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SYNTHESIS OF CHIRAL IMINOALKYL FUNCTIONALISED *N*-HETEROCYCLIC CARBENES AND THEIR USE IN ASYMMETRIC CATALYSIS

THESIS

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Abstract

The steric and electronic properties of *N*-Heterocyclic carbenes and their use as ligands in asymmetric catalysis are reviewed. Key features of enantioselective palladium-catalysed allylic substitution and copper-catalysed conjugate addition reaction are discussed.

A modular design approach was applied to the synthesis of iminoalkyl imidazol-2-ylidenes to enable simple structural modifications and fine-tuning catalytic performance for selected reactions. A range of novel chiral iminoalkyl alkylimidazolium salts and iminoalkyl arylimidazolium salts have been prepared *via* the *N*-alkylation of *N*-substituted imidazoles with iminoalkyl bromides in moderate to good yields. The chiral iminoalkyl bromides were synthesised from amino acids using a five-step procedure, involving reduction, *N*-BOC protection, bromination, *N*-BOC deprotection and imination. The synthesis of chiral iminoalkyl alkylimidazolium salts derived from glycine, alanine, leucine, valine and phenylalanine and *N*-methyl-, *N*-benzyl-, *N*-phenyl and *N*-mesitylimidazoles is reported. The preparation of both benzylideneamine- and benzylhydrylideneamine derivatives was achieved. One example of an imidazolin-2-ylidene ligand precursor, derived from a dihydroimidazole is also reported.

Silver iminoalkyl imidazol-2-ylidene complexes were prepared by deprotonation of the corresponding imidazolium salts with silver(I) oxide. An X-ray crystal structure of one example is reported; it shows the monodentate co-ordination of the iminoalkyl imidazol-2-ylidene to silver. Attempts to use theses complexes to synthesise and isolate palladium complexes failed. Nonetheless, the silver complexes were successfully

employed as carbene transfer reagents for the generation of iminoalkyl imidazol-2-ylidene palladium catalysts for use in asymmetric allylic substitution.

The application and performance of the small library of iminoalkyl imidazol-2-ylidene ligands in asymmetric palladium-catalysed allylic substitution is reported and discussed. Catalytic testing demonstrated that variation of the imidazole substituent had a greater effect on enantioselectivity than changing the alkyl substituent at the stereogenic centre on the ligand backbone. The highest enantiomeric excess obtained for the substitution of 1,3-diphenylprop-3-enyl acetate with dimethyl malonate was 53%. The ligands were also screened for enantioselectivity towards copper catalysed conjugate addition of diethyl zinc to cyclohexenone. Performance for this reaction was poor with a highest enantiomeric excess of 18% being obtained.

Acknowledgements

Firstly, I would like to thank my supervisor, Dr. Neil Williams, for giving me the opportunity to work as a research student and explore the beautiful world of research at Kingston University. His assistance and guidance were decisive to cope with the ups and downs encountered during my studies.

I would like to thank as well the students, and the academic and technical staff in the School of Pharmacy and Chemistry, for their precious advice and help. Special thanks to Dr Jean-Marie Péron who was always ready and willing to help, and Julien Millet, Emma, Sophie and Steve for their kindness when everything was new and difficult.

Finally, but not least, I am deeply grateful to all my family and friends, particularly my wife and my two little boys who have been the catalyst for my ambition and my determination.

Abbreviations

Ad	Adamantyl
BDE	Bond Dissociation Enthalpies
Bn	Benzyl
$(Boc)_2O$	Di-*tert*-butoxy dicarbonate
b.p.	Boiling point
BSA	*N,O*-Bis(trimethylsilyl)acetamide
^{13}C NMR	Carbon nuclear magnetic resonance
cod	Cyclooctadiene
CuTC	Copper thiophenecarboxylate
Cy	Cyclohexane
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DFT	Density Functional Theory
DIOP	2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
e.e.	Enantiomeric excess
Equiv.	Equivalent
ERO	Electron-rich olefin
$Eu(hfc)_3$	Europium tris[3-(heptafluoropropyl hydroxymethylene)-(+)-camphorate]

EWG	Electron-withdrawing group
FAB	Fast atom bombardment
g	Gramme
^{1}H NMR	Proton nuclear magnetic resonance
3-HQD	3-hydroxyquinuclidine
HRMS	High resolution mass spectroscopy
^{i}Bu	*Iso*-Butyl
ImH	Imidazole
^{i}Pr	*Iso*-Propyl
IR	Infrared
LAC	Ligand accelerated catalyst
LAH	Lithium aluminium hydride
LG	Leaving group
LRES	Low Resolution Electrospray Mass Spectroscopy
M-C	Metal-carbon
Me	Methyl
Mes	Mesityl
mL	Millilitre
mmol	Millimole
MO	Molecular orbital
mol%	Mole percentage
M.S.	Molecular sieves
MsCl	Methanesulfonyl chloride (mesyl chloride)
Nap	Naphtalene
NHC	*N*-Heterocyclic Carbene

OAc	Acetate
o.n.	Overnight
OTf	Trifluoromethanesulfonate (Triflate)
PDPI	polystyryl diphenylphosphine iodine
Ph	Phenyl
PHOX	Phosphinooxazoline
pKa	Acid dissociation constant
ppm	Parts per million
PR_3	Tri-substituted Phosphines
PSTPP	Polymer-supported triphenylphosphine
QM/MM	Quantum mechanics/Molecular mechanics
RCM	Ring closing metathesis
ROMP	Ring opening metathesis polymerisation
r.t.	Room temperature
S_N2	Bimolecular nucleophilic substitution
TBDMS	*Tert*-butyldimethylsilyl
TEDA	Triethylenediamine
THF	Tetrahydrofuran
TM	Transition metal
TMSCl	Trimethylsilyl chloride
Y	Yield
ε	Dielectric constant
δ	Chemical shift
υ	Wave number

1. Introduction

N-Heterocyclic Carbenes (NHCs) have been a subject of great interest, since they demonstrated efficiency as spectator ligands in homogeneous catalysis.[1] Their catalytic potential was initially spotted by Lappert who synthesised a range of transition metal (TM)-NHC complexes from enetetramines.[2] The first isolation of a stable free NHC by Arduengo[3] and the synthesis of a range of NHC metal complexes by Herrmann[4] from imidazolium salts, initiated renewed interest in their catalytic application.

NHC ligands have demonstrated their ability to supersede the widely used phosphines in homogeneous catalysis. Phosphines (PR_3), which have proved to be very effective in controlling reactivity and selectivity[5-8] for a wide variety of TM-catalysed reactions, are often prone to air oxidation and P-C bond decomposition at higher temperatures. Higher concentrations of ligand are usually required to prevent catalyst deactivation. Sterically demanding PR_3 ligands are often needed to stabilise the co-ordinately unsaturated, late transition metal centres that act as active catalyst species. Unlike phosphines, NHCs present hydrolytic durability, high thermal stability and high M-C dissociation energies. However, their strong σ-donating character and the variety of steric bulk possible *via* alkyl and aryl *N*-substituents are comparable to those of phosphines.

The success of tertiary phosphines in TM-catalysed enantioselective transformations is mainly based on their easy and predictable steric and electronic tunability, obtained by varying their substituents. Like tertiary phosphines, NHCs are sterically tuneable

by modification of the N^1 and N^3 substituents. The more recent application of novel chiral NHC ligands in enantioselective catalysis initially led to modest asymmetric inductions (hydrosilylation of acetophenone with e.e. = 32%).[9] Soon after, they gained prominence with the remarkable Grubbs metathesis catalyst (e.e. = 91%) (Figure 1.1).[10]

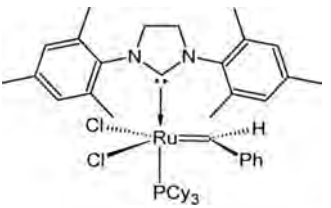
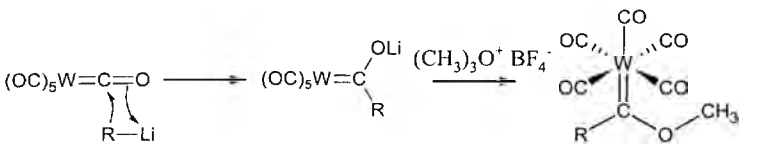


Figure 1.1 Grubbs metathesis catalyst.

Chiral bidentate diphosphines or bidentate *N*, *P* mixed-donor ligands, have often realised higher enantioselectivities than related monodentate ligands (e.g. Chiraphos, Prophos and DIOP).[11] The tight binding, resulting from ligand chelation, diminishes conformational flexibility, favouring a more fixed conformation, resulting in higher selectivity. Although bidentate phosphines have proved to be very successful for a wide range of reactions (e.g. olefin hydrogenation and allylic substitution), there is still further scope for improvement in selectivity and substrate range. Chiral bidentate mixed-donor ligands, bearing an NHC donor, are expected to exhibit improved catalytic performance.

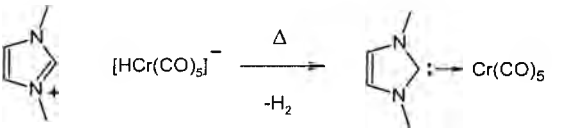
1.1 Synthesis of NHCs

Fischer and his students isolated the first TM-carbene complex *via* treatment of $W(CO)_6$ with RLi and $(CH_3)_3O^+ BF_4^-$ (Scheme 1.1).[12]

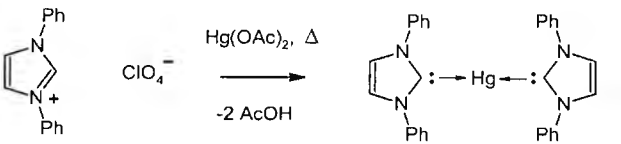


Scheme 1.1 Tungsten carbene complexes.

The first preparations of complexes containing NHC ligands were independently reported by Öfele[13] (Eq.1) and Wanzlick[14] (Eq.2) in 1968 (Scheme 1.2). In both reports, the method involved the deprotonation of imidazolium salts using sufficiently basic metal-containing precursors.



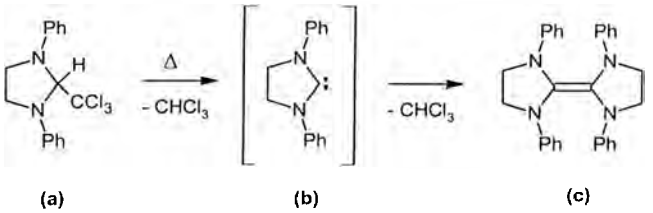
(Eq. 1)



(Eq. 2)

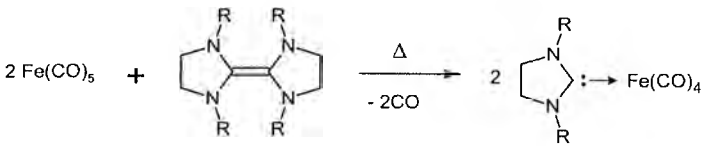
Scheme 1.2 Synthesis of NHC complexes *via* deprotonation of imidazolium salts.

Wanzlick recognised that it was possible to improve the stability of carbenes by having nitrogen atoms as substituents (i.e. diaminocarbenes).[15] Despite the attempts made to isolate monomeric 1,3-diphenylimidazolin-2-ylidene **(b)**, *via* thermal elimination of chloroform from imidazolidene **(a)**, the dimeric electron-rich olefin (ERO) species **(c)** was obtained instead (Scheme 1.3).



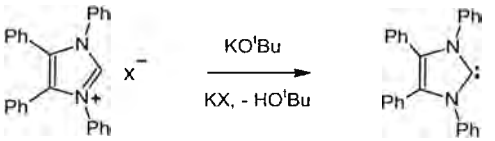
Scheme 1.3 Attempts to isolate the free NHC derived from an imidazoline

The equilibrium between triplet state NHC monomers and their dimeric ERO form was later characterised by Denk.[16] Lappert and co-workers prepared a wide range of metal-NHC complexes from EROs such as enetetramines (Scheme 1.4).[17]



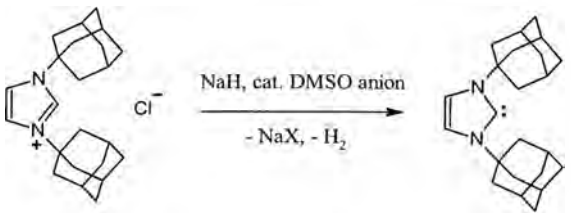
Scheme 1.4 Synthesis of NHC complexes derived from enetetramines.

Wanzlick and Schönherr observed stabilisation of an unsaturated NHC *via* aromatic resonance structures generated by deprotonation of imidazolium salts using KO^{t}Bu (Scheme 1.5).[18]



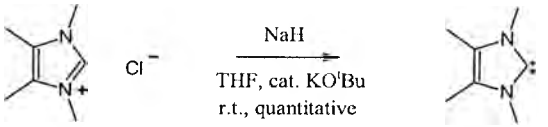
Scheme 1.5 Synthesis of free NHCs stabilised by aromatic resonance.

Despite their effort, no free NHC was isolated. After almost two decades, Arduengo succeeded in isolating the first stable NHC.[3] The free imidazol-2-ylidene carbene was obtained after deprotonation of 1,3-di-1-admantyl imidazolium chloride, using sodium hydride (NaH) in the presence of catalytic amount of dimethylsulfoxide (DMSO) anions (Scheme 1.6).



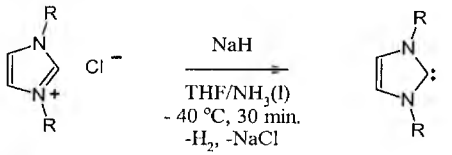
Scheme 1.6 Synthesis of the first stable free NHC.

Later, the synthesis of a stable free 2,3,4,5-tetramethyl-substituted NHC was reported (Scheme 1.7),[19] indicating that steric bulk was not essential for the stabilisation of NHCs.



Scheme 1.7 Synthesis of a free 1,2,3,4-tetramethylimidazol-2-ylidene carbene.

Herrmann *et al.* reported a convenient method to generate free NHCs,[20] *via* deprotonation of imidazolium salts, using sodium hydride in a mixture of liquid ammonia and tetrahydrofuran (THF) (Scheme 1.8). The success of this method was attributed to ammonia's ability to dissolve imidazolium salts.

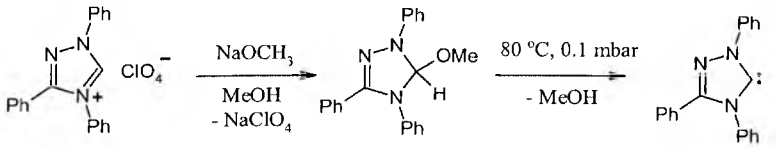


Scheme 1.8 Synthesis of free NHC inTHF/NH_3(liq.) mixture.

Kuhn et *al.* synthesised stable *N*-alkyl substituted NHCs by reduction of imidazol-2-thiones using potassium in THF under reflux (Scheme 1.9).[21]

Scheme 1.9 Synthesis of free NHCs *via* reduction of imidazol-2-thiones.

Ender *et al.* prepared the first crystalline triazole-derived carbenes.[22] They converted triazolium salts to the corresponding 5-methoxy-4,5-dihydro-1*H*-triazoles, using methanolate in methanol. The triazoles formed were subsequently converted to 1,2,4-triazolin-5-ylidenes by methanol elimination under heat and reduced pressure (Scheme 1.10).



Scheme 1.10 Synthesis of an NHC from triazole.

1.2 Carbenes properties

1.2.1 Structure and reactivity

Carbenes are neutral compounds characterised by a divalent carbon atom with six electrons in its valence shell. Their structure, stability and reactivity are strongly related to the electronic configuration of the carbenic atom. Carbenes can present two different geometries; linear or bent, with each geometry featuring a certain level of

hybridisation.[23] The linear geometry presents two non-bonding degenerate orbitals p_x and p_y resulting from sp hybridisation on the carbene centre. The bent geometry involves sp^2 hybridisation given σ and p_π orbitals (Figure 1.2).

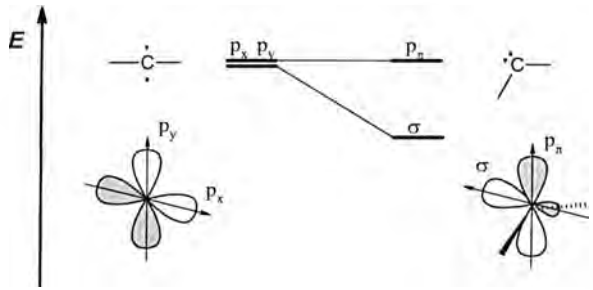


Figure 1.2 The relationship between the carbene bond angle and the nature of the frontier orbitals.

Four different electronic configurations are possible for geometrically bent carbenes; one triplet state resulting from the $\sigma^1 p_\pi^1$ configuration ($^3B_1$ state) with two non-bonding electrons with parallel spins, and three singlet states resulting from the σ^2 ($^1A_1$ state), p_π^2 ($^1A_1$ state) and $\sigma^1 p_\pi^1$ ($^1B_1$ state) configurations with two non-bonding electrons with anti-parallel spins (Figure 1.3).[23] Although four electronic configurations are possible, only the first three have been reported for ground state species.

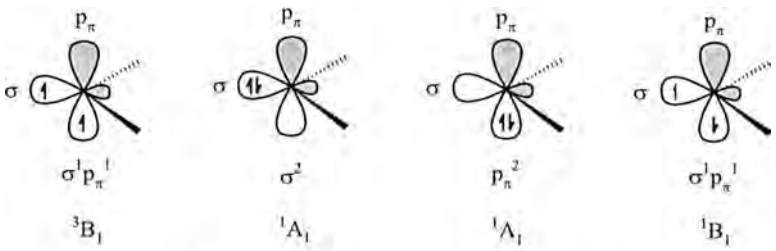


Figure 1.3 Possible electronic configurations for bent carbenes.

Singlet carbenes with a filled σ and a vacant p_π orbital feature ambiphilic character (i.e. electrophilic and nucleophilic), while triplet carbenes can be regarded as diradicals. The relative stability of the triplet and the singlet state is dependent on the difference between the σ and the p_π orbital energies. Hoffmann highlighted that $\sigma - p_\pi$ gap energies higher than 2 eV impose a singlet ground state, while values below 1.5 eV result in a triplet ground state being favoured.[24] Inductive, mesomeric and steric contributions, arising from the substituents adjacent to the carbenic carbon, can influence the $\sigma - p_\pi$ energy gap. Singlet carbenes, which are generally more stable than their triplet analogues, are more widely coveted as spectator ligands in organometallic chemistry.

1.2.2 Inductive effects

It is possible to control the ground state spin multiplicity by varying the electronic properties of the carbenic carbon substituents. σ-Electron withdrawing groups are known to favour the singlet carbenes. Harrison *et al.*[25] reported that changing the

substituent from electropositive (Li & H) to electronegative (F) substituents results in a switch from a triplet ground state to a singlet ground state (Figure 1.4).[23]

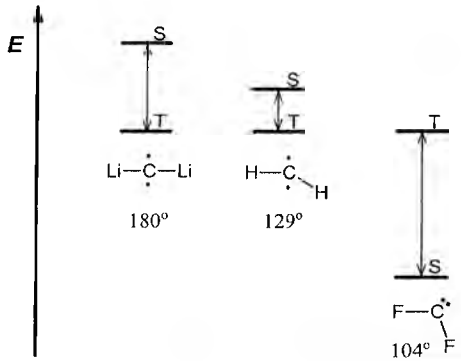


Figure 1.4 Influence of electronegativity of substituents on the carbene ground state spin multiplicity.

The increase in the $\sigma - p_\pi$ gap, from the stabilisation of the σ-nonbonding orbital *via* amplification of its "s" character, favours the singlet ground state (Figure 1.5a).[23] Conversely, smaller $\sigma - p_\pi$ gaps, imposed by σ-electron donating substituents, favour the triplet state (Figure 1.5b).[23]

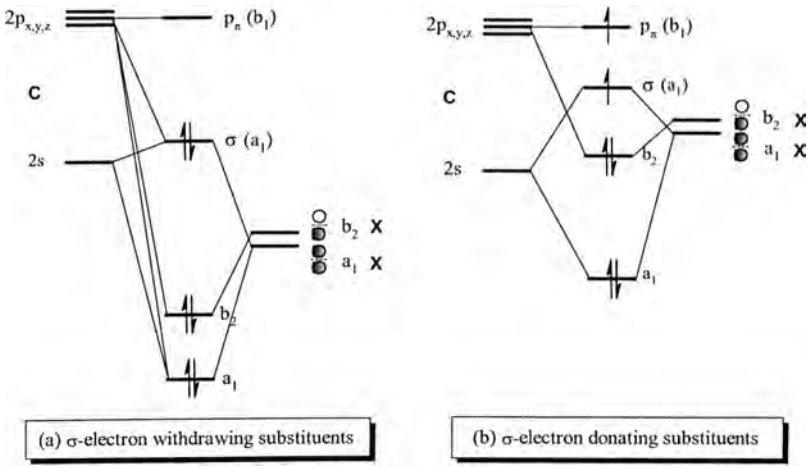


Figure 1.5 Perturbation orbital diagrams.

