solid reaction conditions, there was found to be no background reaction in the absence of catalyst after 16 hours (Table 4.17, entry 1). Dramatic improvements in binaphthyl-urea catalyst activity were found using the solid-liquid reaction conditions. Catalysts (*S*)-**291c**, (*S*)-**291d**, and (*S*)-**291f** were highly efficient promoters yielding close to 50% conversion after just 16 hours (entries 2-4). In contrast to the findings of the JCC studies, the less Lewis-acidic catalyst (*S*)-**291c** was more active than the more acidic catalyst (*S*)-**291f** (entries 2 and 4). Previous experience in the Friedel-Crafts study identified the pentafluorophenyl substituent as an alternative to the *bis* trifluoromethylphenyl group affording similar effects on catalyst efficiency (Section 2.1). As a result both a pentafluorophenyl and saturated binaphthyl component were incorporated into catalyst (*S*)-**297a**. However, these modifications led to a reduction in both activity and selectivity (entry 5).

Table 4.17 Evaluation of chiral catalysts in the liquid-solid KOH reaction conditions in the cyclopropanation reaction

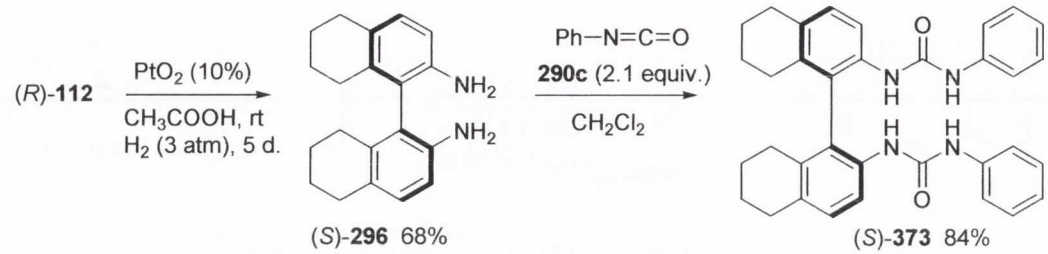


entry	cat.	time (h)	conv. (%)[a]	*ee* (%)
1	-	16	0	-
2	(*S*)-**291c**	16	48	6
3	(*S*)-**291d**	16	47	3
4	(*S*)-**291f**	16	41	6
5	(*S*)-**297a**	16	12	2
6	(*S*)-**373**	16	46	2
7	**363**	16	48	2
8	**361**	16	58	2
9	(*S,R,R,S*)-**367**	12	33	6
10	(*S*,S,*S*,*S*)-**367**	12	20	2

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using chiralcel AS Column.

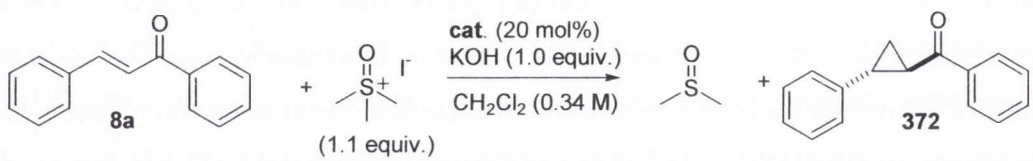
To increase the steric demands of these catalysts with a view to improving the enantioselectivity of the products a new catalyst was synthesised using the general procedure outlined in Scheme 5.0. A saturated version of (*S*)-**291c** was synthesised from the unsaturated amine precursor (*S*)-**296.** Incorporation of the urea functionality *via* the corresponding isocyanate **290c** afforded a brown solid which was purified *via* column chromatography (ethyl acetate:hexane 10:90) to afford (*S*)-**373** as a white solid in 84% yield. (*S*)-**373** Was synthesised in order to probe the influence of the binaphthyl backbone on catalyst efficiency. Catalyst (*S*)-**373** was equally as active as (*S*)-**291c** yet the enantioselectivity reduced slightly from 6% to 2% *ee* (Table 4.17, entry 6). Note: At such low *ee* readings the HPLC instrumental error may be significant.

Scheme 5.0 Synthesis of catalyst (*S*)-**373**



Ricci's catalyst **363** and Jacobsen's catalyst **361** proved efficient promoters of the cyclopropanation reaction, yielding 48% and 58% conversion respectively after just 16 hours akin to the binaphthylurea catalysts **291**, indicating the importance of the 3,5-*bis* trifluoromethyl phenyl group for smooth catalysis (entries 7 and 8). The amino-acid *bis*-urea catalyst **367** was capable of similar levels of activity and enantioselectivty, as expected the (*S,R,R,S*)-**367** catalyst exhibited superior activity (Table 4.17, entries 9 and 10). As the modifications made to catalysts **291** did not improve the enantiomeric excess detected in the products, we decided to perform catalyst screening at sub-ambient temperatures with the aim of improving the enantioselectivity.

Table 4.18 Evaluation of chiral catalysts in the liquid-solid KOH reaction conditions in the cyclopropanation reaction at sub-ambient temperatures



entry	cat.	time (h)	temp (°C)	conv. (%)[a]	*ee* (%)[b]
1	(*S*)-**291c**	16	-20	0	6
2	(*S*)-**291d**	16	-20	23	0
3	(*S*)-**291f**	16	-20	8[c]	4
4	(*S*)-**291f**	16	-20	25	6
5	(*S*)-**291f**	16	35	100	3

[a]Determined using ^{1}H NMR spectroscopy. [b]Determined using chiralcel AS Column.[c]10 mol% of catalyst was used in this experiment.

Sub-ambient temperatures of –20 °C and –30 °C were evaluated, however the products were isolated as near racemic mixtures as before (Table 4.18). In order to verify this result, a reaction at 35 °C was completed which exhibited faster substrate conversion but the enantioselectivty remained constant. The lack of improvement in the *ee* of the cyclopropanes synthesised in these reactions at sub-ambient temperatures indicates that the catalysts synthesised in this study while capable of promoting the reaction are not able to effectively shield one face of the bound chalcone from attack by the sulfoxonium ylide.

4.7 Chapter 4: conclusions

In summary, we have for the first time shown that urea-based catalysts are efficient promoters of both the Johnson-Corey-Chaykovsky epoxidation reaction and the Corey cyclopropanation reaction. This work demonstrates that ureas are excellent motifs to incorporate into either monofunctional or bifunctional catalysts for the promotion of these two very useful reactions. Future work may involve the development of modified chiral catalysts to promote enantioselective versions of these reactions. The catalyst-type **367** has been designed, synthesised and shown to be a highly efficient promoter of both reactions, which until now have been relatively under-utilised in the literature. This study has highlighted the fact that to achieve successful catalysis in both the epoxidation and cyclopropanation reactions the determination of the optimal reaction conditions is paramount.

5.1 General experimental data

Proton Nuclear Magnetic Resonance spectra were recorded on a Bruker Avance 400 or 600 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) or d_6-DMSO referenced relative to residual DMSO (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 or 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation, $KMnO_4$, or anisaldehyde staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of 10^{-1}degcm^{2}g^{-1}. Anhydrous THF was distilled over sodium-benzophenone ketyl radical before use. Methylene chloride, toluene and triethylamine were distilled from calcium hydride. All reactions were carried out under a protective nitrogen, or argon atmosphere unless otherwise stated. Analytical CSP-HPLC was preformed on Daicel CHIRALCEL OD-H (4.6 mm x 25 cm), CHIRALPAK AD-H (4.6 mm x 25 cm) and AS (4.6 mm x 25 cm) columns. *trans*-Cyclohexane-1,2-diamine (**59**) was resolved as per the general procedure outlined by Schanz *et al.*[355] Mass spectroscopy was carried out using a Micromass LCT time-of-flight spectrometer linked to a Waters 2690 HPLC for sample delivery. Analysis was carried out in electrospray positive mode using Leucine Enkephalin for internal lock mass correction. The instrument was operated at a resolution of 5000 FWHM. Data was acquired over a range m/z 100 to m/z 1000. Sample analysis, accurate mass measurements were performed using MassLynx 4.0 software.

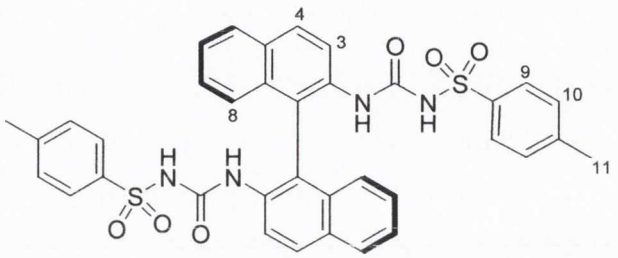
5.2.1 Experimental data for Section 2.1

5.2.1.1 Procedure A: general procedure for the preparation of (thio)urea catalysts in Scheme 2.1

To a solution of (*S*)-1,1-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) in CH_2Cl_2 (1.8 cm^3) under Ar at 0 °C was added the relevant iso(thio)cyanate (2.10 mmol) drop-wise *via*

syringe. The resulting solution was left to stir for 12 h at room temperature with precipitation of the product from solution. The pure product could be obtained by gravity filtration and purified by either recrystallisation (CH_2Cl_2:hexane) or column chromatography to yield the catalyst as a white solid.

5.2.1.2 (*S*)-1,1'-binaphthyl-2-(*para*-toluenesulfonyl) urea (291a)



Procedure A was followed using *para*-toluenesulfonyl isocyanate (**290a**) (246 μL, 1.47 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (200 mg, 0.71 mmol) in CH_2Cl_2 (1.2 cm^3) to yield **291a** as a white powder (449 mg, 94%). M.p. 173-175 °C. $[\alpha]^{20}_D$ -35.67 (*c* 1.8 $CHCl_3$).

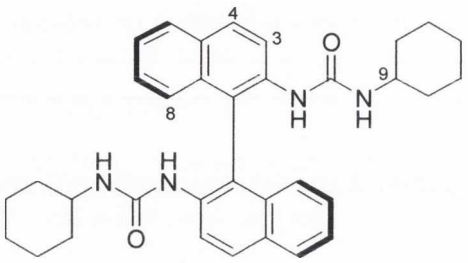
δ_H (400 MHz, $CDCl_3$): 8.68 (d, 2H, J 9.1, H-4), 8.41 (s, 2H, NH), 8.26 (br s, 2H, NH), 8.12 (d, 2H, J 9.1, H-3) 8.01 (d, 2H, J 8.1, H-5), 7.52 (m, 2H, H-6), 7.32 (m, 2H, H-7), 7.09 (d, 2H, J 8.4, H-8), 6.99 (app s, 8H, H-9, H-10, H-12, H-13), 2.22 (s, 6H, CH_3)

δ_C (100 MHz, $CDCl_3$): 149.1 (q), 144.3 (q), 135.4 (q), 134.4 (q), 132.1 (q), 130.8 (q), 130.3, 129.2, 128.2, 127.1, 125.9, 125.1, 124.4, 119.1, 118.4 (q), 20.9

υ (cm^{-1}): KBr 3548, 3299, 3059, 2847, 1919, 1692 (C=O), 1534, 1282 (S=O), 1156 (S=O)

HRMS (ESI): $(M+Na)^+$ calcd. for $C_{36}H_{30}N_4O_6S_2Na$ 701.1504; found 701.1517

5.2.1.3 (*S*)-1,1'-Binaphthyl-2,2'-(cyclohexyl) urea (291b)



Procedure A was followed using (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) and cyclohexyl-isocyanate (**290b**) (282 μL, 2.20 mmol), in CH_2Cl_2 (1.80 cm^3). Column chromatography (1:1 CH_2Cl_2:hexane, R_f 0.5) afforded **291b** as a white powder (309 mg, 55%). M.p. 154-156 °C. $[\alpha]^{20}_D$ -24.66 (*c* 0.5 $CHCl_3$).

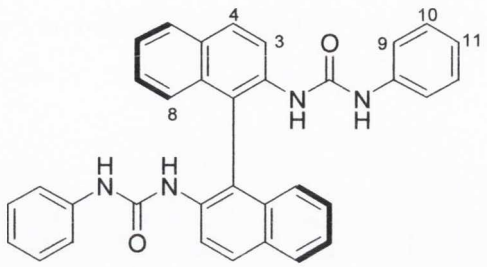
δ_H (400 MHz, DMSO): 8.64 (d, 2H, J 9.0, H-4), 7.98 (d, 2H, J 9.0, H-3), 7.90 (d, 2H, J 8.0, H-5), 7.30 (dd, 2H, J 8.0, 7.0, H-6), 7.15 (dd, 2H, J 8.0, 7.0, H-7) 6.95 (s, 2H, Ar-NH), 6.66 (m, 4H, J 8.0, H-8 and cyclohexyl-NH), 3.30 (m, 2H, H-9), 1.47 (m, 10H, cyclohexyl), 0.86 (m, 10H, cyclohexyl)

δ_C (100 MHz, DMSO): 154.4 (q), 137.9 (q), 132.7 (q), 129.5 (q), 128.6, 128.0, 126.3, 124.1, 123.7, 120.7, 116.6 (q), 48.0, 32.9, 25.2, 24.5.

υ (cm^{-1}): 3638, 3303, 2927,1650 (C=O),1542, 1231.

HRMS (ESI): (M^++Na) Calcd for $C_{34}H_{38}N_4O_2Na$ 557.2892; found 557.2872

5.2.1.4 (*S*)-1,1'-binaphthyl-2,2'-(phenyl)-urea (291c)



Procedure A was followed using phenyl isocyanate (**290c**) (240 μL, 2.20 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) in CH_2Cl_2 (1.80 cm^3). Column chromatography (1:1 CH_2Cl_2:hexane, R_f 0.5) afforded **291c** as a white powder (545 mg, 90%). M.p. 121-124 °C. $[\alpha]_D^{20}$ -50.60 (*c* 0.50 $CHCl_3$)

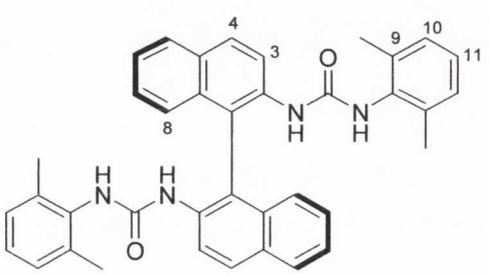
δ_H (400 MHz, $CDCl_3$): 8.26 (d, 2H, J 9.0, H-4) 7.94 (d, 2H, J 9.0, H-3), 7.86 (d, 2H, J 8.0, H-5) 7.36 (app.t, 2H, J 7.5, H-6), 7.28 (br s, 2H, NH), 7.17 (app.t, 2H, J 7.5, H-7), 6.95 (m, 8H, H-8 and H-10-12), 6.87 (d, J 4H, J 7.5, H-9 and H-13), 6.65 (br s, 2H, NH).

δ_C (100 MHz, $CDCl_3$): 153.3 (q) 136.9 (q), 135.1 (q), 132.3 (q), 130.3 (q), 129.0, 128.5, 127.7, 126.6, 124.7, 124.5, 123.8, 121.6, 120.4, 120.1 (q)

υ (cm^{-1}): 3326, 1672 (C=O), 1492, 1241

HRMS (ESI): $(M+Na)^+$ calcd. for $C_{34}H_{26}N_4O_2Na$ 545.1953; found 545.1946

5.2.1.5 (*S*)-1,1'-binaphthyl-2,2'-(2,6 dimethylphenyl)-urea (291d)



Procedure A was followed using 2,6-dimethylphenyl isocyanate (**290d**) (307 μL, 2.20 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) in CH_2Cl_2 (1.8 cm^3). Column chromatography (1:1 CH_2Cl_2:hexane, R_f 0.6) afforded **291d** as a white powder (541 mg, 89 %). M.p. 236-239 °C. $[\alpha]_D^{20}$ -101.38 (*c* 0.51 $CHCl_3$)

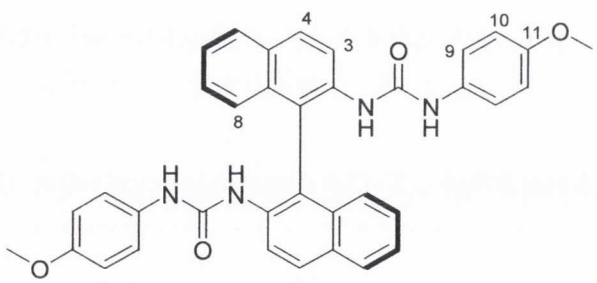
δ_H (400 MHz, $CDCl_3$): 8.54 (d, 2H, J 9.0, H-4), 7.72 (m, 4H, H3 and H-5), 7.30 (app.t, 2H, J 7.5, H-6), 7.09 (app.t, 2H, J 7.5, H-7), 6.82 (app.t, 2H, J 7.5, H-11), 6.74 (d, 2H, J 8.5, H-8), 6.17 (s, 2H, NH), 6.41 (br s, 2H, NH), 5.81 (m, 4H, H-10 and H-12), 1.62 (s, 12H, CH_3)

δ_C (100 MHz, $CDCl_3$): 153.5 (q), 135.9 (q), 135.7 (q), 135.3 (q), 131.3 (q), 131.2 (q), 129.5, 129.4 (q), 127.7, 127.8, 127.6, 126.3, 123.8, 123.4, 118.6, 30.4 (CH_3)

$\upsilon(cm^{-1})$: 3358 (N-H), 1678 (C=O), 1494, 1283

HRMS (ESI): $(M+Na)^+$ calcd for $C_{38}H_{34}N_4O_2Na$ 601.2579; Found 601.2584

5.2.1.6 (*S*)-1,1'-binaphthyl-2,2'-(4-methoxyphenyl)-urea (291e)



Procedure A was followed using 4-methoxyphenyl isocyanate (**290e**) (286 μL, 2.20 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) in CH_2Cl_2 (1.8 cm^3). Column

chromatography (1:1 CH_2Cl_2:hexane, R_f 0.55) afforded **291e** as a white powder (545 mg, 90%). M.p. 131-133 °C. $[\alpha]_D^{20}$ -79.8 (*c* 0.5 $CHCl_3$)

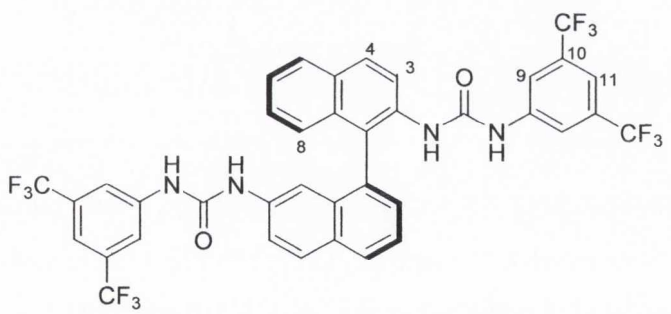
δ_H (400 MHz, DMSO): 8.90 (br s, 2H, NH) 8.61 (d, 2H, J 9.0, H-4), 8.07 (d, 2H, J 9.0, H-3), 7.96 (d, 2H, J 8.0, H-5), 7.35 (app.t, 2H, J 7.3, H-6), 7.21 (app.t, 2H, J 7.3, H-7), 7.17 (d, 2H, J 9.0, H-8), 6.76 (m, 8H, H-9, H-10, H-12 and 13), 3.67 (s, 6H, OCH_3), the other NH was not visible.

δ_C (100 MHz, $CDCl_3$): 156.9 (q), 154.3 (q), 135.7 (q), 132.4 (q), 130.5 (q), 129.4, 129.3 (q), 128.1, 127.0, 124.8, 124.6, 121.8, 119.0 (q), 114.1, 114.2, 55.3 (CH_3)

$\upsilon(cm^{-1})$: 3318, 3055,2833, 1658 (C=O),1544,1492,1231

HRMS (ESI): $(M+Na)^+$ calcd. for $C_{35}H_{28}N_4O_4$ 605.2165 found 605.2153

5.2.1.7 (*S*)-1,1'-binaphthyl-2,2'-(3,5 *bis*-trifluoromethylphenyl)-urea (291f)



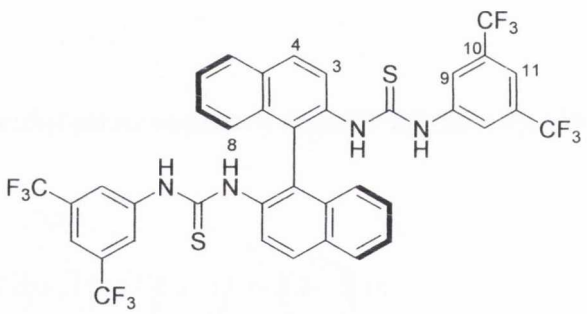
Procedure A was followed using 3,5-*bis* trifluoromethylphenyl isocyanate (**290f**) (381 µL, 2.2 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) in CH_2Cl_2 (1.8 cm^3). Column chromatography (1:1 CH_2Cl_2:hexane, R_f 0.6) afforded **291f** as a white powder (447 mg, 54%). M.p. 155-157 °C. (lit.,[356] 128-130 °C), $[\alpha]_D^{20}$ -136.4 (*c* 1.00 MeOH).

δ_H (400 MHz, $CDCl_3$): 8.31 (d, 2H, J 9.0, H-4), 8.07 (d, 2H, J 9.0, H-3), 7.95 (d, 2H, J 8.0, H-5), 7.73 (s, 4H, H-9 and H-13), 7.46 (app.t, 2H, J 8.0, H-7), 7.43 (s, 2H, H-11), 7.28 (app.t, 2H, J 7.1, H-6), 7.04 (d, 2H, J 8.2, H-8), 6.87 (s, 2H, NH), the other NH signal was coincident with the residual $CHCl_3$ resonance.

δ_C (100 MHz, $CDCl_3$): 153.1 (C=O), 139.2 (q), 134.5 (q), 132.7 (q), 131.9 (qt, J 33.1), 130.9 (q), 129.6, 128.2, 127.3, 125.5, 125.0, 123.5 (q), 122.1, 122.8 (qt, J 276), 118.1, 116.1

HRMS (ESI): $(M+Na)^+$ calcd. for $C_{38}H_{22}N_4O_2F_{12}Na$ 817.1449 found 817.1486

5.2.1.8 (*S*)-1,1'-binaphthyl-2,2'-(3,5-*bis* trifluoromethylphenyl)-thiourea (291g)



Procedure A was followed using 3,5-*bis*-trifluoromethylphenyl isothiocyanate (**290g**) (276 μL, 1.5 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (205 mg, 0.72 mmol) in CH_2Cl_2 (1.2 cm^3). Column chromatography (1:1 CH_2Cl_2:hexane, R_f 0.5) afforded **291g** as a white powder (546 mg, 91%). M.p. 137-138 °C. $[\alpha]_D^{20}$ -125.6 (*c* 0.5 $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 8.24 (br s, 2H, NH), 8.10 (d, 2H, J 8.5, H-4), 7.97 (d, 2H, J 8.5, H-3), 7.88 (d, 2H, J 8.7, H-5), 7.71 (br s, 2H, NH), 7.68 (s, 4H, H-9 and H-13), 7.58 (s, 2H, H-11), 7.50 (m, 2H, H-6), 7.29 (m, 2H, H-7), 7.13 (d, 2H, J 8.7, H-8)

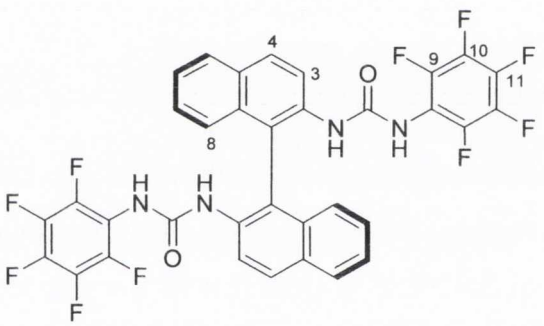
δ_C (100 MHz, $CDCl_3$): 179.8 (q), 138.6 (q), 133.4 (q), 132.6 (q), 132.2 (q), 131.7 (qt, C-C, J 33.7), 130.5, 128.6, 128.0, 127.3 (q), 126.9, 125.2, 124.6, 124.2, 122.6 (qt, C-F, J 272.7), 119.5

δ_F (376 MHz, $CDCl_3$): -63.52 (s, CF_3)

$\upsilon(cm^{-1})$: 3265, 1669 (C=O), 1470, 1377, 1126

HRMS(ESI): $(M+Na)^+$ calcd. for $C_{38}H_{22}F_{12}N_4S_2Na$ 849.0992, found 849.1013

5.2.1.9 (*S*)-1,1'-binaphthyl-2,2'-(pentafluorophenyl) urea (291h)



Procedure A was followed using pentafluorophenyl isocyanate (**290h**) (288 μL, 2.20 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (300 mg, 1.05 mmol) in CH_2Cl_2 (1.80 cm^3). Column chromatography (1:1 CH_2Cl_2:hexane, R_f 0.5) afforded **291h** as a white powder (616 mg, 83%). M.p. 158-160 °C. $[\alpha]_D^{20}$ -78.44 (*c* 0.45 $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 8.17 (d, 2H, J 9.0, H-3), 7.93 (d, 2H, J 9.0, H-4) 7.85 (d, 2H, J 8.0, H-5) 7.38 (dd, 2H, J 8.7, 8.0, H-7), 7.18 (dd, 2H, J 8.7, 8.0, H-6), 6.93 (d, 2H, J 8.7, H-8), 6.34 (s, 2H, NH), 6.61 (s, 2H, NH).

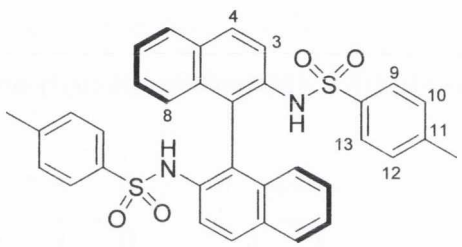
δ_C (100 MHz, $CDCl_3$): 153.0 (q), 143.1 (d, J^1 260, J^2 27.0), 139.7 (app.t, J^1 249), 137.6 (app.t, J^1 252), 134.7 (q), 132.5 (q), 131.0 (q), 129.8, 128.2, 127.3, 125.6, 125.0, 122.1, 121.7 (q), 111.8 (q)

δ_F (376 MHz, $CDCl_3$): -146.8 (d, 4F, 19.0), -157.5 (m, 2F), -163.1 (app.t, 4F, J 20.0)

$\upsilon(cm^{-1})$: 3265, 1688 (C=O), 1498, 980

HRMS (ESI): $(M+Na)^+$ calcd. for $C_{34}H_{16}F_{10}N_4O_2$ 725.1011, found 725.1003

5.2.1.10 (*S*)-1,1'-binaphthyl-2,2'-*para*-toluenesulfonyl amine (295)



Procedure A was followed using *para*-toluenesulfonyl chloride (**294**) (429 mg, 2.25 mmol), (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (200 mg, 0.71 mmol), pyridine (682 μL, 8.40 mmol) in CH_2Cl_2 (4.5 cm^3) to afford (*S*)-**295** as a white powder (64 mg, 15%). M.p. 120-121 °C. (no m.p quoted in the literature reference, all spectra were consistent with the literature data).[357]

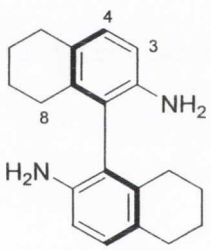
δ_H (400 MHz, $CDCl_3$): 8.11 (d, 2H, J 9.1, H-4), 8.00 (d, 2H, J 9.1, H-3), 7.88 (d, 2H, J 8.0, H-5), 7.45 (d, 4H, J 8.3, H-9, H-13) 7.40 (dd, 2H, J 8.0, 7.5, H-6), 7.17 (d, 4H, J 8.0, H-10, H-12), 7.01 (dd, 2H, J 8.3, 7.5, H-7), 6.48 (d, 2H, J 8.3, H-8), 5.88 (s, 2H, Ar-NH), 2.4 (s, 6H, H-11).

HRMS(ESI) $(M+Na)^+$ calcd. for $C_{34}H_{28}N_2O_4S_2Na$ 615.1388; found 615.1370

5.2.1.11 Procedure B: general procedure for the catalytic hydrogenation of (*S*)-1,1'-binaphthyl-2,2'-diamine

In a hydrogenation flask containing a suspension of (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (1.00 g, 3.5 mmol) in glacial acetic acid (100 cm^3), PtO_2 (150 mg, 0.66 mmol) was added. The hydrogenation flask was subsequently flushed with hydrogen gas and placed under 3 atm of pressure with continuous shaking for 5 days. After releasing the hydrogen gas and removing the solid (PtO_2) by filtration, the resulting dark green liquid was neutralised with saturated sodium bicarbonate solution (500 cm^3) followed by extraction with chloroform (3 x 75 cm^3) and drying ($MgSO_4$). The product was purified using column chromatography on silica gel (CH_2Cl_2/hexane 1.5:1) to afford the saturated amine as a brown solid.