1.2.3 Mesomeric effects.

The influence of the mesomeric effect on the ground state spin multiplicity is more important than that of the inductive effect. The mesomeric effect arises from interactions between (σ, p_π) orbitals of the carbenic carbon, and the p (or π) orbitals of the substituent. The substituents interacting with the carbene centre can be of two types: π-electron donating (X: –F, –Cl, –Br, –I, $-NR_2$, $-PR_2$, –OSR, $-SR_3$ …) or π-electron withdrawing (Z: –COR, –CN, $-CF_3$, $-BR_2$, $-SiR_3$, $-PR_3^+$…). Bertrand envisaged three scenarios: highly bent (a) (X,X)-, and linear or quasi linear (b & c) (Z,Z)- and (X,Z)-carbenes (Figure 1.6).[23]

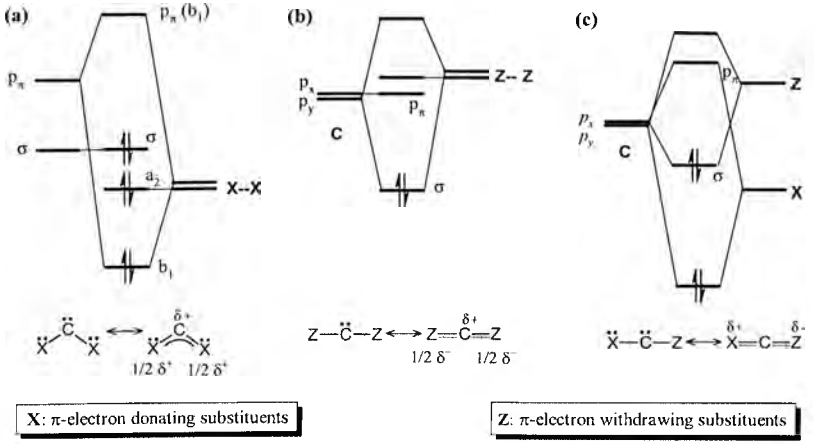


Figure 1.6 Perturbation orbital diagrams highlighting mesomeric effect.

In 1980, Pauling identified three possible ways to favour the singlet ground state (Figure 1.7).[26] The combinations of electronic effects suggested were:

1. Two π-donor/σ-attractor substituents to give a push, push mesomeric effect and a pull, pull inductive effect (e.g. diaminocarbenes).
2. Two π-attractor/σ-donor substituents to give a pull, pull mesomeric effect and a push, push inductive effect (e.g. diborylcarbenes).
3. A π-donor and a π-attractor substituent to give a push, pull mesomeric effect (e.g. phosphinosilylcarbenes).

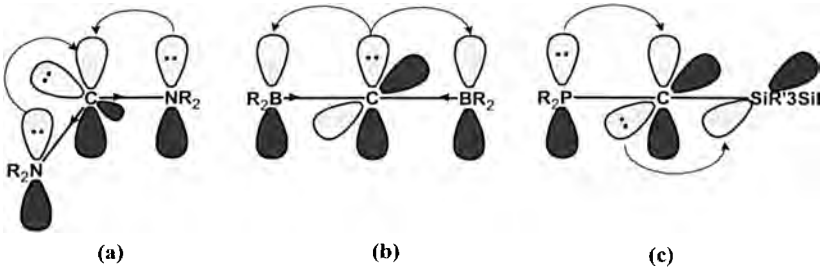


Figure 1.7 Combinations of substituents favouring the carbene single ground state *via* electronic effects.

Carbenes featuring substituents with opposite effects ("push-pull") prevent excessive accumulation of charges on the carbenic carbon. As a result, the electron delocalisation contribution towards the vacant orbitals tends to stabilise the carbene singlet state. Diaminocarbenes are by far the most commonly isolated singlet carbene species (Figure 1.7a).[27] The HOMO-LUMO energy gap is more pronounced with cyclic NHCs than with acyclic diaminocarbenes.[28]

1.2.4 Aromaticity

Although aromatic resonance is not the dominant stabilising effect, it does makes a contribution to the stabilisation of aromatic NHC. This contribution to NHCs stability was initially subject to controversy. Dixon and Arduengo related their higher stability exclusively to inductive effects arising from the adjacent nitrogens.[29] Cioslowski described the stabilising role of the nitrogen lone pair as negligible.[30] It was a few years later that Apeloig[31] and Frenkling[32] investigated the stabilising effect of

aromaticity in NHCs. Frenkling found that unsaturated NHCs (6π electrons) were more stable than their saturated counterparts (4π electrons), due to aromatic resonance within the ring. Cyclic electron delocalisation in unsaturated NHCs imidazol-2-ylidenes was confirmed by inner-shell electron energy loss spectroscopy.[33]

1.2.5 Steric effects

Steric effects may also effect the ground state multiplicity.[34] Bulkier groups on the carbenic carbon were found to broaden the carbene angle, and to favour the triplet ground state.[35,36] Bertrand suggested that steric hindrance created by the NHC *N*-substituents, has a direct influence on the carbene angle.[23]

The different factors stabilising the singlet state of carbenes are depicted in Figure 1.8.[37]

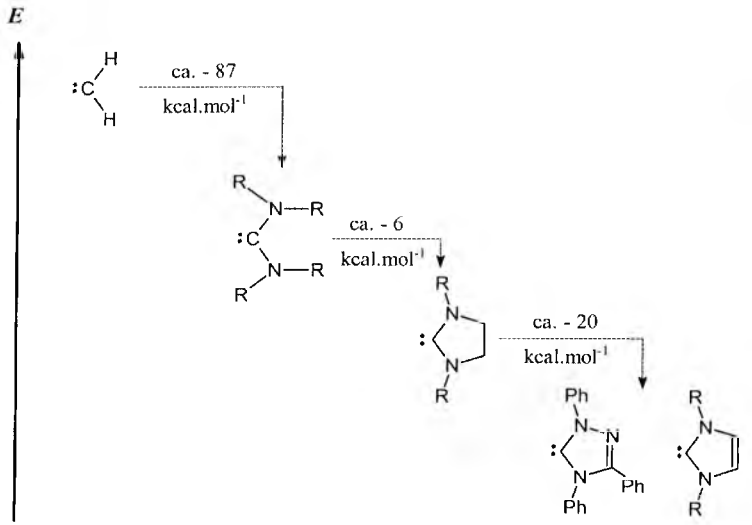


Figure 1.8 Carbene energy diagram presenting the different factors stabilising singlet ground state carbenes.

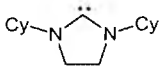
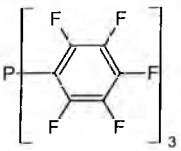
1.3 Coordination chemistry

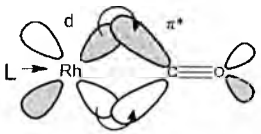
Strictly planar five-membered NHCs are commonly described as pure σ-donors and weak π-acceptors.[38] Comparative studies between PR_3 ligands and NHCs were carried out to quantify steric and electronic contributions to metal-NHC bonding.[39-45]

1.3.1. The σ-donation contribution

The σ-donation strength of NHCs has been characterised by IR analysis of the stretching frequency of carbonyl ligands in transition metal complexes such as $Ni(CO)_3L$ (L = NHC),[39,45] $Cr(CO)_5L$[46] or $RhL_2(CO)Cl$[47] (Figure 1.9). The

substitution of a carbonyl ligand by an NHC pushes more electron density onto the metal, resulting in greater π-acceptance by the remaining carbonyl ligands into the C-O π* orbital. Increased donation to the carbonyl π* orbitals weakens the C-O bonds, as revealed by υ_{CO} shifting to lower frequencies (Figure 1.9).

L	ν (cm^{-1})
	1924
	1929
PCy_3	1939
PMe_3	1957
PPh_3	1983
	2003
$P(o\text{-}Ph)_3$	2018



More e⁻ density on the metal

↓

More π -backbonding on CO density

↓

Longer CO bond

↓

Shorter CO stretching

Figure 1.8 IR analysis of CO bond stretching frequencies *trans* to NHC and PR_3 ligands.

Computational (QM/MM) and experimental measurements of Bond Dissociation Enthalpies (BDE) indicated that stronger coordination to transition metals is observed with NHCs, than that observed with PR_3 ligands.[39,45]

The steric (V_{bur} = amount of volume of a sphere centred on the metal, buried by overlapping ligand atoms) contribution to the metal-ligand bonding was quantified using DFT (Density Functional Theory), BDE and QM/MM calculations.[45] It was concluded that coordination of NHCs was not as dependent on steric effects as the co-ordination of phosphines.

1.3.2 The π-backbonding contribution

The common assumption that NHCs present weak or no π-accepting properties was questioned by Nolan[39,44,45] and Cavallo[44,45]. Their results, based on computational studies, suggested that filled π and empty π* orbitals do contribute to the metal-NHC bond stabilisation.[44] Their views were supported by Meyer who observed the ability of NHCs to accept electron density from electron rich group 11 metal atoms *via* d → π* backdonation.[40,41]

1.4. Catalysis

1.4.1. General catalysis

NHC complexes have been used as pre-catalysts in many catalytic homogeneous reactions.[48] Their application has led to significant advances in well known reactions such as ring opening metathesis polymerisation (ROMP),[49] ring closing metathesis (RCM)[49,50] (NHC based Grubbs' catalysts, Ru ^{II}) (Figure 1.1), and Heck-type olefination (Pd^0)[51] (Figure 1.10).

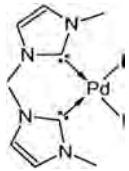
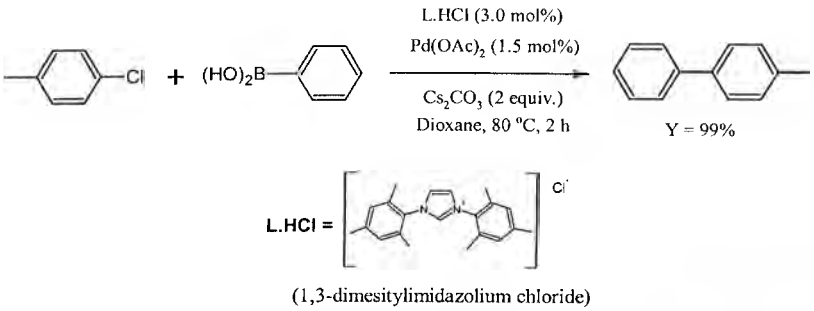
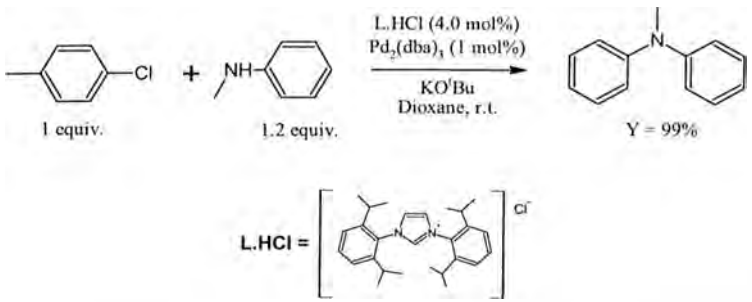


Figure 1.10 A palladium NHC complex used in Heck-type olefination.

Some of the most successful applications of NHCs have been in palladium-catalysed carbon-carbon coupling (Heck, Suzuki and Stille coupling),[52] (Scheme 1.11) and carbon-nitrogen (Hartwig/Buchwald)[53] reactions (Scheme 1.12).



Scheme 1.11 Palladium catalysed C-C cross coupling.[54]

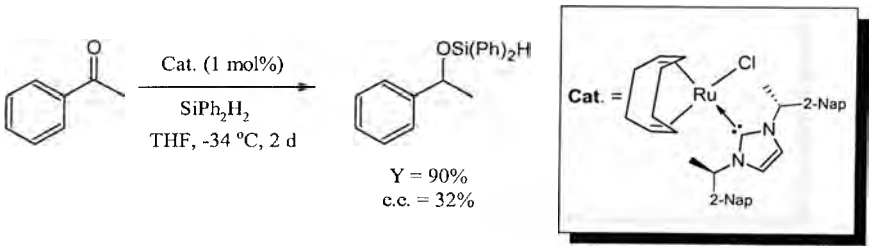


(1,3-bis(2,6-diisopropylphenyl)imidazolium chloride)

Scheme 1.12 Palladium catalysed C-N cross coupling.[55]

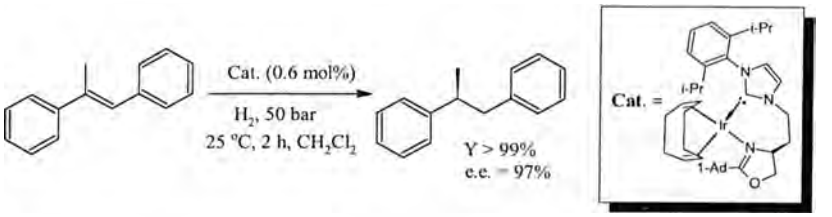
1.4.2. Enantioselective catalysis

The first attempts at enantioselective catalysis in the late 1990s achieved only modest success. For example, hydrosilylation of acetophenone, using a chiral monodentate rhodium imidazol-2-ylidene complex gave an e.e. of 32% (Scheme 1.13).[56]



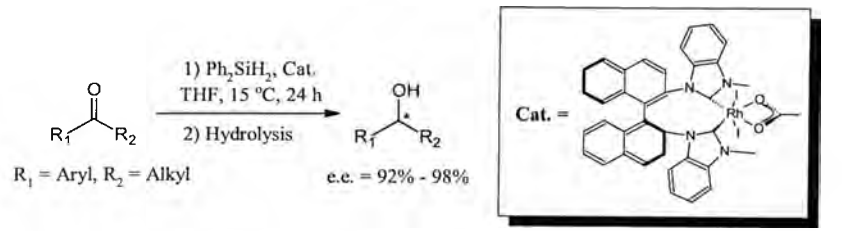
Scheme 1.13 Enantioselective hydrosilylation of acetophenone.

More recently, reports of highly enantioselective catalysis, using chiral NHC donors in Ir-catalysed enantioselective hydrogenation of aryl alkenes, have been published. High activities and high enantioselectivities were achieved using chiral chelating mixed donor imidazol-2-ylidene-oxazoline ligands (Scheme 1.14).[57]



Scheme 1.14 Enantioselective hydrogenation of aryl-alkenes.

High asymmetric inductions were also attained in Rh-catalysed enantioselective hydrosilylation of aryl alkyl ketones, using chiral binaphthyl biscarbene ligands (Scheme 1.15).[58]



Scheme 1.15 Enantioselective hydrosilylation of aryl alkyl ketones.

1.5 Aim of the project

Mixed-donor amino- and imino-phosphines *N*, *P* ligands have previously proved to be effective in enantioselective allylic substitution and copper-catalysed conjugate addition. The similarities between phosphines and imidazolylidene suggested that related amino- and imino-imidazol-2-ylidene ligands may prove to be useful ligands for enantioselective catalysis.

The aim of this project was to synthesise a range of novel chiral bidentate mixed donor imino-NHC ligand precursors (Figure 1.11), derived from amino acids, *N*-substituted imidazoles and carbonyl compounds, and evaluate them in enantioselective palladium-catalysed allylic substitution (a) and copper-catalysed conjugate addition (b) (Scheme 1.16). The rationale for the design of the ligands is described in Chapter 2. Douthwaite *et al.* reported good results (e.e. = 92 %) in enantioselective Pd-catalysed allylic substitution, using chiral imino-NHC ligands,[59] whilst the work in this thesis was being performed.

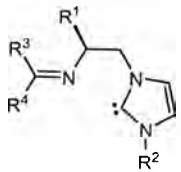
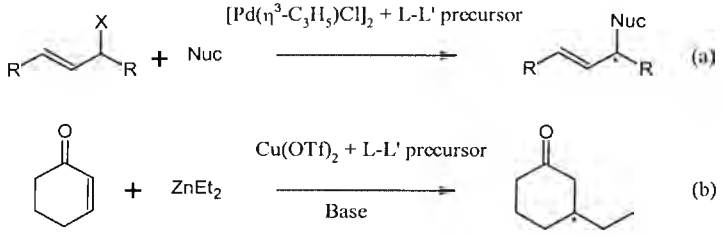


Figure 1.11 Proposed structure of chiral bidentate mixed donor imino-NHC ligands



Scheme 1.16 Enantioselective Pd-catalysed allylic substitution and Cu-catalysed conjugate addition.

1.6 References

1. a) W. A. Herrmann, *Angew. Chem. Int. Ed. Engl.*, 2002, **41**, 1290; b) A. Pfaltz, H. Yamamoto in *Comprehensive Asymmetric Catalysis*, (Eds: E. N. Jacob), Springer, Berlin, 1999; c) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry*, 1998, **9**, 1; d) T. G. Grant, A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297.
2. M. F. Lappert in *Transition Metal Chemistry* (Eds: A. Muller, E. Diemann), Verlag Chemie, Weinheim, 1981.
3. A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.
4. a) W. A. Herrmann, M. Elison, J. Fischer, C. Kocher, G. R. J. Artus, *Chem. Eur. J.*, 1996, **2**, 772; b) W. A. Herrmann, G. M. Kobmaier, M. Elison, *J. Organomet. Chem.*, 1996, **520**, 231.
5. W. A. Herrmann, G. M. Kobmaier, M. Elison, *J. Organomet. Chem.*, 1996, **520**, 231.
6. L. M. Pignolet, *Homogeneous Catalysis with Metal Phosphine Complexes*; Plenum: New York, 1983.
7. R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1993; *Comprehensive Asymmetric Catalysis* (Eds. E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, 1999.
8. G. W. Parshall, *Homogeneous Catalysis*, Wiley-Interscience: New York, 1992.

9. a) A. W. Coleman, P. B. Hitchcock, M. F. Lappert, R. K. Maskell, J. H. Muller, *J. Organomet. Chem.*, 1983, **250**, C9; b) M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953; c) W. A. Herrmann, L. J. Goossen, G. R. J. Artus, C. Kocher, *Organometallics*, 1997, **16**, 2472; d) D. Enders, H. Gielen, G. Raabe, J. Runsink, J. H. Teles, *Chem. Ber.*, 1996, **129**, 1483.
10. T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 1, 18.
11. I. Ogima, *Catalytic Asymmetric Synthesis*: VCH: New York, Cambridge, 1993; R. Noyori, *Asymmetric Catalysis Synthesis in Organic Chemistry*, Wiley, New York, Chichester, 1994.
12. E. O. Fischer, A. Maasböl, *Angew. Chem. Int. Ed. Engl.*, 1964, 580.
13. K. Öfele, *J. Organomet. Chem.*, 1968, **12**, 42.
14. H.-W. Wanzlick, H.-J. Schönherr, *Angew. Chem., Int. Ed. Engl.* 1968, **7**, 141.
15. H.-W. Wanzlick, *Angew. Chem. Int. Ed. Engl.*, 1962, **1**, 75.
16. M. K. Denk, K. Hatano, M. Ma, *Tetrahedron Lett.*, 1999, **40**, 2057.
17. a) M. F. Lappert, *J. Organomet. Chem.*, 1988, **358**, 185; b) M. F. Lappert, P. L. Pye, *J. Chem. Soc. Dalton Trans.*, 1977, 2172; P. B. Hitchcock, M. F. Lappert, P. L. Pye, *J. Chem. Soc. Dalton Trans.*, 1978, 826.
18. H.-W. Wanzlick, H.-J. Schönherr, *Justus Liebigs Am. Chem.*, 1970, **731**, 176.
19. A. J. Arduengo III, H. Dias, R. Harlow, M. Kleine, *J. Am. Chem. Soc.*, 1992, **114**, 5530.
20. W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. Artus, *Chem. Eur. J.*, 1996, **2**, 772.
21. N. Kuhn, T. Kratz, *Synthesis*, 1993, 561.
22. D. Ender, K. Bruer, G. Raabe, J. Runsink, J. H. Teles, J. Melder, K. Ebel, S. Brode, *Angew. Chem., Int. Ed. Engl.* 1995, **34**, 1021.
23. D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.*, 2000, **100**, 39.
24. R. Gleiter, R. Hoffmann, *J. Am. Chem. Soc.*, 1968, **90**, 1475.
25. a) J. F. Harrison, *J. Am. Chem. Soc.*, 1971, **93**, 41; b) J. F. Harrison, Liedtke, J. F. Liebman, *J. Am. Chem. Soc.*, 1979, **101**, 7162.
26. L. J. Pauling, *J. Chem. Soc. Chem. Commun.*, 1980, 688.

27. A. J. Arduengo III, H. Boch, H. Chen, M. Denk, D. A. Dixon, J. C. Green, W. A. Herrmann, N. L. Jones, M. Wagner, R. West, *J. Am. Chem. Soc.*, 1994, **116**, 6641.
28. C. Heinemann, W. Thiel, *Chem. Phys. Lett.*, 1994, **217**, 11.
29. D. A. Dixon, A. J. Arduengo III, *J. Phys. Chem.*, 1991, **95**, 4180.
30. J. Cioslowski, *Int. J. Quantum. Chem., Quantum. Chem. Symp.*, 1993, **27**, 309.
31. C. Heinemann, T. Müller, Y. Apeloig, H. Schwarz, *J. Am. Chem. Soc.*, 1996, **118**, 2023.
32. C. Boehme, G. Frenkling, *J. Am. Chem. Soc.*, 1996, **118**, 2039.
33. J. F. Lehmann, S. G. Urquhart, L. E. Ennis, A. P. Hitchcock, K. Hatano, S. Gupta, M. K. Denk, *Organometallics*, 1999, **18**, 1862.
34. N. C. Baird, K. F. Taylor, *J. Am. Chem. Soc.*, 1978, **100**, 1333.
35. B. C. Gilbert, D. Griller, A. S. Nazran, *J. Org. Chem.*, 1985, **50**, 4788.
36. M.-D. Su, S.-Y. Chu, *Chem. Phys. Lett.*, 1999, **308**, 283.
37. W. A. Herrmann, C. Köcher, *Angew. Chem., Int. Ed. Engl.* 1997, **36**, 2162.
38. W. A. Herrmann, O. Runte, G. Artus, *J. Organomet. Chem.*, 1995, **501**, C1.
39. L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.*, 2005, **690**, 5407.
40. X. Hu, Y. Tang, P. Gantzel, K. Meyer, *Organometallics*, 2003, **22**, 612.
41. X. Hu, I. Casro-Rodriguez, K. Olsen, K. Meyer, *Organometallics*, 2004, **23**, 755.
42. A. C. Hiller, W. J. Sommer, B. S. Yong, J. L. Petersen, L. Cavallo, S. P. Nolan, *Organometallics*, 2003, **22**, 4322.
43. M. S. Viciu, O. Navarro, R. F. Germaneau, R. A. Kelly III, W. J. Sommer, N. Marion, E. D. Stevens, L. Cavallo, S. P. Nolan, *Organometallics*, 2004, **23**, 629.
44. R. Dorta, D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 3516.
45. N. M. Scott, R. Dorta, E. D. Stevens, A. Correa, L. Cavallo, S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 2485.
46. C.-L. Lai, W.-H. Guo, M.-T. Lee, C.-H. Hu, *J. Organomet. Chem.*, 2005, 690, 5867.
47. J. C. Köcher, W. A. Herrmann, *J. Organomet. Chem.*, 1997, **532**, 261.
48. W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290.

49. J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.*, 2002, **124**, 4954.

50. a) M. Scholc, T. M. Trnka, J. P. Morgan, R. H. Grubbs, *Tetrahedron Lett.*, 1999, 40, 2247; b) M. S. Sandford, J. A. Love, R. H. Grubbs, *J. Am. Chem.. Soc.*, 2001, **123**, 6543; c) T. M. Trnka, J. P. Morgan, M. S. Sandford, T. E. Wilhelm, M. Scholl, T. Choi, S. Ding, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 2546; d) J. A. Love, M. S. Sanford, M. W. Day, R. H. Grubbs, *J. Am. Chem.. Soc.*, 2003, **125**, 10103.

51. B. Cornils, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Complexes* (Eds: B. Cornils, W. A. Herrmann), VCH, Weinheim, 1996, Vol. 2, chapter 3, p. 577.

52. a) W. A.Hermann, C. P. Reisinger, *J. Organomet. Chem.*, 1998, **557**, 93; b) C. Zhang, J. Huang, M. T. Trudell, S. P. Nolan, *J. Org. Chem.*, 1999, 64, 3804; c) T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem.*, 1999, 585, 348.

53. a) S. P. Stauffer, L. Sunwao, J. P. Stambulli, S. I. Hauck, J. F. Hartwig, *Org. Lett.*, 2000, **10**, 1423; b) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722; c) B. C. Hamann, J. F. Hartwig, *J. Am Chem. Soc.*, 1998, **120**, 7369.

54. G. A. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell, S. P. Nolan, *Organometallics*, 2002, **21**, 2866.

55. G. A. Grasa, M. S. Viciu, J. Huang, S. P. Nolan, *J. Org. Chem.*, 2001, **66**, 7729.

56. W. A. Herrmann, L. J. Goossen, C. Köcher, G. R. Artus, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 2805.

57. M. C. Perry; X. Cui, M. T. Powell, D.-R. Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.*, 2003, **125**, 114.

58. W.-L. Duan, M. Shi, G.-B. Rong, *Chem. Commun.*, 2003, 2916.

59. L. G. Bonnet, R. E. Douthwaite, B. M. Kariuki, *Organometallics*, 2003, **22**, 4187.

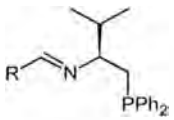
2. Synthesis of iminoalkyl imidazol-2-ylidene ligands

2.1 Introduction

The design of new classes of chiral ligands is of great interest, in order to achieve better results in asymmetric catalysis. Amine and phosphine-based ligands have dominated this area. Their relatively easy synthesis and the wide range of electronic and steric properties they can feature are key elements of their success.[1]

Stable *N*-heterocyclic carbenes (NHCs), characterised by stronger σ-donation and poorer π-back-donation, are valuable alternatives to phosphines.[2] NHCs have demonstrated higher performance than phosphines in numerous metal-catalysed reactions.[3,4] They have superseded phosphines in many transition metal-catalysed reactions, due to their higher activity, ease of preparation, and the high stability of the metal-carbene bond, which decreases ligand dissociation. Recently, very good enantioselectivities were observed in hydrogenation[5] and alkylation[6] reactions using chiral bidentate ligands containing NHC donor groups. The fixed geometry imposed by chelation and a stereogenic centre on the backbone proved critical to attaining very good enantioselection in these reactions.

Chiral mixed-donor imine-phosphine ligands have demonstrated their ability to enable asymmetric induction in a wide range of transition metal-catalysed reactions, such as alkene hydrogenation[7], allylic alkylation[8] and conjugate addition[9] (Figure 2.1).



Asymmetric allylic substitution

R = Me_2N	Y = 98%, ee = 95%
R = *p*-(NMe_2)-C_6H_4	Y = 99%, ee = 92%

Figure 2.1 Chiral iminoalkyl phosphine ligands synthesised by Morimoto *et al.*[8b]

The objective of this work was to substitute the phosphine moiety for a NHC donor group and apply the corresponding ligands to palladium-catalysed allylic alkylation. The stronger σ-donation of the NHC compared to the imine should result in considerable electronic differentiation of the termini of the intermediate palladium allyl species, which enables stereoselectivity (discussed in Chapter 3). The ligand synthesis was designed to permit structural optimisation. A modular approach was adopted using chiral amino acids, carbonyl compounds and *N*-substituted imidazoles as starting materials (Figure 2.2).

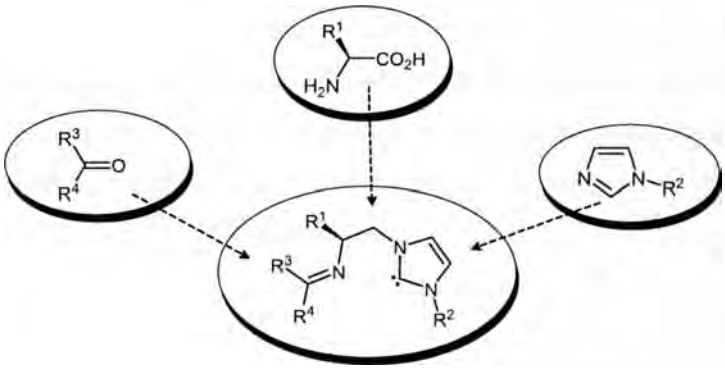
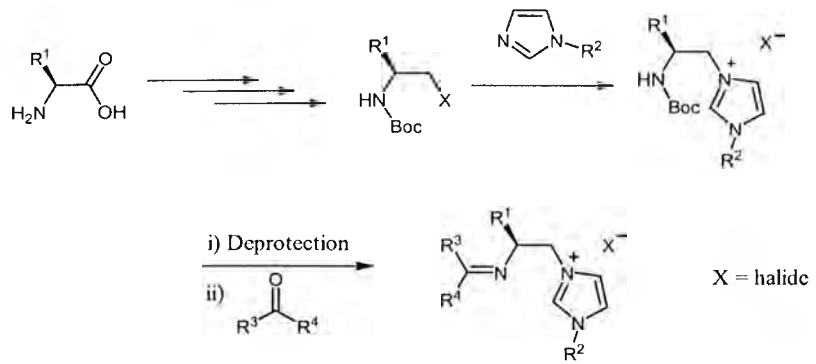


Figure 2.2 Modular design of ligand.

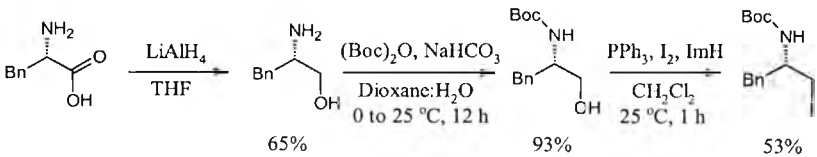
Unlike trialkylphosphines, NHCs have the advantage to be easily generated *in situ* by deprotonation of air-stable imidazolium salts. As a result, the aim was to synthesise iminoalkyl imidazolium salts as precursors to NHC ligands.

Imidazolium salts are easily accessible *via* *N*-alkylation of *N*-substituted imidazoles. Thus, the proposed synthetic route (Scheme 2.1) involved conversion of chiral amino acids into aminoalkyl halides, which could then be used to alkylate *N*-substituted imidazoles. Condensation of the resulting aminoalkyl imidazolium salts with carbonyl compounds was expected to give the desired iminoalkyl imidazolium salts. Given that iodide is the best halide leaving group, the preparation of aminoalkyl iodide derivatives from amino acids, was explored. A number of routes to aminoalkyl iodides involving Boc-protection have been reported.[10-13] In the initial work, it was decided to use the Boc-protected aminoalkyl halides in the alkylation step, in order to avoid any rearrangement of the aminoalkyl halides

Conversion of phenylalanine into the corresponding aminoalkyl iodide has been reported by Knochel *et al.* (Scheme 2.2).[10] Phenylalanine was reduced to phenylalaninol using lithium aluminium hydride (LAH) in THF, which was *N*-protected using di-*tert*-butoxyl dicarbonate $(Boc)_2O$ in dioxane and water in the presence of $NaHCO_3$. *N*-*t*-Boc protected phenylalaninol was then converted into the corresponding protected aminoalkyl iodide using triphenylphosphine (PPh_3), imidazole and iodine in dichloromethane.



Scheme 2.1 The proposed initial synthetic route.

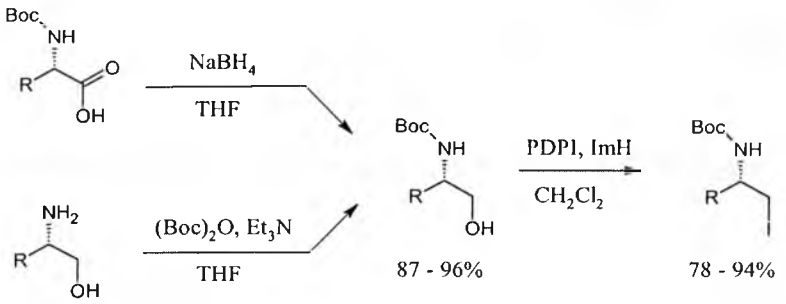


Scheme 2.2 Synthesis of a chiral aminoalkyl iodide.

Likewise, Jackson *et al.* reported the synthesis of aminoalkyl iodides using PPh_3, iodine and imidazole.[11]

Another route, similar to that used by Knochel *et al.* was reported by Longobardo *et al.*[12] *N-t*-Boc protected amino alcohols were obtained *via* reduction of *N-t*-Boc protected amino acids using sodium borohydride, or *via* *N*-protection of amino alcohols using $(Boc)_2O$ in the presence of triethylamine (Scheme 2.3). The *N-t*-Boc protected amino alcohols were subsequently converted to the corresponding

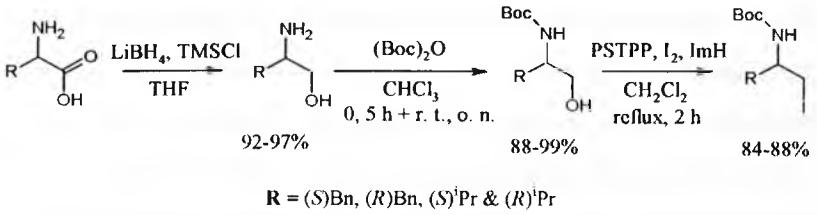
aminoalkyl iodides using polystyryl diphenylphosphine iodine (PDPI) in the presence of imidazole.



R = Me, Et, ^{i}Pr, ^{t}Bu, Bn, etc.

Scheme 2.3 Synthesis of chiral aminoalkyl iodides reported by Longobardo *et al.*[12]

The synthesis of aminoalkyl iodides starting from amino acids has also been reported by Quagliato *et al.* (Scheme 2.4).[13] The reduction of amino acids was achieved using lithium borohydride ($LiBH_4$) and trimethylsilyl chloride (TMSCl). The amino alcohols were subsequently *N*-protected using $(Boc)_2O$, and converted to the corresponding aminoalkyl iodide using polymer-supported triphenylphosphine (PSTPP), I_2 and imidazole.

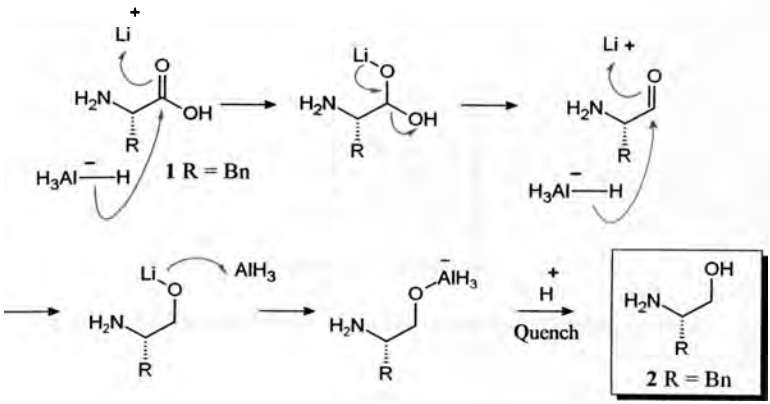


Scheme 2.4 Preparation of chiral aminoalkyl iodides reported by Quagliato *et al.*[13]

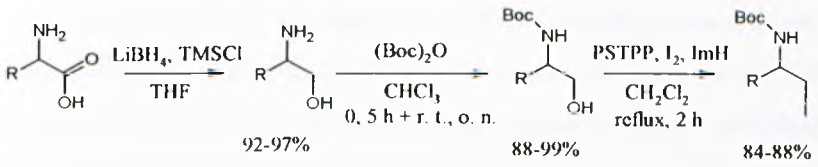
2.2 Results and discussion

2.2.1 Initial route for synthesis of iminoalkyl imidazolium salts

Lithium aluminium hydride was used to reduce amino acids[14] (Scheme 2.5) or the amino alcohols were bought from Sigma-Aldrich.



Scheme 2.5 The mechanism of reduction of amino acids to amino alcohols using $LiAlH_4$.



R = (*S*)Bn, (*R*)Bn, (*S*)^{i}Pr & (*R*)^{i}Pr

Scheme 2.4 Preparation of chiral aminoalkyl iodides reported by Quagliato *et al.*[13]

2.2 Results and discussion

2.2.1 Initial route for synthesis of iminoalkyl imidazolium salts

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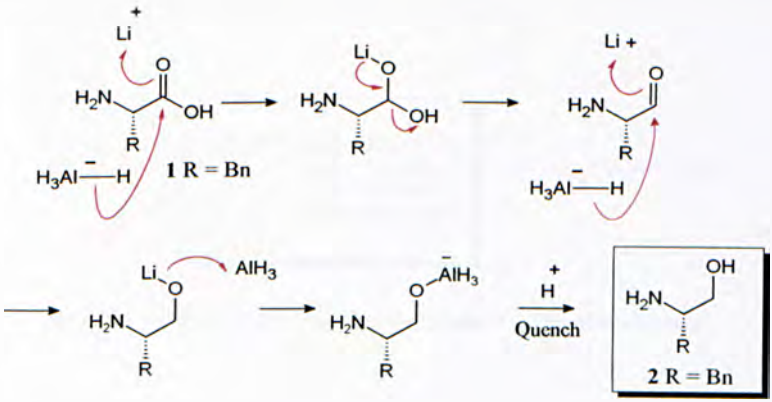
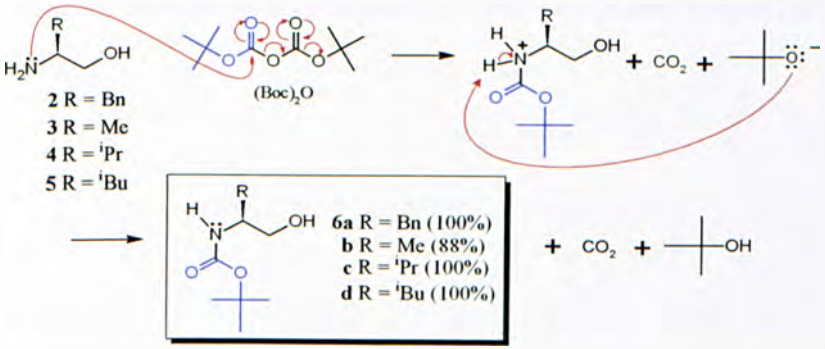
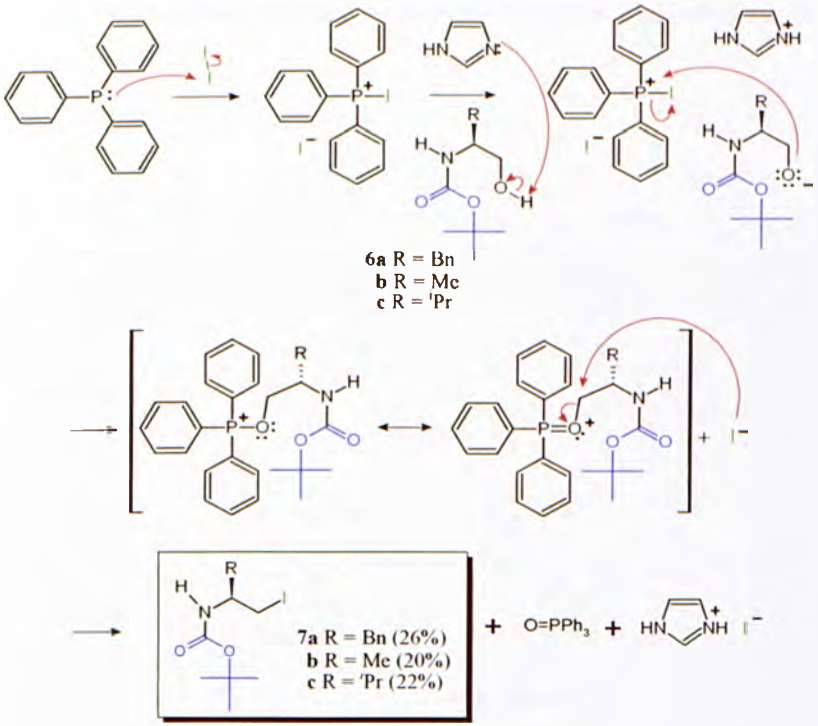


Scheme 2.5 The mechanism of reduction of amino acids to amino alcohols using $LiAlH_4$.

In this work, the amino group of amino alcohols **2-5** was protected to prevent intramolecular substitution. The amino alcohols **2-5** were *N*-*t*-Boc protected in THF using di-*tert*-butyl dicarbonate ($(Boc)_2O$) in the presence of triethylamine (Et_3N) (Scheme 2.6).[8b] Lower yields than expected were obtained for leucinol and valinol using this method.[8b] Another procedure, more convenient and more effective for *N*-protection of valinol, has been reported by Koskinen.[15] Thus *N*-protected amino alcohols **6c-d** derived from valinol **4** and leucinol **5** were prepared by dropwise addition of $(Boc)_2O$ to a solution in CH_2Cl_2 at 0 °C and stirred at room temperature for one hour. The *N*-*t*-Boc protected amino alcohols **6c-d** were obtained in excellent yields (100%). This method has the advantage of being faster and not requiring a base.



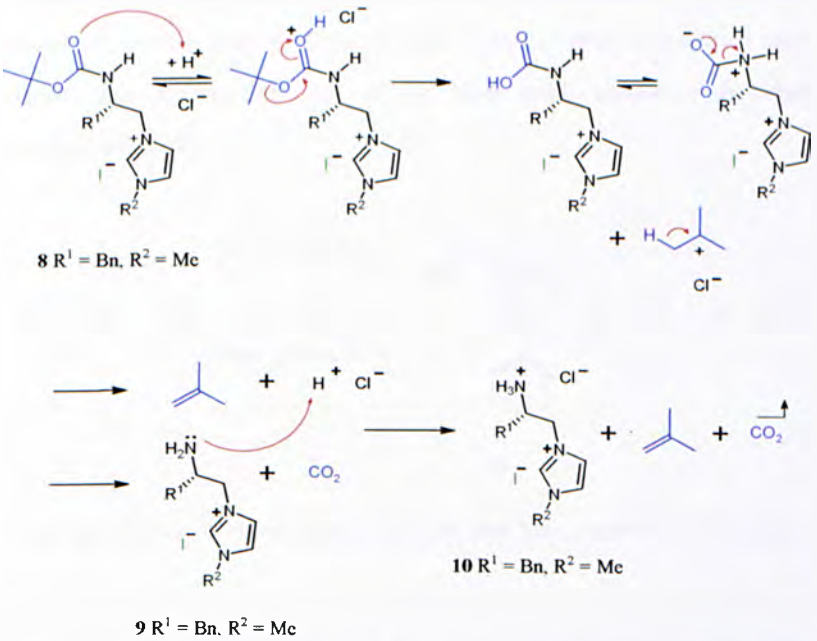
Scheme 2.6 The mechanism of *N*-*t*-Boc protection of amino alcohols.



Scheme 2.7 The mechanism of iodination of amino alcohols.

N-t-Boc protected aminoalkyl iodide **7a** was reacted with 1-methylimidazole in toluene under reflux, to give a mixture of *N-t*-Boc protected aminoalkyl imidazolium salt **8**, and *N*-deprotected aminoalkyl imidazolium salt **9**. The products formed were identified by two ^{1}H NMR signals at $\delta > 9$ ppm in DMSO-d_6, assigned to imidazolium C^2 protons. Deprotection was presumed to be due to thermolytic decomposition. The

mixture of **8** and **9** was treated with 4.0 M hydrogen chloride solution in dioxane to complete the deprotection, affording the dicationic ammonium imidazolium salt **10** (Scheme 2.8).[16]

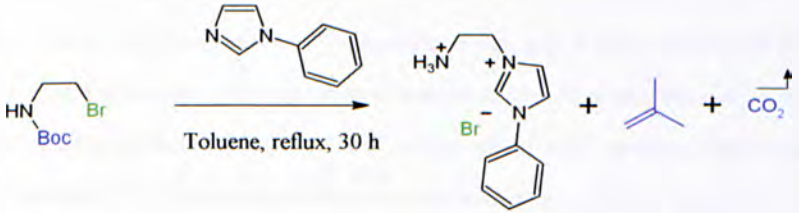


Scheme 2.8 The mechanism of *N*-*t*-Boc deprotection.