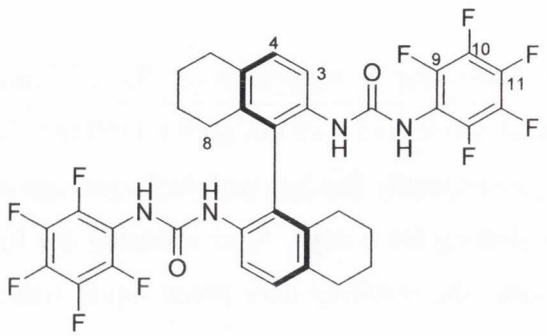
5.2.1.12 (*S*)-5, 5', 6, 6',7, 7',8 ,8'-octahydro-[1,1']binaphtyl-2,2'-diamine (296)



Procedure B was followed using (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**), glacial acetic acid (100 cm^3), and PtO_2 (150 mg, 0.66 mmol) to afford the amine (*S*)-**296** as a brown solid (700 mg, 68%). $[\alpha]^{20}_D$ = - 133 (*c* 1.0, pyridine). M.p 210 °C (no m.p quoted in the literature).[358] The isolated compound exhibited identical spectroscopic data to those in the literature.[358]

δ_H (400 MHz, $CDCl_3$): 6.93 (d, 2H, J 8.0, H-3), 6.64 (d, 2H, J 8.0, H-4), 2.72 (m, 4H, H-8) 2.20 (m, 4H, H-5), 1.67 (m, 8H, H-6 and H-7), NH's not visible in $CDCl_3$

5.2.1.13 (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-(pentafluoro phenyl)-urea (297a)



Procedure A was followed using pentafluorophenyl isocyanate (**290h**) (141 μL, 1.08 mmol), (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-diamine (**296**) (150 mg, 0.51 mmol) in CH_2Cl_2 (1.6 cm^3) yielded **297a** as a white powder (323 mg, 89%). M.p. 67-70 °C. $[\alpha]_D^{20}$ –98 (*c* 0.17 $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 7.66 (d, 2H, J 8.3, H-4), 7.10 (d, 2H, J 8.3, H-3), 6.64 (s, 2H, Ar-NH) 6.37 (s, 2H, Ar-NH), 2.76 (m, 4H, H-5), 2.06 (m, 4H, H-8), 1.64 (m, 8H, H-6 and H-7)

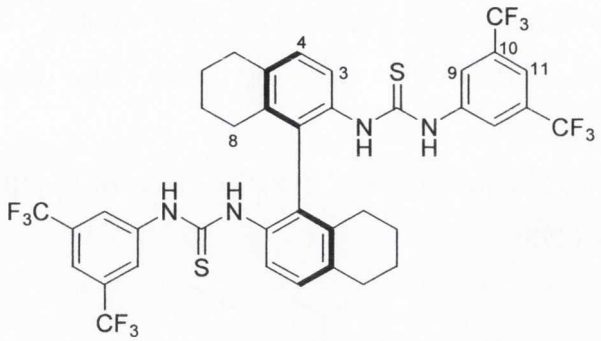
δ_C (100 MHz, $CDCl_3$): 152.5 (q), 143.5 (dd, J^1 260, J^2 30), 138.9 (app.t, J^1 249), 137.8 (app.t, J^1 252), 135.5 (q), 134.1 (q), 132.3 (q), 129.4, 126.6 (q), 124.2 (q), 119.1, 28.9, 26.8, 22.4, 22.2

δ_F (376 MHz, $CDCl_3$): -146.7 (d, 4F, J 19.2), -157.5 (m, 2F), -162.9 (app.t, 4F, J 20.1)

υ (cm^{-1}): 3274, 2935, 1648 (C=O), 1509

HRMS(ESI) (M^++Na) Calcd for $C_{34}H_{24}N_4O_2NaF_{10}$ 733.1637; Found 733.1636

5.2.1.14 (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-(3,5-*bis* trifluoromethyl phenyl)-urea (297b)



Procedure A was followed using 3,5-*bis*-trifluoromethylphenyl isothiocyanate (**290g**) (74 μL, 0.40 mmol), (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-diamine (**296**) (56 mg, 0.19 mmol) in CH_2Cl_2 (1.0 mL) yielded **297b** as a white powder (158 mg, 98 %). m.p. 165-167 °C (lit.,[330] 170-172 °C). $[\alpha]_D^{20}$ -152 (c 0.01 $CHCl_3$). The isolated compound exhibited identical spectroscopic data to those in the literature.[330]

δ_H (400 MHz, $CDCl_3$): 8.02 (s, 4H, H-9, H-13), 7.93 (br s, 2H, NH), 7.58 (s, 2H, H-11) 7.31 (m, 4H, H-3, H-4, overlap with solvent resonance), 7.18 (br s, 2H, NH), 2.89 (m, 4H, H-5), 2.19 (m, 4H, H-8), 1.75 (m, 8H, H-6 and H-7)

HRMS(ESI) (M^++Na) Calcd for $C_{38}H_{30}N_4S_2F_{12}Na$ 857.1618; Found 857.1591

5.2.1.15 Procedure C: general procedure for the mono-bromination of (*S*)-1,1'-binaphthyl-2,2'-diamine (112) to afford 301 and (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-diamine (296) to afford 298

In a 50 cm^3 round bottomed flask fitted with a stirring bar under an atmosphere of N_2 (balloon) at 0 °C was added a 10% bromine in glacial acetic acid solution (10 cm^3/100 cm^3) (1.58 mmol) dropwise to the relevant diamine, (0.70 mmol) in a suspension of sodium acetate (1.4 mmol) in CH_2Cl_2 (1 cm^3). Upon complete addition of the bromine the reaction was allowed warm to room temperature. The resulting mixture was then diluted with ethyl acetate (150

cm^3), washed with saturated sodium bicarbonate solution (2 x 50 cm^3), followed by washing with saturated sodium thiosulfate solution (2 x 20 cm^3), the organic extracts were combined, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/Hexane 1.5:1) to afford the mono-brominated amine.

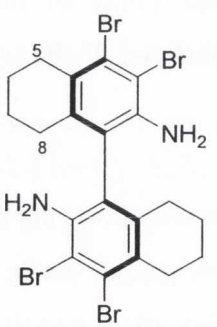
5.2.1.16 (*S*)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthalenyl-2,2'-diamine (298)



Procedure C was followed using (10 cm^3/100 cm^3) bromine in glacial acetic acid solution (31 μL, 0.61 mmol) which was added dropwise to a (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphtyl-2,2'-diamine (**296**) (85 mg, 0.29 mmol) in a CH_2Cl_2 (1.28 cm^3) and sodium acetate (51 mg, 0.63 mmol) suspension. The mono-brominated amine (*S*)-**298** was isolated as a brown solid (105 mg, 80%). m.p. 167-169°C. (lit.[330], 170-172 °C), $[\alpha]_D^{20}$ -49 (*c* 0.5 $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 7.23 (s, 2H, H-4), 3.51 (br s, 4H, 2 x NH_2), 2.7 1(m, 4H, H-5), 2.21 (m, 4H, H-8), 1.65 (m, 8H, H-6 and H-7)

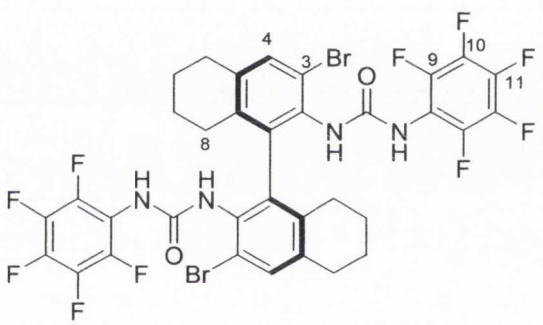
5.2.1.17 (*S*)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-diamine (299)



Procedure C was followed using (10 cm^3/100 cm^3) bromine in glacial acetic acid solution (810 μL, 1.44 mmol) which was added dropwise to a (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphtyl-2,2'-diamine (100 mg, 0.341 mmol) in a CH_2Cl_2 (1.50 cm^3) and sodium acetate (61 mg, 0.73 mmol) suspension. The di-brominated amine (*S*)-**299** was isolated as a brown solid (120 mg, 60%). m.p. 166-168 °C. (lit.,[330] 170-172 °C), $[\alpha]_D^{20}$ -39 (*c* 0.94 $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 3.41 (m, 4H, H-5), 3.01 (m, 4H, H-8), 2.90 (m, 4H, H-6), 2.80 (m, 4H, H-7), NH_2 resonances not visible.

5.2.1.18 (*S*)-3,3'-Dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-phenyl urea (300a)



Using general procedure A, pentafluorophenyl isocyanate (**290h**) (23 μL, 0.17 mmol) was added *via* syringe to a suspension of (*S*)-3,3'-dibromo-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-diamine (**298**) (37.1 mg, 0.082 mmol) in CH_2Cl_2 (400 μL). The resulting solution was left to stir overnight at room temperature with precipitation of the product as a white solid. Purification by column chromatography on silica gel (CH_2Cl_2) afforded **300a** (40 mg, 56%) as a white solid. M.p. 243-245 °C, $[\alpha]_D^{20}$ -72 (*c* 0.4 $CHCl_3$)

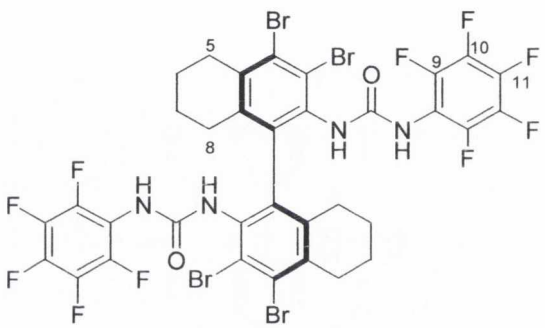
δ_H (400 MHz, $CDCl_3$): 7.43 (s, 2H, H-4), 2.99 (m, 8H, H-5 and H-8), 2.80 (m, 8H, H6 and H7), NH resonances not visible.

δ_C (100 MHz, $CDCl_3$): 152.4 (q), 144.2 (q), 143.6 (d, ^1J 260), 142.5 (app.t, ^1J 250), 138.3 (app.t, ^1J 258), 138.2 (q), 136.7 (q), 130.1 (q), 130.0 (q), 114.2 (q), 109.0 (q), 29.3, 26.9, 25.6, 21.9

υ (cm^{-1}): 3474 (NH), 2935, 1720 (C=O), 1529, 1562

HRMS (ESI): $(M+Na)^+$ calcd. for $C_{34}H_{22}Br_2F_{10}N_4O_2Na$ 888.9848; found 888.9825

5.2.1.19 (*S*)-3,3',4,4'-Bromo-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthalenyl-2,2'-(pentafluorophenyl)-urea (300b)



Procedure A was followed using pentafluorophenyl-isocyanate (**290h**) (23 μL, 0.08 mmol), (*S*)-**299** (37 mg, 0.18 mmol) in CH_2Cl_2 (400 μL) to afford **300b** (40 mg, 56%) as a pale pink solid. m.p. 180-182 °C, $[\alpha]_D^{20}$ -89 (*c* 1.7 $CHCl_3$)

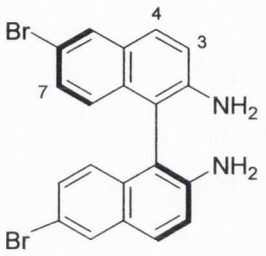
δ_H (400 MHz, $CDCl_3$): 8.42 (s, 2H, NH) 3.31 (m, 4H, H-5), 2.99 (m, 4H, H-8), 2.19 (s, 2H, NH), 1.94 (m, 4H, H-6), 1.74 (m, 4H, H-7)

δ_C (100 MHz, $CDCl_3$): 154.5 (q), 138.0 (q), 135.2 (q), 135.1 (d, J^1 260, J^2 30), 134.1 (app.t, J^1 254), 132.5 (app.t, J^1 245), 131.3 (q), 130.4 (q), 127.1 (q), 124.6 (q), 106.6 (q), 34.7, 34.1, 24.3, 23.9

δ_F (376 MHz, $CDCl_3$): -142.6 (d, 4F, J 16.5), -159.8 (m, 2F), -162.5 (app.t, 4F, J 20.1)

υ (cm^{-1}): 3273, 2735, 1652 (C=O), 1509, 977

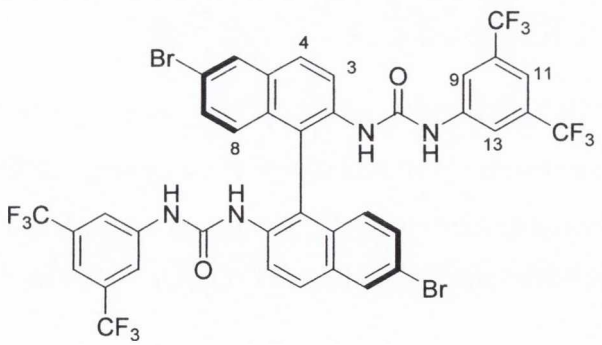
5.2.1.20 (*S*)-6,6'-dibromo[1,1']binaphthylamine (301)



Procedure C was followed using (10 cm^3/100 cm^3) bromine in glacial acetic acid solution (810 μL, 1.44 mmol) was added dropwise to a (*S*)-1,1'binaphthyl-2,2'-diamine (500 mg, 1.75 mmol) in a CH_2Cl_2 (2.5 cm^3) and sodium acetate (303 mg, 3.68 mmol) suspension. The brominated amine (*S*)-**301** was isolated as a brown solid (342 mg, 45%). m.p. 177-180 °C. $[\alpha]_D^{20}$ -16 (*c* 1.43 $CHCl_3$). The spectral data was consistent with those of the literature reference.[359]

δ_H (400 MHz, DMSO): 7.99 (s, 2H, H-5), 7.74 (d, 2H, J 8.8, H-4), 7.22 (m, 4H, H-7 and H-8), 6.66 (d, 2H, J 8.8, H-3), 4.84 (br s, 4H, NH_2)

5.2.1.21 (*S*)-6,6'-dibromo[1,1']binaphthyl-2',2'-(3,5-*bis*-trifluoromethylphenyl-urea (302a)



Procedure A was followed using 3,5-*bis*-trifluoromethyl-isocyanate (**290f**) (82 μL, 0.47 mmol), (*S*)-6,6'-dibromo[1,1']binaphthylamine (**301**) (100 mg, 0.22 mmol) in CH_2Cl_2 (600

μL) to give **302a** as a dark brown solid (55 mg, 26%). m.p. 173-176 °C. $[\alpha]_D^{20}$ -145 (*c* 0.17 $CHCl_3$)

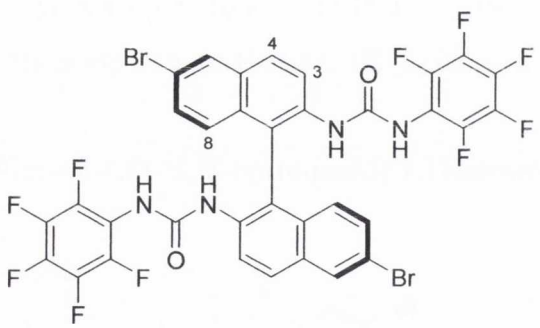
δ_H (400 MHz, $CDCl_3$): 8.29 (d, 2H, J 9.0, H-7), 8.15 (s, 2H, H-5), 8.01 (d, 2H, J 9.3 H-4), 7.76 (s, 4H, H-9 and H-13), 7.48 (m, 2H, H-11) 7.37 (d, 2H, J 9.0, H-8), 7.02 (s, 2H, NH) 6.86 (d, 2H, J 9.3, H-3), 6.58 (s, 2H, NH)

δ_C (100 MHz, $CDCl_3$): 153.1 (q), 139.3 (q), 135.0 (q), 132.1 (qt, C-C, J 33.4), 132.1 (q), 131.2 (q), 130.9, 130.4, 129.0, 126.8, 123.7, 122.8 (qt, C-F, J 271.1), 121.5 (q), 119.9 (q), 118.4, 116.5

υ (cm^{-1}): 3638, 3303, 2927, 1650 (C=O), 1542, 1231.

HRMS (ESI): (M^++Na) Calcd for $C_{38}H_{20}N_4O_2Br_2F_{12}Na$ 972.9659; Found 972.9686

5.2.1.22 (*S*)-6,6'-dibromo[1,1']binaphthyl-2,2'-(pentafluorophenyl)-urea (302b)



Procedure A was followed using pentafluorophenyl isocyanate (**290h**) (37 μL, 0.28 mmol), (*S*)-6,6'-dibromo[1,1']binaphthylamine (**301**) (59 mg, 0.13 mmol) in CH_2Cl_2 (1.0 cm^3) to give **302b** as a dark brown solid (61 mg, 54%). M.p. 74 °C. $[\alpha]_D^{20}$ -169 (*c* 0.17 $CHCl_3$)

δ_H (400 MHz, $CDCl_3$): 8.04 (br d, 2H, J 2.0, H-5), 7.79 (br m, 4H, H-7 and H-8), 7.26 (dd, 2H, J 8.5, 2.0, H-4), 7.11 (s, 2H, NH), 6.94 (s, 2H, NH), 6.79 (d, 2H, J 8.5, H-3)

δ_C (100 MHz, $CDCl_3$): 153.0 (q), 143.4 (d, J^1 250, J^2 29), 142.5 (app.t, J^1 260), 137.1 (app.t, J^1 238), 134.5 (q), 131.8 (q), 130.6 (q), 130.0, 129.8, 128.3, 126.2, 123.5, 122.3 (q), 119.4 (q), 111.2 (q)

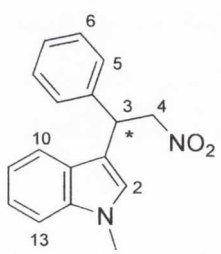
δ_F (376 MHz, $CDCl_3$): -147.0 (d, 4F, 19.0), -157.1 (m, 2F), -163.1 (app. t, 4F, J 20.0)

HRMS (ESI): (M^++Na) Calcd for $C_{34}H_{14}N_4Br_2O_2F_{10}Na$ 880.9222; Found 880.9216

5.2.1.23 Procedure E: general procedure for the organocatalyst-promoted addition of indoles to nitroolefins (Tables 2.1-2.5)

A 1 cm^3 reaction vial containing a stirring bar was charged with the appropriate nitroolefin (0.400 mmol) and catalyst (10-20 mol%). The reaction vessel was then fitted with a septum and placed under an Ar atmosphere. The relevant amount of $CDCl_3$ was added to the reaction *via* syringe. After 5 min the relevant indole (0.800 mmol) was added *via* syringe. The vial was fitted with a sealed cap and stirred for the time and temperature indicated in Tables 2.1-2.5. Samples were taken at intervals and analysed by ^1H NMR spectroscopy. When conversion was adjudged to be complete the solution was diluted with CH_2Cl_2 (1 cm^3) and purified by column chromatography.

5.2.1.24 1-Methyl-3-[2-nitro-1-phenylethyl]-indole (182)



Prepared according to general procedure E using (*E*)-β-nitrostyrene (**27**) (49 mg, 0.33 mmol), **291g** (27 mg, 0.03 mmol), *N*-methylindole (**181**) (84 μL, 0.66 mmol) and $CDCl_3$ (372 μL). The resulting solution was allowed to stir at –30 °C for 117 h. Column chromatography (3:10

CH_2Cl_2-Hexane) afforded **182** (90 mg, 98%) as a clear oil. 30% *ee*. $[\alpha]_D^{20}$ = -13.3 (c 0.1, $CHCl_3$). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 97/3, 0.8 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 18.3 min, minor enantiomer = 15.8 min. The isolated compound exhibited identical spectroscopic data to those in the literature.[168]

δ_H (400 MHz, $CDCl_3$): 7.46 (d, 1H, J 8.0, H-10), 7.23 (m, 7H, Ar-H), 7.07 (m, 1H, Ar-H), 6.88 (s, 1H, H-2), 5.18 (m, 1H, H-3), 5.05 (dd, 1H, J 12.5, 7.5, H-4a) 4.93 (dd, 1H, J 12.5, 8.5, H-4b), 3.77 (s, 3H, CH_3)

υ (cm^{-1}): nujol 1550 (N=O), 1460, 1376 (N=O), 1241, 1083.

5.2.1.25 3-[1-(4-Bromophenyl)-2-nitroethyl]-1-methyl-1H-indole (304a)



Prepared according to general procedure E using 4-bromo nitrostyrene (**103**) (75 mg, 0.33 mmol), **291g** (54 mg, 0.06 mmol), *N*-methylindole (**181**) (84 µL, 0.66 mmol) and $CDCl_3$ (327 µL). The resulting solution was allowed stir at –30 °C for 287 h. Column chromatography (3:10 CH_2Cl_2-hexane, R_f 0.3) afforded **304a** (64 mg, 54 %) as a colourless oil. 28% *ee*. $[\alpha]_D^{20}$ = -1.0 (c 1.0, $CHCl_3$), Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 80/20, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 23.1 min, minor enantiomer = 18.0 min. The isolated compound exhibited identical spectroscopic data to those in the literature.[178]

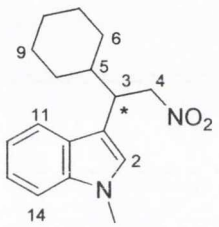
δ_H (400 MHz, $CDCl_3$): 7.46 (d, 2H, J 8.4, H-6 and H-7), 7.41 (d, 1H, J 7.9, H-9), 7.23 (m, 4H, H-5, H-8, H-11, H-12), 7.08 (dd, 1H, J 7.8, 7.1, H-10), 6.86 (s, 1H, H-2), 5.14 (m, 1H, H-3), 5.03 (dd, 1H, J 12.5, 7.5, H-4a), 4.89 (dd, 1H, J 12.5, 9.0, H-4b), 3.78 (s, 3H, CH_3)

δ_C(150 MHz, $CDCl_3$): 138.4 (q), 137.3 (q), 132.0, 129.4, 126.2, 126.3 (q), 122.4, 121.4 (q), 119.6, 118.8, 112.2 (q), 109.6, 79.2, 41.0, 32.9

υ (cm^{-1}): 3054, 2924, 1549 (N=O), 1465, 1376 (N=O), 1334, 1243, 1129, 1073, 816, 740.

HRMS (ESI): (M^++Na) Calcd for $C_{17}H_{15}N_2O_2BrNa$ 381.0215; Found 381.0230

5.2.1.26 3-(1-Cyclohexyl-2-nitroethyl)-1-methyl-1H-indole (304b)

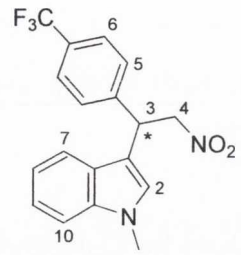


Prepared according to general procedure E using 1-nitro-2-cyclohexyl-ethene (**187**) (43 mg, 0.28 mmol), **291g** (46 mg, 0.056 mmol), *N*-methylindole (**181**) (73 μL, 0.56 mmol) and $CDCl_3$ (313 μL). The resulting solution was allowed stir at –30 °C for 120 h. Column chromatography (3:10 CH_2Cl_2-hexane) afforded **304b** (52 mg, 65 %) as a clear oil. 43% *ee*. $[\alpha]_D^{20}$ = -1.3 (c 0.1, $CHCl_3$), Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 85/15, 0.3 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 32.1 min, minor enantiomer = 30.1 min. The isolated compound exhibited identical spectroscopic data to those in the literature.[178]

δ_H (400 MHz, $CDCl_3$): 7.59 (d, 1H, J 8.0, H-14), 7.20-7.32 (m, 2H, H-11, H-12), 7.11 (app.t, 1H, J 8.0, H-13), 6.86 (s, 1H, H-2), 4.81 (dd, J 12.0, 6.5, H-4a), 4.74 (dd, 1H, J 12.0, 9.0, H-4b) 3.75 (s, 3H, CH_3), 3.65 (m, 1H, H-3) 1.57 (m, 6H, H7-9), 0.85 (m, 5H, H-5, H-6 and H-10)

HRMS (ESI): (M^++Na) Calcd for $C_{17}H_{22}N_2O_2Na$ 309.1579; Found 309.1572

5.2.1.27 3-[1-(4-trifluoromethyl-phenyl)-2-nitro-ethyl]-1-methylindole (304c)



Prepared according to general procedure E using 4-trifluoromethyl-phenyl nitrostyrene (**303a**) (35 mg, 0.16 mmol), **291g** (13 mg, 0.016 mmol), *N*-methylindole (**181**) (42 μL, 0.32 mmol) and $CDCl_3$ (410 μL). The resulting solution was allowed stir at –30 °C for 140 h. Column chromatography (1:1 CH_2Cl_2-hexane) afforded **304c** (50 mg, 89 %) as a brown oil. 36% *ee*. $[\alpha]_D^{20}$ = +0.15 (c 0.25, $CHCl_3$), Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 97/3, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 19.0 min, minor enantiomer = 24.1 min.

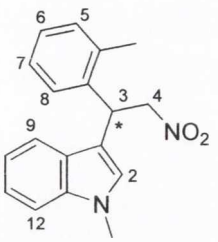
δ_H (400 MHz, $CDCl_3$): 7.60 (d, 2H, J 8.0, H-6), 7.48 (d, 2H, J 8.5, H-5), 7.42 (d, 1H, J 8.0, H-7), 7.32 (d, 1H, J 8.0, H-10), 7.27 (m, 1H, H-9), 7.10 (app.t, 1H, J 8.0, H-8) 6.88 (s, 1H, H-2), 5.25 (m, 1H, H-3) 5.07 (dd, 1H, J 12.5, 7.0, H-4a), 4.95 (dd, 1H, J 12.5, 8.5, H-4b), 3.79 (s, 3H, CH_3)

δ_C (150 MHz, $CDCl_3$): 143.0 (q), 136.8 (q), 129.3 (qt, C-C, J 33), 127.7, 125.9, 125.8, 124.9 (q), 123.6 (qt, C-F, J 272), 122.0, 119.2, 118.2, 111.4 (q), 109.2, 78.5, 40.8, 32.4.

δ_F (376 MHz, $CDCl_3$): -63.0 (s, 3F)

HRMS (ESI): (M^++Na) Calcd for $C_{18}H_{15}N_2O_2F_3Na$ 371.0995; Found 371.0983

5.2.1.28 3-[1-(2-methyl-phenyl)-2-nitro-ethyl]-1-methylindole (304d)



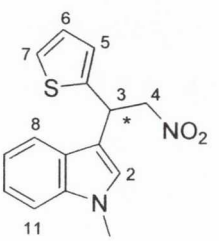
Prepared according to general procedure E using 2-methyl-phenyl nitrostyrene (**303b**) (54 mg, 0.33 mmol), **291g** (54 mg, 0.066 mmol), *N*-methylindole (**181**) (84 μL, 0.66 mmol) and $CDCl_3$ (320 μL). The resulting solution was allowed stir at –30 °C for 115 h. Column chromatography (1:1 CH_2Cl_2-hexane) afforded **304d** (72 mg, 78 %) as an oil. 28% *ee*. $[\alpha]_D^{20}$ = -2.1 (c 0.1, $CHCl_3$), Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 99/1, 0.7 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 39.4 min, minor enantiomer = 36.5 min.

δ_H (400 MHz, $CDCl_3$): 7.50 (d, 1H, J 8.0, H-5), 7.19 (m, 6H, Ar-H), 7.10 (m, 1H, H-6), 6.70 (s, 1H, H-2), 5.42 (m, 1H, H-3), 5.01 (dd, 1H, J 7.4, 7.4, H-4a) 4.91 (dd, 1H, J 8.5, 8.4, H-4b), 3.65 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)

δ_C(150 MHz, $CDCl_3$): 137.3 (q), 137.2 (q), 136.3 (q), 131.1, 127.3, 127.2 (q), 126.6, 126.3, 126.0, 122.2, 119.4, 118.6, 112.5 (q), 109.5, 78.7, 37.1, 32.8, 19.5

HRMS (ESI): (M^++Na) Calcd for $C_{18}H_{18}N_2O_2Na$ 317.1266; Found 317.1260

5.2.1.29 3-(2-nitro-1-thiophen-2-yl-ethyl)-1-methylindole (304e)



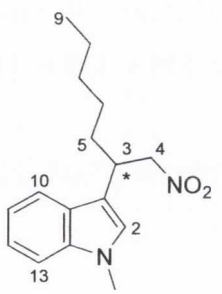
Prepared according to general procedure E using (*E*)-2-(2-nitrovinyl)thiophene (**303c**) (25 mg, 0.16 mmol), **291g** (13 mg, 0.016 mmol), *N*-methylindole **181** (42 μL, 0.32 mmol) and $CDCl_3$ (410 μL). The resulting solution was allowed stir at ambient temperature for 140 h. Column chromatography (CH_2Cl_2) afforded **304e** (27.5 mg, 60 %) as a yellow oil. 12% *ee*. $[\alpha]_D^{20} = -1.9$ (c 0.1, $CHCl_3$), Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA, 97/3, 0.75 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 15.8 min, minor enantiomer = 13.7 min. The isolated compound exhibited identical spectroscopic data to those in the literature.[178]

δ_H (400 MHz, $CDCl_3$): 7.53 (d, 1H, J 8.0, H-8), 7.32 (d, 1H, J 8.0, H-11), 7.27 (m, 1H, H-9), 7.21 (d, 1H, J 5.0, H-5), 7.11 (m, 1H, H-10), 6.96 (m, 3H, H-2, H-6, H-7) 5.45 (m, 1H, H-3), 4.97 (m, 2H, H-4), 3.79 (s, 3H, CH_3)

δ_C(150 MHz, $CDCl_3$): 142.6 (q), 126.4, 126.1, 125.6 (q), 124.6, 124.3, 121.8, 119.1, 118.4, 111.9 (q), 109.1, 79.6, 36.4, 32.4, 30.5 (q).

HRMS (ESI): (M^++Na) Calcd for $C_{11}H_{11}N_aO_2$ 226.0718; Found 226.0641

5.2.1.30 3-(1-nitromethyl-hexyl)-1-Methylindole (304f)



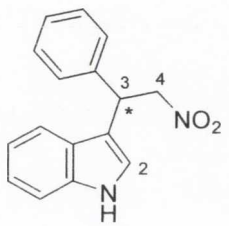
Prepared according to general procedure E using (*E*)-1-nitro-1-octene (**303d**) (52 mg, 0.33 mmol), **291g** (54 mg, 0.066 mmol), *N*-methylindole (**181**) (84 μL, 0.66 mmol) and $CDCl_3$ (321 μL). The resulting solution was allowed stir at –30 °C for 69 h. Column chromatography (CH_2Cl_2) afforded **304f** (72 mg, 76 %) as a colourless oil. 50% *ee*. $[\alpha]_D^{20} = -3.1$ (c 0.5, $CHCl_3$), Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 99/1, 0.30 mL min^{-1}, RT, UV detection at 220

nm, retention times: major enantiomer = 38.3 min, minor enantiomer = 33.0 min. The isolated compound exhibited identical spectroscopic data to those in the literature.[178]

δ_H (400 MHz, $CDCl_3$): 7.62 (d, 1H, J 8.0, H-13), 7.32 (d, 1H, J 8.0, H-10), 7.24 (m, 1H, H-11), 7.13 (app.t, 1H, J 8.0, H-12), 6.91 (s, 1H, H-2), 4.60 (m, 2H, H-4) 3.78 (s, 3H, CH_3), 3.76 (m, 1H, H-3), 1.77 (m, 2H, H-5), 1.22 (m, 6H, H-6, H-7 and H-8), 0.84 (app.t, 3H, J 7.0, H-9)

υ (cm^{-1}): 3431, 2857, 1615, 1550 (N=O), 1469, 1378 (N=O), 1134, 1014, 808, 740.