Unfortunately, attempts to purify **10** by recrystallisation were unsuccessful. Instead, experiments were carried out to investigate the thermolytic *N*-deprotection process as it had the potential to obviate the need for the acid deprotection step.

2.2.2 Investigation of thermolytic *N*-*t*-Boc deprotection

In order to investigate *N*-t-Boc deprotection during the *N*-alkylation, 2-(Boc-amino)ethyl bromide **11** and 1-phenylimidazole were refluxed in toluene for 30 h (Scheme 2.9). A white solid precipitated out during the reaction. The solid was filtered off, washed with Et_2O, recrystallised from hot ethanol, and dried under reduced pressure affording 21% of the white solid, ammonium *N*'-phenyl imidazolium salt **12**.

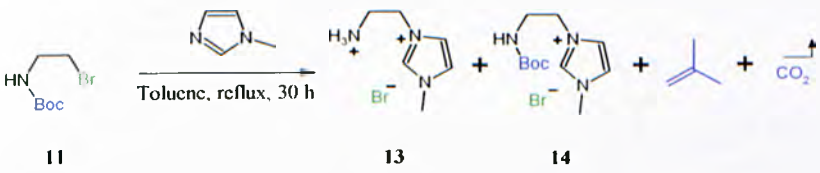


11 **12**

Scheme 2.9 *N*-alkylation of 1-phenylimidazole with 2-(Boc-amino)ethyl bromide.

N-alkylation of 1-methylimidazole with **11** was also carried in toluene under reflux. However, even after prolonged reaction only a mixture of protected and deprotected compounds **13** and **14** was obtained (Scheme 2.10). The highly hygroscopic yellow oily mixture was triturated and washed with dry Et_2O under an inert atmosphere of nitrogen to afford a white solid. The observation of signals at δ 9.32 ppm and 9.22 ppm in CD_3OD, assigned to imidazolium C^2 protons, indicated the presence of two

imidazolium salts **13** and **14** in (7:1) ratio.



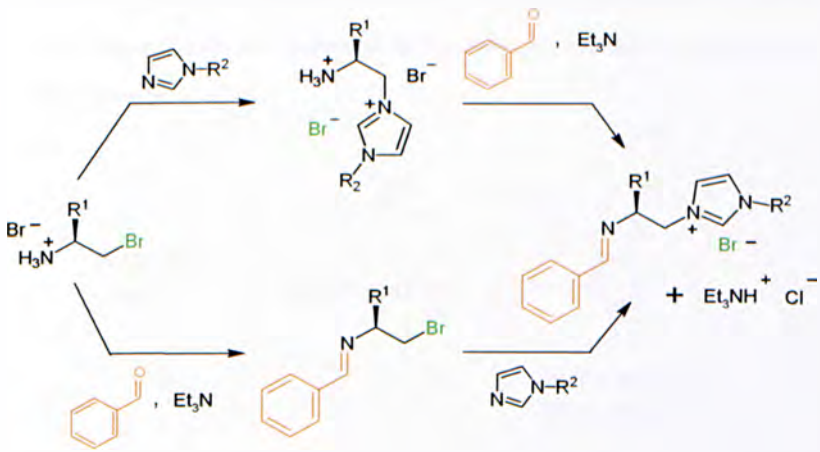
11 **13** **14**

Scheme 2.10 *N*-alkylation of 1-methylimidazole with 2-(Boc-amino)ethyl bromide.

In summary, *N*-deprotection and *N*-alkylation in one step is not general to all *N*-substituted imidazoles. Although the combination of both steps was achieved in the *N*-alkylation of 1-phenylimidazole, only modest yields were obtained, and in the reaction with 1-methylimidazole only partial deprotection was achieved after 30 h.

2.2.3 Alternative routes to the synthesis of iminoalkyl *N*-substituted imidazolium salts

Considering the instability of the *N*-*t*-Boc group during the *N*-alkylation process, two alternative routes were considered, both involving deprotection before the *N*-alkylation step (Scheme 2.11). The first route involved *N*-alkylation of *N*-substituted imidazoles with ammonium alkyl bromides followed by condensation with a carbonyl compound to give the imine. The alternative was to synthesise the iminoalkyl halide and then couple it with an *N*-substituted imidazole.



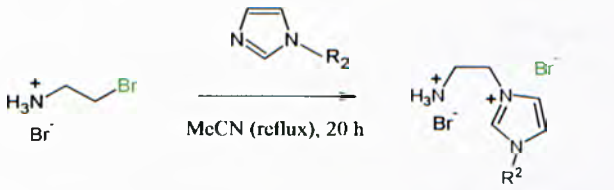
Scheme 2.11 New routes proposed for synthesis of iminoalkyl *N*-substituted imidazolium salts.

Preliminary investigations using an achiral ammonium alkyl halide were carried out to find the best route.

2.2.3.1 *N*-Alkylation followed by condensation with ketones

Deprotection of *N*-*t*-Boc protected aminoalkyl halides with HCl generates aminoalkyl halide hydrochlorides. In order to investigate the *N*-alkylation of *N*-substituted imidazoles with aminoalkyl halide hydrochlorides, commercially available 2-bromoethylamine hydrobromide **15** was used. The achiral *N*-substituted imidazolium salts **12** and **13** were obtained by reacting **15** with *N*-methyl and *N*-phenyl imidazoles in acetonitrile under reflux (Scheme 2.12). The dicationic species **13** was obtained

after 64 h in 17% yield. Compound **13** was very hygroscopic and became oily as soon as it was exposed to the air. Compound **12** which was not hygroscopic, was obtained in 94% yield after 15 h.

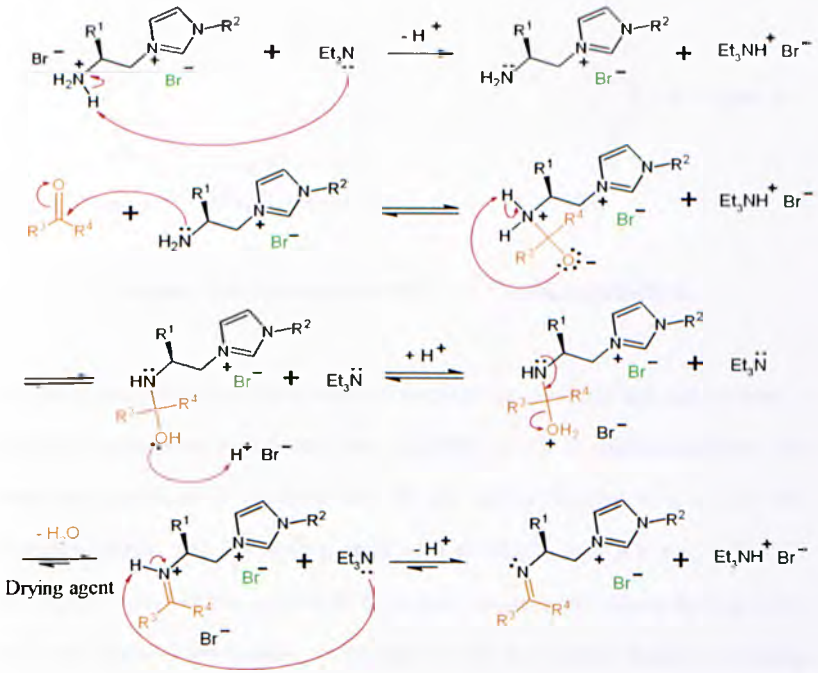


15

12 R^2 = Ph (94%)
13 R^2 = Me (17%)

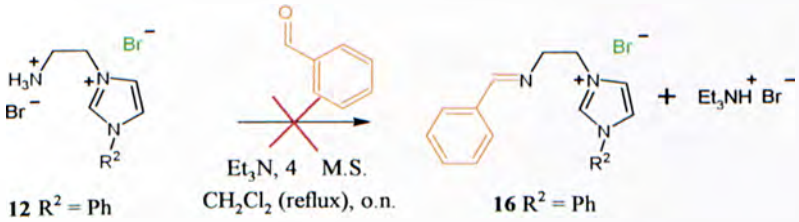
Scheme 2.12 *N*-Alkylation of *N*-substituted imidazoles with 2-bromoethylamine hydrobromide.

After deprotonation of the ammonium moiety and condensation with a carbonyl compound, iminoalkyl *N*-substituted imidazolium salts were expected to be formed (Scheme 2.13). The equilibrium is driven by removal of eliminated water, using a drying agent such as molecular sieves or anhydrous magnesium sulphate.



Scheme 2.13 Synthesis of imino-imidazolium salts starting from ammonium imidazolium salts.

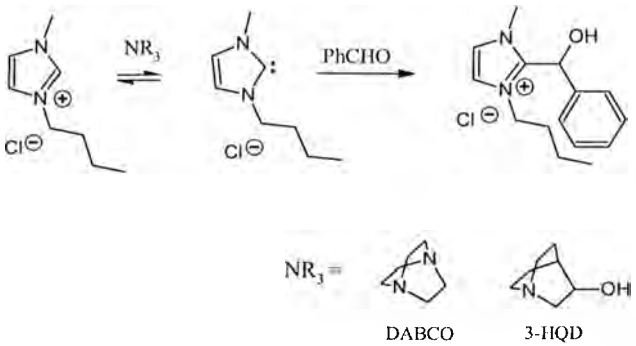
Procedures employed by De Kimpe *et al.* to convert aminoalkyl bromide hydrobromides to the corresponding iminoalkyl bromides were employed.[17] Attempts to convert the ammonium moiety of **12** to the corresponding benzylideneamine group using benzaldehyde were carried out using triethylamine as a base, and activated 4 Å molecular sieves.[17b] Unfortunately, this strategy failed to yield the desired iminoalkyl imidazolium salt **16** (Scheme 2.14).



Scheme 2.14 Condensation reaction of **12** with benzaldehyde.

^{1}H NMR analysis showed that most of the starting materials had not reacted. A plausible explanation is the very low solubility of **12** in dichloromethane. The dicationic species **12** is too polar and did not readily dissolve in a solvent with moderate polarity and low boiling point such as CH_2Cl_2 (ε = 9.1, b.p. = 39.8°C). Attempts to carry out the reaction in more polar solvents with higher boiling points were also made. Unfortunately, compound **12** did not readily dissolve in boiling acetonitrile (ε = 36.6, b.p. = 82°C) and boiling ethanol (ε = 24.3, b.p. = 78°C).

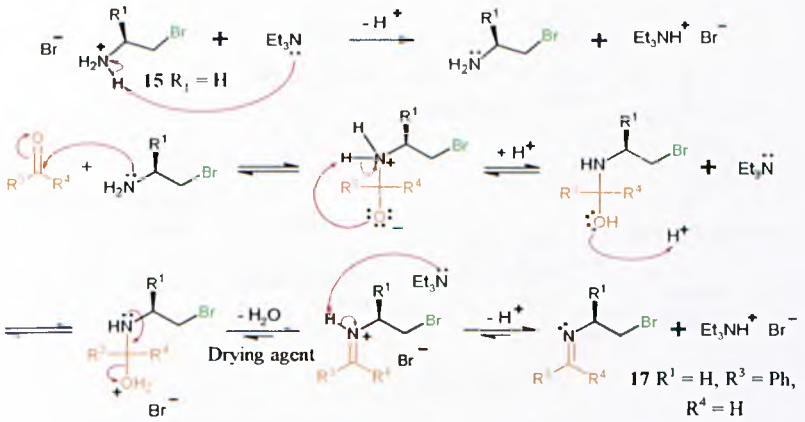
A possible side reaction that could explain the presence of impurities is the deprotonation of the imidazolium moiety instead of the ammonium group. Aggarwal *et al.* reported unexpected deprotonation of imidazolium salt in a Bayliss-Hillman reaction under mild basic conditions[18] using 3-hydroxyquinuclidine (3-HQD, pKa_{II} = 9.5[19] in DMSO) and 1,4-diazabicyclo[2.2.2]octane (DABCO or triethylenediamine = TEDA, pKa_{II} = 8.7[20] in DMSO). The imidazol-2-ylidene formed, subsequently reacted with benzaldehyde (Scheme 2.15). The comparable basicity of triethylamine (Et_3N, pKa_{II} = 9.0[21] in DMSO) suggests that the same reaction could have occurred.



Scheme 2.15 Reaction of imidazolium-based ionic liquid with benzaldehyde in the presence of mild bases.

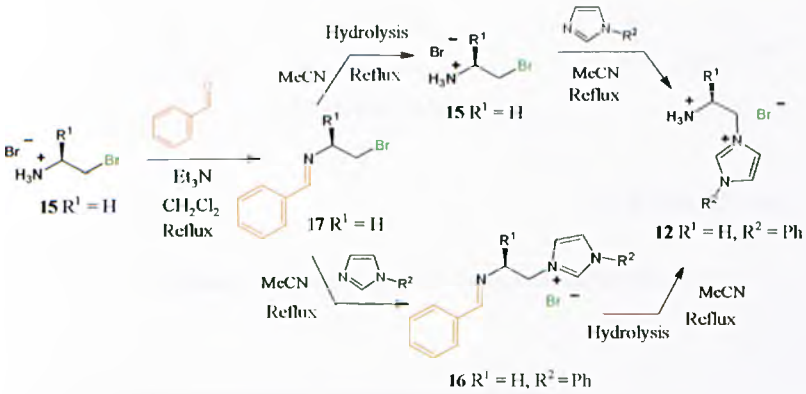
2.2.3.2 Preparation of iminoalkyl halides and their use in *N*-alkylation of imidazoles

Condensation of 2-bromoethylamine hydrobromide **15** with benzaldehyde, in the presence of Et_3N and activated 4 Å molecular sieves, in dichloromethane was carried out under reflux (Scheme 2.16).[17b] The achiral iminoalkyl bromide **17** was obtained in good yield (83%) as a clear yellow oil after 6 h of reflux.



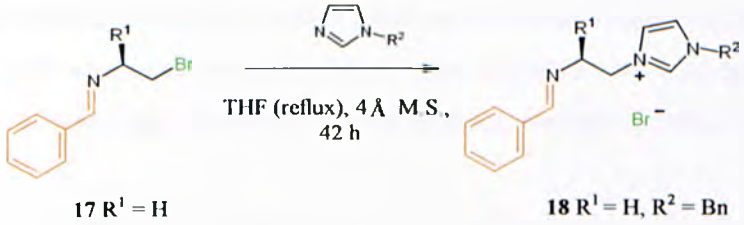
Scheme 2.16 Mechanism of condensation reaction to imines.

Attempts to alkylate 1-phenylimidazole with iminoalkyl bromide **17** resulted in imine hydrolysis and decomposition. Only a small amount **12** was isolated from the reaction as a white solid (Scheme 2.17).



Scheme 2.17 Hydrolysis of imines during *N*-alkylation reactions.

To prevent hydrolysis the coupling reaction of **17** with 1-benzylimidazole was performed in dry THF in the presence of activated 4 Å molecular sieves. The product **18** was obtained in moderate yield (56%) as a clear solid (Scheme 2.18). The synthesis of **18** was confirmed by ^{1}H NMR with characteristic peaks respectively at δ 8.3 and 9.4 ppm assigned to N=C**H**C$_6$H$_5$ and NC**H**N protons. Furthermore, ^{13}C NMR analysis shows a characteristic carbon peak at δ 163.5 ppm confirming the presence of the imine moiety (N=**C**HC$_6$H$_5$).

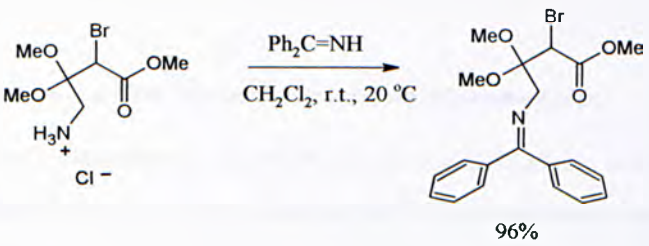


17 $R^1 = H$ **18** $R^1 = H$, $R^2 = Bn$

Scheme 2.18 *N*-alkylation of 1-benzylimidazole with **17**.

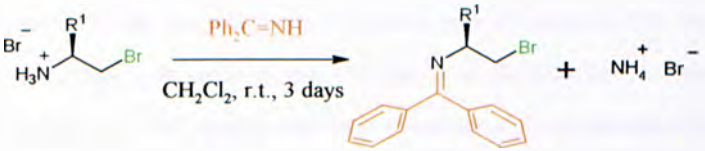
2.2.4 Synthesis of benzylhydrylidene amine derivatives

Compound **18** was hygroscopic and tended to decompose on exposure to air. The synthesis of more stable iminoalkyl halides, featuring bulkier imine carbon substituents was investigated using benzophenone imine. A convenient and effective method to convert ammonium salts to benzylhydrylidene amines using benzophenone imine, was reported by De Kimpe *et al.* (Scheme 2.19).[22]



Scheme 2.19 Preparation of imines using benzophenone imine.

Benzophenone imine was reacted with **15** in dry dichloromethane at room temperature for 3 days affording **19** as a white solid in excellent yields (97%) after recrystallisation from hot hexane or petroleum spirit (Scheme 2.20). The imine double bond formation was confirmed by a ^{13}C NMR signal at δ_C 169.7 ppm in $CDCl_3$.



15 $R^1 = H$ **19** $R^1 = H$

Scheme 2.20 Preparation of imines using benzophenone imine.

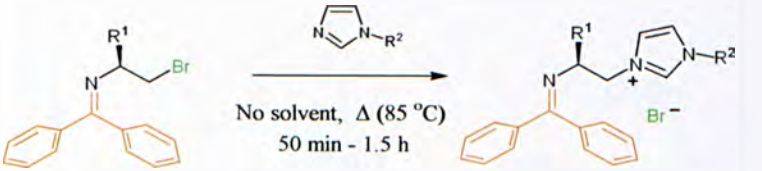
As predicted, bulkier imines were significantly more stable. During the work-up procedure, the crude product withstood treatment with aqueous 10% $NaHCO_3$ and washing with water. Stability towards oligomerisation was also confirmed, with no colourisation being observed after several weeks of storage.

2.2.5 Synthesis of achiral iminoalkyl *N*-substituted imidazolium salts

N-alkylation of 1-benzylimidazole with **19** gave moderate yields of 45% in a range of dry solvents (CH_3Ph, THF, CH_2Cl_2, DMF and MeCN). Low yield could be attributed to steric hindrance.

Bogdal *et al.*[23] and Martin-Aranda *et al.*[24] reported that *N*-alkylation of imidazole with alkyl halides gave better results (up to 89% yield) under solvent free conditions.

Hence, a liquid mixture of **19** and 1-benzylimidazole was stirred and heated at 85 °C under an inert atmosphere until solidification. After 50 minutes, the desired iminoalkyl *N*-benzylimidazolium salt **20a** was successfully formed in 83% yield as a clear solid, after recrystallisation from CH_2Cl_2/Et_2O. Synthesis of **20a** was confirmed by ^1H NMR analysis with a singlet corresponding to the imidazolium C^2 proton at δ 10.37 ppm in CD_2Cl_2. The substitution of bromide with the imidazole ring was also confirmed by C**H**$_2$ signal shifted from δ 3.81 ppm for **19** (CH_2-Br), to δ 4.59 ppm for **20a** (CH_2-N_{Im}). ^{13}C NMR analysis confirmed conservation of the imine double bond with a quaternary carbon signal observed at δ 172.2 ppm. The procedure was subsequently extended to *N*-alkylation of *N*-methyl and *N*-aryl imidazoles with **19**, affording iminoalkyl *N*-substituted imidazolium salts **20b-d** (Scheme 2.21). As for **20a**, the synthesis of **20b-d** and conservation of the imine double bond was confirmed by ^1H NMR (δ 9.26 – 10.5 (NC^2**H**N), δ 4.49 – 4.64 (C**H**$_2$-N_{Im}) and ^{13}C NMR (δ 169.5 – 173.1 (**C**=N)) analyses.



19 R^1 = H

20 a R^1 = H, R^2 = Bn (83%)
b R^1 = H, R^2 = Me (81%)
c R^1 = H, R^2 = Ph (59%)
d R^1 = H, R^2 = Mes (51%)

Scheme 2.21 *N*-alkylation of a range of *N*-alkyl and *N*-aryl imidazoles with **19**.

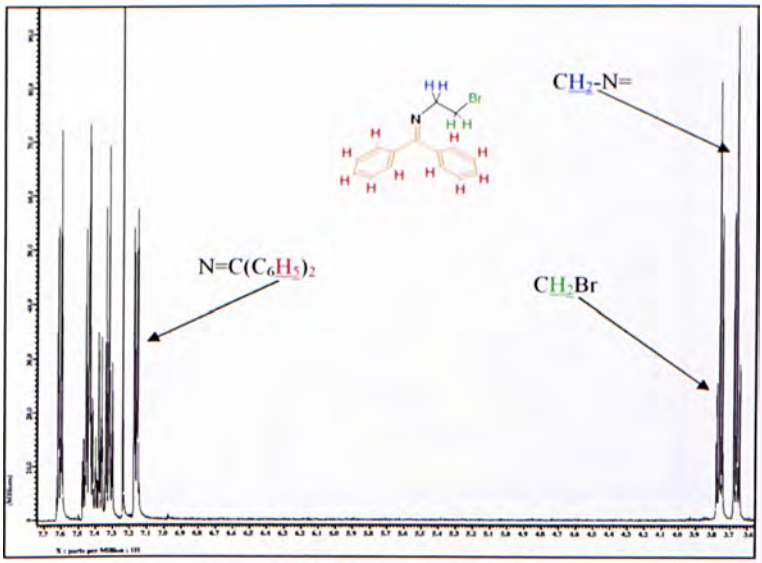


Figure 2.3 ^{1}H NMR spectrum of **19**.

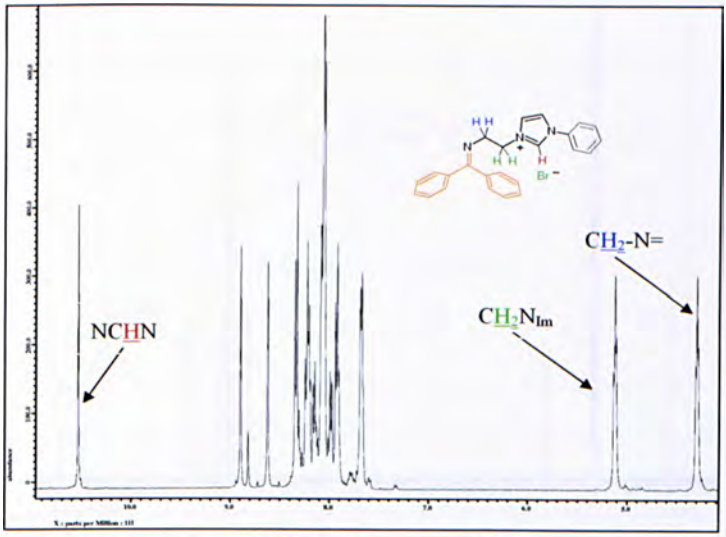


Figure 2.4 ^{1}H NMR spectrum of **20c**.

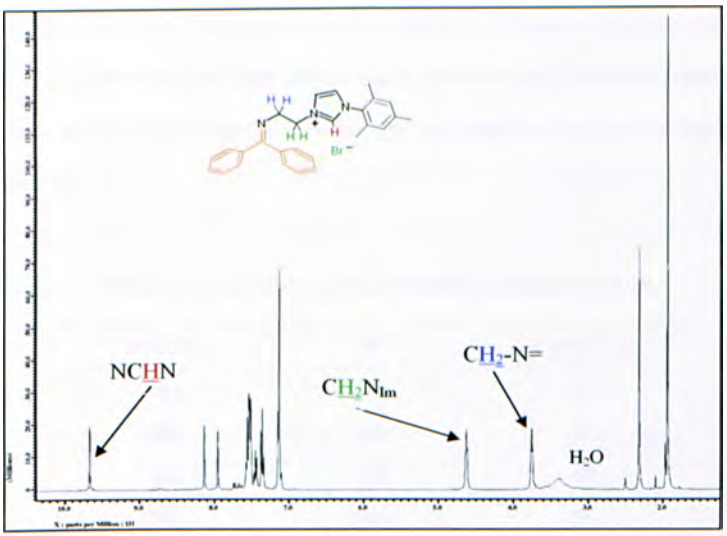


Figure 2.5 ^{1}H NMR spectrum of **20d**.

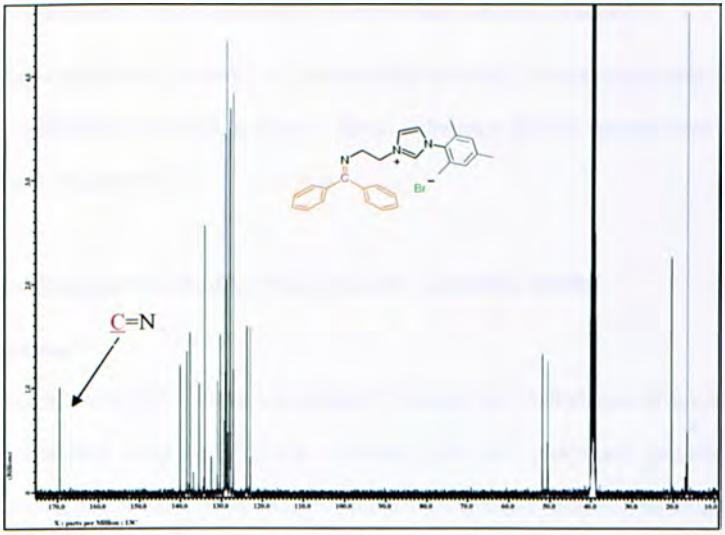


Figure 2.6 ^{13}C NMR spectrum of **20d**.

N-alkylation of *N*-alkyl imidazoles was accomplished in better yields than that of *N*-aryl imidazoles (Table 2.1). This may be due to the steric bulk of the aryl substituents. Electron donating alkyl groups increase the nucleophilicity of *N*-alkyl imidazoles (Table 2.1).

Table 2.1 *N*-alkylation of *N*-substituted imidazoles with **19**.

Products	R^2	Yields (%)
20a	Bn	83
20b	Me	81
20c	Ph	59
20d	Mes	51

2.2.6 Synthesis of chiral iminoalkyl *N*-substituted imidazolium salts

Having established a protocol for synthesising iminoalkyl imidazolium salts starting from iminoalkyl bromides, a route to chiral iminoalkyl halides derived from amino alcohols was devised.

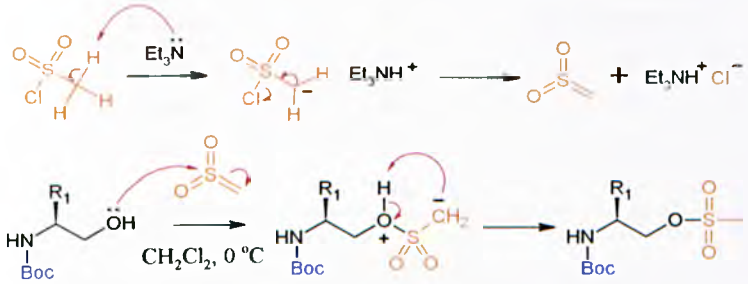
2.2.6.1 Synthesis of chiral *N*-*t*-Boc protected aminoalkyl halides

Iodination

Although aminoalkyl iodides were initially selected for *N*-alkylation of imidazoles, their synthesis using I_2, PPh_3 and imidazole gave low yields and required time consuming purification. Hence, a more efficient halogenation method was sought.

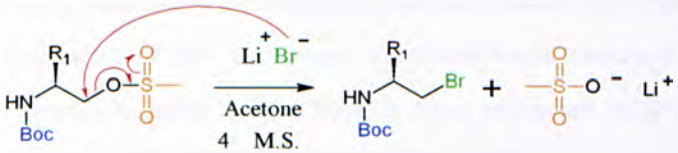
Bromination

Alternatively, amino alcohols can be converted into alkyl halides *via* methane sulfonates. The sulfonyl ester intermediates can then be converted into the corresponding alkyl halides by exchange with halide anions. The synthesis of aminoalkyl bromides and the corresponding ammonium salts *via* sulfonyl derivatives was reported by Ienaga *et al.*[16] Although the conversion of amino alcohols to aminoalkyl bromides requires two steps, the overall yields reported were satisfactory (54%). Moreover, the work-up procedures and purification were not time consuming. *N-t*-Boc amino alcohols **6a-d** were converted into the corresponding methane sulfonate derivatives **21a-d** by reaction with methanesulfonyl chloride (mesyl chloride = MsCl) and Et_3N in CH_2Cl_2 at 0 °C.[16] Compounds **21a-d** were subsequently reacted with lithium bromide in acetone in the presence of 4 Å activated molecular sieves.[16] The crude products were purified by flash chromatography (Hexane : Ethyl acetate, 9:1) affording *N-t*-Boc aminoalkyl bromides **22a-d** as white solids in 38 – 42% overall yield (Scheme 2.22).



6 a R_1 = Bn
b R_1 = Me
c R_1 = ^{i}Pr
d R_1 = ^{t}Bu

21 a R_1 = Bn (93%)
b R_1 = Me (90%)
c R_1 = ^{i}Pr (86%)
d R_1 = ^{t}Bu (86%)



21 a R_1 = Bn
b R_1 = Me
c R_1 = ^{i}Pr
d R_1 = ^{t}Bu

22 a R_1 = Bn (45%)
b R_1 = Me (52%)
c R_1 = ^{i}Pr (44%)
d R_1 = ^{t}Bu (55%)

Scheme 2.22 Bromination of *N-t*-Boc amino alcohols *via* sulfonyl derivatives.

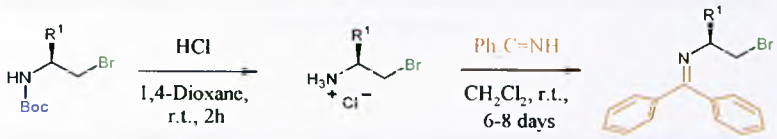
The overall yields of **22a-d** (Table 2.2) from *N-t*-Boc amino alcohols were significantly better than those for the iodides prepared from I_2, PPh_3 and imidazole (Table 2.1).

Table 2.2 Overall yields obtained for bromination of *N*-*t*-Boc amino alcohols.

Products	R^1	Overall yields (%)
22a	Bn	38
22b	Me	47
22c	^{i}Pr	47
22d	^{t}Bu	42

2.2.6.2 Synthesis of chiral iminoalkyl halides

The chiral *N*-*t*-Boc aminoalkyl bromides **22a-d** were deprotected by stirring in a 4 M hydrogen chloride solution in 1,4-dioxane at room temperature for 2 hours, to give the corresponding chiral aminoalkyl bromide hydrochlorides **23a-d** in good yields (85 - 95%) (Scheme 2.23).[16] The chiral ammonium alkylhalide salts **23a-d** were reacted with benzophenone imine in dry CH_2Cl_2 at room temperature to give chiral iminoalkyl bromides **24a-d** in excellent yields (Scheme 2.23).[21]



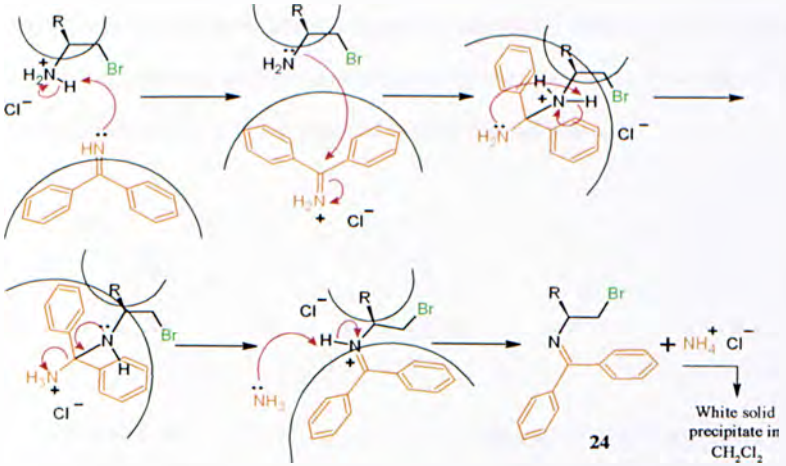
22 **a** R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu

23 **a** R^1 = Bn (86%)
b R^1 = Me (95%)
c R^1 = ^{i}Pr (88%)
d R^1 = ^{t}Bu (93%)

24 **a** R^1 = Bn (90%)
b R^1 = Me (92%)
c R^1 = ^{i}Pr (88%)
d R^1 = ^{t}Bu (87%)

Scheme 2.23 Synthesis of chiral iminoalkyl bromides derived from chiral *N*-*t*-Boc aminoalkyl bromides.

Longer reaction times were required for chiral iminoalkyl bromides **24a-d** (6-8 days) compared to the achiral iminoalkyl bromide **19** (3 days) (Scheme 2.20). This can be explained by the additional steric hindrance created by the group at the stereogenic centre (Scheme 2.24).

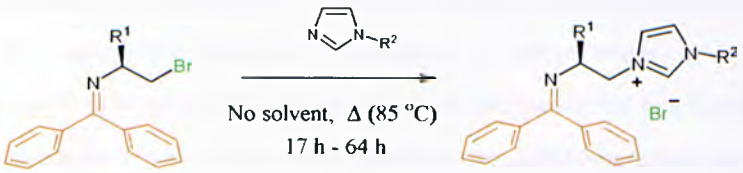


Scheme 2.24 Suggested mechanism for the synthesis of chiral imines derived from chiral ammonium salts.

The synthesis of chiral iminoalkyl bromides was confirmed by the ^{13}C NMR analysis. The spectra revealed characteristic quaternary carbon signals between δ 168.5 ppm and δ 170.1 ppm corresponding to the carbon of the imine moiety.

2.2.6.3 *N*-alkylation of *N*-substituted imidazoles

The protocol for *N*-alkylation of *N*-substituted imidazoles with **19** (Scheme 2.21) was adopted for the *N*-alkylation of 1-benzylimidazole with chiral iminoalkyl bromides **24a-d**. The corresponding chiral iminoalkyl *N*-benzylimidazolium salts **25a-d** were produced in satisfactory yields after recrystallisation from CH_2Cl_2/Et_2O (Scheme 2.25). The lower yields for **25a-d** compared to **20a** (83%) (Scheme 2.21) were likely to be due to additional steric hindrance created by the group at the stereogenic centre. Elimination reactions E_2 were suspected to lower the yields as well.

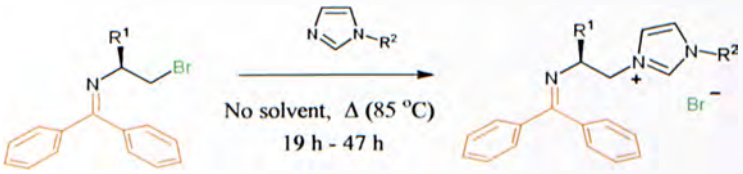


24 a R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu

25 a R^1 = Bn, R^2 = Bn (44%)
b R^1 = Me, R^2 = Bn (66%)
c R^1 = ^{i}Pr, R^2 = Bn (57%)
d R^1 = ^{t}Bu, R^2 = Bn (79%)

Scheme 2.25 Synthesis of chiral iminoalkyl *N*-benzylimidazolium salts.

The reaction of **24a-d** with 1-phenylimidazole gave imidazolium salts **26a-d** in lower yields than imidazolium salts **25a-d** (Scheme 2.26), as previously observed for *N*-alkylation of *N*-aryl imidazoles with **19** (Scheme 2.21, Table 2.1).



24 **a** R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu

26 **a** R^1 = Bn, R^2 = Ph (43%)
b R^1 = Me, R^2 = Ph (28%)
c R^1 = ^{i}Pr, R^2 = Ph (21%)
d R^1 = ^{t}Bu, R^2 = Ph (25%)

Scheme 2.26 Synthesis of chiral iminoalkyl *N*-phenylimidazolium salts.

The formation of chiral iminoalkyl *N*-substituted imidazolium salts was identified by ^{1}H NMR analysis with imidazolium C^2 protons singlets observed between δ 9.43 ppm and δ 10.53 ppm. Substitution products **26a-d** were also characterised by a doublet of doublets in the ^{1}H NMR spectra, due to CH_2-N_{Im} proton shifted from approximately δ 3.5 ppm for the aminoalkyl bromides **24** (CH_2-Br), up to δ 4.5 ppm for the aminoalkyl *N*-substituted imidazolium salts **25** and **26** (CH_2-N_{Im}). Diastereotopic methyl groups in compounds derived from valine (**25c** & **26c**) and leucine (**25d** & **26d**), gave a rise to a pair of doublets in the ^{1}H NMR spectra at δ 0.92 – 1.01 ppm and δ 0.58 – 0.73 ppm. ^{1}H NMR spectra of **25** and **26** revealed signals, usually two singlets, corresponding to aromatic protons shifted from the aromatic region (δ 7.2 – 7.6 ppm) down to δ 5.79 – 6.92 ppm. This could be related to the configuration of the two phenyl rings on the imine moiety. Increased shielding of protons due to exposure to a ring current is a possibility. ^{13}C NMR analysis confirmed conservation of the imine double bond, with the quaternary carbon signals observed between δ 168.5 and 170.1 ppm.

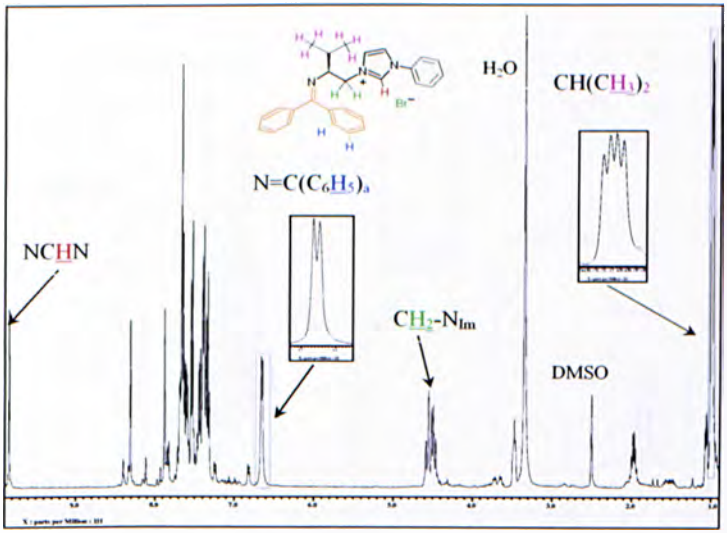


Figure 2.7 ^{1}H NMR spectrum of **26c**.

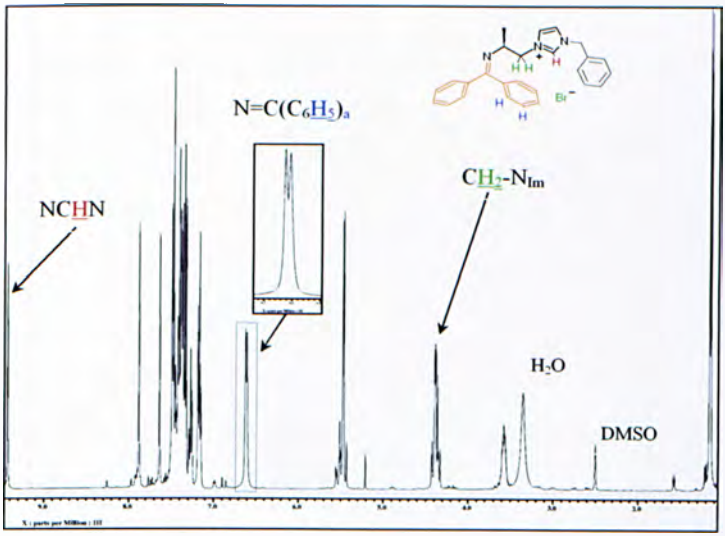


Figure 2.8 ^{1}H NMR spectrum of **25b**.

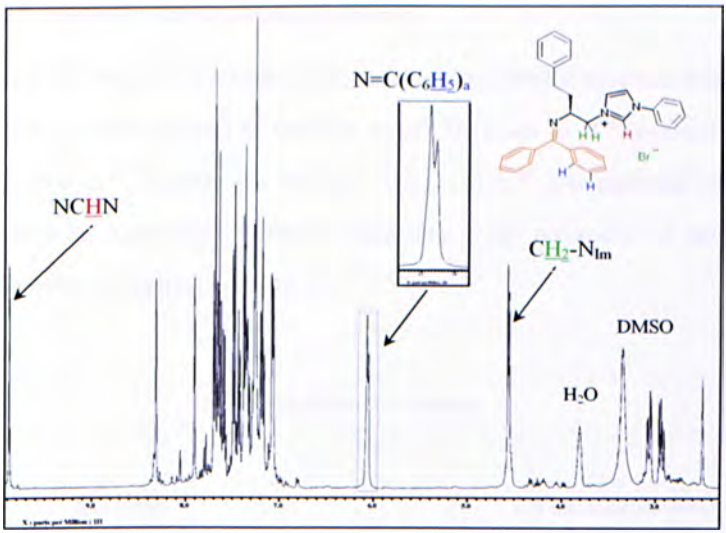


Figure 2.9 ^{1}H NMR spectrum of **26a**.

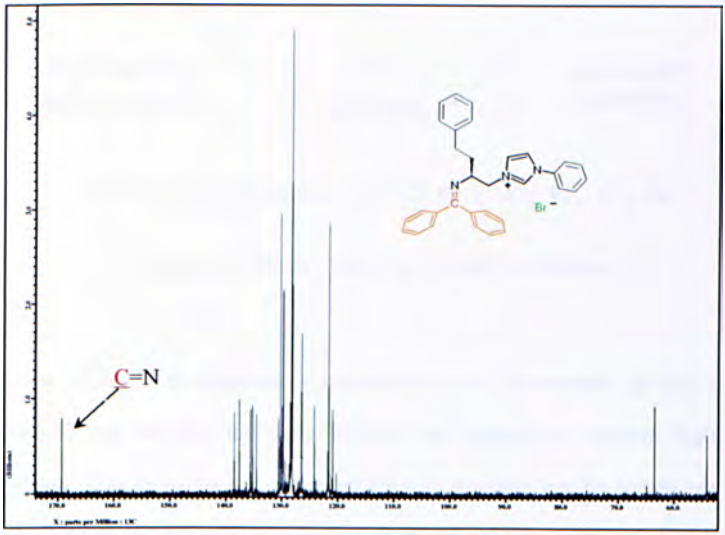


Figure 2.10 ^{13}C NMR spectrum of **26a**.