5.2.1.31 3-(2-Nitro-1-phenyl-ethyl)-1*H*-indole (180)



Prepared according to general procedure E using (*E*)-β-nitrostyrene (**27**) (29 mg, 0.20 mmol), **306** (20 mg, 0.039 mmol) and indole (**162**) (34 mg, 0.29 mmol). The resulting solution was allowed stir at ambient temperature for 10 d. Column chromatography (3:10 CH_2Cl_2-Hexane) afforded **180** (29.8 mg, 56 %) as a clear oil. 10% *ee*. $[\alpha]_D^{20}$ = -10.3 (c 0.1, $CHCl_3$), Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.75 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 36.4 min, minor enantiomer = 33.2 min. The isolated compound exhibited identical spectroscopic data to those in the literature[178]

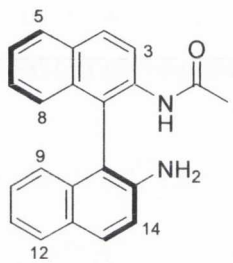
δ_H (400 MHz, $CDCl_3$): 8.10 (br s, 1H, NH), 7.46 (d, 1H, J 8.0, H-5), 7.29 (m, 6H, Ar-H), 7.20 (m, 1H, H-7), 7.07 (m, 1H, H-6), 5.20 (app.t, 1H, J 7.5, H-3), 5.07 (dd, 1H, J 12.5, 8.0, H-4a), 4.94 (dd, 1H, J 12.5, 8.5, H-4b)

δ_C (150 MHz, $CDCl_3$): 138.7 (q), 136.0 (q), 128.4, 127.3, 127.1, 125.6 (q), 122.2, 121.1, 119.5, 118.4, 114.0 (q), 110.9, 79.0, 41.0

5.2.3 Experimental for Section 2.3

5.2.3.1 Procedure F: general procedure for the preparation of the precursor amine 307c for the synthesis of the binaphthyl-based catalysts (*S*)-305 and (*S*)-306 using the literature procedure.[342]

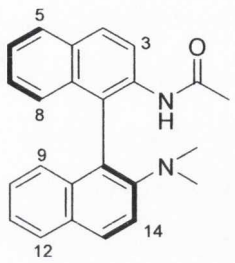
5.2.3.2 (*S*)-*N*-acetyl-1,1'-binaphthyl-2,2'-diamine (307a).



To a solution of (*S*)-1,1'-binaphthyl-2,2'-diamine (**112**) (800 mg, 2.8 mmol) and acetic acid (1.6 cm^3, 28.0 mmol) in CH_2Cl_2 (48 cm^3) was added acetic anhydride (318 μL, 3.37 mmol) at 0 °C under N_2. The resulting solution was stirred for overnight at room temperature, then 2M NaOH aqueous solution was added until the pH of the resulting solution was neutral. The reaction mixture was extracted with CH_2Cl_2 (3 × 150 cm^3) and the combined organic phases were washed with saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product purified using flash chromatography (CH_2Cl_2:hexane = 1/1) to afford **307a** (0.548 mg, 60%) as a white solid. Mp 239-242 °C (lit., 240-241 °C).[342] The isolated compound exhibited identical spectroscopic data to those in the literature.[342]

δ_H (400 MHz, $CDCl_3$): 8.62 (d, 1H, J 9.0, H-4), 8.01 (d, 1H, J 9.0, H-3), 7.85 (m, 3H, H-5, H-9 and H-12), 7.41 (app.t, 1H, J 7.5, H-6), 7.22 (m, 3H, H-7, H-10 and H-11 (overlap with $CDCl_3$)), 7.10 (m, 2H, H-13 and H-14), 6.94 (d, 1H, J 8.5, H-8), 1.86 (s, 3H, CH_3)

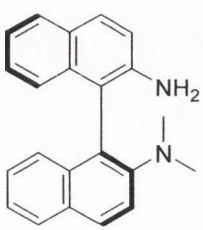
5.2.3.3 (*S*)-*N*-Acetyl-*N*',*N*'-dimethyl-1,1'-binaphthyl-2,2'-diamine (307b).



A solution of (*S*)-*N*-acetyl-1,1'-binaphthyl-2,2'-diamine (**307a**) (0.472 g, 1.45 mmol) in THF (20 cm^3) and $NaBH_4$ (383 mg, 10.0 mmol) were simultaneously added to a stirred solution of 20% H_2SO_4 (1.4 cm^3) and 40% formaldehyde aqueous solution (0.48 cm^3, 17.4 mmol) at 0 °C over a period of 15 min. The reaction mixture was allowed to stir for an additional 1.5 h upon which time 1M NaOH aqueous solution was added until the pH of the resulting solution was neutral. The reaction mixture was extracted using ethyl acetate (3 × 100 cm^3) and the combined organic phases were washed with saturated brine solution (3 x 20 cm^3) and dried ($MgSO_4$). The solvent was removed under pressure to afford **307b** (501 mg, 98%) as a white solid which did not require further purification. m.p 186-189 °C (lit., 187-189 °C).[342] The isolated compound exhibited identical spectroscopic data to those in the literature.[342]

δ_H (400 MHz, $CDCl_3$): 8.48 (d, 1H, J 9.0, H-4), 7.98 (d, 1H, J 8.5, H-3), 7.91 (d, 1H, J 8.0, H-5), 7.86 (d, 1H, J 8.0, H-12), 7.39 (dd, 1H, J 8.0, 7.0, H-6), 7.33 (dd, 1H, J 7.5, 7.0, H-10), 7.12 (m, 3H, H-7, H-8 and H-11), 6.95 (m, 3H, J 8.5, H-12, H-13 and H-14), 2.59 (s, 6H, $2CH_3$), 1.89 (s, 3H, CH_3)

5.2.3.4 (*S*)-*N*,*N*-dimethyl-1,1'-binaphthyl-2,2'-diamine (307c)



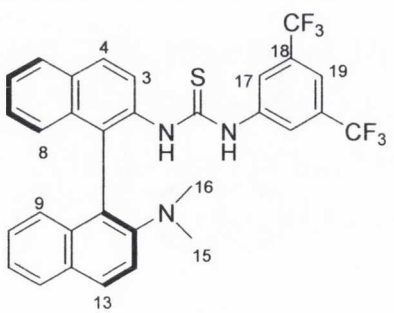
To a solution of (*S*)-*N*-acetyl-*N*',*N*'-dimethyl-1,1'-binaphthyl-2,2'-diamine (**307b**) (362 mg, 1.02 mmol) in 30 cm^3 of ethanol was added 4M HCl (11 cm^3). The resulting solution was stirred for 12h at ambient temperature. 2M NaOH aqueous solution was added until l the pH of the resulting solution was neutral. The reaction mixture was extracted using CH_2Cl_2 (3 × 70 cm^3) and the combined organic phases were washed with saturated brine solution (3 x 10 cm^3) and dried ($MgSO_4$). The solvent was removed under pressure and the crude product was purified using flash chromatography (CH_2Cl_2:hexane = 1/1) to afford **307c** (174 mg, 55%) as a pale yellow solid. m.p 115-117 °C (lit., 116-118 °C).[342] The isolated compound exhibited identical spectroscopic data to those in the literature.[342]

δ_H (400 MHz, $CDCl_3$): 7.91 (d, 1H, J 8.0, H-5), 7.79 (m, 3H, H-8, H-13 and H-14), 7.50 (d, 1H, J 9.0, H-12), 7.31 (m, 1H, H-10), 7.13 (m, 5H, H-3, H-4, H-6, H-7, and H-11), 7.04 (d, 1H, J 8.0, H-9)), 3.73 (br s, 2H, NH_2), 2.59 (s, 6H, $2CH_3$)

5.2.3.5 Procedure G: general procedure for the preparation of the binaphthyl-based catalysts (*S*)-305 and (*S*)-306-incorporation of the (thio)urea motif

To a solution of (*S*)-*N*,*N*-dimethyl-1,1'-binaphthyl-2,2'-diamine (**307c**) in CH_2Cl_2 in a sealed flask under N_2 was added *via* syringe the relevant iso(thio)cyanate at 0 °C. The reaction mixture was allowed to stir to warm to room temperature and stirred for 12 h. The solvent was then removed under reduced pressure and the crude product purified using flash chromatography.

5.2.3.6 (*S*)-1-1(3,5-*Bis*(trifluoromethyl)phenyl)-3-(1-(2-dimethylamino)naphthyl-thiourea (305)



Prepared according to general procedure G using (*S*)-1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-amine (**307c**) (365 mg, 1.16 mmol) in CH_2Cl_2 (5 cm^3) and 3,5-*bis*-trifluoromethyl isothiocyanate (**290g**) (223 μL, 1.22 mmol). Column chromatography (CH_2Cl_2/hexane 1:1) afforded (*R*)-**305** as a yellow solid (600 mg, 89 %). M.p 102-105 °C (m.p not specified in the literature references).[341,360] $[\alpha]_D^{20}$ = -87 (*c* 1.6, $CHCl_3$). The isolated compound exhibited identical spectroscopic data to those in the literature.[341]

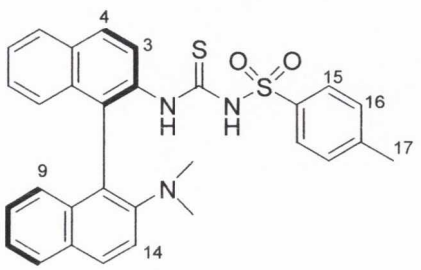
δ_H (400 MHz, $CDCl_3$): 8.37 (s, 1H, NH), 8.08 (d, 1H, J 8.5, H-4), 7.99 (app.t, 2H, J 8.5, H-5 and H-6), 7.84 (d, 1H, J 8.5, H-3), 7.74 (d, 1H, J 8.5, NH), 7.51 (m, 5H, H9-H-13), 7.38 (s, 2H, H-17 and H-21), 7.28 (m, 2H, H-19 and H-7, overlap with $cdcl_3$), 7.11 (app.t, 1H, J 8.0, H-8), 6.92 (d, 1H, J 8.5, H-14), 2.58 (s, 6H, $2CH_3$)

δ_C (100 MHz, $CDCl_3$): 179.3 (q), 173.8 (q), 165.3 (q), 159.4 (q), 139.1, 133.5 (q), 132.7 (q), 132.4 (q), 131.4 (q), 131.2 (qt, C-C, J 33.8), 130.0, 129.5, 128.1, 128.0, 127.5, 127.2 ,126.8, 124.9, 124.6, 124.4, 124.2, 124.0, 123.8, 123.5 (qt, C-F, J 272), 118.9, 44.0

ν_{max} Diff: 2926, 1619 (C=O), 1504, 1472, 1378, 1274, 1171, 1127, 983, 815, 747, 680

HRMS (ESI): (M^++H) Calcd for $C_{31}H_{24}N_3SF_6$ 584.1595; Found 584.1581

5.2.3.7 (*S*)-1-1(4-toluene-sulfonyl)-3-(1-(2-dimethylamino)naphthalene-1-yl)naphthalene-2-yl)thiourea (306)



Prepared according to general procedure G using (*S*)-*N*,*N*-dimethyl-1,1'-binaphthyl-2,2'-diamine (**307c**) (400 mg, 1.4 mmol) in CH_2Cl_2 (3 cm^3) and para-toluenesulfonyl-isothiocyanate (**308**) (492 μL, 3.2 mmol). Column chromatography (CH_2Cl_2/hexane 1:1) afforded (*R*)-**306** (247 mg, 87 %) as a white solid. m.p 202-204 °C. $[\alpha]_D^{20}$ = -35.6 (c 1.8, $CHCl_3$).

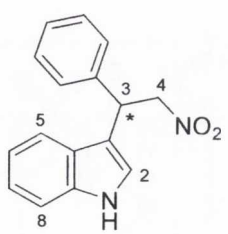
δ_H (400 MHz, $CDCl_3$): 8.70 (s, 1H, tosyl NH), 8.41 (d, 1H, J 8.5, H-4), 8.04 (d, 1H, J 8.5, H-3), 7.89 (m, 3H, H-5, H-6 and H-7), 7.61 (d, 1H, J 9.0, H-8), 7.40 (m, 2H, H-9 and H-10), 7.18 (m, 3H, H-11, H-12 and H-13), 6.90 (d, 1H, J 8.5, H-14), 6.74 (d, 2H, J 8.5, H-15), 6.68 (d, 2H, J 8.5, H-16), 2.60 (s, 6H, $2CH_3$), 2.24 (s, 3H,CH_3), the other NH was not visible.

δ_C (100 MHz, $CDCl_3$): 150.1 (q), 148.4 (q), 144.0 (q), 135.4 (q), 133.5 (q), 133.2 (q), 132.5 (q), 130.7 (q), 129.5 (q), 129.2, 129.3, 128.2, 127.7, 127.6, 126.1, 126.1, 126.0, 126.0, 125.0, 124.8 (q), 124.5, 123.2, 120.7, 120.4 (q), 119.3, 43.0, 21.0

ν_{max} Diff 2924, 1687, 1596, 1503, 1427, 1340 (S=O), 1264, 1155 (S=O), 1047

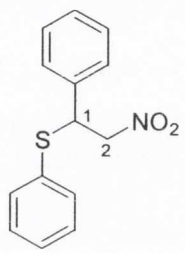
HRMS (ESI): (M^++H) Calcd for $C_{30}H_{28}N_3O_3S$ 510.1836; Found 510.1851

5.2.3.8 3-(2-Nitro-1-phenyl-ethyl)-1*H*-indole (180)



Prepared according to general procedure E using (*E*)-β-nitrostyrene (**27**) (29 mg, 0.20 mmol), **306** (20 mg, 0.039 mmol) and indole (**162**) (34 mg, 0.29 mmol). The resulting solution was allowed stir at ambient temperature for 266 h. Column chromatography (3:10 CH_2Cl_2-Hexane) afforded **180** (23.9 mg, 45 %) as a clear oil. 4% *ee*. $[\alpha]_D^{20}$ = +1.4 (c 1.0, $CHCl_3$), Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.75 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 36.4 min, minor enantiomer = 33.2 min. The isolated compound exhibited identical spectroscopic data to those in the literature.[178] See Section 5.2.1.31 for spectral data.

5.2.3.9 3-(3-Nitro-2-phenyl-ethyl)-1-thiophenol (309c)



To a solution of (*E*)-β-nitrostyrene (34 mg, 0.23 mmol) in CH_2Cl_2 (2.0 cm^3) was added **306** (23 mg, 0.045 mmol) followed by the addition of thiophenol (23 cm^3, 0.23 mmol) *via* syringe. After stirring for 71 h at –30 °C the reaction was diluted with CH_2Cl_2 (2.0 cm^3). Flash chromatography (CH_2Cl_2:hexane 1:1) afforded **309c** as a yellow solid. 0% *ee*. m.p 73-74 °C (lit., 72-73 °C)[361] The isolated compound exhibited identical spectroscopic data to those in the literature.[361]

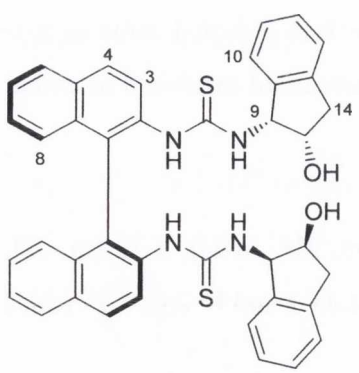
δ_H (400 MHz, $CDCl_3$): 6.41 (m, 2H, Ar-H), 7.32 (m, 5H, Ar-H), 7.27 (m, 3H, Ar-H), 4.89 (m, 2H, H-1 and H-2a), 4.71 (dd, 1H, J 4.6, 4.6, H-2b)

5.2.4 Experimental for Section 2.4

5.2.4.1 Procedure I: general procedure for the preparation of the binaphthyl-indanol based catalysts (*S,R,S*)-310 and (*S,S,R*)-310

To a solution of (*S*)-1,1'-binaphthyl-2, 2'-diamine (**112**) (256 mg, 0.90 mmol) in CH_2Cl_2 (5 cm^3) was added a saturated sodium carbonate solution (5 cm^3) at 0 °C. This solution was allowed stir for 5 min after which the reaction stirrer was stopped and thiophosgene (207 μL, 1.89 mmol) was added *via* syringe to the organic layer of the reaction at 0 °C, upon which addition the reaction turned a bright orange colour. The stirring of the reaction was re-commenced for a further 4 hours after which time the reaction appeared a bright yellow colour. At this stage the reaction was washed with CH_2Cl_2 (3 x 20 cm^3), the organic extracts were dried ($NaSO_4$) and the solvent reduced under reduced pressure to afford the isothiocyanate intermadiate (*S*)-**311** as a yellow liquid. No purification was necessary and (1*R*, 2*S*) or (1*S*, 2*R*)-*cis*-1-amino-2-indanol (282 mg, 1.89 mmol) was added *via* syringe in CH_2Cl_2 (2 cm^3) and the rseulting solution allowed to stir for 12 h under an inert atmosphere. The solvent was removed under reduced pressure to afford a pale yellow solid which was purified *via* column chromatography (7:3 ethyl acetate:hexane) to yield the thiourea catalyst **310** as a pale yellow solid.

5.2.4.2 (*S*)-1,1'-binaphthyl-2, 2'-(hydroxy indanol)-thiourea (*S,R,S*-310)



Prepared according to general procedure I using (*S*)-1,1'-binaphthyl-2, 2'-diamine (**112**) (256 mg, 0.90 mmol), saturated sodium carbonate (5 cm^3) and thiophosgene (207 μL, 1.89 mmol) in CH_2Cl_2 (5 cm^3), and (1*R*, 2*S*)-*cis*-1-amino-2-indanol (**312**) (282 mg, 1.89 mmol). Column

chromatography (7:3 Ethyl acetate:hexane) afforded (*S,R,S*)-**310** (450 mg, 75 %) as a white solid. m.p 201-204 °C, $[\alpha]_D^{20} = -110$ (c 1.16, $CHCl_3$).

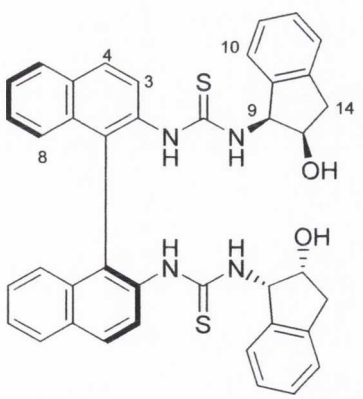
δ_H (400 MHz, DMSO): 9.09 (s, 2H, NH), 8.06 (d, 2H, J 9.0, H-4), 7.93 (m, 4H, H-3 and H-10), 7.58 (dd, 2H, J 8.0, 7.0, H-11), 7.45 (d, 2H, J 8.0, H-13), 7.31 (dd, 2H, J 8.0, 7.0, H-12), 7.05 (m, 4H, H-5 and H-6), 6.86 (dd, 2H, J 7.5, 7.0, H-8), 6.12 (d, 2H, J 7.0, H-8), 5.67 (m, 2H, H-9), 5.25 (m, 2H, H-15), 4.39 (m, 2H, OH), 2.97 (app d, 2H, J 16.0, H-14a), 2.67 (app d, 2H, J 16.0, H14b), the other NH not visible.

δ_C (100 MHz, DMSO): 181.9 (q), 142.0 (q), 139.8 (q), 137.2 (q), 132.1 (q), 131.3 (q), 127.8, 127.6, 126.7, 126.5, 126.1, 126.0 (q), 125.8, 125.7, 125.3, 124.5, 124.1, 72.1, 61.3, 40.1

ν_{max} (Diff)/cm^{-1} 3295, 1737, 1601 (C=O), 1522, 1503, 1430, 1284, 1043, 983

HRMS (ESI): (M^++Na) Calcd for $C_{40}H_{34}N_4O_2NaS_2$ 689.2045; Found 689.2021

5.2.4.3 (*S*)-1,1'-binaphthyl-2, 2'-(hydroxy indanol)-thiourea (*S,S,R*-310)



Prepared according to general procedure I using (*S*)-1,1'-binaphthyl-2, 2'-diamine (**112**) (256 mg, 0.90 mmol), saturated sodium carbonate (5 cm^3) and thiophosgene (207 µL, 1.89 mmol) in CH_2Cl_2 (5 cm^3), and (1*S*, 2*R*)-*cis*-1-amino-2-indanol **312** (282 mg, 1.89 mmol). Flash

chromatography (7:3 Ethyl acetate:hexane) afforded **310b** (390 mg, 65 %) as a white solid. m.p 185-187°C. $[\alpha]_D^{20} = -120$ (c 0.4, $CHCl_3$).

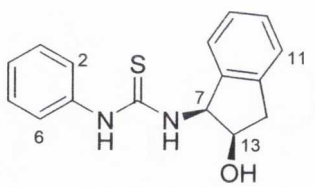
δ_H (400 MHz, DMSO): 9.30 (s, 2H, NH), 8.11 (m, 4H, H-4 and H-10), 8.02 (d, 2H, J 8.5, H-3), 7.89 (d, 2H, J 7.5, H-13), 7.48 (dd, 2H, J 7.5, 7.0, H-11), 7.26 (dd, 2H, J 8.0, 7.5, H-12), 7.06 (m, 6H, H-5-H-7), 6.97 (d, 2H, J 8.0, H-8), 5.65 (m, 2H, H-9), 5.30 (m, 2H, H-15), 4.40 (m, 2H, OH), 2.97 (app.d, 2H, J 16.0, H-14a), 2.68 (app.d, 2H, J 16.0, H14b), the other NH resonance was not visible.

δ_C (100 MHz, $CDCl_3$): 178.3 (q), 139.9 (q), 139.7 (q), 132.6 (q), 131.7 (q), 131.4 (q), 131.1, 128.4, 127.8, 126.8, 126.7, 126.6, 126.4 (q), 124.9, 124.8, 123.9, 122.3, 70.8, 62.5, 39.5

ν_{max} (Diff)/cm^{-1} 3285, 3041, 1594 (C=O), 1503, 1428, 1268, 1155, 1046, 985

HRMS (ESI): (M^++Na) Calcd for $C_{40}H_{34}N_4O_2NaS_2$ 689.2024; Found 689.2021

5.2.4.4 (*S*)-1-(2-Hydroxy-indanol)-3-phenyl)-thiourea (314)



Prepared according to general procedure A using phenylisocyanate (**290c**) (200 μL, 1.67 mmol), in CH_2Cl_2 (1 cm^3) and (1*S*, 2*R*)-*cis*-1-amino-2-indanol (**312**) (250 mg, 1.67 mmol). The resulting solution was allowed stir at ambient temperature for 12 h. Column chromatography (1:1 CH_2Cl_2:hexane.R_f 0.6) afforded **314** (470 mg, 99 %) as a white solid. M.p. 209-212 °C

δ_H (400 MHz, $CDCl_3$): 8.05 (s, 1H, NH), 7.38 (m, 3H, Ar-H), 7.29 (m, 6H, Ar-H), 6.76 (d, 1H, J 8.0, OH), 5.99 (dd, 1H, J 7.0, 5.0, H-7), 4.81 (m, 1H, H-13), 3.21 (dd, 1H, J 16.5, 5.0, H-12a), 2.90 (dd, 1H, J 16.5, 5.0, H-12b)

δ_C (100 MHz, $CDCl_3$): 180.4 (q), 139.4 (q), 139.3 (q), 135.4 (q), 129.8, 128.0, 126.9, 126.8, 125.0, 124.4, 124.2, 73.1, 62.7, 39.3

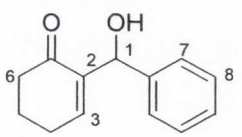
υ (cm^{-1}): 3401, 3209, 1590 (C=O), 1526, 1489, 1240, 1046.

HRMS (ESI): (M^++Na) Calcd for $C_{16}H_{16}N_20Na$ 307.0881; Found 307.0876

5.2.4.5 Procedure H: general procedure for the Baylis-Hillman reaction catalysed by catalysts (*S*)-**291g**, (*S,R*)-**314** and (*S,R,S*)-**310 (Table 2.6-2.8)**

Using a 10 cm^3 vial containing the relevant aldehyde (1.0 equiv.) the relevant catalyst (10-20 mol%) was added and the vial flushed with nitrogen. The cyclohexen-1-one (**93**) (4.0 equiv.) was subsequently added *via* syringe under N_2. After 62-210 h stirring, the reaction mixture was quenched by dilution with CH_2Cl_2. The residue was then subsequently purified using flash chromatography.

5.2.4.6 2-(1-Hydroxy-1-phenylmethyl)-2-cyclohexen-l-one (151)

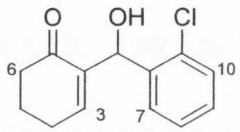


Prepared according to general procedure H using benzaldehyde (**32**) (23 μL, 0.22 mmol), DABCO (5 mg, 0.044 mmol) and cyclohexen-1-one (**93**) (87 μL, 0.90 mmol) and (*S,S,R*)-**310** (30 mg, 0.044 mmol). 23% Conversion. Column chromatography (CH_2Cl_2/hexane 1:1) afforded **151** as a colourless oil. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 85/15, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 7.5 min, minor enantiomer = 9.5 min. 21% *ee*. The isolated compound exhibited identical spectroscopic data

to those in the literature.[362] $[\alpha]_D^{20}$ = +12.8 (c 0.1, $CHCl_3$). An identical procedure was followed in the evaluation of catalyst (*S*,*R*,*S*)-**310**.

δ_H (400 MHz, $CDCl_3$): 7.36 (m, 5H, H-7-11), 6.75 (d, 1H, J 4.0, H-3), 5.58 (s, 1H, H-1), 3.70 (br s, 1H, OH), 2.40 (m, 4H, H-4, H-6), 2.00 (m, 2H, H-5)

5.2.4.7 2-[1-Hydroxy-1-(2-chlorophenyl)methyl]-2-cyclohexen-1-one (309a)

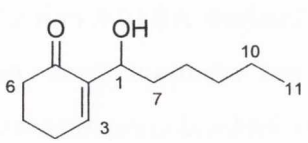


Prepared according to general procedure H using 2-chlorobenzaldehyde (**47**) (25.3 μL, 0.22 mmol) and cyclohexen-1-one (**93**) (86.7 μL, 0.90 mmol), (*S*,*S*,*R*)-**310** (30.0 mg, 0.045 mmol) and DABCO (5 mg, 0.045 mmol). 85% Conversion. Column chromatography (CH_2Cl_2:hexane 1:1) afforded **309a** as a colourless oil. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 85/15, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 11.2 min, minor enantiomer = 8.3 min. 11% *ee*. The isolated compound exhibited identical spectroscopic data to those in the literature.[341] $[\alpha]_D^{20}$ = +10.5 (c 0.1, $CHCl_3$). An identical procedure was followed in the evaluation of catalysts (*S*)-**291g**, (*S*,*R*)-**314** and (*S*,*R*,*S*)-**310**.

δ_H (400 MHz, $CDCl_3$): 7.29 (m, 4H, Ar-H), 6.74 (app.t, 1H, J 4.0, H-3), 5.57 (d, 1H, J 5.0, H-1), 3.46 (d, 1H, J 5.0, OH), 2.48 (m, 2H, H-6), 2.39 (m, 2H, H-4), 2.00 (m, 2H, H-5)

HRMS (ESI): (M^++Na) Calcd for $C_{13}H_{13}O_2ClNa$ 259.0502; Found 259.0513

5.2.4.8 2-(1-Hydroxypentyl)cyclohex-2-enone (309b)



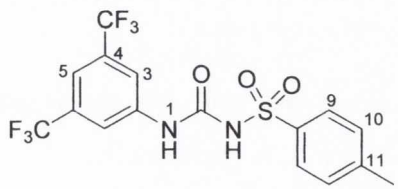
Prepared according to general procedure H using hexanal (**80**) (27.6 μL, 0.22 mmol) and cyclohexen-1-one (**93**) (86.7 μL, 0.90 mmol), (*S,S,R*)-**310** (30.0 mg, 0.045 mmol) and DABCO (5 mg, 0.045 mmol). Conversion 32%. Column chromatography (ethyl acetate/hexane 1:1) afforded **309b** as a brown oil. Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 90/10, 1.0 mL min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 6.45 min, minor enantiomer = 8.50 min. 62% *ee*. The isolated compound exhibited identical spectroscopic data to those in the literature.[341] $[\alpha]_D^{20} = +9.5$ (c 0.1, $CHCl_3$). An identical procedure was followed in the evaluation of catalysts (*S*)-**291g**, (*S,R*)-**314** and (*S,R,S*)-**310**.

δ_H (400 MHz, $CDCl_3$): 6.87 (app.t, 1H, J 4.0, H-3), 4.29 (m, 1H, H-1), 2.90 (br d, 1H, J 7.0, OH), 2.38 (m, 4H, H-5, H-6), 1.99 (m, 2H, H-4), 1.50 (m, 2H, H-7), 1.36 (m, 1H, H-8a), 1.22 (m, 5H, H-8b-H-10), 0.88 (m, 3H, H-11)

ν(neat NaCl) 3431, 2857, 1615, 1550, 1469, 1378, 1329, 1134, 1014, 808, 740

5.3.1 Experimental for Section 3.1

5.3.1.1 *N*-benzoyl-4-methyl-(3,5-bistrifluoromethyl)urea (316)



Prepared according to general procedure A using *p*-toluenesulfonyl isocyanate (643 μL, 4.22 mmol), in CH_2Cl_2 (5.0 cm^3) and 3,5-trifluoromethylaniline (600 μL, 3.84 mmol). A white precipitate was observed after 10 min. The resulting solution was stirred for 12 h. The reaction was filtered, and purified by recystallisation (CH_2Cl_2-hexane, R_f 0.1) to afford **316** (1.52 g, 93%) as a white solid. M.p 185-187 °C

δ_H (400 MHz, $CDCl_3$): 8.92 (br s, 1H, NH), 7.95 (s, 2H, H-3 and H-7), 7.84 (d, 2H, J 5.4, H-9 and H-13), 7.66 (s, 1H, H-5), 7.39 (d, 2H, J 5.4, H-10 and H-12), 2.48 (s, 3H, CH_3), the other NH resonance was not visible.

δ_C (100 MHz, $CDCl_3$): 148.4 (q), 145.9 (q), 138.2 (q), 136.0 (q), 132.6 (qt, C-C, J 33.9), 130.4, 126.9, 122.9 (qt, C-F, J 273.0), 119.8, 118.1, 21.6.