2.2.7 Synthesis of silver carbene complexes

Silver (I) complexes of *N*-heterocyclic carbenes (Ag(I)-NHCs) have been widely used as NHC transfer reagents to transition metals. Herrmann *et al.*[25], Bertrand *et al.*[26], Arnold *et al.*[27], Garrison and Youngs[28], and Lin *et al.*[29] have published interesting reviews on Ag(I)-NHCs. Different approaches to the preparation of silver-NHC complexes are depicted in Figure 2.11.[29b]

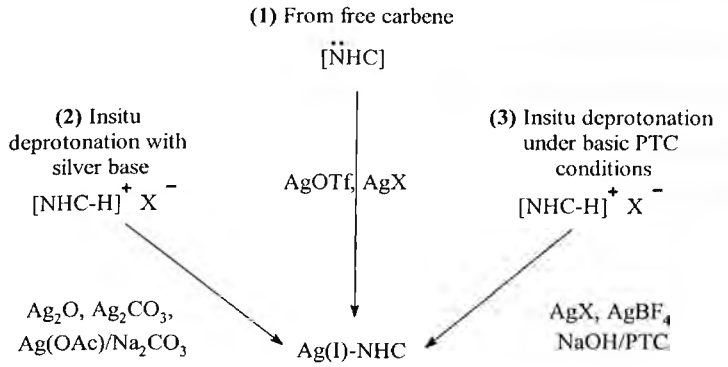
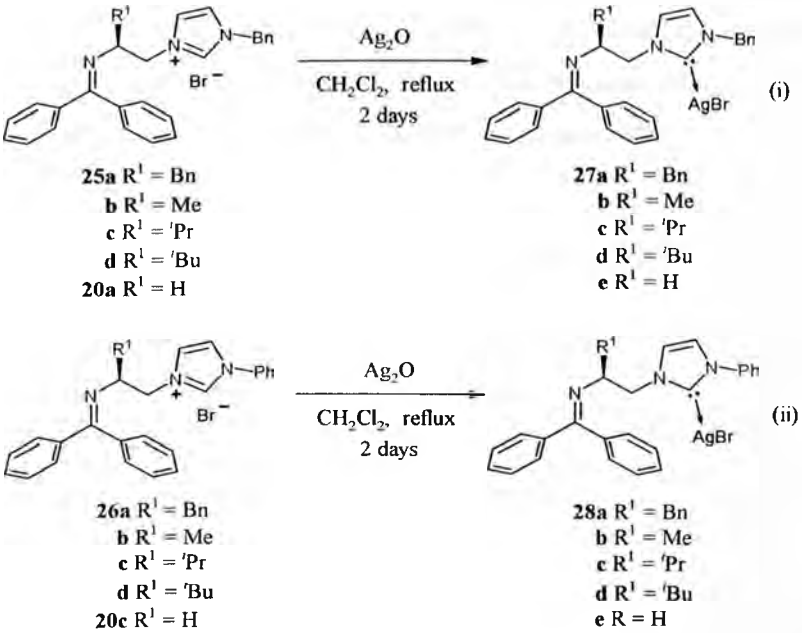


Figure 2.11 Preparation of Ag(I)-NHC complexes.

The use of Ag_2O to deprotonate imidazolium salts, developed by Lin and co-workers,[29a] has become the most widely used method to prepare Ag(I)-NHC complexes. This technique is convenient because reactions can be carried out in air, without solvent pre-treatment and without additional base. It also favours

deprotonation at C^2 carbon with a good tolerance of other active hydrogen atoms. Other methods used to prepare Ag(I)-NHC complexes have generally encountered practical difficulties. Danopoulos *et al.* for instance, reported that the synthesis of Ag(I)-NHC complexes starting from azolium salts required longer reaction times when Ag_2CO_3 was used instead of Ag_2O.[30]

The imidazolium salt **20a** was deprotonated by silver (I) oxide (Ag_2O) in dry CH_2Cl_2 under reflux, in the presence of activated 4 Å molecular sieves.[30,31] The reaction was carried out in the dark to prevent photodecomposition of the silver complex. After 2 days, the achiral silver imidazol-2-ylidene complex **27e** was obtained in good yield (79%). The method was subsequently extended to chiral iminoalkyl *N*-benzyl- and *N*-phenyl imidazolium salts **25a-d** and **26a-d** (Scheme 2.27). The corresponding silver imidazol-2-ylidene complexes **27a-d** and **28a-d** were obtained after 2 days under reflux in the dark (Scheme 2.27, Table 2.3).



25a R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu
20a R^1 = H

27a R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu
e R^1 = H

26a R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu
20c R^1 = H

28a R^1 = Bn
b R^1 = Me
c R^1 = ^{i}Pr
d R^1 = ^{t}Bu
e R = H

Scheme 2.27 Synthesis of chiral imidazol-2-ylidene silver complexes.

Table 2.3 Synthesis of chiral silver imidazol-2-ylidene complexes.

Ag(I)-NHC	Yields (%)	Ag(I)-NHC	Yields (%)
27a	50	**28a**	66
27b	84	**28b**	91
27c	45	**28c**	64
27d	68	**28d**	60
27e	79	**28e**	78

As reviewed by Lin,[29b] the deprotonation of *N*-functionalised monoazolium halides and their coordination to Ag(I) can lead to a variety of structures, including: ion pairs (a), mononuclear neutral complexes (b), halide bridged complexes (c), bridged tetranuclear complexes (d), or biscarbene complexes (e) (Figure 2.12).[29b]

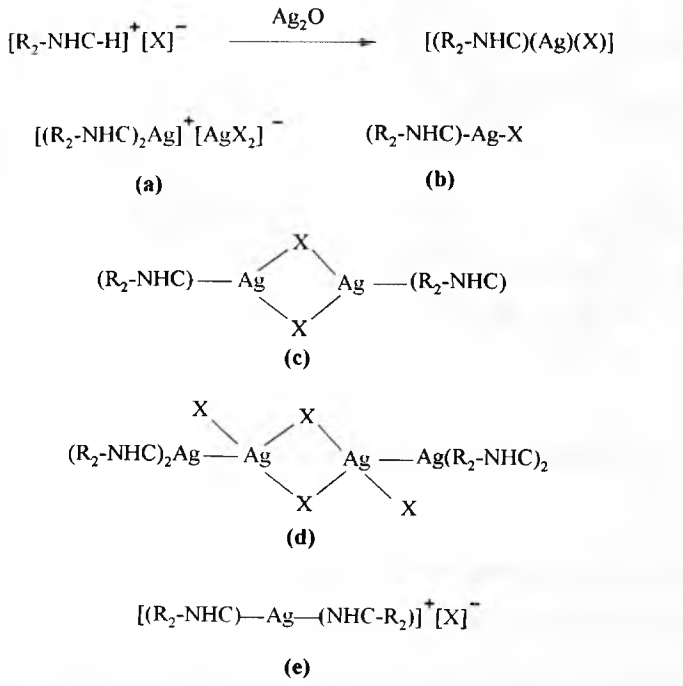


Figure 2.12 Common structures of Ag(I)-NHC complexes obtained from monoazolium salts.

The structure of silver iminoalkyl *N*-substituted imidazol-2-ylidene complex **27e** was deduced from single crystal X-ray diffraction analysis (Figure 2.13). Single crystals of **27e** were grown by slow diffusion of diethyl ether into a saturated equivolume solution of CH_2Cl_2/Et_2O.

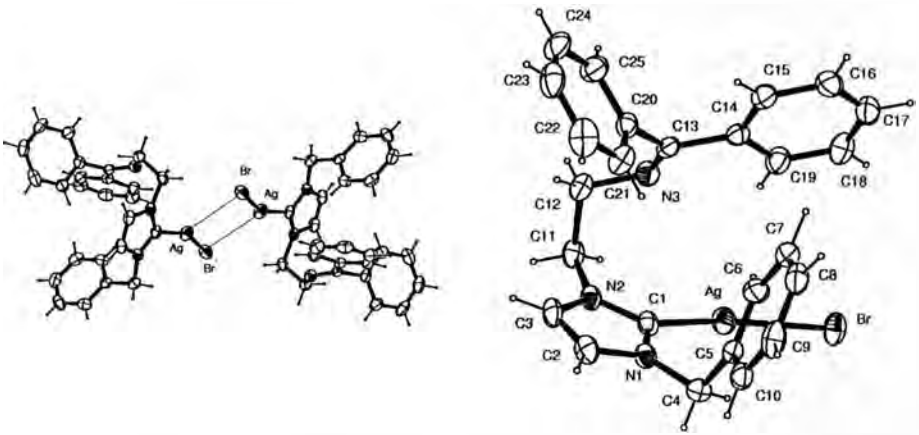


Figure 2.13 X-ray crystal structure of silver carbene complex **27e**.

X-ray crystallographic data of **27e** indicates that the distance between the imine nitrogen (N(3)) and the Ag atom (3.402 Å) is significantly longer than that between the carbene carbon (C(1)) and Ag (2.105 Å) (Table 2.4). Although the imine nitrogen is directed toward the Ag atom, the two atoms are too far away to significantly interact. The structure of **27e** with no imine N(3)-Ag coordination, is in agreement with the general trend of silver to form linear and low coordinate complexes.[32] The orientation of the imine moiety away from the metal centre is assumed to be due to steric hindrance.

The deprotonation of imidazolium salts **20a**, **25a-d** and **26a-d** was evidenced by the disappearance of imidazolium C^2 proton singlet in the ^1H NMR spectra between 9 and 10 ppm (Figure 2.14). The coordination of the carbene carbon to the Ag(I) centre was characterised by ^{13}C NMR. The characteristic C^2 carbon signals of **27a-e** and **28a-d** were generally shifted from c.a. δ 136 ppm for imidazolium compounds, to δ 180 ppm with no apparent coupling between the silver and the carbon atoms (Figure 2.15). The carbene ^{13}C signals were generally not detected for chiral silver iminoalkyl *N*-phenylimidazol-2-ylidene complexes **28**.

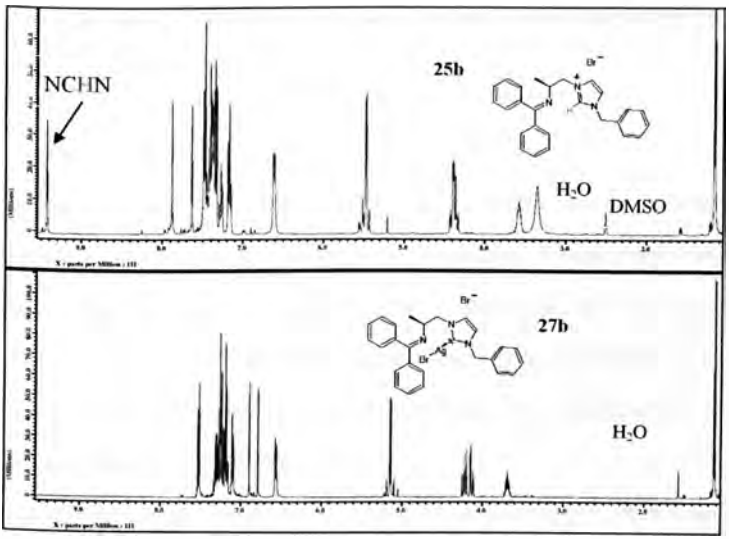


Figure 2.14 ^1H NMR spectra of **25b** and **27b**.

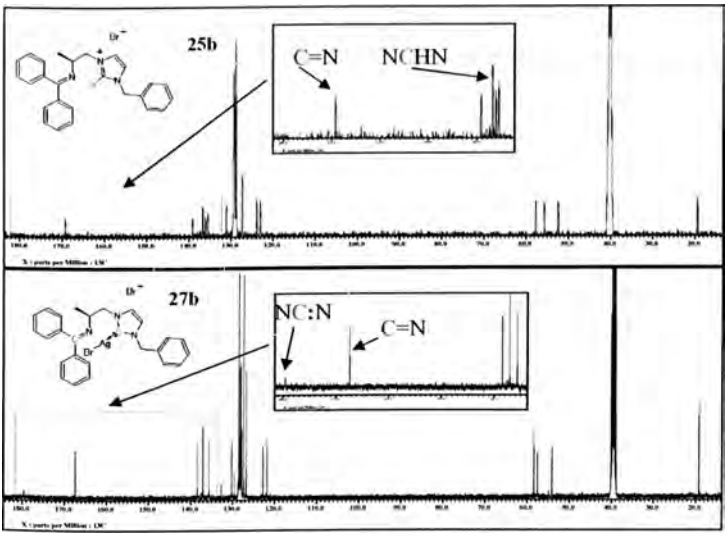
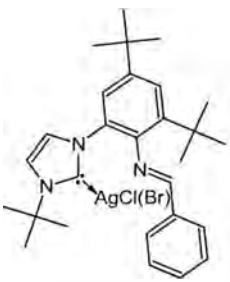


Figure 2.15 ^{13}C NMR spectra of **25b** and **27b**.

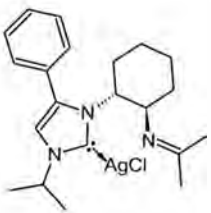
Danopoulos *et al.*[30] and Douthwaite *et al.*[33] reported similar structural and spectroscopic observations for chiral silver iminoalkyl *N*-substituted imidazol-2-ylidene complexes depicted in Figure 2.16. As for compound **27e**, X-ray structures of compounds **29**[30] and **30**[33] indicated mononuclear neutral complexes of type (b) (Figure 2.12). For both compounds, the disappearance of the characteristic C^2 proton singlet was identified by ^{1}H NMR analysis.

No HRMS data were provided for the Ag(I)-NHC complexes. No suitable techniques such as FAB were available amongst the national facilities. Element analysis was not

provided for most of the Ag(I)-NHC complexes. Decomposition of the Ag(I)-NHC complexes was observed (AgBr precipitation) after multiple recrystallisations.



29



30

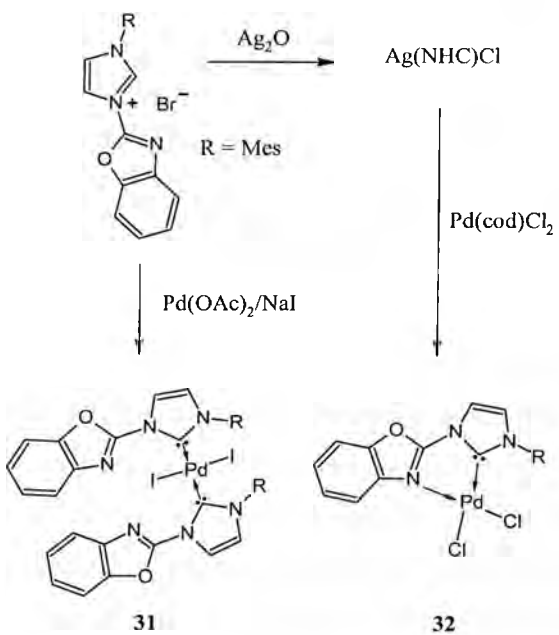
Figure 2.16 Structures of chiral silver iminoalkyl *N*-substituted imidazol-2-ylidene complexes.

The lack[35,36] of Ag(I) – ^{13}C coupling is indicative of labile nature of the NHC ligand in silver complexes.[36] The literature contains many examples of NHC transfer from Ag(I)-NHC complexes to various metal ions such as Au(I), Pd(II), Cu(I), Cu(II), Ni(II), Pt(II), Ir(I), Ir(III), Rh(I), Rh(III), Ru(II), Ru(III) and Ru(IV).[29b] The NHC transfer method has been mainly used to prepare Au(I), Pd(II) and Rh(I)-NHC complexes.

2.2.8 Synthesis of palladium (II) carbene complexes

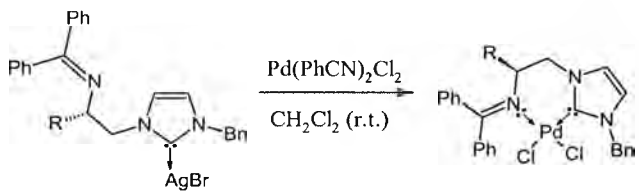
As iminoalkyl imidazol-2-ylidene ligands were designed for palladium-catalysed allylic substitution, the preparation of their palladium (II) complexes was explored in order to investigate their coordination behaviour.

A range of palladium (II) NHC complexes have been prepared by treating $Pd(PhCN)_2Cl_2$ with silver carbene complexes.[31] This method has been proven to be successful in the preparation of palladium complexes with chelating *N*-functionalised ligands. Poyatos *et al.* observed that *N*-oxalate imidazolium salts can be converted to a chelated NHC-Pd(II) complex **32** *via* transmetallation, and to a non-chelated NHC-Pd(II) complex **31** *via* direct metallation (Scheme 2.28).[37] In several cases, the synthesis of Pd(II)-NHCs *via* direct metallation of azolium salts with Pd(OAc), or with other Pd(II) precursors failed.[28b] Therefore, the synthesis of Pd(II)-NHCs complexes *via* transmetallation from Ag(I)-NHC was investigated.



Scheme 2.28 Preparation of Pd(II)-NHC complexes *via* direct metallation and transmetallation.

To assess the chelating ability of the mixed donor imino-NHC ligand, ligand transfer to palladium was explored by reacting silver iminoalkyl *N*-substituted imidazol-2-ylidene complexes **27d** and **27e**, with bis(benzonitrile) palladium(II) dichloride ($Pd(PhCN)_2Cl_2$) in dry dichloromethane, in the dark at room temperature (Scheme 2.29).[31,33] The solution of Ag(I)-NHC reagents changed colour from dark orange, after addition of $Pd(PhCN)_2Cl_2$, to clear yellow suggesting the carbene transfer.



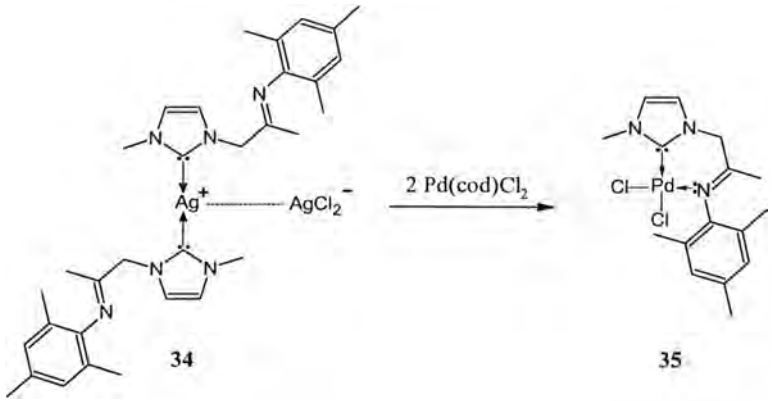
27 d: R = ^{t}Bu
e: R = H

33 a R = ^{t}Bu
b R = H

Scheme 2.29 Palladium carbene complexes expected after NHC transfer from silver complexes **27d-e**.

The products **33a-b** obtained after slow recrystallisation from CH_2Cl_2/hexane were insoluble in most solvents. Although **33a-b** were sparingly soluble in pyridine, NMR characterisation was still possible for **33b**. Attempts to grow X-ray quality crystals were unsuccessful. An indication of imine coordination may be deducible from shift in $\nu_{(C=N)}$ of approximately 10-15 cm^{-1} in accordance with observations made by Tilset *et al.* on complexation of an imino-carbene ligand with palladium.[38] They observed that the C=N stretch absorption in the IR spectrum was shifted from $\nu_{(C=N)}$ = 1665,

1685 cm^{-1} for the Ag(I)-NHC complex **34** (Scheme 2.30) featuring NHC mono-coordination, to $\nu_{(C=N)}$ = 1637 cm^{-1} for the corresponding chelated Pd(II)(imino-NHC)Cl_2 complex **35** (Scheme 2.30). The structure of the Pd(II)(imino-NHC)Cl_2 complex **35** was confirmed by X-ray crystal structure determination.



Scheme 2.30 Preparation of Pd(II)-NHC *via* transmetallation starting using Ag(I)-NHC.

Low Resolution Electrospray Mass Spectroscopy (LRES) of the reaction product derived from **27e** (Figure 2.16), contains a fragment $[M\text{-}Cl]^+$ m/z = 564.1, 562.1; which corresponds to $[Pd(imino\text{-}NHC)Cl]^+$ (Figure 2.17).

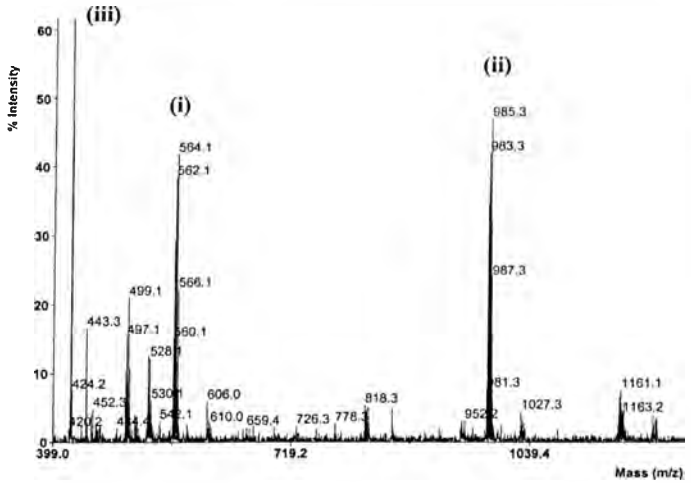


Figure 2.17 LRES of palladium (II) imino-carbene species.