ν_{max} (Nujol)/cm^{-1} 3157, 1693 (C=O), 1276, 1162 (S=O), 1147

HRMS(ESI) (M^++Na) Calcd for $C_{16}H_{12}N_2O_3SF_6Na$ 449.0371; Found 449.0389

5.3.1.2 Procedure I: general procedure for the synthesis of epoxides using *m*CPBA (Scheme 3.1)

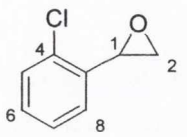
An oven-dried 50 cm^3 round bottomed flask containing a stirring bar was charged with the appropriate alkene (2.77 mmol), and CH_2Cl_2 (10 cm^3) which were stirred for 15 min at 0 °C. To the cooled reaction solution *m*CPBA (2.91 mmol) was added in two equal amounts. The resultant solution was fitted with a septum, flushed with argon gas and allowed to stir for 5 h while warming to ambient temperature. The reaction was washed with Na_2CO_3 (3 x 20 cm^3), the organic layer was then extracted with CH_2Cl_2 (2 x 50 cm^3), dried ($MgSO_4$) and the organic extracts concentrated *in vacuo*. Purification was carried out using column chromatography.

5.3.1.3 Procedure J: general procedure for the synthesis of epoxides using trimethylsulfonium iodide (Scheme 3.2)

An oven-dried 50 cm^3 round bottomed flask containing a stirring bar was charged with trimethylsulfonium iodide (1.0 equiv.), *tert*-butanol (500 µL), distilled water (100 µL) and CH_2Cl_2 (1.4 cm^3) and allowed to stir for 15 min at ambient temperature. To this mixture the appropriate aldehyde (1.0 equiv.) and KOH (1.70 equiv.) were added, the reaction was allowed to stir at ambient temperature for 12 h. A further aliquot of KOH (2.4 mmol) was added and the resulting mixture heated under reflux at 60 °C for 3 h after which time the reaction was diluted with 5 cm^3 of water, followed by extraction of the organic layer with

CH_2Cl_2 (2 x 10 cm^3), the organic layer dried ($MgSO_4$) and the reaction concentrated *in vacuo* to afford the epoxide. If necessary, purification was carried out using column chromatography.

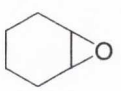
5.3.1.4 2-Chlorostyrene oxide (130b)



Prepared according to general procedure J using trimethylsulfonium iodide (726 mg, 3.55 mmol), 2-chlorobenzaldehyde (500 mg, 3.55 mmol) and KOH (339 mg, 6.03 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **361b** (367 mg, 67 %) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[363]

δ_H (400 MHz, $CDCl_3$): 7.36 (d, 1H, J 8.0, H-5), 7.23 (m, 3H, Ar-H), 4.23 (dd, 1H, J 4.5, 2.5, H-1), 3.20 (dd, 1H, J 6.0, 4.5, H-2a), 2.68 (dd, 1H, J 6.0, 2.5, H-2b)

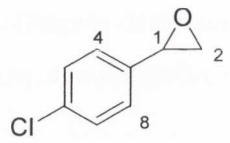
5.3.1.5 Cyclohexene oxide (130d)



Prepared according to general procedure I using cyclohexene (280 μL, 2.77 mmol), and *m*CPBA (500 mg, 2.91 mmol) in CH_2Cl_2 (10 cm^3) which were stirred at 0 °C for 5 h. General procedure K workup afforded pure **130d** (258 mg, 95%) as a colourless oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[364]

δ_H (400 MHz, $CDCl_3$): 3.14 (br s, 2H), 1.93 (m, 2H), 1.79 (m, 2H), 1.29 (m, 2H), 1.22 (m, 2H)

5.3.1.6 4-Chlorostyrene oxide (261b)

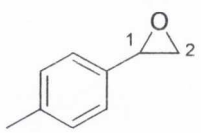


Prepared according to general procedure J using trimethylsulfonium iodide (726 mg, 3.55 mmol), 4-chlorobenzaldehyde (500 mg, 3.55 mmol) and KOH (339 mg, 6.03 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **361b** (411 mg, 75 %) as a clear oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[365]

δ_H (400 MHz, $CDCl_3$): 7.32 (d, 2H, J 8.5 H-4 and H-8), 7.21 (d, 2H, J 8.5, H-5 and H-7), 3.84 (dd, 1H, J 4.0, 2.5, H-1), 3.15 (dd, 1H, J 5.5, 4.0, H-2a,), 2.76 (dd, 1H, J 5.5, 2.5, H-2b)

δ_C (100 MHz, $CDCl_3$): 136.1 (q), 133.9 (q), 128.7, 126.8, 51.8, 51.2

5.3.1.7 4-Methylstyrene oxide (261c)

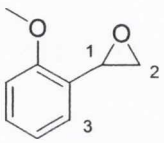


Prepared according to general procedure J using trimethylsulfonium iodide (1.09 g, 5.34 mmol), 4-methylbenzaldehyde (600 µL, 5.09 mmol) and KOH (486 mg, 8.65 mmol). Column chromatography was not necessary therefore the epoxide was dried under high vacuum for 1 h to afford **261c** (691 mg, 99%) as a yellow liquid. The isolated compound exhibited identical spectroscopic data to those in the literature.[365]

δ_H (400 MHz, $CDCl_3$): 7.18 (m, 4H, Ar-H), 3.84 (dd, 1H, J 4.0, 2.7, H-1), 3.14 (dd, 1H, CH, J 5.5, 4.0, H-2a), 2.81 (dd, 1H, CH. J 5.5, 2.7, H-2b), 2.36 (s, 3H, CH_3)

δ_C (100 MHz, $CDCl_3$): 137.5 (q), 134.0 (q), 128.7, 125.0, 51.9, 50.7, 20.7

5.3.1.8 2-Methoxystyrene oxide (325a)

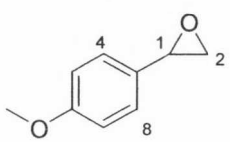


Prepared according to general procedure J using trimethylsulfonium iodide (9.06 g, 44.0 mmol), 2-methoxybenzaldehyde (1.20 g, 8.88 mmol) and KOH (4.98 g, 88.8 mmol). (Epoxide **325a** decomposes during column chromatography therefore the reaction solution was allowed to reflux for a further 2 h (5 h in total) to ensure complete conversion of the aldehyde. General workup in procedure L afforded **325a** (1.29 g, 98 %) as a yellow oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[365]

δ_H (400 MHz, $CDCl_3$): 7.27 (m, 1H, H-5), 7.16 (d, 1H, J 7.5, H-3), 6.95 (app.t, 1H, J 7.5, 7.5, H-4), 6.90 (d, 1H, J 8.0, H-6), 4.23 (m, 1H, H-1), 3.90 (s, 3H, OCH_3), 3.16 (dd, 1H, J 4.5, 5.0, H-2a), 2.72 (dd, 1H, J 4.5, 2.0, H-2b)

δ_C (100 MHz, $CDCl_3$): 158.0 (q), 128.6, 125.9 (q), 124.8, 120.5, 109.9, 55.2, 50.4, 48.0

5.3.1.9 4-Methoxy styrene oxide (325b)

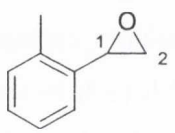


Prepared according to general procedure J using trimethylsulfonium iodide (749 mg, 3.67 mmol), 4-methoxybenzaldehyde (500 mg, 3.67 mmol) and KOH (350 mg, 6.24 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **325b** (251 mg, 46%) as a yellow liquid. The isolated compound exhibited identical spectroscopic data to those in the literature.[365]

δ_H (400 MHz, $CDCl_3$): 7.22 (d, 2H, J 8.5, H-4 and H-8), 6.90 (d, 2H, J 8.5, H-5 and H-7), 3.85 (m (dd and s), 4H, H-1 and OCH_3), 3.14 (dd, 1H, J 5.0, 4.5, H-2a), 2.82 (dd, 1H, J 5.0, 2.5, H-2b)

δ_C (100 MHz, $CDCl_3$): 159.5 (q) 129.3 (q), 126.7, 113.8, 55.1, 52.0, 50.8

5.3.1.10 2-Methylstyrene oxide (325c)

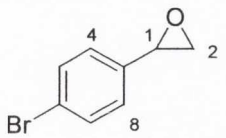


Prepared according to general procedure J using trimethylsulfonium iodide (1.11 g, 5.45 mmol), 2-methylbenzaldehyde (600 μL, 5.18 mmol) and KOH (494 mg, 8.80 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **325c** (643 mg, 93%) as a yellow liquid. The isolated compound exhibited identical spectroscopic data to those in the literature.[366]

δ_H (400 MHz, $CDCl_3$): 7.21 (m, 4H, Ar-H), 4.01 (dd, 1H, J 4.0, 2.5, H-1), 3.17 (dd, 1H, J 5.8, 4.0, H-2a), 2.70 (dd, 1H, J 5.8, 2.5, H-2b), 2.44 (s, 3H, CH_3)

δ_C (100 MHz, $CDCl_3$): 136.1 (q), 135.8 (q), 128.9, 127.6, 126.1, 124.0, 50.4, 50.1, 18.7

5.3.1.11 4-Bromostyrene oxide (325d)

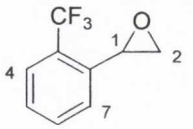


Prepared according to general procedure J using trimethylsulfonium iodide (551 mg, 2.70 mmol), 4-bromobenzaldehyde (500 mg, 2.70 mmol) and KOH (258 mg, 4.60 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **261b** (478 mg, 89 %) as an orange liquid. The isolated compound exhibited identical spectroscopic data to those in the literature.[367]

δ_H (400 MHz, $CDCl_3$): 7.48 (d, 2H, J 8.5, H-4 and H-8), 7.16 (d, 2H, J 8.5, H-5 and H-7), 3.84 (dd, 1H, J 4.0, 2.5, H-1), 3.16 (dd, 1H, J 5.5, 4.0, H-2a), 2.76 (dd, 1H, J 5.5, 2.5, H-2b)

δ_C (100 MHz, $CDCl_3$): 136.7 (q), 131.6, 127.1, 122.0 (q), 51.8, 51.2

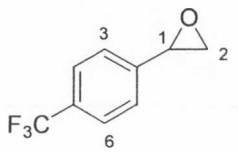
5.3.1.12 2-(Tri-fluoromethyl)-styrene oxide (325e)



Prepared according to general procedure J using trimethylsulfonium iodide (586 mg, 2.87 mmol), 2-trifluoromethyl benzaldehyde (500 mg, 2.87 mmol) and KOH (274 mg, 4.88 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **325e** (378 mg, 70%) as a yellow liquid. The isolated compound exhibited identical spectroscopic data to those in the literature.

δ_H (400 MHz, $CDCl_3$): 7.66 (d, 1H, J 7.5, H-4), 7.55 (m, 1H, H-6), 7.47 (d, 1H, J 8.0, H-7), 7.40 (app.t, 1H, J 7.5, H-5), 4.23 (m, 1H, H-1), 3.20 (dd, 1H, J 6.0, 4.5, H-2a), 2.66 (dd, 1H, J 6.0, 2.5, H-2b)

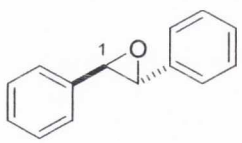
5.3.1.13 4-(Tri-fluoromethyl)-styrene oxide (325f)



Prepared according to general procedure J using trimethylsulfonium iodide (1.19 g, 5.85 mmol), 4-trifluoromethylbenzaldehyde (800 μL, 5.85 mmol) and KOH (558 mg, 9.95 mmol). Column chromatography was not necessary and the epoxide was dried under high vacuum for 1 h to afford **325f** (747 mg, 68%) as a red liquid. The isolated compound exhibited identical spectroscopic data to those in the literature.

δ_H (400 MHz, $CDCl_3$): 7.62 (m, 2H, H-4 and H-6), 7.50 (d, 1H, J 8.0, H-3), 7.41 (d, 1H, J 8.0, H-7), 3.93 (m, 1H, H-1), 3.20 (dd, 1H, J 5.5, 4.0, H-2a), 2.78 (dd, 1H, J 5.5, 2.5, H-2b)

5.3.1.14 *trans*-1,2-Diphenyl epoxide (342)



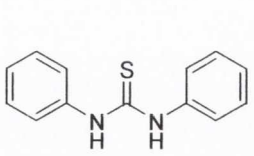
Prepared according to general procedure I using *(E)*-stilbene (500 mg, 2.77 mmol), and *m*CPBA (500 mg, 2.91 mmol) in CH_2Cl_2 (10 cm^3) which were stirred at 0 °C for 5 h. General procedure I workup afforded pure **342** (462 mg, 95%) as a white solid. M.p 64-66 °C (lit., 62 °C).[368]

δ_H (400 MHz, $CDCl_3$): 7.37 (m, 10H, Ar-H), 3.89 (s, 2H, H-1)

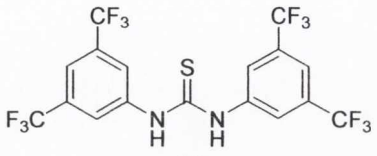
δ_C (100 MHz, $CDCl_3$): 136.6 (q), 128.1, 127.8 (q), 125.0, 62.4

5.3.2 Experimental for Section 3.2

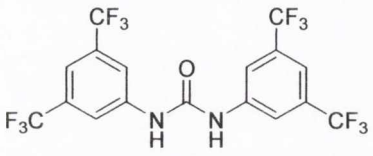
5.3.2.1 *N,N*-Di-(3,5-*bis*-trifluoromethyl-phenyl)-urea (46), (thio)urea (20) and *N,N*-Di-(phenyl)-urea (321)



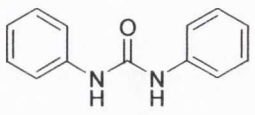
18



20



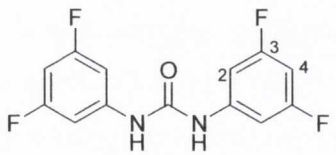
46



321

These compounds were readily available within the group. For synthesis and characterisation of catalysts **18**,[369] **20**,[63] **46**, [64] and **321**,[43] see the associated references.

5.3.2.2 1,3-*Bis*-(3,5-difluoro-phenyl)-urea (320)



Prepared according to the procedure outlined by Connon *et al.*[64] To a solution of 1,1'-carbonyldiimidazole (55.4 mg, 0.34 mmol) (in CH_2Cl_2, 100 μL) under Ar was added a solution of 3,5-difluoroaniline (92.7 mg, 0.71 mol) in CH_2Cl_2 (2 cm^3) *via* syringe and the resulting solution was stirred for 24 h at room temperature with precipitation of a white solid which was filtered, washed sequentially with CH_2Cl_2 (2 cm^3), 0.1 M HCl (3 x 2 cm^3), sat. $NaHCO_3$ (3 x 2 cm^3) and H_2O (1 x 5 cm^3). The resulting solid was dried under high vacuum to afford **320** (52.5 mg, 54% yield) as a white solid. m.p 210 °C.

δ_H(400 MHz, $CDCl_3$): 7.53 (br s, 2H, Ar-NH), 7.04 (m, 4H, H-2, H-6), 6.50 (m, 2H, H-4)

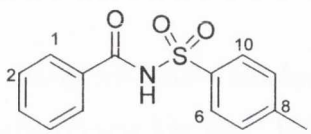
δ_C (100 MHz, DMSO): 162.5 (d, J 240.0), 151.9 (q), 141.9 (t, J 21.1), 101.3 (d, J 29.2), 97.2 (t, J 26.0)

δ_F (100 MHz, DMSO): -110.0 (s, 4F)

ν_{max} (diff)/cm^{-1} 2921, 1574 (C=O), 1382, 1229, 1116, 976

HRMS (ESI): (M $^+$+ Na) Calcd for $C_{13}H_8N_2OF_4Na$ 307.0470; Found 307.0484

5.3.2.3 *N*-benzoyl-4-methyl-benzene sulfonamide (323)



A 25 cm^3 reaction vessel containing a stirring bar was charged with *p*-toluenesulfonamide (1.0 g, 5.84 mmol) and CH_2Cl_2 (3.0 cm^3) and the resulting suspension was allowed to stir for 10 min. To this suspension benzoyl chloride (712 µL, 6.13 mmol) and triethylamine (590 µL, 7.30 mmol) were added dropwise, simultaneously. The reaction vessel was flushed with argon and allowed to stir for 12 h. The reaction was then diluted with CH_2Cl_2 (10 cm^3), the organic layer separated with CH_2Cl_2 (2 x 10 cm^3), dried ($MgSO_4$) and the solvent reduced *in vacuo* to afford an oil which was purifed using column chromatography (CH_2Cl_2-hexane,1:1, R_f 0.4) to afford **323** (926 mg, 58 %) as a white solid. The isolated compound showed identical spectroscopic data to those in the literature.[370]

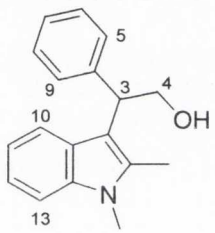
δ_H (400 MHz, DMSO): 7.94 (d, 2H, J 8.0, H-6 and H-10), 7.70 (d, 2H, J 8.5, H-1 and H-5), 7.61 (m, 1H, H-3), 7.50 (m, 2H, H-2 and H-4), 7.28 (s, 1H, NH), 7.36 (d, 2H, J 8.0, H-7 and H-9), 2.38 (s, 3H, CH_3)

δ_C (100 MHz, DMSO): 167.2 (q), 141.7 (q), 141.4 (q), 132.8, 130.7 (q), 129.3, 129.2, 128.5, 125.5, 20.8

5.3.2.4 Procedure J: general procedure for the organocatalyst promoted addition of indoles to epoxides (Tables 3.3-3.5)

A 1 cm^3 reaction vial containing a stirring bar was charged with the appropriate indole (1.37 mmol) and catalyst **315** (10 mol%). The reaction vessel was charged with 5 Å molecular sieves (40 mg), a septum and flushed with argon gas. The appropriate amount of $CDCl_3$ and the relevant epoxide (0.688 mmol) was then added *via* syringe. The vial was fitted with a sealed cap and stirred for the time indicated in Tables 3.3-3.5. Samples were taken at regular intervals, when conversion was adjudged to be complete the solution was diluted with CH_2Cl_2 (1 cm^3) and purified using column chromatography.

5.3.2.5 3-(2-hydroxy-1-phenylethyl)-1,2-dimethylindole (319)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), styrene oxide (**130a**) (78.5 μL, 0.688 mmol) in CH_2Cl_2 (40 μL) and **316** (29.3 mg, 0.069 mmol). The reaction was allowed to stir for 72 h at ambient temperature. Column chromatography (4:1 hexane:ethyl acetate, R_f 0.3) afforded **319** (129 mg, 71 %) as a pale yellow oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[205]

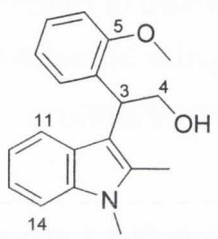
δ_H (400 MHz, $CDCl_3$): 7.41 (d, 1H, J 8.0, H-10), 7.27 (m, 5H, H5-9), 7.16 (m, 2H, H-12 and H-13), 7.02 (dd, 1H, J 8.0, 7.0, H-11), 4.52 (dd, 1H, J 8.0, 7.5, H-3), 4.36 (m, 2H, H-4), 3.71 (s, 3H, N-CH_3), 2.41 (s, 3H, Ar-CH_3), the OH was not visible.

δ_C (100 MHz, $CDCl_3$): 141.9 (q), 137.0 (q), 135.3 (q), 128.4, 127.9, 126.7 (q), 126.3, 120.7, 119.3, 119.2, 109.2 (q), 108.9, 65.2, 45.4, 29.7, 10.7

ν_{max} (neat)/cm^{-1} 3399, 2936, 1600, 1177, 1031

HRMS (ESI): (M^+ + Na) Calcd for $C_{18}H_{19}NONa$ 288.1364; Found 288.1358

5.3.2.6 3-(2-hydroxy-1-(2-methoxyphenyl)ethyl)-1,2-dimethylindole (326)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), 2-methoxyphenyl oxirane (**325a**) (103.3 mg, 0.688 mmol) in CH_2Cl_2 (40 μL) and **316** (29.3 mg, 0.0688 mmol). The resulting solution was stirred at ambient temperature for 26 h. Column chromatography (CH_2Cl_2, R_f 0.5) afforded **326** (183 mg, 90 %) as a pale yellow solid. M.p 124-126 °C.

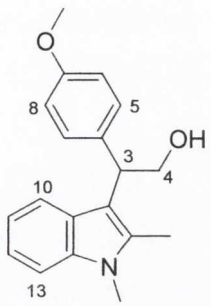
δ_H (400 MHz, DMSO): 7.48 (m, 2H, H-6 and H-11), 7.28 (d, 1H, J 8.5, H-14), 7.10 (app.t, 1H, J 7.5, H-12), 6.95 (app.t, 1H, J 8.5, H-13), 6.83 (m, 3H, H-7-H-9), 4.58 (m, 2H, H-3 and OH), 4.16 (dd, 1H, J 10.0, 9.0, H-4a), 3.94 (dd, 1H, J 9.0, 8.5 H-4b), 3.72 (s, 3H, O-CH_3), 3.62 (s, 3H, CH_3), 2.40 (s, 3H, CH_3)

δ_C (100 MHz, DMSO): 157.0 (q), 136.2 (q), 133.9 (q), 130.8 (q), 127.9, 126.7, 119.7, 119.8, 119.5, 118.9, 118.0 (q), 110.6, 110.4, 108.9, 62.7, 55.3, 38.6, 29.3, 10.3

ν_{max} (Nujol)/cm^{-1} 3327, 2917, 1596, 1462, 1117, 1027

HRMS(ESI) (M^+ + Na) Calcd for $C_{19}H_{21}NO_2Na$ 318.1470; Found 318.1464

5.3.2.7 3-(2-hydroxy-1-(4-methoxyphenyl)ethyl)-1,2-dimethylindole (327)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.7 mmol), **325a** (78.5 μL, 0.688 mmol) in CH_2Cl_2 (40.4 μL) and **316** (29.3 mg, 0.0688 mmol). The resulting solution was stirred at ambient temperature for 26 h. Column chromatography (CH_2Cl_2, R_f 0.5) afforded **327** (183 mg, 90 %) as a pale yellow oil.

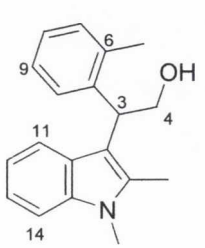
δ_H (400 MHz, DMSO): 7.31(d, 2H, J 8.5, H-6 and H-8), 7.22 (d, 2H, J 8.5, H-5 and H-9), 6.98 (app.t, 1H, J 7.5, H-12), 6.83 (dd, 1H, J 8.0, 7.0, H-11), 6.79 (m, 2H, H-10 and H-13), 4.67 (br s, 1H, OH), 4.25 (dd, 1H, J 7.5, 6.5, H-3), 4.18 (br m, 1H, H-4a), 3.94 (br m, 1H, H-4b), 3.69 (s, 3H, O-CH_3), 3.64 (s, 3H, N-CH_3), 2.36 (s, 3H, Ar-CH_3)

δ_C (100 MHz, $CDCl_3$): 157.1 (q), 136.3 (q), 135.4 (q), 133.6 (q), 128.9, 126.5 (q), 119.7, 118.8, 118.2, 113.3, 111.6 (q), 109.0, 64.0, 55.0, 44.1, 29.3, 10.4.

ν_{max} (neat)/cm^{-1} 3399, 3048, 2933, 1610, 1511, 1034

HRMS (ESI): (M^+ + Na) Calcd for $C_{19}H_{21}NO_2Na$ 318.1470; Found 318.1461

5.3.2.8 3-(2-hydroxy-1-(2-methylphenyl)ethyl)- 1,2-dimethylindole (328)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), epoxide **325c** (92.3 μL, 0.688 mmol) in CH_2Cl_2 (78 μL) and **316** (29.3 mg, 0.0688 mmol). The resulting solution was stirred at ambient temperature for 48 h. Column chromatography (CH_2Cl_2 R_f 0.45) afforded **328** (188 mg, 98 %) as a pale yellow oil.

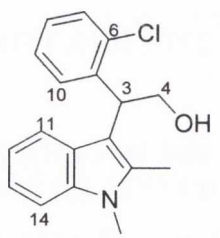
δ_H (400 MHz, DMSO): 7.58 (d, 1H, J 7.8, H-11), 7.28 (app.t, 2H, J 7.8, H-12 and H-13), 7.18 (d, 1H, J 7.8, H-14), 7.06 (m, 2H, H-7 and H-10), 6.96 (app.t, 1H, J 7.8, H-9), 6.80 (dd, 1H, J 7.8, 6.8, H-8), 4.68 (app.t, 1H, J 4.8, OH), 4.37 (dd, 1H, J 7.8, 6.8, H-3), 4.12 (m, 1H, H-4a), 3.91 (m, 1H, H-4b), 3.62 (s, 3H, N-CH_3), 2.33 (s, 3H, CH_3), 2.12 (s, 3H, CH_3)

δ_C (100 MHz, DMSO): 140.8 (q), 136.6 (q), 136.3 (q), 134.0 (q), 130.1, 127.3, 126.7 (q), 125.6, 125.3, 119.6, 118.4, 118.1, 109.6 (q), 108.9, 63.5, 41.7, 29.3, 19.3, 10.4

ν_{max} (neat)/cm^{-1} 3410, 3049, 2251, 1657, 1470, 1008

HRMS (ESI): (M^+ + Na) Calcd for $C_{19}H_{21}NONa$ 302.1521; Found 302.1511

5.3.2.9 3-(2-hydroxy-1-(2-chlorophenyl)ethyl)-1,2-dimethylindole (329)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), 2-chlorophenyl oxirane (106.4 mg, 0.688 mmol) in CH_2Cl_2 (64 μL) and **316** (29.3 mg, 0.0688 mmol). The resulting solution was stirred at ambient temperature for 621 h. Column chromatography (4:1 hexane: ethyl acetate, R_f 0.3) afforded **329** (165 mg, 80 %) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 7.62 (d, 1H, J 8.0, H-11), 7.57 (d, 1H, J 7.5, H-7), 7.35 (d, 1H, J 8.0, H-14), 7.29 (m, overlap with solvent 1H, H-13), 7.14 (m, 2H, H-8 and H-10), 7.04 (dd, 1H, J 8.0, 7.0, H-12), 4.85 (dd, 1H, J 9.0, 6.5, H-3), 4.37 (dd, 1H, J 10.5, 9.0, H-4a), 4.27 (dd, 1H, J 10.5, 6.0, H-4b), 3.70 (s, 3H, N-CH_3), 2.43 (s, 3H, Ar-CH_3), OH signal not visible.

δ_C (150 MHz, $CDCl_3$): 139.3 (q), 136.8 (q), 135.5 (q), 134.1 (q), 129.7, 129.1, 127.5, 126.7 (q), 126.6, 120.5, 119.2, 118.8, 108.9, 107.8 (q), 64.2, 43.0, 29.5, 10.6

ν_{max} (neat)/cm^{-1} 3400, 2935, 1611, 1468, 1040

HRMS (ESI): (M^+ + Na) Calcd for $C_{18}H_{18}NONaCl$ 322.0984; Found 322.0975

5.3.2.10 3-(2-hydroxy-1-(4-chlorophenyl)ethyl)-1,2-dimethylindole (330)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), oxirane **261b** (137 mg, 0.688 mmol) in CH_2Cl_2 (66 μL) and **316** (29.3 mg, 0.0688 mmol). The resulting solution was stirred at ambient temperature for 163 h. Column chromatography (CH_2Cl_2, R_f 0.3) afforded **330** (191 mg, 93 %) as a clear oil.

δ_H (400 MHz, DMSO): 7.28 (m, 6H, H-6, H-7, H-9, H-10, H-11 and H-14), 6.99 (app.t, 1H, J 7.8, H-13), 6.85 (app.t, 1H, J 7.5, H-12), 4.80 (m, 1H, OH), 4.32 (app.t, 1H, J 6.0, H-3), 4.20 (m, 1H, H-4a), 3.91 (m, 1H, H-4b), 3.64 (s, 3H, N-CH_3), 2.37 (s, 3H, Ar-CH_3)

δ_C (100 MHz, DMSO): 142.6 (q), 136.3 (q), 133.8 (q), 130.0, 129.8, 127.8, 126.3 (q), 119.9, 118.6, 118.4, 110.9 (q), 109.1, 63.6, 44.3, 29.4, 10.4

ν_{max} (neat)/cm^{-1} 3434, 2250, 1661, 1056

HRMS (ESI): (M^+ + Cl) Calcd for $C_{18}H_{19}NOCl$ 300.1147; Found 300.1155

5.3.2.11 3-(2-hydroxy-1-(4-methylphenyl)ethyl)- 1,2-dimethylindole (331)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), epoxide **261c** (92.3 mg, 0.688 mmol) in CH_2Cl_2 (78 μL) and **316** (29.3 mg, 0.0688 mmol). The resulting solution was stirred at ambient temperature for 48 h. Column chromatography (4:1 hexane:ethyl acetate, R_f 0.3) afforded **331** (181 mg, 94 %) as a pale yellow oil.

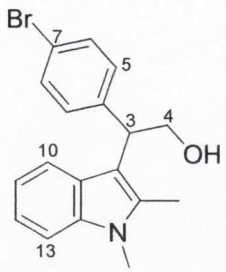
δ_H (400 MHz, DMSO): 7.31 (m, 2H, H-11 and H-14), 7.20 (d, 2H, J 8.0, H-7 and H-9), 6.98 (m, 3H, H-6, H-10 and H-13), 6.83 (app.t, 1H, J 7.5, H-12), 4.66 (m, 1H, H-3), 4.26 (app.t, 1H, J 7.3, H-4a), 4.18 (m, 1H, H-4b), 3.63 (s, 3H, N-CH_3), 2.36 (s, 3H, Ar-CH_3), 2.22 (s, 3H, CH_3).

δ_C (100 MHz, DMSO): 140.5 (q), 136.3 (q), 134.3 (q), 133.6 (q), 128.5, 128.0, 127.9, 126.5 (q), 119.7, 118.8, 118.2, 111.5 (q), 108.9, 63.8, 44.6, 29.3, 20.6.

ν_{max} (neat)/cm^{-1} 3392, 3047, 2923, 1470, 1036

HRMS (ESI): (M^+ + Na) Calcd for $C_{19}H_{21}NONa$ 302.1521; Found 302.1516

5.3.2.12 3-(2-hydroxy-1-(4-bromophenyl)ethyl)- 1,2-dimethylindole (332)



Prepared according to general procedure J using 1,2-dimethylindole (**318**) (200 mg, 1.37 mmol), epoxide **325d** (137 mg, 0.688 mmol) in CH_2Cl_2 (66 μL) and **316** (29.3 mg, 0.0688 mmol) was stirred for 77 h at room temperature. Column chromatography (CH_2Cl_2-R_f 0.3) afforded **332** (218 mg, 92 %) as a pale yellow oil.