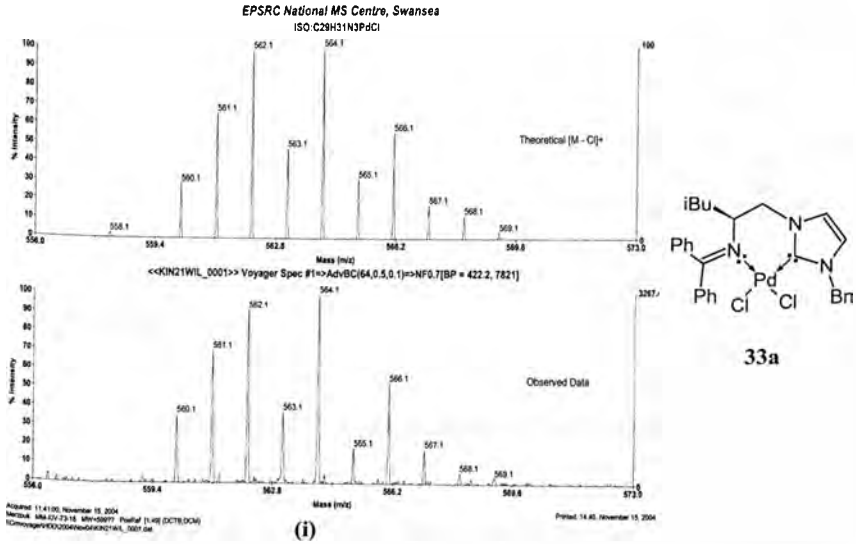
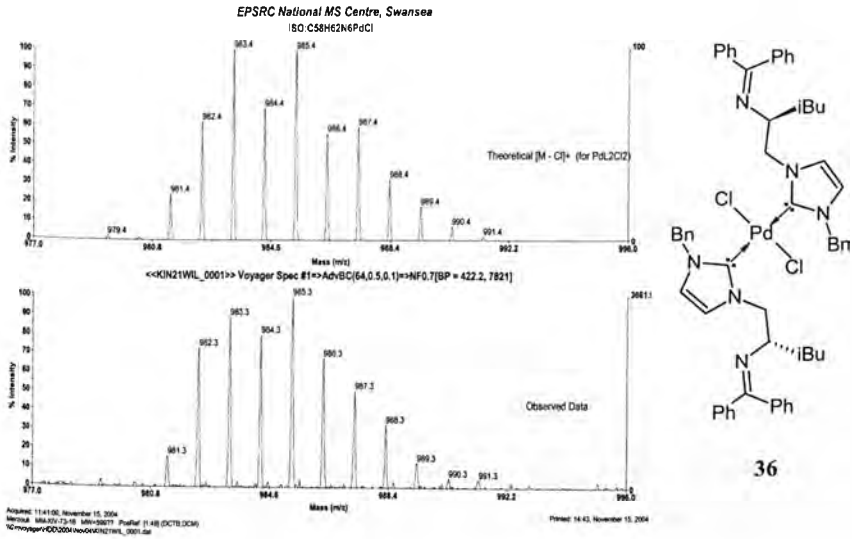


Figure 2.18 LRES of $[Pd(II)(imino\text{-}NHC)Cl]^+$ **[33a-Cl]**$^+$.

However, a signal corresponding to a higher mass species was also observed. The signal observed corresponded to the exact mass of a $[Pd(II)(imino\text{-}NHC)_2Cl]^+$ ion, obtained after loss of Cl^- from **36** (Observed: $[M\text{-}Cl]^+$ m/z = 985.3, 983.3; Theoretical: $[M\text{-}Cl]^+$ m/z = 985.4, 983.4) (Figure 2.19). This suggests that the signal observed for $[M\text{-}Cl]^+$ m/z = 564.1, 562.1 (Figure 2.18), may be due to a mass fragment of the molecular ion $[Pd(II)(imino\text{-}NHC)Cl_2]^+$, resulting from the loss of one imino-NHC ligand.

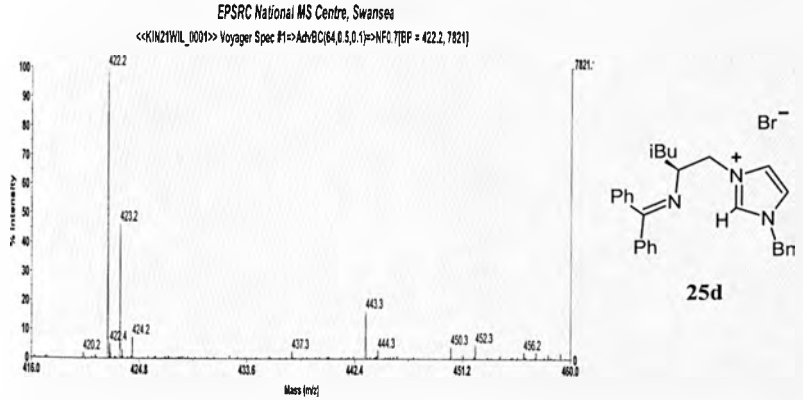


(ii)

Figure 2.19 LRES of $[Pd(II)(imino\text{-}NHC)_2Cl]^+$ **[36-Cl]$^+$**.

The signal observed at m/z = 422.2, 423.2 matches the molecular ion mass of imidazolium salt $[(imino\text{-}NHC)+H]^+$ (Theoretical: m/z = 422.3, 423.3), obtained after

protonation of the carbene ligand (Figure 2.20). These observations further supported the suggestion that ligand may not be chelated to palladium.



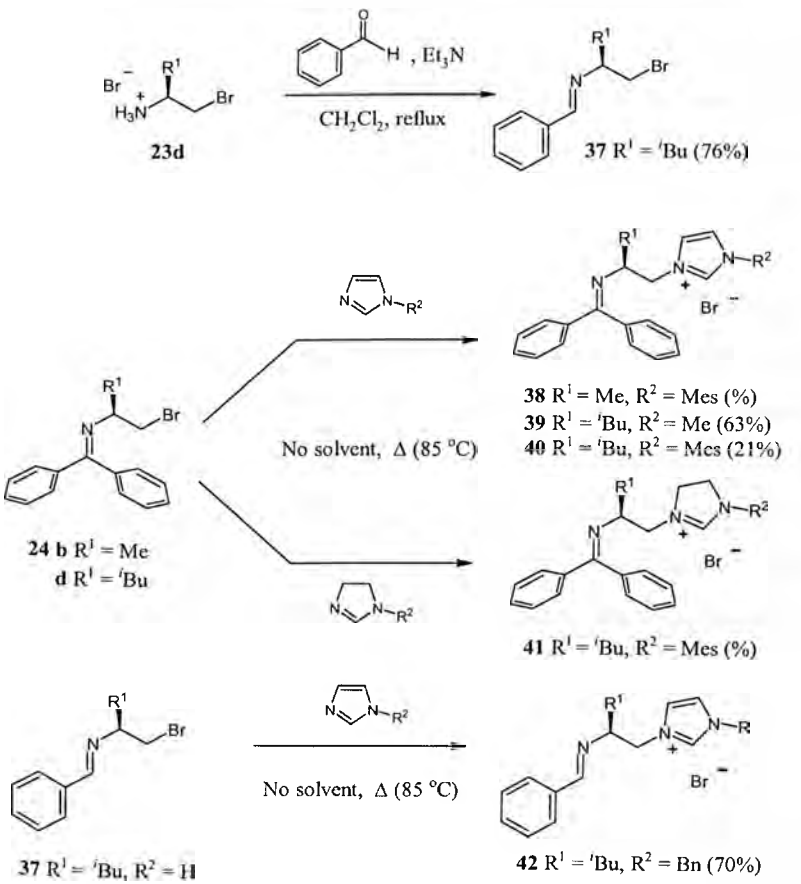
(iii)

Figure 2.20 LRES of imidazolium salt [(imino-NHC)+H]$^+$ [**25d-Br**]$^+$.

2.2.9 Synthesis of additional ligand precursors for catalysis

To optimise enantioselectivity in asymmetric catalysed reactions (i.e. allylic substitution and conjugate addition), an additional range of chiral imidazolium, imidazolinium salts and silver carbene complexes were synthesised. Chiral iminoalkyl bromide **37** was prepared by reacting **23d** with benzaldehyde in dry CH_2Cl_2 under reflux, in the presence of activated 4 Å molecular sieves (Scheme 2.31).[17b] Chiral imidazolium salts **38** – **40** were prepared after *N*-alkylation of 1-methyl- and 1-mesityl imidazoles using chiral iminoalkyl bromides **24b** and **24d** at 85 °C without solvent

(Scheme 2.31). Solvent-free conditions were also used to synthesise the chiral iminoalkyl *N*-mesitylimidazolinium salt **41** starting from **24d**. The chiral iminoalkyl bromide **37** was reacted with 1-benzylimidazole *via N*-alkylation to yield **42** (Scheme 2.31).

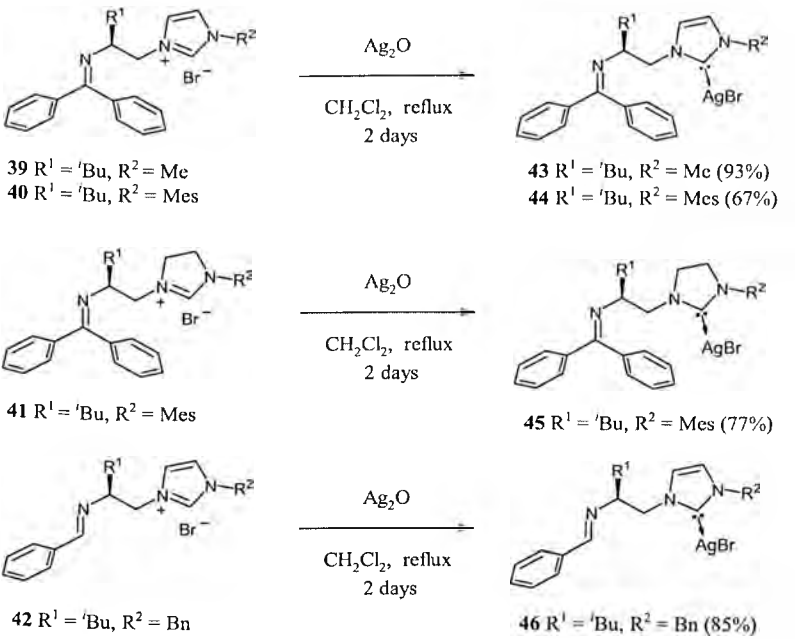


Scheme 2.31 Synthesis of additional chiral iminoalkyl *N'*-substituted imidazolium and imidazolinium salts.

The imine bond formation for compound **37** was confirmed by ^{1}H NMR analysis, with a singlet at δ 8.28 ppm attributed to N=C**H**C_6H_5. ^{13}C NMR also indicated the imine bond formation with the signal observed at δ 169.9 ppm, attributed to the imine carbon.

Imidazolium and imidazolinium salts (**38 – 42**) were characterised by ^{1}H NMR, with C^2 proton singlet signals appearing between δ 9.92 and 10.19 ppm. Diastereotopic methyl groups in imidazolium salts derived from leucine (**39 – 42**), appeared as a pair of doublets between δ 0.60 and 1.04 ppm. Conservation of the imine double bond after *N*-alkylation reactions was confirmed by ^{13}C NMR analysis, showing C=N carbon signals between δ 162.6 and 169.8 ppm.

Chiral iminoalkyl *N*-substituted imidazolium (**38, 39, 40** and **42**) and imidazolinium (**41**) salts were subsequently deprotonated by silver (I) oxide (Ag_2O) in dry CH_2Cl_2 under reflux, in the presence of activated 4 Å molecular sieves. The silver carbene complexes **43 – 46** were obtained in satisfactory yields (Scheme 2.32).[31,33] The C^2 deprotonation was inferred from C^2 proton signal disappearance in ^{1}H NMR spectra. The carbene carbon signal was generally visible at around δ 180 ppm in the ^{13}C NMR spectra. Diastereotopic methyl groups were observed as two separate doublet signals between δ 0.76 and 0.93 ppm.



39 R^1 = ^{t}Bu, R^2 = Me
40 R^1 = ^{t}Bu, R^2 = Mes

43 R^1 = ^{t}Bu, R^2 = Me (93%)
44 R^1 = ^{t}Bu, R^2 = Mes (67%)

41 R^1 = ^{t}Bu, R^2 = Mes

45 R^1 = ^{t}Bu, R^2 = Mes (77%)

42 R^1 = ^{t}Bu, R^2 = Bn

46 R^1 = ^{t}Bu, R^2 = Bn (85%)

Scheme 2.32 Synthesis of additional chiral silver NHC complexes.

2.3 Conclusion

Different routes to synthesise iminoalkyl *N*-substituted imidazolium salts have been investigated. The synthesis of a range of chiral iminoalkyl *N*-aryl and *N*-alkyl substituted imidazolium salts was achieved. Chiral silver imidazol-2-ylidene complexes were readily generated by deprotonation of chiral iminoalkyl *N*-substituted imidazolium salts using silver (I) oxide. They were isolated but accurate elemental

analysis data were not obtained for some of them. Nonetheless, in subsequent catalytic reactions, Ag_2O was used to deprotonate chiral imidazolium salts to generate imidazolylidenes for co-ordination to palladium in Chapter 3. The modular design allowed for variation of R^1, R^2, R^3 and R^4 (Figure 2.2) and fine tuning of ligand structure for application in enantioselective allylic alkylation and conjugate addition. Attempts to isolate palladium complexes **33a-b** (Scheme 2.29) were unsuccessful. Infra red measurements did provide some evidence of iminoalkyl imidazol-2-ylidene ligands chelating to palladium.

2.4 References

1. *Catalytic Asymmetric Synthesis*, I. Ojima (eds), Wiley VCH, New York, 2000.
2. W. A. Herrmann, *Angew. Chem. Int. Ed. Engl.*, 2002, **41**, 1290.
3. a) O. Navarro, R. A. Kelly, S. P. Nolan, *J. Am. Chem. Soc.*, 2003, 125, 16194; b) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem. Int. Ed. Engl.*, 2003, **42**, 3690.
4. T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.
5. M. C. Perry, X. Cui, M. T. Powell, D.-R Hou, J. H. Reibenspies, K. Burgess, *J. Am. Chem. Soc.*, 2003, **125**, 113.
6. L. G. Bonnet, R. E. Douthwaite, B. M. Karuiki, *Organometallics*, 2003, **22**, 4187.
7. A. Pfaltz, J. Blankestein, R. Hilgraf, E. Hormann, S. Mcintyre, F. Menges, M. Schonleber, S. P. Smidt, B. Wustenberg, N. Zimmermann, *Adv. Synth. Catal.*, 2003, **345**, 33.
8. a) G. J. Dawson, C. G. J. M. J. Williams, *Tetrahedron Lett.*, 1993, **34**, 3149; b) A. Saitoh, K. Achiwa, K. Tanaka, T. Morimoto, *J. Org. Chem.*, 2000, **65**, 4227.
9. G. Helmchen, A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336.
10. R. Duddu, M. Eckhardt, M. Furlong, H. P. Knoess, S. Berger, P. Knochel, *Tetrahedron*, 1994, **50**, 2415.

11. a) R. Appel, *Angew. Chem. Int. Ed.*, 1975, **14**, 801; b) C. Hunter, R. F. W. Jackson, H. K. Rami, *J. Chem. Soc., Perkin Trans. 1*, 2000, 219.
12. R. Caputo, E. Cassano, L. Longobardo, G. Palumbo, *Tetrahedron*, 1995, **51**, 12337.
13. D. A. Quagliato, P. M. Andrea, E. M. Matelan, *J. Org. Chem.*, 2000, **65**, 5037.
14. T. Hayashi, M. Konishi, M. Fukushima, K. Kanchira, T. Hioki, M. Kumada, *J. Org. Chem.*, 1983, **48**, 2195.
15. V. T. Myllymäki, M. K. Lindvall, A. M. P. Koskinen, *Tetrahedron*, 2001, **57**, 4629.
16. H. Higashirua, H. Morino, H. Matsuura, Y. Toyomaki, K. Ienaga, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1479.
17. a) N. De Kimpe, K. De Smaele, *Tetrahedron Lett.*, 1994, **35**, 8023; b) N. De Kimpe, K. De Smaele, *Tetrahedron*, 1995, **51**, 2387; c) N. De Kimpe, D. De Smaele, P. Bogaert, *Synlett*, 1994, 287; d) N. De Kimpe, R. Jolie, D. De Smaele, *J. Chem. Soc., Chem. Commun.*, 1994, 1221; e) N. De Kimpe, D. De Smaele, Z. Szakonyi, *J. Org. Chem.*, 1997, **62**, 2448.
18. V. K. Aggarwal, I. Emme, A. Mereu, *Chem. Commun.*, 2002, 1612.
19. J. S. Hine, S. Isaacs, *Tetrahedron Lett.*, 1986, **41**, 5007.
20. J. Hine, Y.-J Chen, *J. Org. Chem.*, 1987, **52**, 2091.
21. I. M., Kolthoff, J. K. Chantooni, S. J. Bhowmik, *J. Am. Chem. Soc.* **1968**, *90*, 23.
22. A. Salgado, M. Boeykens, C. Gauthier, J.-P. Declercq, N. De Kimpe, *Tetrahedron*, 2002, **58**, 2763.
23. D. Bogdal, J. Pielichowski, K. Jaskot, *Heterocycles*, 1997, **45**, 715.
24. J. M. López-Pestaña, M. J. Ávila-Rey, R. M. Martin-Aranda, *Green Chemistry*, 2002, **4**, 628.
25. T. Weskamp, V. P. W. Böhm, W. A. Herrmann, *J. Organomet. Chem.*, 2000, **600**, 12.
26. D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.*, 2000, **100**, 39.
27. P. L. Arnold, *Heteroatom Chem.*, 2002, **13**, 534.
28. J. C. Garrison, W. J. Youngs, *Chem. Rev.*, 2005, **105**, 3978.
29. a) I. J. B. Lin, C. S. Vasam, *Comment. Inorg. Chem.*, 2004, **25**, 75; b) I. J. B. Lin, C. S. Vasam, *Coord. Chem. Rev.*, 2007, **251**, 642.

30. A. A. D. Tulloch, A. A. Danopoulos, S. Winston, S. Kleinhenz, G. Eastham, *Dalton Trans.*, 2000, 4499.

31. K. S. Coleman, H. T. Chamberlayne, S. Turberville, M. L. H. Green, A. R. Cowley, *Dalton Trans.*, 2003, 2917.

32. G. Van Koten, S. L. James, J. T. B. H. Jasrzebski, Copper and Silver. In *Comprehensive Organometallic Chemistry*; E. W. Abel, F. G. A. Stone, G., Wilkinson, Eds.; Pergamon Press: Oxford, 1995; Vol. 3, p. 57.

33. L. G. Bonnet, R. E. Douthwaite, B. M. Kariuki, *Organometallics*, 2003, **22**, 4187.

34. (a) J. C. Garrison, R. S. Simons, J. M. Talley, C. Wesdemiotis, C. A. Tessier, W. J. Youngs, *J. Organomet. Chem.*, 2001, **20**, 1276; b) A. Malaiye, Z. Sun, K. Hindi, A. Milsted, D. Ely, D. H. Reneker, C. A. Tessier, W. J. Youngs, *J. Am. Chem. Soc.*, 2005, **127**, 2285.

35. X. Hu, Y. Tang, P. Gantzel, K. Meyer, *Organometallics*, 2003, **22**, 612.

36. H. M. J. Wang, I. J. B. Lin, *Organometallics*, 1998, **17**, 972.

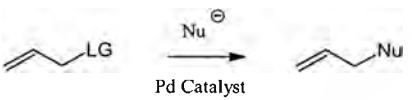
37. M. Poyatos, A. Maisse-Francois, S. Bellemin-Laponnaz, L. H. Gade, *Organometallics*, 2006, 25, 300.

38. M. Frøseth, A. Dhindsa, H. Røise, M. Tilset, *Dalton Trans.*, 2003, 4516.

3. Enantioselective palladium-catalysed allylic substitution

3.1 Introduction

Transition metal catalysed asymmetric synthesis using chiral ligands has become more and more important in organic chemistry. In 1973, Trost *et al.* reported a palladium-mediated allylic alkylation[1], and the application of chelating bisphosphine ligands in stoichiometric asymmetric allylic substitution.[2] A few years later, Trost[3,4] and Tsuji[5] reported a catalytic process (Scheme 3.1).



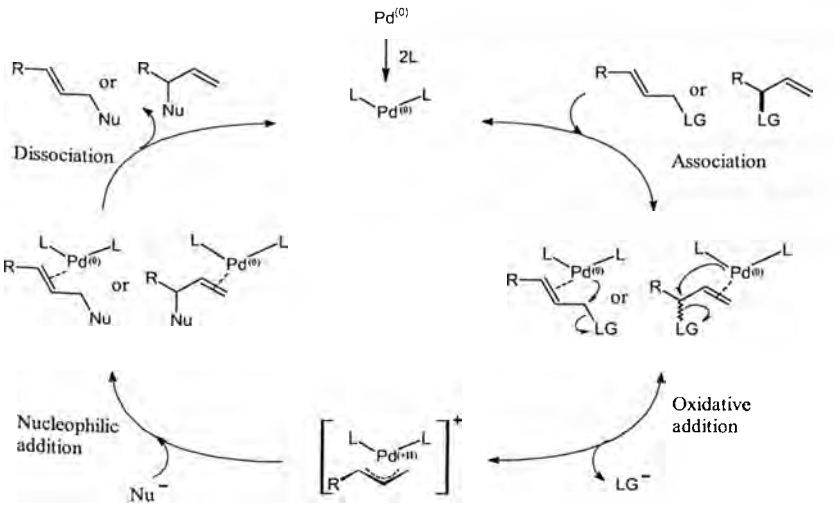
Scheme 3.1 Palladium-catalysed allylic substitution.