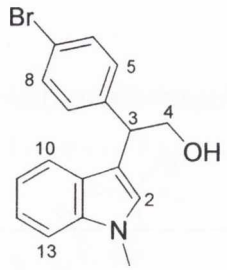
δ_H (400 MHz, DMSO): 7.41 (d, 2H, J 8.0, H-6 and H-8), 7.28 (m, 4H, H-5, H-9, H-10 and H-13), 6.99 (app.t, 1H, J 7.5, H-12), 6.85 (app.t, 1H, J 7.5, H-11), 4.81 (m, 1H, OH), 4.29 (m, 1H, H-3), 4.20 (m, 1H, H-4a), 3.92 (m, 1H, H-4b), 3.44 (s, 3H, CH_3), 2.36 (s, 3H, CH_3)

δ_C (100 MHz, DMSO): 143.0 (q), 136.3 (q), 133.8 (q), 130.7, 130.3, 126.3 (q), 119.9, 118.6, 118.5, 118.3, 110.8 (q), 109.0, 63.5, 44.3, 29.3, 10.3

ν_{max} (neat)/cm^{-1} 3435, 2251, 2125, 1661, 1055, 822

HRMS(ESI) (M^+ + Na) Calcd for $C_{18}H_{18}NONaBr$ 366.0461; Found 366.0469

5.3.2.13 3-(2-hydroxy-1-(4-methylphenyl)ethyl)- *N*-methylindole (335a)



Prepared according to general procedure J using *N*-methylindole (**181**) (200 μL, 1.56 mmol), 4-bromophenyl epoxide (**325d**) (155.7 mg, 0.782 mmol) in CH_2Cl_2 (424 μL) and **315** (33.3 mg, 0.0782 mmol) stirred at ambient temperature for 7.8 days. Column chromatography (3:1 hexane:ethyl acetate R_f 0.5) afforded **335a** (235 mg, 91 %) as a white solid. M.p 141-143°C

δ_H (400 MHz, $CDCl_3$): 7.42 (m, 3H, H-10, H-12 and H-13), 7.22 (m, 4H, H-5, H-6, H-8 and H-9), 7.05 (app.t, 1H, J 7.5, 7.0, H-11), 6.97 (s, 1H, H-2), 4.44 (app.t, 1H, J 7.0, H-3), 4.21 (dd, 1H, J 11.0, 7.0, H-4a), 4.13 (dd, 1H, J 11.0, 7.0, H-4b), 3.80 (s, 3H, N-CH_3), OH not visible.

δ_C (150 MHz, $CDCl_3$): 140.9 (q), 137.2 (q), 131.6, 130.0, 127.2 (q), 126.7, 122.0, 120.4 (q), 119.2, 119.1, 113.8 (q), 109.3, 66.1, 45.0, 32.7

ν_{max} (Nujol)/cm^{-1} 3302, 2923, 1377, 1053, 1007

HRMS(ESI) (M^+ + H) Calcd for $C_{17}H_{17}NOBr$ 330.0494; Found 330.0495

5.3.2.14 3-(2-hydroxy-1-(4-bromophenyl)ethyl)-2-methy-1*H*-indole (335b)



Prepared according to general procedure J using 2-methylindole (200 mg, 1.52 mmol), 4-bromophenyl oxirane (151.7 mg, 0.762 mmol) in CH_2Cl_2 (261 μL) and **315** (32.5 mg, 0.0762 mmol) stirred at ambient temperature for 7.2 days. Column chromatography (CH_2Cl_2 R_f 0.5) afforded **335b** (221 mg, 89 %) as a yellow wax.

δ_H (400 MHz, DMSO): 10.8 (br s, 1H, NH), 7.41 (d, 2H, J 8.5, H-6 and H-8), 7.28 (m, 3H, H-5, H-9 and H-10), 7.20 (d, 1H, J 8.0, H-13), 6.91 (app.t, 1H, J 7.5, H-12), 6.80 (app.t, 1H, J 7.5, H-11), 4.78 (m, 1H, OH), 4.17 (m, 2H, H-3 and H-4a), 3.91 (m, 1H, H-4b), 2.34 (s, 3H, CH_3)

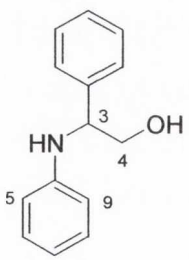
δ_C (100 MHz, DMSO): 143.2 (q), 135.2 (q), 132.2 (q), 130.7, 130.4, 127.3 (q), 119.6, 118.5 (q), 118.4, 118.2, 110.7 (q), 110.5, 63.6, 44.3, 12.0

υ (cm^{-1})neat: 3399, 3325, 2926,1618, 1487, 1010

HRMS (ESI): (M^+ + H) Calcd for $C_{17}H_{17}NOBr$ 302.0498; Found 330.0494

5.3.3 Experimental for Section 5.3

5.3.3.1 2-Phenyl-2-phenylamino ethanol (337)



Prepared according to general procedure J using aniline (**209**) (80 μL, 0.877 mmol), styrene oxide (**130a**) (100 μL, 0.877 mmol) in CH_2Cl_2 (240 μL) and **315** (37.4 mg, 0.087 mmol) stirred at ambient temperature for 91 h. Column chromatography (1:1 CH_2Cl_2:hexane R_f 0.5) afforded **337** (161 mg, 86 %) as a pale brown wax. The isolated compound exhibited identical spectroscopic data to those in the literature.[371]

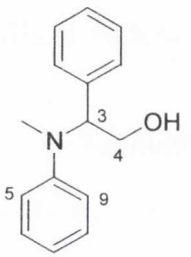
δ_H (400 MHz, $CDCl_3$): 7.29 (m, 5H, Ar-H), 7.11 (dd, 2H, J 8.5, 7.5, H-6 and H-8), 6.69 (t, 1H, J 7.5, H-7), 6.59 (d, 2H, J 8.5, H-5 and H-9), 4.53 (dd, 1H, J 7.0, 4.0, H-3), 3.96 (dd, 1H, J 11.0, 4.0, H-4a), 3.77 (dd, 1H, J 11.0, 7.0, H-4b), OH and NH not visible.

δ_C (100 MHz, $CDCl_3$): 146.7 (q), 139.6 (q), 128.7, 128.4, 127.2, 126.2, 117.4, 113.4, 66.9, 59.4

υ (cm^{-1})neat: 3399, 3025, 2874, 1599, 1501, 1316, 1066

HRMS (ESI): (M^+ + Na) Calcd for $C_{14}H_{16}NO$ 214.1227; Found 214.1232

5.3.3.2 2-Phenyl-2-*N*-methylphenylamino ethanol (major isomer) (338)



Prepared according to general procedure J using *N*-methyl aniline (**336c**) (895 μL, 0.877 mmol), styrene oxide (**130a**) (100 μL, 0.877 mmol) and **315** (37.4 mg, 0.087 mmol) in CH_2Cl_2 (225 μL) stirred at ambient temperature for 91 h. Column chromatography (1:1 CH_2Cl_2:hexane R_f 0.4) afforded **338** (177 mg, 78 %) as a pale yellow viscous oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[372]

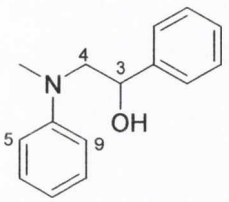
δ_H (400 MHz, $CDCl_3$): 7.26 (m, 5H, Ar-H), 7.15 (app.t, 2H, J 8.0, 7.5, H-6 and H-8), 6.96 (d, 2H, J 8.0, H-5 and H-9), 6.83 (app.t, 1H, J 7.5, H-7), 5.10 (app.t, 1H, J 9.0, 6.0, H-3), 4.13 (m, 2H, H-4), 2.73 (s, 3H, CH_3)

δ_C (150 MHz, $CDCl_3$): 151.0 (q), 137.3 (q), 129.1, 128.4, 127.4, 127.0, 118.2, 114.6, 64.4, 61.5, 31.8

υ (cm^{-1})neat: 3383, 2884, 1597, 1503, 1030

HRMS (ESI): (M^+ + Na) Calcd for $C_{15}H_{18}NO$ 228.1388; Found 228.1387

5.3.3.3 2-Phenyl-2-*N*-methylphenylamino ethanol (minor isomer) (338)



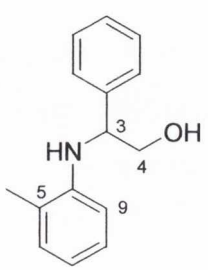
Prepared according to general procedure J using *N*-methyl aniline (**336c**) (895 μL, 0.877 mmol), styrene oxide (**130a**) (100 μL, 0.877 mmol) and **315** (37.4 mg, 0.087 mmol) in CH_2Cl_2 (225 μL) stirred at ambient temperature for 91 h. Flash chromatography (1:1 CH_2Cl_2:hexane R_f 0.4) afforded **338** (8 mg, 3 %) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 7.39 (m, 4H, Ar-H), 7.28 (m, 3H, Ar-H), 6.87 (d, 2H, J 8.5, H-5 and H-9), 6.79 (t, 1H, J 7.3, H-7), 5.02 (dd, 1H, J 9.0, 4.5, H-3), 3.44 (m, 2H, H-4), 2.86 (s, 3H, CH_3), 2.55 (br s, 1H, OH), the NH resonance was not visible.

δ_C (100 MHz, $CDCl_3$): 149.5 (q), 141.4 (q), 128.8, 128.1, 127.4, 125.4, 117.0, 112.8, 71.3, 61.6, 38.9.

HRMS (ESI): (M^+ + H) Calcd for $C_{15}H_{18}NO$ 228.1388; Found 228.1379

5.3.3.4 2-Phenyl-2-*N*-methylphenylamino ethanol (339)



Prepared according to general procedure J using 2-methyl aniline (**336d**) (93 μL, 0.877 mmol), styrene oxide (**130a**) (100 μL, 0.877 mmol) and **315** (37.4 mg, 0.0877 mmol) in CH_2Cl_2 (386 μL) stirred at ambient temperature for 90 h. Column chromatography (CH_2Cl_2 R_f 0.5) afforded **339** (183 mg, 99 %) as a pale grey-green solid. M.p 81-83 °C

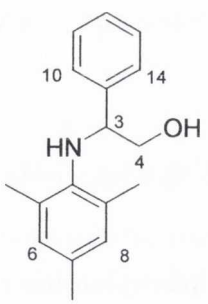
δ_H (400 MHz, $CDCl_3$): 7.35 (m, 4H, Ar-H), 7.28 (m, 1H, Ar-H), 7.10 (d, 1H, J 7.0, H-6), 6.96 (t, 1H, J 7.6, H-7), 6.65 (t, 1H, J 7.6, H-8), 6.41 (d, 1H, J 7.6, H-9), 4.57 (dd, 1H, J 7.0, 4.0, H-3), 3.99 (dd, 1H, J 11.0, 4.0, H-4a), 3.80 (dd, 1H, J 11.0, 7.0, H-4b), 2.31 (s, 3H, CH_3), OH and NH not visible

δ_C (100 MHz, $CDCl_3$): 144.6 (q), 139.7 (q), 129.6, 128.4, 127.1, 126.5, 126.2, 122.1, 117.0, 111.0, 67.0, 59.3, 17.2

υ (cm^{-1})nujol: 3302, 2922, 1605, 1376, 1048

HRMS (ESI): (M^+ + H) Calcd for $C_{15}H_{17}NO$ 228.1388; Found 228.1384

5.3.3.5 2-Phenyl-2-*N*-methylphenylamino ethanol (340)



Prepared according to general procedure J using 2,4,6-trimethyl aniline (**336e**) (246 μL, 1.75 mmol), styrene oxide (**130a**) (100 μL, 0.877 mmol) and **315** (74.8 mg, 0.175 mmol) in CH_2Cl_2 (93 μL) stirred at ambient temperature for 147 h. Column chromatography (CH_2Cl_2, R_f 0.5) afforded **340** (206 mg, 92 %) as a pale yellow oil.

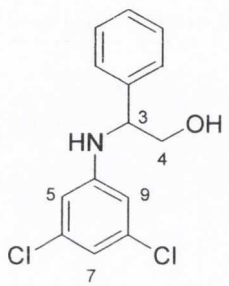
δ_H (400 MHz, DMSO): 7.32 (d, 2H, J 7.0, H-10 and H-14), 7.24 (t, 2H, J 7.0, H-11 and H-13), 7.16 (t, 1H, J 7.0, H-12), 6.66 (s, 2H, H-6 and H-8), 4.81 (m, 1H, H-3), 4.07 (m, 1H, H-4a), 3.68 (m, 1H, H-4b), 2.08 (m, 9H, $3CH_3$), NH and OH not visible.

δ_C (100 MHz, DMSO): 143.2 (q), 142.8 (q), 129.1, 128.8 (q), 128.4 (q), 127.7, 127.3, 126.4, 65.0, 62.9, 20.1 18.7

υ (cm^{-1})neat: 3368, 2920, 1484, 1026

HRMS (ESI): (M^+ + Na) Calcd for $C_{17}H_{22}NONa$ 256.1701; Found 256.1691

5.3.3.6 2-Phenyl-2-*N*-methylphenylamino ethanol (341)



Prepared according to general procedure J using 3,5-dichloroaniline (**336f**) (283 µL, 1.75 mmol), styrene oxide (**130a**) (100 µL, 0.877 mmol) and **315** (37.4 mg, 0.0877 mmol) in CH_2Cl_2 (340 µL) stirred at ambient temperature for 71 h. Column chromatography (CH_2Cl_2, R_f 0.7) afforded **341** (207 mg, 84 %) as a pale yellow solid. M.p 79-81 °C.

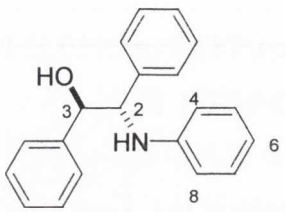
δ_H (400 MHz, $CDCl_3$): 7.31(m, 5H, Ar-H), 6.66 (s, 1H, H-7), 6.44 (s, 2H, H-5 and H-9), 4.46 (dd, 1H, J 6.0, 5.0, H-3), 3.97 (dd, 1H, J 4.0, 11.0, H-4a), 3.79 (dd, 1H, J 6.0, 11.0, H-4b), NH and OH not visible

δ_C (100 MHz, $CDCl_3$): 148.7 (q), 138.7 (q), 135.1 (q), 128.9, 127.8, 126.4, 117.4, 111.7, 66.9, 59.2

υ (cm^{-1})neat: 3431, 2930, 1593, 1451, 1316, 1069

HRMS (ESI): (M $^{+}$+ H) Calcd for $C_{14}H_{14}NOCl_2$ 282.0452; Found 282.0461

5.3.3.7 2-Phenyl-2-*N*-methylphenylamino ethanol (343)



Prepared according to general procedure J using aniline (**209**) (186 μL, 2.04 mmol), (*E*)-stilbene oxide (**342**) (200 mg, 1.02 mmol) and **315** (86.9 mg, 0.20 mmol) in CH_2Cl_2 (324 μL) stirred at 30 °C for 142 h. Flash chromatography (1:1 CH_2Cl_2:hexane R_f 0.1) afforded **343** (270 mg, 92 %) as a pale pink solid. M.p 127-128 °C (lit., 122-124 °C).[373] The isolated compound exhibited identical spectroscopic data to those in the literature. [373]

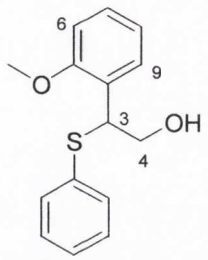
δ_H (400 MHz, $CDCl_3$): 7.25 (m, 6H, Ar-H), 7.08 (m, 6H, Ar-H), 6.67 (t, 1H, J 7.3, H-6), 6.51 (d, 2H, J 7.5, H-4 and H-8), 5.09 (d, 1H, J 4.5, H-3), 4.70 (d, 1H, J 4.5, H-2)

δ_C (100 MHz, $CDCl_3$): 146.3 (q), 139.5 (q), 138.0 (q), 128.6, 127.9, 127.8, 127.5, 127.4, 127.1, 126.1, 117.4, 113.4, 76.7, 63.2

υ (cm^{-1})nujol: 3345, 3255, 1601, 1057

HRMS (ESI): (M $^{+}$+ H) Calcd for $C_{20}H_{20}NO$ 290.1545; Found 290.1552

5.3.3.8 2-Phenyl-2-*N*-methylphenylamino ethanol (344)



Prepared according to general procedure J using thiophenol (**223**) (141 μL, 1.38 mmol), 2-methoxy styrene oxide (**325a**) (103.3 mg, 0.69 mmol) and **315** (58.7 mg, 0.138 mmol) stirred at ambient temperature for 20 h. Column chromatography (CH_2Cl_2 R_f 0.6) afforded **344** (153mg, 85 %) as a pale yellow oil.

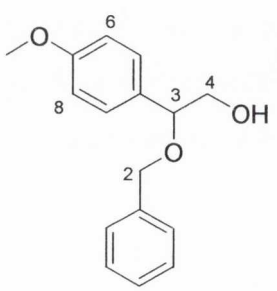
δ_H (400 MHz, $CDCl_3$): 7.37 (m, 2H, H-7 and H-9), 7.23 (m, 6H, Ar-H), 6.91 (m, 2H, H-6 and H-8), 4.84 (t, 1H, J 6.5, H-3), 3.89 (m, 2H, H-4), 3.87 (s, 3H, OCH_3), 1.76 (br s, 1H, OH)

δ_C (100 MHz, $CDCl_3$): 156.4 (q), 134.1 (q), 131.6, 128.4, 128.3, 127.9, 126.7, 126.6 (q), 120.2, 110.3, 64.0, 55.1, 48.7

υ (cm^{-1})nujol: 3429, 2937, 1584, 1491, 1246, 1026

HRMS (ESI): (M^+ + Na) Calcd for $C_{15}H_{16}O_2NaS$ 283.0769; Found 283.0769

5.3.3.9 2-Phenyl-2-*N*-methylphenylamino ethanol (347)



Prepared according to general procedure J using benzyl alcohol (**213a**) (143 μL, 1.38 mmol), 4-methoxystryene oxide (**325b**) (103.3 mg, 0.69 mmol) and **315** (58.7 mg, 0.138 mmol) stirred at ambient temperature for 20 h. Column chromatography (CH_2Cl_2 R_f 0.2) afforded **347** (146 mg, 82%) as a pale yellow oil.

δ_H (400 MHz, $CDCl_3$): 7.31 (m, 7H, Ar-H), 6.94 (d, 2H, J 6.0, H-6 and H-8), 4.54 (d, 1H, J 11.5, H-2a), 4.50 (dd, 1H, J 9.0, 4.0, H-3), 4.33 (d, 1H, J 11.5 H-2b), 3.85 (s, 3H, OCH_3), 3.73 (dd, 1H, J 11.5, 9.0, H-4a), 3.64 (m, 1H, H-4b), OH resonance not visible.

δ_C (150 MHz, $CDCl_3$): 55.2, 67.3, 70.4 , 81.7, 114.0, 127.7, 127.8, 128.2, 128.4 130.3 (q), 138.0 (q), 159.6 (q)

υ (cm^{-1})neat: 3435, 2932, 1610, 1512, 1247, 1099, 1034, 832

HRMS (ESI): (M^+ + Na) Calcd for $C_{16}H_{18}O_3Na$ 281.1154; Found 281.1160

5.4.1 Experimental for Section 4.1

5.4.1.1 General procedure K for the epoxidation of aldehydes under liquid-liquid reaction conditions (Tables 4.1-4.4, 4.6, 4.9 and 4.11)

A carousel flask containing a magnetic stirring bar was charged with trimethylsulfonium iodide (165.7 mg, 0.81 mmol) and then 50% NaOH/H_2O solution (1.77 cm^3, 44.3 mmol) *via* syringe. The resulting suspension was allowed to stir for 10 min. (*E*)-Stilbene (66.5 mg, 0.37 mmol) and the appropriate catalyst (0.037 mmol) were then added and the flask was fitted with a cap and placed under an atmosphere of argon (balloon). CH_2Cl_2 (2.175 cm^3) and freshly distilled aldehyde (0.74 mmol) were then added sequentially *via* syringe and the reacton stirred at ambient temperature for the time indicated in the relevant table. When ^1H NMR spectroscopy indicated completion of the reaction the mixture was diluted with CH_2Cl_2 and the organic phase separated using a separating funnel. The aqueous layer was washed with CH_2Cl_2 (2 x 10 cm^3) then the organic phases were combined, dried ($MgSO_4$) and the solvent

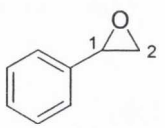
evaporated under reduced pressure to afford the crude epoxide which was purified *via* column chromatography.

5.4.1.2 General procedure L for the epoxidation of aldehydes under liquid-solid reaction conditions (Tables 4.2, 4.5, 4.7, 4.10 and 4.12).

A carousel flask containing a magnetic stirring bar was charged with trimethylsulfonium iodide (86.12 mg, 0.42 mmol), CH_2Cl_2 (3.50 cm^3) and KOH (21.5 mg, 0.384 mmol). The resulting suspension was allowed to stir for 10 min. (*E*)-Stilbene (34.6 mg, 0.19 mmol) and the appropriate catalyst (0.038 mmol) were then added and the flask was fitted with a cap and placed under an atmosphere of argon (balloon). Freshly distilled aldehyde (0.38 mmol) was then added sequentially *via* syringe and the reaction stirred at ambient temperature for the time indicated in the Table. When ^1H NMR spectroscopy indicated completion of the reaction the mixture was diluted with H_2O and the organic phase separated using a separating funnel. The aqueous layer was washed with CH_2Cl_2 (2 x 10 cm^3) then the organic phases were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude epoxide that was purified *via* column chromatography.

Note: These reactions must be carried out under rigorously identical conditions (flask- and stirring bar size, stirring rate and temperature) to achieve reproducible results. A Radley's discovery Technologies 12-station carousel reactor (No. RR98030) in conjunction with a heater-stirrer (No. RR98072, stirring setting 4) was used which provided uniform stirring in each reaction 24 x 150 mm vessels. Each reaction vessel was fitted with a cross-shaped stirring bar measuring 16.5 mm across.

5.4.1.3 Styrene oxide (130a)



Prepared according to general procedures K and L. Flash chromatography (CH_2Cl_2, R_f 0.8) afforded the isolation of **130a** as a clear liquid. Chiralpak OD-H (4.6 mm x 25 cm), hexane (100%), 1.0 cm^3 min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer =

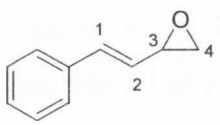
17.70 min, minor enantiomer = 19.09 min. No attempt was made to determine the optical rotation due to the low *ee* recorded for this product. The isolated compound exhibited identical spectroscopy data to that in the literature.[313,374]

δ_H (400 MHz, $CDCl_3$): 7.25 (m, 5H, Ar-H), 3.88 (dd, 1H, J 4.0, 2.5, H-1), 3.16 (dd, 1H, J 5.5, 4.0, H-2a), 2.82 (dd, 1H, J 5.5, 2.5, H-2b)

υ (cm^{-1}) neat (NaCl): 2923, 2853, 1463, 1276, 1134

5.4.2 Experimental for Section 4.2

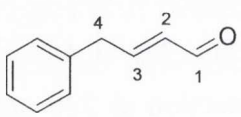
5.4.2.1 (*2E*)-2-Styryl-Epoxide (353a)



Prepared according to general procedure K using (*E*)-cinnamaldehyde (465 μL, 3.69 mmol), trimethylsulfonium iodide (828 mg, 4.06 mmol), 50% $NaOH_{(aq)}$ solution (8.85 cm^3, 0.22 mol), catalyst **46** (89 mg, 0.184 mmol) and CH_2Cl_2 (11 cm^3). The resulting solution was allowed to stir at room temperature for 42 h. Flash chromatography (hexane:ethyl acetate, 5:1, R_f 0.6) allowed the isolation of **353a** (485 mg, 90%) as a clear oil. The isolated compound showed identical spectroscopic data to those in the literature.[375]

δ_H (400 MHz, $CDCl_3$): 7.41 (m, 2H, Ar-H), 7.33 (m, 2H, Ar-H), 6.79 (d, 1H, J 12.0, H-1), 5.87 (dd, 1H, J 12.0, 8.0, H-2), 3.53 (m, 1H, H-3), 3.08 (dd, J 8.0, 4.0, H-4a), 2.79 (dd, 1H, J 8.0, 4.0, H-4b)

5.4.2.2 4-Phenyl-but-2-enal (353b)



The synthesis of epoxide **353a** was performed exactly detailed above on 3.69 mmol scale with 11 cm^3 of CH_2Cl_2 as solvent. When the reaction was complete (analysis by ^1H NMR spectroscopy) the mixture was diluted with water (20 cm^3) and transferred to a separating funnel. As the molarity of the organic phase of the subsequent reaction is 0.095 M the work up was done so that the final organic phase volume was 39 cm^3. The aqueous phase was extracted with CH_2Cl_2 (3 x 8 cm^3), leaving 4 cm^3 for washings. The combined organic extracts were then washed with water (2 x 30 cm^3s) and brine (1cm^3). The organic phase was then dried ($MgSO_4$) and the solution filtered. An oven dried 50cm^3 round bottomed flask containing a stirring bar and molecular sieves (4 Å) was fitted with a septum and placed under argon. Using an oven dried glass syringe, the filtrate was then transferred to the flask. The catalyst, copper tetrafluoroborate hydrate (218.8 mg, 0.923 mmol, 0.25 eq.) was then added to the reaction flask and the resulting mixture stirred for 30 mins at ambient temperature. The reaction mixture was diluted with CH_2Cl_2 (50 cm^3) and filtered to remove the molecular sieves. The organic phase was then washed with water (3 x 50 cm^3) and brine (3 x 50 cm^3). The organic phase was then dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The product was purified by column chromatography (60:40 hexane:CH_2Cl_2) to yield **353b** as a colourless oil (323 mg, 60 %). The isolated compound exhibited identical spectroscopic data to those in the literature.[376]

δ_H (400 MHz, $CDCl_3$): 9.73 (d, 1H, J 8.0, H-1), 7.32 (m, 5H, Ar-H), 6.73 (dt, 1H, J 12.0, 8.0, H-3), 6.35 (m, 1H, H-2), 3.36 (dd, 2H, J 12.0, 8.0, H-4)

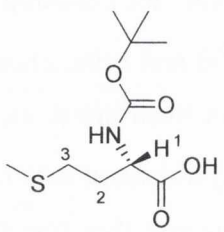
5.4.3. Experimental for Section 4.4

5.4.4. General procedure M: protection of the amine group of amino acids using the *tert*-butoxycarbonyl (Boc) group.

To a solution of the appropriate amino acid (0.022 mol) in 50% MeOH/H_2O solution (20 cm^3) and Na_2CO_3 (0.022 mol) under Ar at 0 °C was added di-*tert*-butyl dicarbonate (**354b**) (0.022 mol) with stirring. The resulting solution was allowed to stir at room temperature for 12 h. 1M HCl was added to the reaction mixture until pH 1 was attained. The organic layer was

extracted using CH_2Cl_2 (2 x 25 cm^3) and dried ($MgSO_4$) to afford the Boc-protected amino acid.

5.4.4.1. *N-tert*-Butoxycarbonylamino-*L*-methionine (354c)



Prepared according to general procedure M using *L*-methionine (6.0 g, 40.21 mmol) in 50% MeOH/H_2O solution (30 cm^3), Na_2CO_3 (4.26 g, 40.19 mmol) under Ar at 0 °C, and di-*tert*-butyl dicarbonate (**354b**) (8.77 g, 40.18 mmol). 1M HCl was added to the reaction mixture until pH 1 was reached. The organic layer was extracted using CH_2Cl_2 (2 x 100 cm^3) and dried ($MgSO_4$) to afford *N*-Boc-*L*-methionine **354c** (9.02 g, 90 %) as a viscous oil. The isolated compound exhibited identical spectroscopic data to those in the literature.[377]

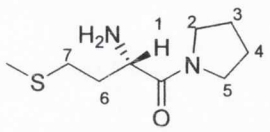
δ_H (400 MHz, $CDCl_3$): 7.13 (d, 1H, J 8.0, NH), 3.97 (m, 1H, H-1), 2.44 (m, 2H, H-3), 2.03 (s, 3H, CH_3), 1.80 (m, 2H, H-2), 1.38 (s, 9H, $3CH_3$)

5.4.4.2 General procedure N: Boc-protected amino acid coupling with an amine (using HTBU) and subsequent Boc group removal using TFA

Part I: To a solution of *N*-Boc-amino acid (8.39 mmol) in CH_2Cl_2 (75 cm^3) was added *O*-benzotriazole-1-*N*,*N*,*N*',*N*'-tetraethyluronium hexafluorophosphate (**354d**) (HTBU, 3.5 g, 9.23 mmol.). The white suspension was stirred for 5 min, followed by the addition of diisopropylethylamine (1.75 cm^3, 10.06 mmol) and the appropriate amine (9.23 mmol). The reaction mixture was then stirred for 24 h at room temperature. The mixture was combined with CH_2Cl_2 (20 cm^3) and water (10 cm^3) and the organic layer separated, washed with 1M hydrochloric acid (3 x 50 cm^3) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the crude Boc-protected amide.

Part II: The amide was then dissolved in CH_2Cl_2 (10 cm^3) and trifluoroacetic acid (10 cm^3) was added *via* syringe at 0 °C under nitrogen. The reaction was allowed to stir for 1 h at room temperature. The resulting solution was diluted with water (10 cm^3) and treated with 10% aqueous solution of KOH at 0 °C. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers dried ($MgSO_4$). Concentration of the organic phases *in vacuo* afforded the crude amine as a residue which was purified by column chromatography.

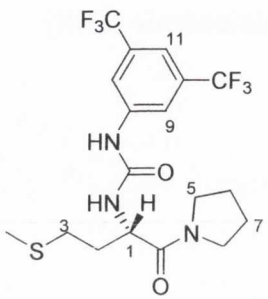
5.4.4.3. *L*-methionine pyrollidinamide (354f)



Prepared according to general procedure N using *N*-Boc-*L*-methionine (0.858 mg, 3.44 mmol) in CH_2Cl_2 (30 cm^3) and added *O*-benzotriazole-1-*N*,*N*,*N*',*N*'-tetraethyluronium hexafluorophosphate (1.35 g, 3.56 mmol). The white suspension was allowed to stir for 5 min, followed by the addition of diisopropylethylamine (719 µl, 4.13 mmol) and pyrollidine (287 µl, 3.44 mmol). The reaction mixture was then stirred for 24 h at room temperature. The mixture was combined with CH_2Cl_2 (10 cm^3) and water (5 cm^3) and the organic layer separated, washed with 1M hydrochloric acid (3 x 50 cm^3) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the crude Boc-protected amide **354e** as a pale yellow oil which was dissolved in CH_2Cl_2 (1 cm^3) and trifluoroacetic acid (4.3 cm^3) at 0 °C. The reaction mixture was allowed to stir for 1 h at room temperature followed by dilution of the reaction with water (15 cm^3) and treatment with KOH (10% aqueous solution) until pH ~ 7 at 0 °C. The resulting mixture was extracted with CH_2Cl_2 (2 x 10 cm^3) and the combined organic layers dried ($MgSO_4$). After filtration and concentration of the organic phases *in vacuo*, crude **354f** was obtained as a yellow oil which was purified using column chromatography (1:1 Hexane:ethyl acetate) to afford *L*-methionine pyrollidinamide (**354f**) as a yellow oil (180 mg, 26%). The isolated compound exhibited identical spectroscopic data to those in the literature.[378]

δ_H (400 MHz, $CDCl_3$): 3.42 (m, 5H, H-2, H-5, and H-1), 2.19 (br s, 2H, NH_2), 2.14 (s, 3H, CH_3), 1.96 (m, 2H, H-7), 1.86 (m, 2H, H-6), 1.60 (br s, 4H, H-3 and H-4)

5.4.4.4. (*S*)-1-(3,5-*bis*trifluoromethylphenyl)-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (355a)



Prepared according to procedure A using 3,5-*bis*trifluoromethylphenylisocyanate (**290f**) (287 µL, 1.66 mmol) and *L*-methionine pyrollidinamide (**354f**) (333 mg, 1.64 mmol) in CH_2Cl_2 (3 cm^3). The resulting solution was stirred for 12 h, upon which time the reaction was concentrated *in vacuo* to afford a beige residue which was purified *via* column chromatography (ethyl acetate: hexane 1:1, R_f 0.1) to afford **355a** (600 mg, 80 %) as a white solid after drying under high vacuum for 4 h. M.p. 118-119 ° C. $[\alpha]_D^{20}$ +12.0 (*c* 1.40 $CHCl_3$)

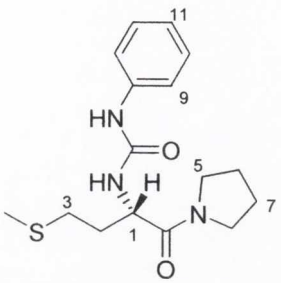
δ_H (400 MHz, $CDCl_3$): 8.66 (br s, 1H, NH), 7.77 (s, 2H, H-9 and H-13), 7.37 (s, 1H, H-11), 7.07 (d, 1H, J 8.7, NH), 4.94 (m, 1H, H-1), 3.96 (m, 1H, H-5a), 3.51 (m, 3H, H-5b and H-8), 2.65 (m, 2H, H-3), 2.14 (s, 3H, CH_3), 1.91 (m, 6H, H-6, H-7 and H-2b)

δ_C (100 MHz, $CDCl_3$): 172.5 (q), 154.9 (q), 140.9 (q), 131.7 (qt, C-C, J 32.8), 123.3 (qt, C-F, J 271.2), 117.6, 114.9, 50.3, 47.3, 46.8, 32.7, 30.4, 25.9, 24.1, 15.8

HRMS (ESI): (M^+ + Na) Calcd for $C_{18}H_{21}N_3O_2F_6SNa$ 480.1156; Found 480.1180

υ (cm^{-1})Diff: 3329, 1703, 1609, 1387, 1276, 1166, 1111

5.4.4.5. (*S*)-1-Phenyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (355b)



Prepared according to procedure A using phenylisocyanate (**290c**) (221 μL, 2.00 mmol) and *L*-methionine pyrollidinamide (**354f**) (412 mg, 2.00 mmol) in CH_2Cl_2 (2 cm^3). The resulting solution was stirred for 12 h, upon which time the reaction was concentrated *in vacuo* to afford a beige residue which was purified *via* column chromatography (ethyl acetate: hexane 1:1, R_f 0.1) to afford **355b** as a white solid (438 mg, 68 %). M.p. 104-106 °C. $[\alpha]_D^{20}$ +11.2 (*c* 0.17 $CHCl_3$)

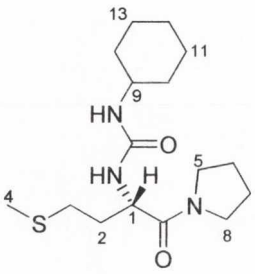
δ_H (400 MHz, $CDCl_3$): 7.91 (br s, 1H, NH), 7.34 (d, 2H, J 7.6, H-9 and H-13), 7.22 (m, 2H, H-10 and H-12), 6.94 (m, 2H, H-11 and NH), 4.96 (m, 1H, H-1), 3.60 (m, 1H, H-5a), 3.48 (m, 3H, H-8 and H-5b), 2.63 (dt, 2H, J 7.4, 7.1, H-3), 2.09 (s, 3H, CH_3), 1.90 (m, 6H, H-2b, H-6 and H-7)

δ_C (100 MHz, $CDCl_3$): 171.6 (q), 155.2 (q), 138.9 (q), 128.4, 121.9, 118.8, 49.7, 46.6, 45.9, 32.7, 29.9 25.5, 23.8, 15.3

υ (cm^{-1})Diff: 3337, 2881, 1701, 1611, 1544, 1443, 1309, 1211, 1176

HRMS(ESI) (M^+ + Na) Calcd for $C_{16}H_{23}N_3O_2SNa$ 344.1409; Found 344.1424

5.4.4.7 (*S*)-1-Cyclohexyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (355c)



Prepared according to procedure A using cyclohexylisocyanate (**290b**) (141 μL, 1.1o mmol) and *L*-methionine pyrollidinamide (**354f**) (203 mg, 1.00 mmol) in CH_2Cl_2 (2 cm^3). The resulting solution was stirred for 12 h, upon which time the reaction was concentrated *in vacuo* to afford a beige residue which was purified *via* column chromatography (CH_2Cl_2: hexane, R_f 0.1) to afford **355c** as a white solid which was dried under high vacuum for 1d. (302 mg, 84 %). M.p. 80-81 °C. $[\alpha]_D^{20}$ +2.05 (*c* 1.40 $CHCl_3$).

δ_H (400 MHz, $CDCl_3$): 5.54 (d, 1H, J 8.0, NH), 4.75 (m, 2H, H-1 and H-9), 4.67 (d, 1H, J 8.0, NH), 3.75 (m, 1H, H-8a), 3.39 (m, 3H, H-8b and H-5), 2.58 (app.t, 2H, H-3), 2.20 (s, 3H, *S*-CH_3), 1.69 (m, 8H, H-2, H-6, H-7, H-12), 1.28 (m, 4H, H-10), 1.10 (m, 4H, H-11 and H-13)

δ_C (100 MHz, $CDCl_3$): 171.8 (q), 157.2 (q), 49.8, 48.3, 46.3, 45.6, 33.6, 33.4, 32.7, 29.9, 25.5, 25.2, 24.6, 24.5, 23.7, 15.1

υ (cm^{-1})Diff: 3342, 2924, 2851, 1611 (C=O), 1546, 1445, 1226

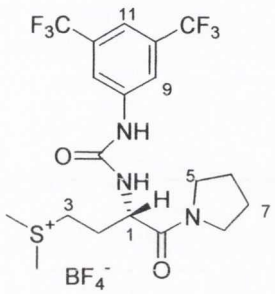
HRMS (ESI): (M^+ + Na) Calcd for $C_{16}H_{29}N_3O_2SNa$ 350.1878; Found 350.1880

5.4.4.8 General procedure O: for the alkylation of the Methionine-derived urea catalysts using Meerweins reagent

A solution of methionine-derived urea catalysts (0.250 mmol) in CH_2Cl_2 (2.0 cm^3) was cooled to 0 °C under N_2. After 10 min $(CH_3)_3OBF_4$ (0.250 mmol) was added with stirring. The

resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by recrystallisation (1:1 hexanes:CH_2Cl_2) to yield **356** as hydroscopic solids. The product was dried on the high vacuum line to afford the alkylated methionine-derived catalyst as a tetrafluoroborate salt in the form of an amorphous hydroscopic white solid.

5.4.4.9 (*S*)-1-(3,5-*bis*trifluoromethyl-phenyl)-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea-tetrafluoro borate salt (356a)



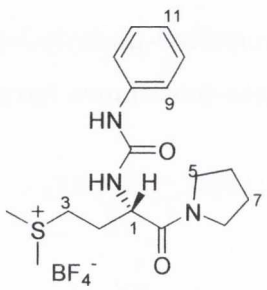
Prepared according to general procedure O using (*S*)-1-(3,5-*bis*trifluoromethyl)phenyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (88 mg, 0.19 mmol) in CH_2Cl_2 (4.0 cm^3) and $(CH_3)_3OBF_4$ (29 mg, 0.19 mmol). The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by recrystallisation (1:1 hexanes:CH_2Cl_2) to yield **356b** as a clear hydroscopic solid. The crude solid was dried further under high vacuum to afford (3-(3,5-*bis*trifluoromethyl-phenyl)-L-urea)-4-pyrrolidinamide-1-yl-butyl-dimethyl sulfonium tetrafluoroborate salt (97 mg, 90 %) as a white solid. M.p 121-122 °C

δ_H (400 MHz, DMSO): 9.54 (s, 1H, NH), 8.05 (s, 2H, H-9 and H-13), 7.49 (s, 1H, H-11), 6.95 (d, 1H, J 8.0 NH), 4.60 (m, 1H, H-1), 3.52 (m, 2H, H-5), 3.27 (m, 4H, H-3 and H-8), 2.80 (s, 6H, $2CH_3$), 2.09 (m, 1H, H-2a), 1.90 (m, 3H, H-2b and H-6), 1.80 (m, 2H, H-7)

δ_C (100 MHz, $CDCl_3$): 168.2 (q), 154.4 (q), 142.0 (q), 130.8, 130.7 (qt, C-C, J 32.3), 130.5, 123.3 (qt, C-F, J 273.1), 117.3, 114.0, 49.8, 45.8, 38.8, 26.5, 25.6, 24.2, 23.7

υ (cm^{-1})Diff: 3340, 1620 (C=O), 1565, 1473, 1387, 1276, 1172, 1122, 1033

5.4.4.10 (*S*)-1-Phenyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-L-urea tetrafluoroborate salt (356b)



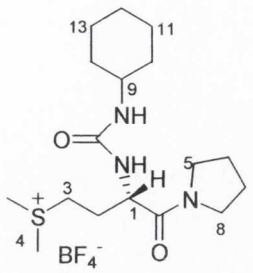
Prepared according to general procedure O using (*S*)-1-Phenyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (176 mg, 0.547 mmol) in CH_2Cl_2 (4.0 cm^3) and $(CH_3)_3OBF_4$ (82 mg, 0.55 mmol). The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by recrystallisation (1:1 Hexanes:CH_2Cl_2) to yield **356b** as a clear hydroscopic solid. The crude solid was dried further under high vacuum to afford (3-Phenylurea)-4-pyrrolidinamide-1-yl-butyl-dimethyl-sulfonium BF_4^- salt (206 mg, 89 %) as an amorphous hygroscopic white solid. M.p. 64-65 °C. $[\alpha]_D^{20}$ +10.0 (*c* 1.40 $CHCl_3$).

δ_H (400 MHz, DMSO): 8.79 (s, 1H, NH), 7.37 (d, 2H, J 8.0, H-9 and H-13), 7.21 (dd, 2H, J 8.0, 7.4, H-10 and H-12), 6.90 (app.t, 1H, J 7.4, H-11), 6.64 (d, 1H, J 8.2, NH), 4.60 (m, 1H, H-1), 3.52 (m, 2H, H-5), 3.20 (m, 4H, H-3 and H-8), 2.80 (s, 6H, CH_3), 2.10 (m, 1H, H-2a), 1.90 (m, 3H, H-2b and H-6), 1.8 (m, 2H, H-7)

δ_C (100 MHz, DMSO): 168.6 (q), 154.7 (q), 140.0 (q), 128.7, 121.4, 117.6, 49.6, 45.9, 45.8, 38.2, 26.8, 25.6, 24.3, 24.2, 23.7

υ (cm^{-1})Diff: 3084, 1656 (C=O), 1594, 1447, 1399, 1343, 1222, 1029, 987

5.4.4.11 (*S*)-1-Cyclohexyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (356c)



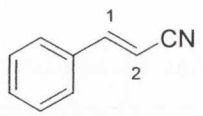
Prepared according to general procedure O using (*S*)-1-Cyclohexyl-3-[3-methylsulfanyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (81 mg, 0.247 mmol) in CH_2Cl_2 (1.0 cm^3) and $(CH_3)_3OBF_4$ (37 mg, 0.247 mmol). The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by recrystallisation (1:1 Hexane:CH_2Cl_2) to yield **356a** as a clear hydroscopic solid. The crude solid was dried on the high vacuum line to afford (3-Cyclohexylurea)-4-pyrrolidinamide-1-yl-butyl-dimethyl sulfonium BF_4^- salt (70 mg, 60 %) as an amorphous hygroscopic white solid. M.p 30-32 °C. $[\alpha]_D^{20}$ +2.05 (*c* 1.40 $CHCl_3$).

δ_H (400 MHz, DMSO): 6.14 (d, 1H, J 8.0, NH), 6.03 (d, 1H, J 8.0, NH), 4.48 (m, 1H, H-1), 3.47 (m, 2H, H-5a and H-9), 3.23 (m, 3H, H-5b, H-8), 2.87 (s, 6H, $2CH_3$, H-4), 2.04 (m, 1H, H-3a), 1.77 (m, 4H, H-6, H-7), 1.74 (m, 2H, H-2), 1.62 (m, 2H, H-10a and H-14a), 1.50 (m, 1H, H-3b), 0.58 (m, 6H, H-11, H-12 and H-13)

δ_C (100 MHz, DMSO): 169.1 (q), 156.7 (q), 54.9, 49.6, 47.7, 45.8, 45.7, 44.9, 33.1, 26.9, 25.5, 25.2, 24.2, 23.7

υ (cm^{-1})Diff: 3350, 2932, 2855, 1617 (C=O), 1546, 1448, 1231, 1030

5.4.4.13 Cinnamonitrile (359)

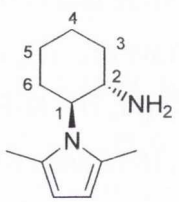


Prepared by the addition of benzaldehyde (30 μL, 0.296 mmol), KOH (33 mgs, 0.592 mmol), methyl iodide (22 μL, 0.355 mmol) and CH_3CN (930 μL) to a reaction flask with a stirrer bar. The resulting solution was allowed to stir at room temperature for 112 h. Flash chromatography (CH_2Cl_2:hexane 1:1, R_f 0.5) isolated **259** as a colourless liquid. The isolated compound showed identical data as that in the literature.[379]

δ_H (400 MHz, $CDCl_3$): 7.39 (m, 5H, Ar-H), 7.41 (d, 1H, J 16.5, H-1), 5.89 (d, 1H, J 16.5, H-2)

δ_C (150 MHz, $CDCl_3$): 150.9 (q), 133.8 (q), 131.5, 129.5, 127.7, 118.4, 96.7

5.4.4.14 (*R*,*R*)-2-(2,5-Dimethyl-pyrrol-1-yl)-cyclohexylamine (360a)

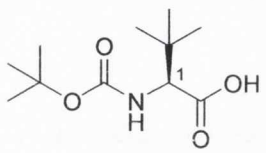


Prepared according to the general procedure described by Jacobsen *et al.*[78] In a round bottomed flask, acetic acid (469 μL, 8.2 mmol), and 2,5-hexanedione (962 μL, 8.2 mmol) were added to a solution of (*R*,*R*)-diaminocyclohexane (937 mg, 8.2 mmol) in methanol (47 cm^3). The mixture was heated to 50 °C and stirred for 1 h, then cooled to 23 °C and concentrated *in vacuo*. The residue was partioned between CH_2Cl_2 (160 cm^3) and 4M aqueous sodium hydroxide (160 cm^3). The organic phase was separated, and the aqueous phase extracted with CH_2Cl_2 (2 x 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting residue was purified using column chromatography (50% MeOH

in CH_2Cl_2, R_f 0.35) to afford **360** as a dark brown liquid (1.26 g, 80%). The isolated compound showed identical spectroscopic data to those in the literature.[78]

δ_H (400 MHz, $CDCl_3$): 5.75 (br s, 2H, Ar-H), 3.59 (m, 1H, H-1), 3.25 (m, 1H, H-2), 2.36 (br s, 3H), 2.23 (br s, 3H, CH_3), 2.06 (m, 1H, H-6a), 1.75 (m, 4H, H-4 and H-5), 1.36 (m, 2H, H-3), 1.20 (m, 1H, H-6b), NH_2 not visible

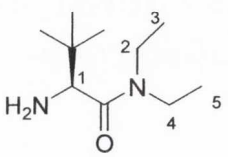
5.4.4.15 *N*-Boc-L-*tert*-leucine (368b)



Prepared according to general procedure M using *L*-tert leucine (**368a**) (3.0 g, 0.022 mol), *tert* butyl carbonate (4.99 g, 0.022 mol) in 50% MeOH/H_2O (20 cm^3) and sodium carbonate (2.42 g, 0.0228 mol) to afford boc protected *L*-tert leucine (**368b**) (4.22 g, 80%) as a colourless oil which solidified to a white solid on standing. The isolated compound showed identical spectroscopic data to those in the literature.[380]

δ_H (400 MHz, $CDCl_3$): 12.4 (br s, 1H, OH), 6.82 (d, 1H, J 9.0, NH), 3.74 (d, 1H, J 9.0, H-1), 1.38 (s, 9H, $C(CH_3)_3$), 0.93 (s, 9H, $C(CH_3)_3$)

5.4.4.16 L-*tert*-leucine diethylamide (368c)

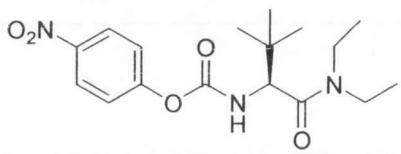


Prepared according to general procedure N using *N*-Boc-*L*-tert leucine (**368b**) (1.94 g, 8.39 mmol), HTBU (3.5 g, 9.23 mmol), in CH_2Cl_2 (74 cm^3). To this mixture diethylamine (955 µL, 9.23 mmol) and *N,N*-diisopropylethylamine (1.75 cm^3, 10.06 mmol) was added *via* syringe. The resulting solution was allowed to stir for 12 h at ambient temperature. General workup

and acid deprotection using TFA (1.4 cm^3) afforded a residue which was purified by column chromatography (5% MeOH in CH_2Cl_2) to give **368c** (1.50 g, 96 %) as a colourless oil. The isolated compound showed identical spectroscopic data to those in the literature.[381]

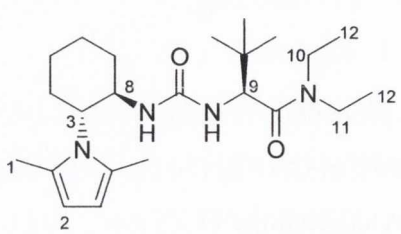
δ_H (400 MHz, $CDCl_3$): 3.68 (m, 1H, H-2a), 3.57 (m, 1H, H-2b), 3.40 (s, 1H, H-1), 3.19 (m, 1H, H-4a), 3.05 (m, 1H, H-4b), 1.54 (br s, 2H, NH_2), 1.20 (app.t, 3H, J 7.0, H-3), 1.13 (app.t, 3H, J 7.0, H-5), 0.97 (s, 9H, $C(CH_3)_3$)

5.4.4.17 (*S*)-1-Diethylcarbomoyl-2,2-dimethyl-propyl)-carbamic acid 4-nitro phenyl ester (370)



Prepared by analogy to the procedure reported by Jacobsen *et al.*[348] for the coupling of amines. In a round bottomed flask fitted with a stirrer bar L-*tert* leucine diethylamine (400 mg, 2.15 mmol) in CH_2Cl_2 (10 cm^3) and triethylamine (300 µL, 2.15 mmol) were stirred at 0 °C for 15 mins. *Para*-nitro phenyl chloroformate (**369**) (432.7 mg, 2.15 mmol) a solution in CH_2Cl_2 (10 cm^3) was added *via* syringe to the reaction flask causing the solution to turn a deep orange colour, indicative of the carbamate ester **370** intermediate. Upon complete formation of **370** (adjudged by ^1H NMR), the solution was concentrated *in vacuo* to afford crude **370** was which used without purification.

5.4.4.18 (*S*)-2-(3-((1*R*,2*R*)-2-(2,5-dimethyl-pyrrol-1-yl)cyclohexyl)urea)-*N*,*N*-diethyl-3,3-dimethylbutamide (360b)



In a round bottomed flask equipped with a stirrer bar (*S*)-1-diethylcarbomoyl-2,2-dimethyl-propyl)-carbamic acid 4-nitro phenyl ester (**370**) (755 mg, 2.15 mmol) and triethylamine (599 μL, 4.29 mmol) were dissolved in CH_2Cl_2 (5 cm^3). The resulting solution was allowed stir at ambient temperature for 15 min. (*R*,*R*)-2-(2,5-dimethyl-pyrrol-1-yl)-cyclohexylamine (**360**) (413 mg, 2.15 mmol) was added dropwise *via* syringe to the reaction and allowed to stir for 12 h. All volatile components were evaporated *in vacuo* to afford crude **360b** as a brown solid. Purification *via* column chromatography (1:10 hexane:ethyl acetate, R_f 0.1) afforded **360** (696 mg, 80 %) as a white solid. M.p 151-152 °C

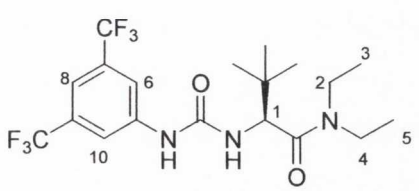
δ_H (600 MHz, DMSO): 6.08 (d, 1H, J 9.5, NH), 5.85 (d, 1H, J 8.0, NH), 5.71 (s, 2H, Ar-H), 5.00 (d, 1H, J 9.5, H-9), 4.55 (m, 1H, H-3), 4.20 (m, 1H, H-8), 4.10 (m, 1H, H-10a), 3.65 (m, 1H, H-11a), 3.55 (m, 1H, H-10b), 3.26 (m, 1H, H-11b), 3.05 (m, 1H, cyclohexyl), 2.23 (m, 6H, H-1), 1.92 (m, 4H, cyclohexyl), 1.35 (m, 3H, cyclohexyl), 1.22 (app.t, 3H, J 7.0, H-12a), 1.10 (app.t, 3H, J 7.0, H-12b), 0.96 (s, 9H, CH_3)

δ_C (100 MHz, DMSO): 171.4 (q), 156.7 (q), 107.3 (q), 105.5 (q), 59.7, 54.9, 52.1, 42.7, 40.1, 35.3, 34.4, 32.1, 30.7, 26.4, 25.8, 24.9, 14.0, 12.8

ν (cm^{-1})Diff 3401, 3205, 1622 (C=O), 1527, 1488, 1385, 1293, 1046

HRMS (ESI): (M^++Na) Calcd for $C_{23}H_{40}N_4O_2Na$ 427.3049; Found 427.3039

5.4.4.19 (*S*)-*N*,*N*-diethyl-3,3-dimethyl-2-(3-(3,5-*bis*-trifluoromethylphenyl)urea) butamide (361)



Prepared according to general procedure A using 3,5-*bis*-trifluormethylphenylisocyanate (**290f**) (372 μL, 2.15 mmol), in CH_2Cl_2 (25 cm^3) and L-*tert*-leucine diethylamide (**368**) (400

mg, 2.15 mmol). The resulting solution was stirred for 12 h. The reaction volume was reduced *in vacuo* to afford a white residue which was purified *via* flash chromatography (CH_2Cl_2, R_f 0.1) to afford **361** as a white solid (805 mg, 85 %). $[\alpha]_D^{20}$ = -4.3 (c 1.1, $CHCl_3$). M.p 186-188 °C

δ_H (400 MHz, $CDCl_3$): 8.31 (s, 1H, NH), 7.79 (s, 2H, H-6 and H-10), 7.42 (s, 1H, H-8), 6.53 (d, 1H, J 9.3, NH), 4.91 (d, 1H, J 9.3, H-1), 3.79 (m, 2H, H-2), 3.30 (m, 1H, H-4a), 3.03 (m, 1H, H-4b), 1.33 (app.t, 3H, J 7.0, H-3), 1.15 (app.t, 3H, J 7.0, H-5), 1.06 (s, 9H, CH_3)

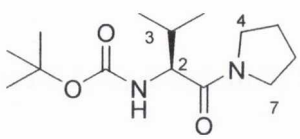
δ_C (100 MHz, $CDCl_3$): 172.0 (q), 154.5 (q), 140.5 (q), 131.3 (qt, C-C, J 32.8), 122.8 (qt, C-F, J 271),118.2, 114.8, 55.1, 42.9, 39.9, 35.3 (q), 26.5, 13.7, 12.3

δ_F (376 MHz, $CDCl_3$): -63.4 (s, 3F)

ν (cm^{-1})Diff 3329, 2976, 1655 (C=O), 1570, 1469,1386, 1270, 1126

HRMS (ESI): (M^++Na) Calcd for $C_{19}H_{25}N_3O_2F_6Na$ 464.1749; Found 464.1726

5.4.4.20 (*S*)-1-(3,5-*Bis*-trifluoromethyl-phenyl)-3-[2-methyl-1-(pyrrolidine-1-carbonyl)-propyl]-L-urea (362d)



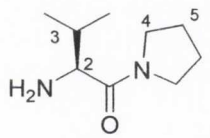
Step 1. Using general procedure M for the boc-protection of amino acids using *L*-valine (2.0 g, 17.0 mmol) in MeOH/H_2O (1:1,10 cm^3), Na_2CO_3 (1.80 g, 17.0 mmol) and di-*tert*-butyl dicarbonate (3.72 g, 17.0 mmol). The resulting solution was allowed to stir at room temperature overnight. 1M HCl was added to the reaction mixture until pH 1 was reached. The organic layer was extracted using CH_2Cl_2 (2 x 25 cm^3) and dried using $MgSO_4$ to afford the *tert*-butoxycarbonyl protected valine (**362b**) (2.93 g, 85%) as a viscous yellow liquid.

Step 2. DCC coupling of pyrrolidine to **362b**-(exception to general procedure M).

To a solution of **362b** (231 mg, 1.15 mmol) in CH_2Cl_2 (1.76 cm^3) the DCC coupling agent was added dropwise *via* pipette at 0 °C. The resulting solution was allowed stir for 15 min when pyrrolidine (76 μL, 0.91 mmol) was added dropwise *via* syringe. The reaction was allowed stir at room temperature for 12 h. The reaction was washed with an aqueous saturated Na_2CO_3 solution (2 x 10 cm^3), extracted with CH_2Cl_2 (2 x 10 cm^3) and the solvent evaporated *in vacuo* to afford a white semi-solid which was purified by column chromatography (75:25 hexane:ethyl acetate, R_f 0.3) to afford **362d** (61 mg, 22%) as a white solid. M.p. 69-70 °C (lit., 69-72 °C).[362]

δ_H (400 MHz, $CDCl_3$): 5.28 (br d, 1H, J 9.0, NH), 4.24 (m, 1H, H-2), 3.67 (m, 1H, H-3), 3.40 (m, 3H, H-4a and H-7), 1.85 (m, 5H, H-5, H-6, H-4b), 1.44 (s, 9H, CH_3, ^{t}Bu), 0.97 (d, 3H, J 7.0, CH_3), 0.93 (d, 3H, J 7.0, CH_3)

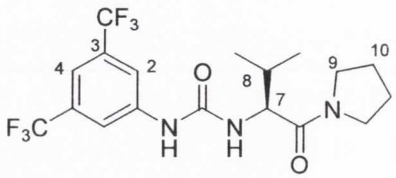
5.4.4.21 (*S*)-1-(3,5-*Bis*-trifluoromethyl-phenyl)-3-[2-methyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (362e)



Deprotection as per general procedure N-part II using **362d** (300 mg, 1.1 mmol), CH_2Cl_2 (5 cm^3) and trofluoroacetic acid (1.1 cm^3), the resulting solution was allowed to stir for 48 h at room temperature. Neutralisation was carried out using a concentrated aqueous solution of Na_2CO_3. The aqueous layer was washed with ethyl acetate (2 x 15 cm^3), the organic washings were combined and dried ($MgSO_4$) and concentrated *in vacuo* to afford **362e** (100 mg, 54%) as a white solid.M.p 68-70 °C (no m.p data in the literature).[382] No further purification was necessary. All spectral data was in agreement with the literature data.[382]

δ_H (400 MHz, $CDCl_3$): 4.20 (br s, 2H, NH_2), 4.20 (br s, 1H, H-2), 3.46 (m, 4H, H-4 and H-7), 2.22 (m, 1H, H-3), 1.96 (m, 4H, H-5 and H-6), 1.10 (d, 3H, J 7.0, CH_3), 1.09 (dd, 3H, J 7.0, CH_3)

5.4.4.22 (*S*)-1-(3,5-*Bis*-trifluoromethyl-phenyl)-3-[2-methyl-1-(pyrrolidine-1-carbonyl)-propyl]-urea (362f)



Prepared according to general procedure A using 3,5-*bis* trifluoromethylisocyanate (**290f**) (163 μL, 0.94 mmol) in CH_2Cl_2 (2 cm^3) and *L*-valine-pyrollidino-amide (**362e**) (145 mg, 0.85 mmol). Flash chromatography (1:1 CH_2Cl_2-Hexane, R_f 0.5) afforded **362f** (285 mg, 78 %) as a beige solid. M.p. 188-190 °C.$[\alpha]_D^{20}$ = -20.7 (c 0.6, $CHCl_3$).

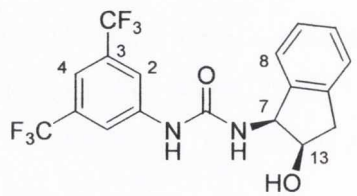
δ_H (400 MHz, $CDCl_3$): 8.83 (br s, 1H, NH), 7.84 (s, 2H, H-2 and H-6), 7.39 (s, 1H, H-4), 6.98 (d, 1H, J 9.0, NH), 4.55 (dd, 1H, J 9.0, 8.1, H-7), 4.01 (m, 1H, H-8), 3.59 (m, 3H, H-9 and one H-12a), 1.93 (m, 5H, H-10, H-11 and H-12b), 1.09 (d, 3H, J 7.0, CH_3), 1.06 (d, 3H, J 7.0, CH_3)

δ_C (100 MHz, $CDCl_3$): 170.2 (q), 155.0 (q), 142.6 (q), 131.1 (q, C-C, J 32.3), 123.7 (qt, C-F, J 271.1), 117.5, 114.1, 56.0, 46.6, 45.9, 30.9, 26.0, 24.1, 19.8, 18.0

HRMS (ESI): (M^+ + Na) Calcd for $C_{18}H_{21}N_3O_2NaF_6$ 448.1436; Found 448.1425

υ (cm^{-1})Diff: 3344, 1705, 1606 (C=O), 1386, 1274, 1114, 873

5.4.4.23 1-(2-Hydroxy-indan-1-yl)-3-(3,5 *bis* trifluoromethylphenyl) urea (363)



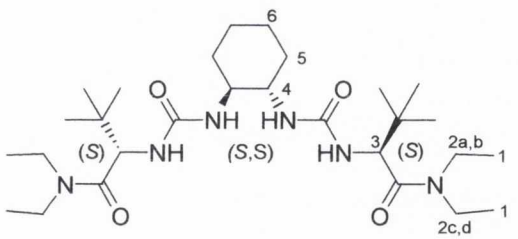
Prepared according to general procedure A using 3,5-*bis* trifluoromethylisocyanate (**290f**) (307 μL, 1.77 mmol) in CH_2Cl_2 (1 cm^3) and (1*S*, 2*R*)-*cis*-1-amino-2-indanol (**312**) (252 mg, 1.77 mmol). Flash chromatography (1:1 CH_2Cl_2-hexane, R_f 0.5) afforded **363** (572 mg, 80 %) as a white solid. M.p. 80-82 °C (lit., 82-84 °C). The isolated compound showed identical spectroscopic data to those in the literature.[192]

δ_H (400 MHz, $CDCl_3$): 8.15 (br s, 1H, NH), 7.94 (br s, 2H, H-2 and H-6), 7.53 (br s, 1H, H-4), 7.36 (m, 1H, Ar-H), 5.26 (m, 3H, Ar-H), 5.66 (d, 1H, J 7.5, OH), 5.34 (m, 1H, H-7), 4.67 (m, 1H, H-13), 3.21 (dd, 1H, J 16.5, 5.0, H-12a), 2.94 (app.d, 1H, J 16.5, H-12b), the other NH not visible.

υ (cm^{-1}): 3321, 1642 (C=O), 1565, 1471, 1384, 1276, 1169, 1124, 886, 701, 682

HRMS (ESI): (M^++Na) Calcd for $C_{18}H_{14}N_2O_2NaF_6$ 427.0857; Found 427.0930

5.4.4.24 Diaminocyclohexamin *L*-tert leucine-derived urea (*S,S,S,S*)-367



In a 50 cm^3 round bottomed flask which was charged with 1-diethylcarbomoyl-2,2-dimethyl-propyl)-carbamic acid 4-nitro phenyl ester (**370**)(347 mg, 0.987 mmol) in CH_2Cl_2 (3 cm^3) was added (1*S*, 2*S*)-cyclohexyldiamine (**59**) (56.4 mg, 0.494 mmol). The reaction was allowed to stir for 5 min. DIPEA (181 μL, 1.04 mmol) was added dropwise with stirring. The reaction was allowed to stir at ambient temperature for 12 h. As the reaction was adjudged to be incomplete at this stage by ^1H NMR spectroscopy a further portion of DIPEA (181 μL, 1.04 mmol) was added and the reaction allowed to stir at ambient temperature for 4 d. All volatile solvents were reduced *in vacuo* to afford a yellow residue which was purified using flash

chromatography (1:10 MeOH-Ethyl acetate, R_f 0.3) to afford (*S*,*S*,*S*,*S*)-**367** (150 mg, 56 %) as a white solid. M.p. 150-152 °C.

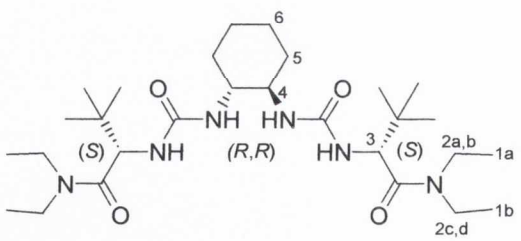
δ_H (600 MHz, $CDCl_3$): 5.32 (br s, 2H, NH-cycl), 5.25 (d, 2H, J 9.4, NH), 4.72 (d, 2H, J 9.4, H-3), 3.79 (m, 2H, H-2a), 3.69 (m, 2H, H-2b), 3.52 (m, 2H, H-4), 3.42 (br m, 2H, H-5a), 3.30 (m, 2H, H-2c), 3.03 (m, 2H, H-2d), 2.01 (m, 2H, H-5b), 1.93 (m, 2H, H-6a), 1.71 (m, 2H, H-6b), 1.25 (m, 6H, 2 x CH_3, H-1), 1.16 (m, 6H, 2 x CH_3, H-1), 1.01 (s, 18H, 6 x CH_3)

δ_C (150 MHz, $CDCl_3$): 171.6 (q), 157.8 (q), 54.5, 54.3, 42.7, 40.0, 35.5 (q), 33.0, 26.5, 24.7, 14.3, 12.8

HRMS (ESI): (M^+ + Na) Calcd for $C_{28}H_{54}N_6O_4Na$ 561.4105; Found 561.4099

υ (cm^{-1})Diff: 3372, 2937, 1622 (C=O), 1546, 1450, 1432, 1335, 1216, 694

5.4.4.25 Diaminocyclohexamin *L*-tert leucine-derived urea (*S*,*R*,*R*,*S*)-367



In a 50 cm^3 round bottomed flask which was charged with 1-diethylcarbomoyl-2,2-dimethyl-propyl)-carbamic acid 4-nitro phenyl ester (**370**)(604 mg, 1.71 mmol) in CH_2Cl_2 (3 cm^3) was added (1*R*, 2*R*)-cyclohexyldiamine (**59**) (98.1 mg, 0.859 mmol). The reaction was allowed to stir for 5 min. DIPEA (314 µL, 1.80 mmol) was added dropwise with stirring. The reaction was allowed to stir at ambient temperature for 12 h. As the reaction was adjudged to be incomplete at this stage by ^1H NMR spectroscopy a further portion of DIPEA (314 µL, 1.80 mmol) was added and the reaction allowed to stir at ambient temperature for 4 d. All volatile solvents were reduced *in vacuo* to afford a yellow residue which was purified using flash

chromatography (1:10 MeOH-Ethyl acetate, R_f 0.3) to afford (*S*,*R*,*R*,*S*)-**367** (133 mg, 50 %) as a pale yellow solid. M.p. 142-143 °C.

δ_H (600 MHz, $CDCl_3$): 6.38 (br s, 2H, NH), 6.22 (br s, 2H, NH), 4.44 (d, 2H, J 7.5, H-3), 3.64 (m, 6H, H-2a and H-4), 3.38 (m, 2H, H-2b), 2.96 (m, 4H, H-5a and H-2c), 2.19 (m, 2H, H-2d), 1.71 (m, 2H, H-5b), 1.50 (m, 2H, H-6), 1.27 (m, 6H, $2CH_3$, H-1), 1.12 (m, 6H, CH_3, H-1), 1.03 (s, 18H, 6 x CH_3)

δ_C (150 MHz, $CDCl_3$): 172.7 (q), 157.4 (q), 56.0, 54.4, 43.0, 40.5, 33.1, 31.2 (q), 26.7, 24.4, 13.6, 12.6

HRMS (ESI): (M^+ + Na) Calcd for $C_{28}H_{54}N_6O_4Na$ 561.4104; Found 561.4098

υ (cm^{-1})Diff: 3372, 3302, 2937, 1621, 1546, 1450, 1216, 1097, 840

5.4.6 Experimental data for Section 4.6

5.4.6.1 General Procedure P: for the urea catalysed cyclopropanation reaction of 1,3-diphenyl propenone under liquid-solid reaction conditions (Tables 4.15, 4.17 and 4.18)

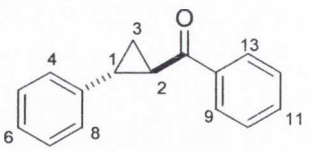
A carousel flask containing a magnetic stirring bar was charged with trimethylsulfoxonium iodide (105.7 mg, 0.528 mmol), the appropriate catalyst (0.048 mmol), powdered KOH (27 mg, 0.480 mmol) and CH_2Cl_2 (1.4 cm^3). The resulting suspension was allowed to stir for 10 min. 1,3-Diphenyl propenone (100 mg, 0.480 mmol) was then added and the flask was fitted with a cap and placed under an atmosphere of argon (balloon). The reaction was then stirred at ambient temperature for the time indicated in Tables 4.15, 4.17 and 4.18. When ^1H NMR spectroscopic analysis indicated completion of the reaction it was diluted with H_2O and the organic phase separated using a separating funnel. The aqueous layer was washed with CH_2Cl_2 (2 x 10 cm^3), then the organic phases were combined, dried ($MgSO_4$) and the solvent

evaporated under reduced pressure to afford the crude cyclopropane that was purified *via* column chromatography.

5.4.6.2 General Procedure Q: for the urea catalysed cyclopropanation reaction of 1,3-diphenyl propenone under liquid-liquid reaction conditions (Tables 4.13, 4.14 and 4.16)

A carousel flask containing a magnetic stirring bar was charged with trimethylsulfoxonium iodide (52.8 mg, 0.26 mmol), 50% $NaOH/H_2O$ solution (96 μL, 2.40 mmol) *via* syringe, the appropriate catalyst (0.024 mmol) and CH_2Cl_2 (1.4 cm^3). The resulting suspension was allowed to stir for 10 min. 1,3-diphenyl propenone (50 mg, 0.240 mmol) was then added and the flask was fitted with a cap and placed under an atmosphere of argon (balloon). The reaction was then stirred at ambient temperature for the time indicated in Tables 4.13 to 4.14 and Table 4.16. When ^1H NMR spectroscopic analysis indicated completion of the reaction it was diluted with H_2O and the organic phase separated using a separating funnel. The aqueous layer was washed with CH_2Cl_2 (2 x 10 cm^3), then the organic phases were combined, dried ($MgSO_4$) and the solvent evaporated under reduced pressure to afford the crude cyclopropane that was purified *via* column chromatography.

5.4.6.3 *trans*-Phenyl(2-phenylcyclopropyl)methanone (372)



Prepared using general procedures P and Q. Conversions up to 100%. Purification was *via* column chromatography (CH_2Cl_2, R_f 0.6). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 97/3, 1.0 cm3 min^{-1}, RT, UV detection at 220 nm, retention times: major enantiomer = 5.5 min, minor enantiomer = 6.0 min. M.p 46-48 °C (lit., 43-44 °C).[323] An identical experimental procedure was followed using catalysts **46**, **291**, **297**, **321**, **361**, **363**, **367**, **373**.

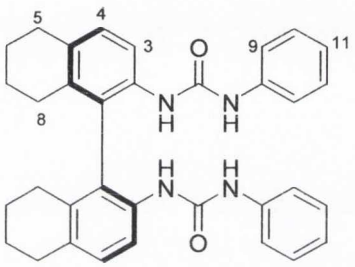
δ_H (400 MHz, $CDCl_3$): 8.03 (d, 2H, J 7.9, H-9 and H-13), 7.58 (app t, 1H, J 7.3, H-11), 7.48 (t, 2H, J 7.6, H-10 and H-12), 7.34 (m, 2H, J 7.5, H-5 and H-7), 7.22 (m, 1H, H-6), 7.22 (d, 2H, J 7.7, H-4 and H-8), 2.91 (ddd, 1H, J 8.0,

5.0, 4.0, H-2), 2.70 (ddd, 1H, CH, J 9.0, 6.5, 4.0, H-1), 1.96 (ddd, 1H, CH, J 4.0, 5.0, 9.0, H-3a), 1.62 (m, 1H, H-3b)

δ_C (100 MHz, $CDCl_3$): 198.1 (C=O), 140.0 (q), 137.3 (q), 132.5, 128.2, 128.1, 128.0, 127.6, 125.8, 29.6 (CH), 28.9 (CH), 18.8 (CH_2)

υ (cm^{-1})Diff: 3084, 1656 (C=O), 1594, 1447, 1398, 1343, 1221, 1029, 986

5.4.6.4 (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphthyl-2,2'-phenyl urea (373)



Procedure A was followed using phenylisocyanate (**290c**) (34.4 mg, 0.316 mmol), (*S*)-5,5',6,6',7,7',8,8'-octahydro-[1,1']binaphtyl-2,2'-diamine (46 mg, 0.157 mmol), in CH_2Cl_2 (1.0 cm^3). The resulting solution was left to stir overnight at room temperature with precipitation of the product (*S*)-**373** as a yellow solid (70 mg, 84 %). The product was purified *via* column chromatography on silica gel (CH_2Cl_2:hexane, R_f 0.5) M.p. 142-143 °C, $[\alpha]_D^{20}$ – 9.8 (*c* 1.4, $CHCl_3$)

δ_H (600 MHz, DMSO): 7.91 (d, 2H, J 8.5, H-4), 7.45 (br s, 2H, NH), 7.33 (d, 4H, J 7.5, H-9 and H-13), 7.27 (t, 2H, J 8.1, H-11), 7.20 (dd, 4H, J 8.1, 7.5, H-10 and H-12), 7.09 (d, 2H, J 8.5, H-3), 6.91 (m, 2H, NH), 2.74 (m, 4H, H-6), 2.05 (m, 2H, H-5a), 1.88 (m, 2H, H-5b), 1.66 (m, 4H, H-7), 1.58 (m, 4H, H-8)

δ_C (150 MHz, $CDCl_3$): 152.7 (C=O), 139.7 (q), 135.0 (q), 134.8 (q), 131.5 (q), 128.9, 128.7, 125.6 (q), 121.6, 118.9, 118.2, 28.9, 26.7, 22.7, 22.4

HRMS(ESI) (M^+ + Na) Calcd for $C_{34}H_{34}N_4O_2Na$ 553.2579; Found 553.2592

υ (cm^{-1})Diff: 3318, 2924, 2854, 1649, 1596, 1495, 1441, 1312, 1230

1. J. B. Biot, *Bull.Soc. Philomath. Paris.,* 1815.
2. P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.,* 2004, **43**, 5138.
3. P. I. Dalko and and L. Moisan, *Angew. Chem. Int. Ed.,* 2001, **40**, 3726.
4. *Comprehensive Asymmetric Catalysis*, ed, E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999 Vol. Vols. 1-3,
5. S.J. Connon, *Chem. Eur. J.,* 2006, **12**, 5418.
6. M. S. Taylor and E. N. Jacobsen, *Angew. Chem. Int. Ed.,* 2006, **45**, 1520.
7. M. J. Gaunt, C. C. C. Johansson, A. McNally and N. T. Vo, *Drug. Discov. Today,* 2007, **12**, 8.
8. B. List, *Chem. Commun.,* 2006, 819.
9. H. Wynberg and R. Helder, *Tetrahedron Lett.,* 1975, **16**, 4057.
10. A. M. Thayer, *Chem. Eng. News.,* 2007, **85**, 11.
11. B. M. Trost, *Proc. Natl. Acad. Sci. USA.,* 2004, **101**, 5348.
12. L. Pasteur, *Ann. Chim. Phys,* 1853, **38**, 437.
13. L. Pasteur, *C.R. Acad. Sci,* 1853, **37**, 162.
14. L. Pasteur, *C.R. Acad. Sci,* 1858, **46**, 615.
15. P. Sykes, in A Guidebook to Mechanism in Organic Chemistry, Pearson, England, 1986
16. S. Jaroch, H. Weinmann and K. Zeitler, *ChemMedChem.,* 2007, **2**, 1261.
17. M. T. Reetz, *Proc. Natl. Acad. Sci. USA.,* 2004, **101**, 5716.
18. P. A. Frey and A. D. Hegeman, in Enzymatic Reaction Mechanisms, Oxford University Press, New York, 2007
19. A. Peracchi, *ChemBioChem.,* 2005, **6**, 1316.
20. L. Polgar, *Cell. Mol. Life Sci.,* 2005, **62**, 2161.
21. Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem. Int. Ed. Engl.,* 1997, **36**, 1871.
22. T. Mallat, E. Orglmeister and A. Baiker, *Chem. Rev.,* 2007, **107**, 4863.

23. Z. Chen, H. Morimoto, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.,* 2008, **130**, 2170.
24. E. M. McGarrigle and D. G. Gilheany, *Chem. Rev.,* 2005, **105**, 1563.
25. S. J. Connon, *Angew. Chem. Int. Ed.,* 2006, **45**, 3909.
26. H. Yamamoto and K. Futatsugi, *Angew. Chem. Int. Ed.,* 2005, **44**, 1924.
27. P. M. Pihko, *Angew. Chem. Int. Ed.,* 2004, **43**, 2062.
28. J. F. Blake and W. L. Jørgensen, *J. Am. Chem. Soc.,* 1991, **113**, 7430.
29. J. F. Blake, D. Lim and W. L. Jørgensen, *J. Org. Chem.,* 1994, **59**, 803.
30. T. P. Yoon and E. N. Jacobsen, *Science,* 2003, **299**, 1691.
31. E. J. Corey and M. J. Grogan, *Org. Lett.,* 1999, **1**, 157.
32. T. Schuster, M. Kurz and M. W. Göbel, *J. Org. Chem.,* 2000, **65**, 1697.
33. T. R. Kelly, P. Meghani and S. V. Ekkundi, *Tetrahedron Lett.,* 1990, **31**, 3381.
34. L. Zu, J. Wang, H. Li, H. Xie, W. Jiang and W. Wang, *J. Am. Chem. Soc.,* 2007, **129**, 1036.
35. A. G. Doyle and E. N. Jacobsen, *Chem. Rev.,* 2007, **107**, 5713.
36. S. Saito and H. Yamamoto, *Acc. Chem. Res.,* 2004, **37**, 570.
37. J. Hine, S.-M. Linden and V.M. Kanagasabapathy, *J. Am. Chem. Soc.,* 1984, **107**, 1082.
38. J. Hine, K. Ahn, J. C. Gallucci and S. -M. Linden, *J. Am. Chem. Soc.,* 1984, 7980.
39. J. Hine, S. Hahn, D. E. Miles and K. Ahn, *J. Org. Chem.,* 1985, **50**, 5092.
40. D. L. Severance and W. L. Jørgensen, *J. Am. Chem. Soc.,* 1992, **114**, 10966.
41. Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.,* 2002, **124**, 9662.
42. Y. Huang, A. K. Unni and A. N. Thadani, *Nature,* 2003, **424**, 146.
43. M. C. Etter, Z. Urbañczyk-Lipkowska, M. Zia-Ebrahimi and T. W. Panunto, *J. Am. Chem. Soc.,* 1990, **112**, 8415.
44. M. C. Etter and T. W. Panunto, *J. Am. Chem. Soc.,* 1988, **110**, 5896.
45. D. P. Curran and L. H. Kuo, *J. Org. Chem.,* 1994, **59**, 3259.
46. C. S. Wilcox, E. Kim, D. Romano, L. H. Kuo, A. L. Burt and D. P. Curran, *Tetrahedron,* 1995, **51**, 621.
47. D. P. Curran and L. H. Kuo, *Tetrahedron Lett.,* 1995, **36**, 6647.
48. A. Wittkopp and P. R. Schreiner, *Chem. Eur. J.,* 2003, **9**, 407.
49. A. Wittkopp and P. R. Schreiner, *Org. Lett.,* 2002, **4**, 217.
50. P. R. Schreiner, *Chem. Soc. Rev.,* 2003, **32**, 289.

51. T. Weil, M. Kotke, C. M. Kleiner and P. R. Schreiner, *Org. Lett.,* 2008, **10**, 1513.
52. F. G. Bordwell, D. J. Algrim and J. A. Harrelson, *J. Am. Chem. Soc.,* 1988, **110**, 5903.
53. T. Okino, Y. Hoashi and Y. Takemoto, *Tetrahedron Lett.,* 2003, **44**, 2817.
54. P. E. Harrington and M. A. Kerr, *Synlett,* 1996, 1047.
55. I. Komoto and S. Kobayashi, *Org. Lett.,* 2002, **4**, 111.
56. M. M. Alam, R. Varala and S. R. Adapa, *Tetrahedron Lett.,* 2003, **44**, 5115.
57. G. Dessole, R. P. Herrera and A. Ricci, *Synlett,* 2004, 2374.
58. S. C. Pan, J. Zhou and B. List, *Synlett,* 2006, 3275.
59. M. Kotke and P. R. Schreiner, *Tetrahedron,* 2006, **62**, 434.
60. C. M. Kleiner and P. R. Schreiner, *Chem. Commun.,* 2006, 4315.
61. M. Kotke and P. Schreiner, *Synthesis,* 2007, 779.
62. Z. Zhang and P. Schreiner, *Synlett,* 2007, 1455.
63. M. Kirsten, J. Rehbein, M. Hiersemann and T. Strassner, *J. Org. Chem.,* 2007, **72**, 4001.
64. S. J. Connon and D. J. Maher, *Tetrahedron Lett.,* 2004, **45**, 1301.
65. G. Bredig and P. S. Fiske, *Biochem. Z.,* 1912, **46**, 7.
66. M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *J. Am. Chem. Soc.,* 1996, **118**, 4910.
67. H. Danda, H. Nishikawa and K. Otaka, *J. Org. Chem.,* 1991, **56**, 6740.
68. K. Tanaka, A. Mori and S. Inoue, *J. Org. Chem.,* 1990, **55**, 181.
69. E. R. Jarvo and S. J. Miller, *Tetrahedron,* 2002, **58**, 2481.
70. M. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.,* 1998, **120**, 4901.
71. J. T. Su, P. Vachal and E. N. Jacobsen, *Advanced Synthetic Catalysis,* 2001, **343**, 197.
72. I. T. Raheem and E. N. Jacobsen, *Adv. Synth. Catal.,* 2005, **347**, 1701.
73. P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2002, **124**, 10012.
74. Y. Takemoto, *Org. Biomol. Chem.,* 2005, **3**, 4299.
75. A. G. Wenzel, M. P. Lalonde and E. N. Jacobsen, *Synlett,* 2003, **12**, 1919.
76. T. P. Yoon and E. N. Jacobsen, *Angew. Chem.,* 2005, **117**, 470.
77. T. P. Yoon and E. N. Jacobsen, *Angew. Chem. Int. Ed.,* 2005, **44**, 466.
78. M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2004, **126**, 10558.
79. M. S. Taylor, N. Tokunaga and E. N. Jacobsen, *Angew. Chem.,* 2005, **117**, 6858.
80. Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem.,* 2005, **117**, 4100.
81. Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem. Int. Ed.,* 2005, **44**, 4032.

82. T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.,* 2004, **6**, 625.

83. A. Berkessel, F. Cleesman, S. Mukherjee, T. N. Muller and J. Lex, *Angew. Chem.,* 2005, **117**, 817.

84. A. Berkessel, F. Cleesman, S. Mukherjee, T. N. Muller and J. Lex, *Angew. Chem. Int. Ed.,* 2005, **44**, 817.

85. A. Berkessel, S. Mukherjee, F. Cleesman, T. N. Muller and J. Lex, *Chem. Commun.,* 2005, 1898.

86. Y. Sohtome, A. Tanatani, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.,* 2004, **45**, 5589.

87. S. H. McCooey, T. McCabe and S. J. Connon, *J. Org. Chem.,* 2006, **71**, 7494.

88. D. E. Fuerst and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2005, **127**, 8964.

89. K. L. Tan and E. N. Jacobsen, *Angew. Chem. Int. Ed.,* 2007, **46**, 1315.

90. B. Procuranti and S. J. Connon, *Chem. Commun.,* 2007, 1421.

91. E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994

92. J. H. van't Hoff, *Arch. Neerl. Sci. Exactes Nat.,* 1874, **9**, 445.

93. J. A. leBel, *Bull. Soc. Chim.,* 1874, **22**, 337.

94. IUPAC Compendium of Chemical Terminology and Electronic version http://goldbook.iupac.org/A00547.html, 1996

95. V. von Richter, *Chem. Ber.,* 1873, **6**, 1252.

96. J. Jacques and C. Fouquey, *Tetrahedron Lett.,* 1971, **12**, 4617.

97. M. Hovorka, R. Scigel, J. Gunterova, M. Tichy and J. Zavada, *Tetrahedron,* 1992, **48**, 9503.

98. M. O. Rasmussen, O. Axelsson and D. Tanner, *Synth. Commun.,* 1997, **27**, 4027.

99. P. Mastrorilli, F. Muscio, G. P. Suranna, C. F. Nobile and M. Latronico, *J. Mol. Catal. A:,* 2001, **165**, 81.

100. J. Doussot, A. Guy and C. Ferroud, *Tetrahedron Lett.,* 2000, **41**, 2545.

101. D. Villemin and F. Sauvaget, *Synlett,* 1994, 435.

102. B. E. Love and R. A. Bills, *Synth. Commun.,* 2002, **32**, 2067.

103. S. J. Ji, J. Lu, X. Zhu, J. Yang, J. P. Lang and L. Wu, *Synth. Commun.,* 2002, **32**, 3069.

104. D. R. Hwang, C. P. Chen and B. J. Uang, *Chem. Commun.,* 1999, 1207.

105. V. B. Sharma, S. L. Jain and B. Sain, *Tetrahedron Lett.,* 2003, **44**, 2655.

106. T. Sakamoto, H. Yonehara and C. Pac, *J. Org. Chem.,* 1997, **62**, 3194.

107. T. Sakamoto, H. Yonehara and C. Pac, *J. Org. Chem.,* 1994, **59**, 6859.

108. M. L. Kantam and P. L. Santhi, *Synth. Commun.,* 1996, **26**, 3075.

109. G. M. S. R. O. Rocha, R. A. W. Johnstone and M. G. P. M. S. Neves, *J. Mol. Catal. A: Chem.,* 2002, **187**, 95.

110. M. R. Prasad, G. Kamalakar, S. J. Kulkarni and K. V. Raghavan, *J. Mol. Catal. A:,* 2002, **180**, 109.

111. M. Juarez-Hernandez, D. V. Johnson, H. L. Holland, J. McNulty and A. Capretta, *Tetrahedron: Asymmetry,* 2003, **14**, 289.

112. F. Toda and K. Tanaka, *J. Org. Chem.,* 1988, **53**, 3607.

113. Y. Wang, J. Sun and K. Ding, *Tetrahedron,* 2000, **56**, 4447.

114. S. W. Hon, C. H. Li, J. H. Kuo, N. B. Barhate, Y. H. Liu, Y. Wang and C. T. Chen, *Org. Lett.,* 2001, **3**, 869.

115. Z. Luo, Q. Liu, L. Gong, X. Cui, A. Mi and Y. Jiang, *Angew. Chem. Int. Ed.,* 2002, **41**, 4532.

116. P. Kočovsky, Š. Vyskočil and M. Smrčina, *Chem. Rev.,* 2003, **103**, 3213.

117. A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, *J. Am. Chem. Soc.,* 1980, **102**, 7932.

118. R. Noyori and T. Ohkuma, *Angew. Chem. Int. Ed.,* 2001, **40**, 40.

119. H. Takaya, T. Ohta, N. Sayo, H. Kumobayashi, S. Akutagawa, S.Inoue, I. Kasahara and R. Noyori, *J. Am. Chem. Soc.,* 1987, **109**, 1597.

120. J. M. Brown and R. G. Naik, *J. Chem. Soc., Chem. Commun.,* 1982, 348.

121. D. A. Evans and M. M. Morrissey, *Tetrahedron Lett.,* 1984, **25**, 4637.

122. K. Mashima, T. Akutagawa, X. Zhang, H. Takaya, T. Taketomi, H. Kumobayashi and S. Akutagawa, *J. Organomet. Chem.,* 1992, **428**, 213.

123. T. Ohkuma, M. Koizumi, H. Doucet, T. Pham, M. Kozawa, K. Murata, E. Katayama, T. Yokozawa, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.,* 1998, **120**, 13529.

124. R. Noyori, I. Tomino and Y. Tanimoto, *J. Am. Chem. Soc.,* 1979, **101**, 3129.

125. M. Nishizawa and R. Noyori, *Tetrahedron Lett.,* 1980, **21**, 2821.

126. R. Noyori, I. Tomino and Y. Tanimoto, *J. Am. Chem. Soc.,* 1979, **101**, 5843.

127. R. Noyori, *Chem. Soc. Rev.,* 1989, **18**, 187.

128. J. M. Brunel, *Chem. Rev.,* 2005, **105**, 857.

129. R. O. Hutchins, A. Abdel-Magid, Y. P. Stercho and A. Wambsgans, *J. Org. Chem.,* 1987, **52**, 702.

130. A. Berkessel and M. Frauenkron, *Tetrahedron: Asymmetry,* 1996, **7**, 671.

131. T. Nemoto, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.,* 2001, **123**, 9474.

132. T. Nemoto, T. Ohshima, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.,* 2001, **123**, 2725.

133. T. Ohshima, V. Gnanadesikan, T. Shibuguchi, Y. Fukuta, T. Nemoto and M. Shibasaki, *J. Am. Chem. Soc.,* 2003, **125**, 11206.

134. T. Nemoto, H. Kakei, V. Gnanadesikan, S. y. Tosaki, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.,* 2002, **124**, 14544.

135. G. D. Sala, A. Lattanzi, T. Severino and A. Scettri, *J. Mol. Catal. A,* 2001, **170**, 219.

136. Y. Iwabuchi, M. Nakatani, N. Yokoyama and S. Hatakeyama, *J. Am. Chem. Soc.,* 1999, **121**, 10219.

137. Y. M. A. Yamada and S. Ikegami, *Tetrahedron Lett.,* 2000, **41**, 2165.

138. G. Kumaraswamy, M. N. V. Sastry and N. Jena, *Tetrahedron Lett.,* 2001, **42**, 8515.

139. K. Matsui, S. Takizawa and H. Sasai, *Synlett,* 2006, 761.

140. N. T. McDougal and S. E. Schaus, *J. Am. Chem. Soc.,* 2003, **125**, 12094.

141. G. Guillena, M. D. C. Hita and C. Najera, *Tetrahedron: Asymmetry,* 2006, **17**, 729.

142. C. Friedel and J. M. Crafts, *C. R. Hebd. Seances. Acad. Sci.,* 1877, **84**, 1392.

143. C. Friedel and J. M. Crafts, *C. R. Hebd. Seances. Acad. Sci.,* 1877, **84**, 1450.

144. G. A. Olah, in *Friedel-Crafts Chemistry*, Wiley Interscience, New York 1973

145. M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem. Int. Ed.,* 2004, **43**, 550.

146. M. Bandini, A. Melloni, S. Tommasi and A. Umani-Ronchi, *Synlett,* 2005, 1199.

147. H. Dalton King, Z. Meng, D. Denhart, R. Mattson, R. Kimura, D. Wu, Q. Gao and J. E. Macor, *Org. Lett.,* 2005, **7**, 3437.

148. J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2002, **124**, 1172.

149. A. Kleeman, J. Engel, B. Kutscher and D. Reichert, in *Pharmaceutical Substances*, 4th ed, Thieme, New York, 2001

150. N. Ono, in *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001

151. F. Bigi, C. Casiraghi, G. Casnati and G. Sartori, *J. Org. Chem.,* 1985, **50**, 5018.

152. K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem.,* 2001, **113**, 164.

153. K. B. Jensen, J. Thorhauge, R. G. Hazell and K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2001, **40**, 160.

154. M. P. A. Lyle, N. D. Draper and P. D. Wilson, *Org. Lett.,* 2005, **7**, 901.

155. J. Zhou, M. C. Ye, Z. Z. Huang and Y. Tang, *J. Org. Chem.,* 2004, **69**, 1309.
156. M. C. Ye, B. Li, J. Zhou, X. L. Sun and Y. Tang, *J. Org. Chem.,* 2005, **70**, 6108.
157. S. Yamazaki and Y. Iwata, *J. Org. Chem.,* 2006, **71**, 739.
158. R. Rasappan, M. Hager, A. Gissibl and O. Reiser, *Org. Lett.,* 2006, **8**, 6099.
159. W. Zhuang, N. Gathergood, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.,* 2001, **66**, 1009.
160. W. Zhuang, T. Hansen and K. A. Jørgensen, *Chem. Commun.,* 2001, 347.
161. G. Desimoni, G. Faita, M. Toscanini and M. Boiocchi, *Chem. Eur. J.,* 2008, **14**, 3630.
162. D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam and J. Wu, *J. Am. Chem. Soc.,* 2003, **125**, 10780.
163. D. A. Evans, K. R. Fandrick, H. J. Song, K. A. Scheidt and R. Xu, *J. Am. Chem. Soc.,* 2007, **129**, 10029.
164. N. Takenaka, J. P. Abell and H. Yamamoto, *J. Am. Chem. Soc.,* 2007, **129**, 742.
165. H. Yang, Y-T. Hong and S. Kim, *Org. Lett.,* 2007, **9**, 2281.
166. G. Blay, I. Fernandez, J. R. Pedro and C. Vila, *Org. Lett.,* 2007, **9**, 2601.
167. Y. X. Jia, J. H. Xie, H-F. Duan, L-X. Wang and Q-L. Zhou, *Org. Lett.,* 2006, **8**, 1621.
168. S-F. Lu, D-M. Du and J. Xu, *Org. Lett.,* 2006, **8**, 2115.
169. Y. X. Jia, S. F. Zhu, Y. Yang and Q. L. Zhou, *J. Org. Chem.,* 2006, **71**, 75.
170. P. K. Singh, A. Bisai and V. K. Singh, *Tetrahedron Lett.,* 2007, **48**, 1127.
171. M. Bandini, A. Garelli, M. Rovinetti, S. Tommasi and A. Umani-Ronchi, *Chirality,* 2005, **17**, 522.
172. G. Desimoni, G. Faita and K. A. Jørgensen, *Chem. Rev.,* 2006, **106**, 3561.
173. B. Trost and C. Muller, *J. Am. Chem. Soc.,* 2008, **130**, 2438.
174. M. Bandini, M. Fagioli, P. Melchiorre, A. Melloni and A. Umani-Ronchi, *Tetrahedron Lett.,* 2003, **44**, 5843.
175. M. Johannsen, *Chem. Commun.,* 1999, 2233.
176. D. A. Evans, K. R. Fandrick and H. J. Song, *J. Am. Chem. Soc.,* 2005, **127**, 8942.
177. G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.,* 2003, **103**, 3119.
178. W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Org. Biomol. Chem.,* 2005, **3**, 2566.
179. M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva and A. Umani-Ronchi, *J. Org. Chem.,* 2002, **67**, 3700.
180. M. Bandini, P. Melchiorre, A. Melloni and A. Umani-Ronchi, *Synthesis,* 2002, 1110.
181. N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2001, **123**, 4370.

182. S. Lee and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2007, **129**, 15438.

183. D-P. Li, Y-C. Guo, Y. Ding and W-J. Xiao, *Chem. Commun.,* 2006, 799.

184. G. Bartoli, M. Bosco, A. Carlone, F. Pesciaioli, L. Sambri and P. Melchiorre, *Org. Lett.,* 2007, **9**, 1403.

185. M. Terada and K. Sorimachi, *J. Am. Chem. Soc.,* 2006, **129**, 292.

186. Q. Kang, Z-A. Zhao and S-L. You, *J. Am. Chem. Soc.,* 2007, **129**, 1484.

187. M. Terada, S. Yokoyama, K.Sorimachi and D. Uraguchi, *Adv. Synth. Catal.,* 2007, **349**, 1863.

188. H. Li, Y-Q. Wang and L. Deng, *Org. Lett.,* 2006, **8**, 4063.

189. W. Zhuang and K. A. Jørgensen, *Chem. Commun.,* 2002, 1336.

190. T-Y. Liu, H-L. Cui, Q. Chai, J. Long, B-J. Li, Y. Wu, L-S. Ding and Y-C. Chen, *Chem. Commun.,* 2007, 2228.

191. E. M. Fleming, T. McCabe and S. J. Connon, *Tetrahedron Lett.,* 2006, **47**, 7037.

192. R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem. Int. Ed.,* 2005, **44**, 6576.

193. W. Zhuang, T. B. Poulsen and K. A. Jørgensen, *Org. Biomol. Chem.,* 2005, **3**, 3284.

194. L-T. An, J-P. Zou, L-L. Zhang and Y. Zhang, *Tetrahedron Lett.,* 2007, **48**, 4297.

195. J. P. Dirlam, D. A. Clark and S. J. Hecker, *J. Org. Chem.,* 1986, **51**, 4920.

196. H. Kotsuki, K. Hayashida, T. Shimanouchi and H. Nishizawa, *J. Org. Chem.,* 1990, **55**, 2969.

197. H. Kotsuki, K. Hayashida, T. Shimanouchi and H. Nishizawa, *J. Org. Chem.,* 1996, **61**, 984.

198. M. Bandini, P. G. Cozzi, P. Melchiorre and A. Umani-Ronchi, *J. Org. Chem.,* 2002, **67**, 5386.

199. J. S. Yadav, B. V. S. Reddy, S. Abraham and G. Sabitha, *Synlett,* 2002, 1550.

200. E. C. Blossey, L. M. Turner and D.C. Neckers, *J. Org. Chem.,* 1975, **40**, 959.

201. S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.,* 1996, **118**, 8977.

202. S. Kobayashi and S. Nagayama, *J. Org. Chem.,* 1996, **61**, 2256.

203. L. Yu, D. Chen, J. Li and P. G. Wang, *J. Org. Chem.,* 1997, **62**, 3575.

204. S. Kobayashi and S. Nagayama, *J. Am. Chem. Soc.,* 1998, **120**, 2985.

205. M. Bandini, M. Fagioli, A. Melloni and A. Umani-Ronchi, *Adv. Synth. Catal.,* 2004, **346**, 573.

206. M. L. Kantam, S. Laha, J. Yadav and B. Sreedhar, *Tetrahedron Lett.,* 2006, **47**, 6213.

207. N. Azizi, S. Mehrazma and M. R. Saidi, *Can. J. Chem.*, 2006, **84**, 800.

208. A. K. Chakraborti and A. Kondaskar, *Tetrahedron Lett.*, 2003, **44**, 8315.

209. E. N. Jacobsen, W. Zhuang, A. R. Muci, J. R. Ecker and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063.

210. J. F. Larrow, S. E. Schaus and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 7420.

211. L. E. Martinez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897.

212. J. L. Leighton and E. N. Jacobsen, *J. Org. Chem.*, 1996, **61**, 389.

213. E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421.

214. D. A. Annis, O. Helluin and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 1998, **37**, 1907.

215. F. Benfatti, G. Cardillo, L. Gentilucci, R. Perciaccante, A. Tolomelli and A. Catapano, *J. Org. Chem.*, 2006, **71**, 9229.

216. E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow and M. Tokunaga, *Tetrahedron Lett.*, 1997, **38**, 773.

217. D. J. Ager, I. Prakash and D. R. Schaad, *Chem. Rev.*, 1996, **96**, 835.

218. M. Fujiwara, M. Imada, A. Bab and H. Matsuda, *Tetrahedron Lett.*, 1989, **30**, 739.

219. G. Sekar and V. K. Singh, *J. Org. Chem.*, 1999, **64**, 287.

220. M. Meguro, N. Asao and Y. Yamamoto, *J. Chem. Soc., Perkin Trans 1*, 1994, 2597.

221. N. R. Swamy, T. V. Goud, S. M. Reddy, P. Krishnaiah and Y. Venkateswarlu, *Synth. Commun.*, 2004, **34**, 727

222. S. K. De and R. A. Gibbs, *Synth. Commun.*, 2005, **35**, 2675.

223. A. Kamal, R. Ramu, M. Ameruddin Azhar and G. B. Ramesh Khanna, *Tetrahedron Lett.*, 2005, **46**, 2675.

224. C. L. Kissel and B. Rickborn, *J. Org. Chem.*, 1972, **37**, 2060.

225. L. E. Overman and L. A. Flippin, *Tetrahedron Lett.*, 1981, **22**, 195.

226. M. Chini, P. Crotti and F. Macchia, *Tetrahedron Lett.*, 1990, **31**, 4661.

227. J. S. Yadav, B. V. S. Reddy, A. K. Basak and A. Venkat Narsaiah, *Tetrahedron Lett.*, 2003, **44**, 1047.

228. M. W. C. Robinson, D. A. Timms, S. M. Williams and A. E. Graham, *Tetrahedron Lett.*, 2007, **48**, 6249.

229. S. Sagawa, H. Abe, Y. Hase and T. Inaba, *J. Org. Chem.*, 1999, **64**, 4962.

230. C. Schneider, A. R. Sreekanth and E. Mai, *Angew. Chem. Int. Ed.*, 2004, **43**, 5691.

231. F. Carree, R. Gill and J. Collin, *Org. Lett.*, 2005, **7**, 1023.

232. X-L. Hou, J. Wu, L-X. Dai, L-J. Xia and M-H. Tang, *Tetrahedron Asymmetry,* 1998, **9**, 1747.

233. B. Saha, M. H. Lin and T. V. RajanBabu, *J. Org. Chem.,* 2007, **72**, 8648.

234. M. LakshmiKantam, B. Neelima, C. VenkatReddy and R. Chakravarti, *Ind. Eng. Chem. Res.,* 2007, **46**, 8614.

235. K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.,* 2007, **129**, 8103.

236. S. Ozaki, E. Matsui, H. Yoshinaga and S. Kitagawa, *Tetrahedron Lett.,* 2000, **41**, 2621.

237. V. Kesavan, D. Bonnet-Delpon and J.-P. Bégué, *Tetrahedron Lett.,* 2000, **41**, 2895.

238. C. G. Aifheli and P. T. Kaye, *Synth. Commun.,* 1996, **26**, 4459.

239. A. Schwartz, P. B. Madan, E. Mohacsi, J. P. O'Brien, L. J. Todaro and D. L. Coffen, *J. Org. Chem.,* 1992, **57**, 851.

240. J. P. Bégué, D. Bonnet-Delpon and A. Kornilov, *Synthesis,* 1996, 529.

241. E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson and S. Hammarstrom, *J. Am. Chem. Soc.,* 1980, **102**, 1436.

242. V. Polshettiwar and M. P. Kaushik, *Catal. Commun.,* 2004, **5**, 515.

243. F. Fringuelli, F. Pizzo, S. Tortoioli and L. Vaccaro, *J. Org. Chem.,* 2003, **68**, 8248.

244. F. P. S. T. L. V. Francesco Fringuelli, *Advanced Synthesis & Catalysis,* 2002, **344**, 379.

245. M. V. Nandakumar, A. Tschop, H. Krautscheid and C. Schneider, *Chem. Commun.,* 2007, 2756.

246. V. Pironti and S. Colonna, *Green Chem.,* 2005, **7**, 43.

247. J. Chen, H. Wu, C. Jin, X. Zhang, Y. Xie and W. Su, *Green Chem.,* 2006, **8**, 330.

248. R-H. Fan and X-L. Hou, *J. Org. Chem.,* 2003, **68**, 726.

249. W. Su, J. Chen, H. Wu and C. Jin, *J. Org. Chem.,* 2007, **72**, 4524.

250. N. Iranpoor, M. Shekarriz and F. Shiriny, *Synth. Commun.,* 1998, **28**, 347.

251. D. Bradley, G. Williams and M. Lawton, *Org. Biomol. Chem.,* 2005, **3**, 3269.

252. A. Gansauer, C-A. Fan, F. Keller and J. Keil, *J. Am. Chem. Soc.,* 2007, **12**, 3484.

253. J. M. Ready and E. N. Jacobsen, *J. Am. Chem. Soc.,* 1999, **121**, 6086.

254. J. M. Ready and E. N. Jacobsen, *J. Am. Chem. Soc.,* 2001, **123**, 2687.

255. J. Barluenga, H. Vazquez-Villa, A. Ballesteros and J. M. Gonzalez, *Org. Lett.,* 2002, **4**, 2817.

256. E. Thiery, J. LeBras and J. Muzart, *Green Chem.,* 2007, **9**, 326.

257. F. Fringuelli, F. Pizzo, S. Tortoioli and L. Vaccaro, *J. Org. Chem.,* 2004, **69**, 8780.

258. F. Fringuelli, F. Pizzo and L. Vaccaro, *J. Org. Chem.,* 2004, **69**, 2315.

259. Z. Wang, Y. T. Cui, Z. B. Xu and J. Qu, *J. Org. Chem.,* 2008, **73**, 2270.

260. H-Y. Kim, A. Talukdar and M. Cushman, *Org. Lett.,* 2006, **8**, 1085.

261. A. Sekine, T. Ohshima and M. Shibasaki, *Tetrahedron,* 2002, **58**, 75.

262. A. Kamal, M. Arifuddin and M. V. Rao, *Tetrahedron Asymmetry,* 1999, **10**, 4261.

263. D. C. Braddock, I. D. MacGilp and B. G. Perry, *Adv. Synth. Catal.,* 2004, **346**, 1117.

264. R-H. Fan and X-L. Hon, *Org. Biomol. Chem.,* 2003, **1**, 1565.

265. W. Xu, J-H Xu, J. Pan, Q. Gu and X-Y. Wu, *Org. Lett.,* 2006, **8**, 1737.

266. F. Rüdiger, *Angew. Chem. Int. Ed.,* 2001, **40**, 2251.

267. S. Chandrasekhar, C. R. Reddy, B. N. Babu and G. Chandrashekar, *Tetrahedron Lett.,* 2002, **43**, 3801.

268. S. Chandrasekhar, C. Narasihmulu, V. Jagadeshwar and K. V. Reddy, *Tetrahedron Lett.,* 2003, **44**, 3629.

269. E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.,* 2007, **107**, 5841.

270. A. W. Johnson and R. B. LaCount, *J. Am. Chem. Soc.,* 1961, **83**, 417.

271. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.,* 1962, **84**, 867.

272. E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.,* 1965, **87**, 1353.

273. V. K. Aggarwal, J. N. Harvey and J. Richardson, *J. Am. Chem. Soc.,* 2002, **124**, 5747.

274. V. K. Aggarwal and J. Richardson, *Chem. Commun.,* 2003, 2644.

275. C. R. Johnson, C. W. Schroeck and J. R. Shanklin, *J. Am. Chem. Soc.,* 1973, **95**, 7424.

276. C. R. Johnson and E. R. Janiga, *J. Am. Chem. Soc.,* 1973, **95**, 7692.

277. D. R. Edwards, J. Du and C. M. Crudden, *Org. Lett.,* 2007, **9**, 2397.

278. V. K. Aggarwal, J. G. Ford, S. Fonquerna, H. Adams, RVH. Jones and R. Fieldhouse, *J. Am. Chem. Soc.,* 1998, **120**, 8328.

279. V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J. L. Vasse and C. L. Winn, *J. Am. Chem. Soc.,* 2003, **125**, 10926.

280. N. Furukawa, Y. Sugihara and H. Fujihara, *J. Org. Chem.,* 1989, **54**, 4222.

281. L. Breau and T. Durst, *Tetrahedron Asymmetry,* 1991, **2**, 367.

282. L. Breau, W. W. Ogilvie and T. Durst, *Tetrahedron Lett.,* 1990, **31**, 35.

283. B. Trost and R. Hammen, *J. Am. Chem. Soc.,* 1973, **95**, 962.

284. A. Solladié-Cavallo and A. Adib, *Tetrahedron,* 1992, **48**, 2453.

285. A. Solladié-Cavallo, M. Roje, T. Isarno, V. Sunjic and V. Vinkovic, *Eur. J. Org. Chem.,* 2000, 1077.

286. A. Solladié-Cavallo, A. Adib, M. Schmitt, J. Fischer and J. DeCian, *Tetrahedron Asymmetry,* 1992, **3**, 1597.

287. A-H. Li, L-X. Dai and V. K. Aggarwal, *Chem. Rev.,* 1997, **97**, 2341.

288. V. K. Aggarwal, A. Thompson, R. V. H. Jones and M. Standen, *Tetrahedron: Asymmetry,* 1995, **6**, 2557.

289. V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Am. Chem. Soc.,* 1996, **118**, 7004.

290. V. K. Aggarwal, *Synlett,* 1998, 329.

291. K. Julienne, P. Metzner and V. Henyron, *J. Chem. Soc., Perkin Trans. 1,* 1999, 731.

292. J. Zanardi, C. Leriverend, D. Aubert, K. Julienne and P. Metzner, *J. Org. Chem.,* 2001, **66**, 5620.

293. A-H. Li, L-X. Dai, X-L. Hou, Y-Z. Huang and F-W. Li, *J. Org. Chem.,* 1996, **61**, 489.

294. X-M. Deng, P. Cai, S. Ye, X-L. Sun, W-W. Liao, K. Li, Y. Tang, Y-D. Wu and L-X. Dai, *J. Am. Chem. Soc.,* 2005, **128**, 9730.

295. R. Hayakawa and M. Shimizu, *Synlett,* 1999, 1328.

296. C. L. Winn, B. R. Bellenie and J. M. Goodman, *Tetrahedron Lett.,* 2002, **43**, 5427.

297. T. Saito, D. Akiba, M. Sakairi and S. Kanazawa, *Tetrahedron Lett.,* 2001, **42**, 57.

298. V. K. Aggarwal and C. L. Winn, *Acc. Chem. Res.,* 2004, **37**, 611.

299. T. Durst, L. Breau and R. N. Ben, *Phosphorus, Sulfur and Silicon.,* 1993, **74**, 215.

300. V. K. Aggarwal, M. P. Coogan, R. A. Stenson, R. V. H. Jones, R. Fieldhouse and J. Blacker, *Eur. J. Org. Chem.,* 2002, 319.

301. J. Zanardi, D. Lamazure, S. Miniere, V. Reboul and P. Metzner, *J. Org. Chem.,* 2002, **67**, 9083.

302. V. K. Aggarwal, H. Abdel-Rahman, L. Fan, R. V. H. Jones and M. C. H. Standen, *Chem. Eur. J.,* 1996, **2**, 1024.

303. V. K. Aggarwal, H. Abdel-Rahman, R. V. H. Jones and M. C. H. Standen, *Tetrahedron Lett.,* 1995, **36**, 1731.

304. V. K. Aggarwal, H. Abdel-Rahman, R. V. H. Jones, H. Y. Lee and B. D. Reid, *J. Am. Chem. Soc.,* 1994, **116**, 5973.

305. V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni and J. R. Studley, *Angew. Chem. Int. Ed.,* 2001, **40**, 1430.

306. V. K. Aggarwal, I. Bae, H-Y. Lee, J. Richardson and D. T. Williams, *Angew. Chem. Int. Ed.,* 2003, **42**, 3274.

307. A-H. Li and L-X. Dai, *Chem. Rev.,* 1997, **97**, 2341.

308. F. Toda and N. Imai, *J. Chem. Soc., Perkin Trans 1,* 1994, 2673.

309. T. Hiyama, T. Mishima, H. Sawada and H. Nozaki, *J. Am. Chem. Soc.,* 1975, **97**, 1626.

310. Y. Zhang and W. Wu, *Tetrahedron Asymmetry,* 1997, **8**, 2723.

311. M. Rosenberger, W. Jackson and G. Saucy, *Helv. Chim. Acta.,* 1980, **63**, 1665.

312. S. A. Kavanagh and S. J. Connon, *Tetrahedron Asymmetry,* 2008, accepted.

313. V. K. Aggarwal, A. Ali and M. P. Coogan, *J. Org. Chem.,* 1997, **62**, 8628.

314. V. K. Aggarwal, L. Bell, M. P. Coogan and P. Jubault, *J. Chem. Soc., Perkin Trans 1,* 1998, 2037.

315. B. R. Bellenie and J. M. Goodman, *Chem. Commun.,* 2004, 1076.

316. Y. G. Gololobov, A. N. Nesmeyanov, V. P. Lysenko and I. E. Boldeskul, *Tetrahedron,* 1987, **43**, 2609.

317. Y. Kazuta, H. Abe, T. Yamamoto, A. Matsuda and S. Shuto, *J. Org. Chem.,* 2003, **68**, 3511.

318. W. A. Donaldson, *Tetrahedron,* 2001, **57**, 8589.

319. H. Lebel, J-F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.,* 2003, **103**, 977.

320. Y. Kazuta, A. Matsuda and S. Shuto, *J. Org. Chem.,* 2002, **67**, 1669.

321. G. A. Molander and C. Alonso-Alija, *Tetrahedron,* 1997, **53**, 8067.

322. D. B. Reddy, P. V. R. Reddy, S. Vijayalakshmi and M. V. R. Reddy, *Phosphorus, Sulfur and Silicon.,* 1993, **84**, 63

323. R. J. Paxton and R. J. K. Taylor, *Synlett,* 2007, 633.

324. V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd and M. Porcelloni, *Angew. Chem. Int. Ed.,* 2001, **40**, 1433.

325. V. K. Aggarwal, H. W. Smith, R. V. H. Jones and R. Fieldhouse, *Chem. Commun.,* 1997, 1785.

326. V. K. Aggarwal, H. W. Smith, G. Hynd, R. V. H. Jones, R. Fieldhouse and S. E. Spey, *J. Chem. Soc., Perkin Trans 1,* 2000, 3267.

327. S. E. Denmark and L. R. Marcin, *J. Org. Chem.,* 1993, **58**, 3850.

328. S. H. McCooey and S. J. Connon, *Angew. Chem. Int. Ed.,* 2005, **44**, 6367.

329. M. Shi and X-G. Liu, *Org. Lett.*, 2008, **10**, 1043.

330. X.-G. Liu, J.-J. Jiang and M. Shi, *Tetrahedron: Asymmetry,* 2007, **18**, 2773.

331. M. L. Clarke, C. E. S. Jones and M. B. France, *Beilstein. J. Org. Chem.*, 2007, **3**, No. 24.

332. M. E. Kraft and J. A. Wright, *Chem. Commun.*, 2006, 2977.

333. D. Basavaiah, A. J. Rao and T. Satyanarayana, *Chem. Rev.*, 2003, **103**, 811.

334. G. Masson, C. Housseman and J. Zhu, *Angew. Chem. Int. Ed.*, 2007, **46**, 4614.

335. J. S. Hill and N. S. Isaacs, *J. Phys. Org. Chem.*, 1990, **3**, 285.

336. K. E. Price, S. J. Broadwater, H. M. Jung and D. T. McQuade, *Org. Lett.*, 2005, **7**, 147.

337. K. E. Price, S. J. Broadwater, B. J. Walker and D. T. McQuade, *J. Org. Chem.*, 2005, **70**, 3980.

338. V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem. Int. Ed.*, 2005, **44**, 1706.

339. R. Robiette, V. K. Aggarwal and J. N. Harvey, *J. Am. Chem. Soc.*, 2007, **129**, 15513.

340. P. Buskens, J. Klankermayer and W. Leitner, *J. Am. Chem. Soc.*, 2005, **127**, 16762.

341. J. Wang, H. Li, X. Yu, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4293.

342. C-J. Wang and M. Shi, *Eur. J. Org. Chem.*, 2003, 2823.

343. A. K. Audin, *Aziridines and Epoxides in Organic Synthesis*, Wiley & Sons, Weinheim, 2006

344. R. F. W. Bader, *Atoms in Molecules. A Quantum Theory*, Oxford University, New York, 1990

345. B. P. Bandgar and A. V. Patil, *Tetrahedron Lett.*, 2007, **48**, 173.

346. I. Rozas, *Phys. Chem. Chem. Phys.*, 2007, **9**, 2782.

347. F. D. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.

348. P. Vachal and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 867.

349. D. Mauzerall and F. H. Westheimer, *J. Am. Chem. Soc.*, 1955, **77**, 2261.

350. A. Hantzsch, *Justus Liebigs Ann. Chem.*, 1882, **215**, 1.

351. S. A. Kavanagh, A. Piccinini, E. M. Fleming and S. J. Connon, *Org. Biomol. Chem.*, 2008, **6**, 1339.

352. J. Meinwald, S. S. Labana and S. S. Chadha, *J. Am. Chem. Soc.*, 1963, **85**, 582.

353. M. W. C. Robinson, K. S. Pillinger and A. E. Graham, *Tetrahedron Lett.*, 2006, **47**, 5919.

354. N-J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976.

355. H.-J. Schanz, M. A. Linseis and D. G. Gilheany, *Tetrahedron Asymmetry,* 2003, **14**, 2763.

356. I. Stibor, R. Holakovský, A. R. Mustafina and P. Lhoták, *Collect. Czech. Commun.,* 2004, **69**, 365.

357. J. Y. Jamieson, R. R. Schrock, W. M. Davis, P. J. Bonitatebus, S. S. Zhu and A. H. Hoveyda, *Organometallics,* 2000, **19**, 925.

358. X-G. Zhou, J-S. Huang, P-H. Ko, K-K. Cheung and C-M. Che, *J. Chem. Soc., Dalton Trans.,* 1999, 3303.

359. P. Yan, A. C. Millard, M. Wei and L. M. Loew, *J. Am. Chem. Soc.,* 2006, **128**, 11030.

360. J. Wang, H. Li, W. Duan, L. Zu and W. Wang, *Org. Lett.,* 2005, **7**, 4713.

361. L. F. Cason and C. C. Wanser, *J. Am. Chem. Soc.,* 1951, **73**, 142.

362. T. Kataoka, T. Iwama, S.-I. Tsujiyama, T. Iwamura and S.-I. Watanabe, *Tetrahedron,* 1998, **54**, 11813.

363. J. H. Lutje Spelberg, R. Rink, R. M. Kellogg and D. B. Jansen, *Tetrahedron Asymmetry,* 1998, **9**, 459.

364. D. Casarini, *J. Org. Chem.,* 2000, **65**, 3207.

365. Y. Tsuchiya, T. Kumamoto and T. Ishikawa, *J. Org. Chem.,* 2004, **69**, 8504.

366. W. Krimse and K. Kund, *J. Am. Chem. Soc.,* 1989, **111**, 1465.

367. S. Pedragosa-Moreau, C. Morisseau, J. Zylber, A. Archelas, J. Baratti and R. Furstoss, *J. Org. Chem.,* 1996, **61**, 7402.

368. R. I. Kureshy, S. Singh, N.-u. H. Khan, S. H. R. Abdi, S. Agrawal and R. V. Jasra, *Tetrahedron: Asymmetry,* 2006, **17**, 1638.

369. H. Shipley Fry, *J. Am. Chem. Soc.,* 1913, **35**, 1539.

370. J. Chan, K. D. Baucom and J. A. Murry, *J. Am. Chem. Soc.,* 2007, **129**, 14106.

371. J. Barluenga, F. J. Fananas and M. Yus, *J. Org. Chem.,* 1979, **40**, 4798.

372. M. Chini, P. Crotti and F. Macchia, *J. Org. Chem.,* 1991, **56**, 5939.

373. G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, M. Massaccesi, P. Melchiorre and L. Sambri, *Org. Lett.,* 2004, **6**, 2173.

374. Y. Kurosaki, T. Fukuda and M. Iwao, *Tetrahedron,* 2005, **61**, 3289.

375. M. Lautens, M. L. Maddess, E. L. O. Sauer and S. G. Ouellet, *Org. Lett.,* 2002, **4**, 83.

376. P. G. Bulger, M. G. Moloney and P. C. Trippier, *Org. Biomol. Chem.,* 2003, **1**, 3726.

377. R. L. E. Furlán, E. G. Mata, O. A.Mascaretti, C. Peña and M. P. Coba, *Tetrahedron,* 1998, **54**, 13023.

378. E. A. A. Wallen, J. A. M. Christiaans, E. M. Jarho, M. M. Forsberg, J. I. Venalainen, P. T. Mannisto and J. Gynther, *J. Med. Chem.,* 2003, **46**, 4543.

379. E. M. Zippi and E. Kamperman, *J. Label Compd Radiopharm,,* 2002, **45**, 103.

380. S. M. Ali, M. Z. Hoemann, J. Aube, L. A. Mitscher, G. I. Georg, R. McCall and L. R. Jayasinghe, *J. Med. Chem.,* 1995, **38**, 3821.

381. J. Christoffers and A. Mann, *Chem. Eur. J.,* 2001, **7**, 1014.

382. K. Senten, P. Van der Veken, I. De Meester, A-M. Lambeir, S. Scharpé, A. Haemers and K. Augustyns, *J. Med. Chem.,* 2003, **46**, 5005.