The most commonly used transition metal in enantioselective allylic substitution is palladium (Pd); however, the use of other transition metals such as Mo, W, Ir, Pt and Ni has also been reported.[6]

3.1.1 Mechanism of palladium-catalysed allylic substitution

The established mechanism is described in Scheme 3.2.[6] The first step of the catalytic process is the formation of an η^2-alkene $Pd^{(0)}$ complex obtained after association of the allyl substrate with a palladium(0) species.[7] The subsequent step is the oxidative

addition to $Pd^{(0)}$ that affords a π-allyl $Pd^{(II)}$ intermediate after displacement of the leaving group (LG). In the presence of neutral ligands such as phosphines, the cationic intermediate species, identified by spectroscopic[8], crystallographic[9] and NMR[10] analyses, is more reactive to nucleophilic addition.[11] Nucleophilic addition takes place at either terminus of the allyl group to generate a $Pd^{(0)}$ alkene species. Finally, the alkene product dissociates from the palladium centre and the $Pd^{(0)}$ catalyst is regenerated.

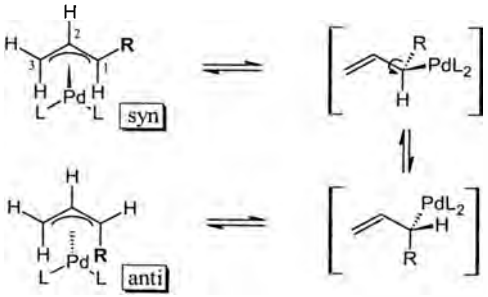


Scheme 3.2 Catalytic cycle of palladium-catalysed allylic substitution.

Alkene association is reversible as is oxidative addition if the leaving group (LG) is a good nucleophile, such as the acetate ion.[12] Oxidative addition and nucleophilic attack both take place with inversion of configuration leading to an overall retention of

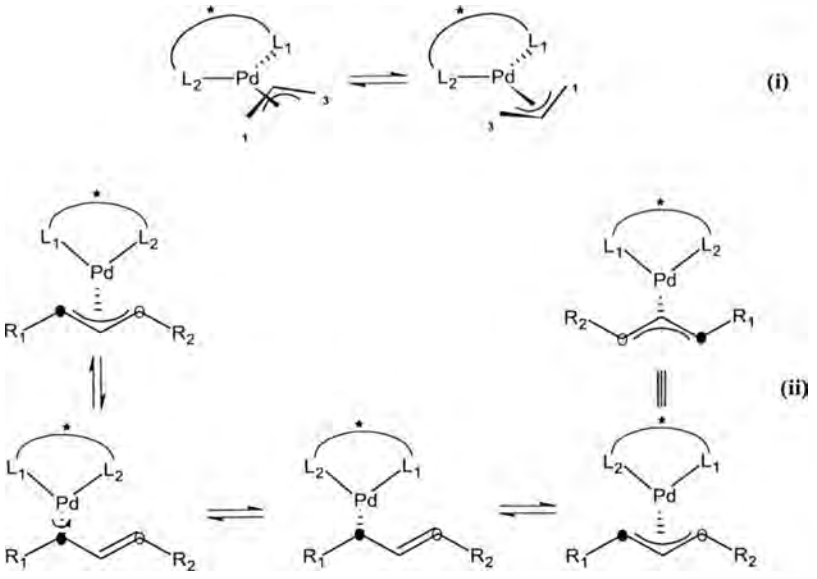
stereochemistry. The mechanism is in fact more complicated since the η^3-π-allyl $Pd^{(+II)}$ complex is involved in a number of dynamic equilibrium processes. The processes of particular interest are π-σ-π isomerisation and an apparent allyl rotation processes.[13] The rates of these processes are usually faster or comparable to that of the nucleophilic addition, which means that the nucleophilic attack generally takes place under Curtin-Hammett conditions.

The π-σ-π (η^3-η^1-η^3) isomerisation, also called *syn/anti* interconversion, occurs *via* rotation around the carbon-carbon σ-bond in the η^1-π-allyl $Pd^{(+II)}$ intermediate (*syn* and *anti* correspond to the position of the substituents relative to the C^2 carbon) (Scheme 3.3). This process is also an *endo/exo* isomerisation because the direction of the bond between the central allylic carbon and its protons changes. Further rotation normally leads to the *anti/anti*-isomer. However, with substrates featuring large **R** substituents such as phenyl groups, the *syn/syn*-isomer is strongly favoured due to steric hindrance. Cyclic substrates are restrained to the *anti/anti* conformation.



Scheme 3.3 π-σ-π isomerisation.

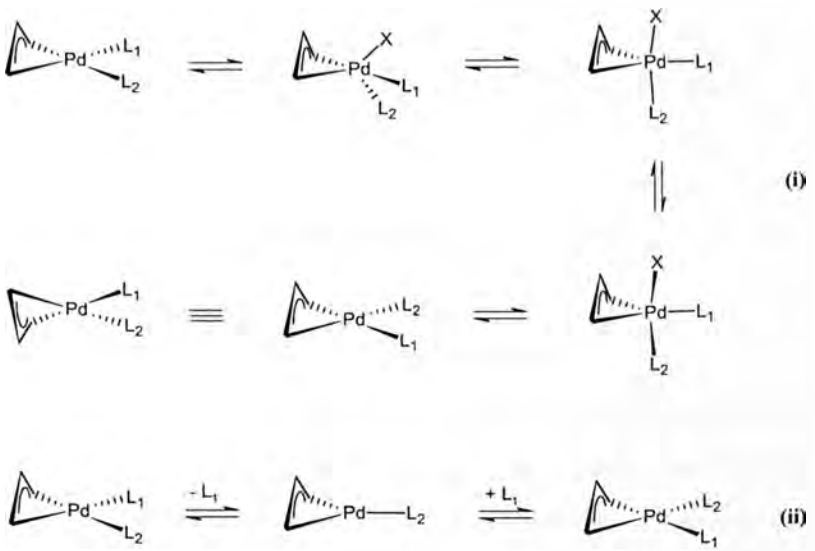
In the apparent allyl rotation, the two termini of the allyl group are exchanged with respect to the two other coordination sites (Scheme 3.4 (i)). In this process, the central allyl carbon is displaced from one side of the coordination plane to the other. This explains why the apparent allyl rotation is also described as an *endo/exo* isomerisation. If the ligands L_1 and L_2 are different, as in unsymmetrical or C_1-symmetrical chiral bidentate mixed donor ligands, isomerisation leads to a diastereoisomeric allyl complex, even if the groups on each of the allyl termini are identical. The two diastereoisomers can undergo nucleophilic addition with different rates and regioselectivities. Therefore, the relative rate of the apparent allyl rotation between the two diastereoisomers can control the distribution of allylic substitution products (i.e. enantiomeric excess). On the other hand, if L_1 and L_2 are identical, as in C_2-symmetrical chiral bidentate ligands, η^3-π-allyl $Pd^{(+II)}$ intermediates in equilibrium *via* apparent allyl rotation will be identical. In this particular case, the apparent allyl rotation process does not influence the outcome of the reaction.



Scheme 3.4 Apparent allyl rotation.

Several mechanisms have been suggested for the apparent allyl rotation. One of them involves a combination of π-σ-π isomerisation with rotation around the palladium-carbon bond in the η^1-π-allyl $Pd^{(II)}$ intermediate (Scheme 3.4 (ii)).[14] Another mechanism involves coordination of external ligands such as anions (X = Cl^-, F^-, etc.) or polar solvents (X = DMSO, MeCN, etc.) to the pseudo-square planar allyl palladium (II) complex. The "pentacoordinated" complex formed subsequently undergoes geometrical modification *via* pseudorotation (Scheme 3.5 (i)).[15] Unlike π-σ-π isomerisation, the η^3-coordination mode of the π-allyl group to the $Pd^{(+II)}$ remains unchanged during the entire process. A third mechanism involves formation of a

tricoordinated η^3-π-allyl $Pd^{(+II)}$ complex. One ligand is successively dissociated and re-associated to the palladium (II) atom, leading to the allyl rotation isomer (Scheme 3.5 (ii)).[16]



Scheme 3.5 Mechanisms suggested for apparent allyl rotation.

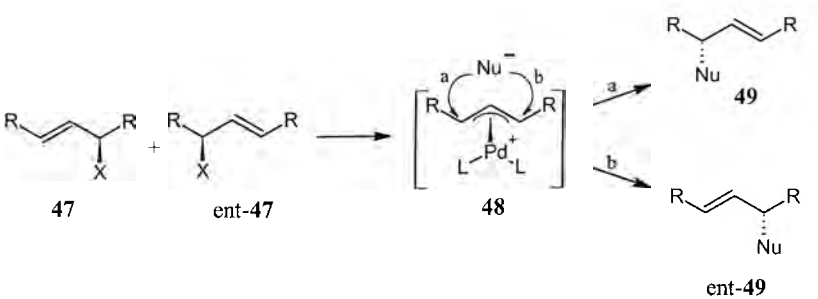
Another type of isomerisation through a metal exchange reaction is depicted in scheme 3.6.[17] The $Pd^{(0)}$ complex can react with the electrophilic allyl group in the η^3-π-allyl $Pd^{(+II)}$ species *via* an S_N2 substitution route. Addition of the $Pd^{(0)}$ results in $Pd^{(II)}$ displacement on the backside, and inversion of configuration at all three carbon atoms (enantioface exchange). Unlike the apparent allyl rotation, this process does not change the configuration of the allyl group. However, this process depends on the

concentration of palladium species being lower than that of substrate and nucleophile. Therefore, isomerisation by allyl exchange is usually slower than the product formation, or does not even occur.

Scheme 3.6 Metal exchange isomerisation.

3.1.2 The (*E*)-1,3-diphenylprop-2-en-1-ylacetate substrate

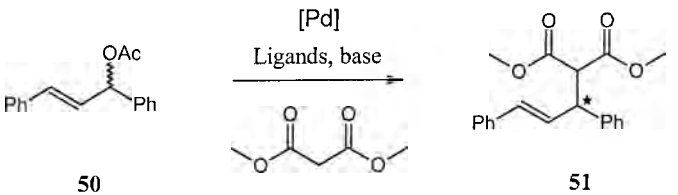
There are many ways to achieve enantiocontrol in palladium-catalysed allylic substitution. The choice of an adequate substrate is an important matter to consider. Symmetrically substituted substrates ($R_1 = R_2$) are commonly employed to evaluate ligand performance in asymmetric allylic substitution. The same *meso*-η^3-π-allyl $Pd^{(+II)}$ complex (**48**) is formed starting from either enantiomer (**47** or ent-**47**) (Scheme 3.7). The two faces of the resulting allyl group in the η^3-π-allyl $Pd^{(+II)}$ intermediate (**48**) are enantiotopic. If the catalyst used is chiral, the two termini of the allyl group become diastereotopic. The resulting termini are likely to differ in terms of reactivity towards nucleophiles. The use of suitable ligands (L) attached to the palladium will influence the regioselectivity of nucleophilic attack, favouring one enantiomer (**49**) or the other (ent-**49**) (Scheme 3.7). The standard test substrate is (*E*)-1,3-diphenylprop-2-en-1-ylacetate (R = Ph, X = OAc).



Scheme 3.7 Allylic substitution *via meso*-complexes.

3.1.3 The nucleophile

Many different carbon and heteroatom nucleophiles have been used in transition metal-catalysed allylic substitutions.[18] The most commonly employed are of the type $RXYC^-$, where the carbanion is stabilised by X and Y π-acceptors. The basicity of the nucleophile plays an important role in the catalytic mechanism. Indeed, the mechanism described in Scheme 3.2 only holds for "soft" nucleophiles with pKas < 25.[6] These attack at the allyl face opposite to the palladium. "Hard" nucleophiles on the other hand, characterised by pKas > 25 (e.g. organozinc reagents), directly coordinate to the metal. Coordination is followed by intramolecular transfer to the allyl group with retention of configuration.[19] Addition of dimethyl malonate to *rac*-(*E*)-1,3-diphenylprop-2-en-1-ylacetate (**50**) has become a benchmark reaction to evaluate ligands in enantioselective allylic substitution (Scheme 3.8).

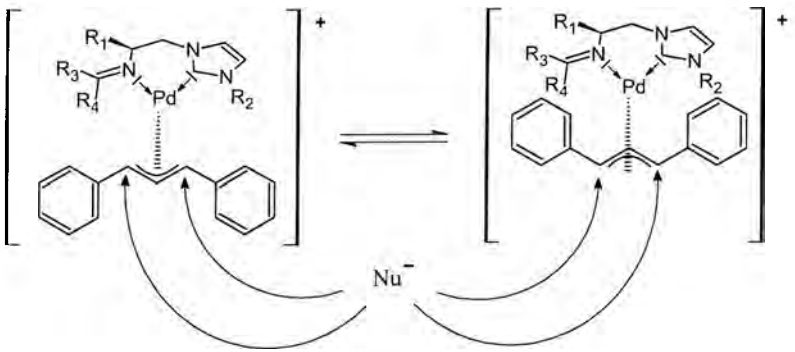


50 51

Scheme 3.8 A typical asymmetric allylic substitution reaction.

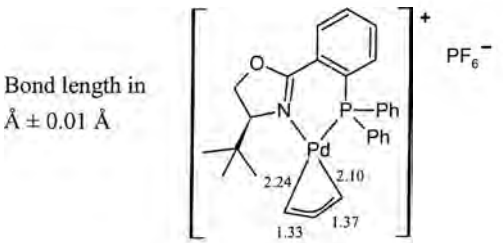
3.1.4 Asymmetric induction

The ligands designed in this work are commonly described as bidentate C_1-symmetric (or unsymmetrical) ligands. The mechanism rationalising asymmetric induction using this type of ligands is not straightforward. Having a good knowledge of the transition state nature is essential to understand the origin of enantiocontrol. Bosnich *et al.* strongly suggested that the substitution reaction proceeds through an early transition state.[20] His argument was based on the fact that the π-allyl palladium (II) complex energy is higher than that of the product. Under these conditions, the transition state resembles the π-allyl complex according to the Hammond postulate.[21] As a result, the nucleophile preferably attacks the most electrophilic terminus of the most reactive π-allyl palladium complex intermediate. The formation of two isomeric (*exo* and *endo*) η^3-π-allyl palladium (II) intermediates complicates the analysis (Scheme 3.4). Indeed, the two π-allyl palladium (II) complexes can both be attacked at the two termini of the allyl group. Four different pathways are then possible; two leading to the (*R*)-enantiomer of the product and two to the (*S*)-enantiomer (Scheme 3.9).



Scheme 3.9 Possible nucleophilic attack pathways.

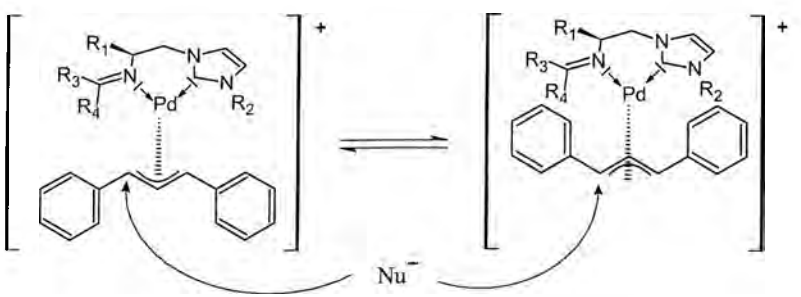
Extensive NMR[22a,23] studies and X-ray[24,25] analyses have given an insight into the mechanism involved using C_1-symmetric bidentate mixed-donor ligands. The crystal structure of a typical chiral C_1-symmetric PHOX (phosphinooxazoline)-π-allyl palladium complex **52** depicted in Figure 3.1, revealed electronic differentiation at the π-allyl termini.[22,23] The Pd-C bond *trans* to the phosphorus is longer (2.24 Å) than the Pd-C bond *trans* to the nitrogen (2.10 Å), highlights the greater *trans* influence of the phosphorus. Preferential nucleophilic attack at the allyl terminus carbon *trans* to the donor featuring the strongest *trans* influence (phosphine atom), is strongly supported by NMR[22a] and computational[26,27] studies.



52

Figure 3.1 X-ray crystal structure of an allyl-palladium complex bearing a PHOX ligand.

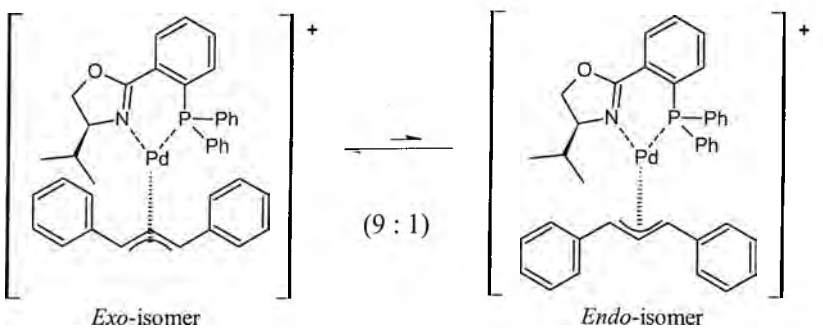
NHCs, like phosphines, present strong *trans*-influence properties. As a result, the nucleophile is expected to preferably attack at the terminus *trans* to the NHC donor (Scheme 3.10).



Scheme 3.10 Expected nucleophilic attack *trans* to the carbon carbene using chiral C_1-symmetric bidentate imino-carbene ligands.

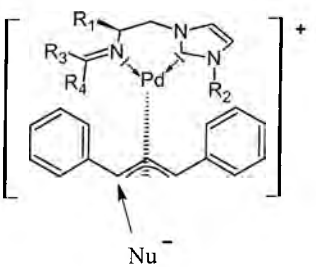
The equilibrium between the *exo*- and *endo*-π-allyl complexes remains a barrier to higher enantioselectivities. Steric effects are required to favour either *endo*- or *exo*-η^3-

π-allyl palladium (II) allyl intermediates. According to NMR studies on PHOX ligand intermediates, *exo*- and *endo*-isomers coexist in a rapid equilibrium, with the *exo*-isomer being the more stable one (Scheme 3.11).[22a] The interaction between the allyl group and the equatorial phosphine phenyl substituent is assumed to be the main factor influencing reaction enantioselection. The stereogenic centre in the oxazoline moiety and the axial phosphine phenyl substituent were found to be too far from the allyl group.



Scheme 3.11 Exo/endo interconversion observed with a PHOX ligand.

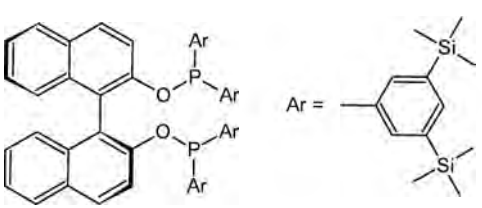
Based on these observations, it is possible to predict at which π-allyl terminus the nucleophile is most likely to attack. The proposed structure of the *exo*-η^3-π-allyl palladium (II) complex intermediate is depicted in Scheme 3.12, with the nucleophile approaching the π-allyl terminus carbon *trans* to NHC donor. Under these conditions, the product (**51**-(*R*)) is expected to be preferably formed.



Scheme 3.12 Proposed η^3-π-allyl palladium (II) complex intermediate.

3.1.5 Ligands and catalysts used in palladium-catalysed allylic substitution

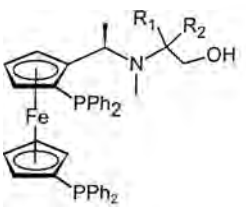
Early ligand design focussed on the synthesis of bulky ligands that would block the approach of a nucleophile at one of the terminal positions of the allyl group (Figure 3.2).[28] C_2-symmetric phosphite ligand **53** exhibited enantiomeric excesses of up to 69% in allylic substitution.



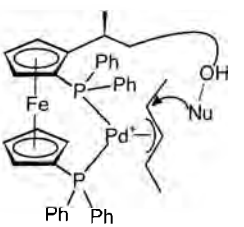
53

Figure 3.2 Chiral bidentate phosphine ligands used in asymmetric allylic substitution.

The bifunctional phosphinoferrocene ligands **54a-c** were designed to interact with the incoming nucleophile *via* hydrogen bonding with the hydroxyalkyl group present on the side chain (Figure 3.3).[29] The approaching nucleophile is preferentially directed to one of the termini. High enantioselectivities (96% e.e.) were obtained using **54c**.



54a $R_1 = R_2 = H$
54b $R_1 = H$, $R_2 = CH_2OH$
54c $R_1 = R_2 = CH_2OH$



55

Figure 3.3 Bifunctional bisphosphine ligands developed by Hayashi *et al.*[29]

Pfaltz *et al.* reported the synthesis and application of C_2-symmetric ligands designed to sterically distort the allyl group in η^3-π-allyl palladium (II) intermediates.[30] The repulsion between R and R' results in one palladium-carbon bond being longer and weaker than the other, as supported by X-ray crystal structure studies.[30] Thus, nucleophilic attack is favoured at this site (Figure 3.4).

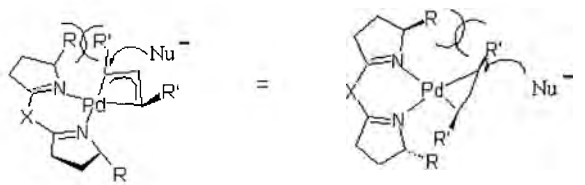


Figure 3.4 Influence of steric effects on enantioselectivity

Other examples of successful bidentate C_2-symmetric nitrogen-based ligands in enantioselective allylic substitution are depicted in Figure 3.5. High enantioselectivities were observed using **56** (95% e.e.) and **57** (97% e.e.).[30,31]

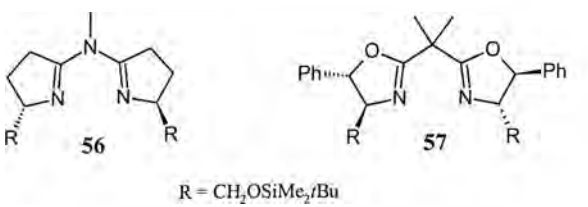
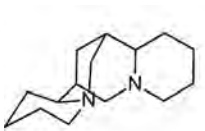
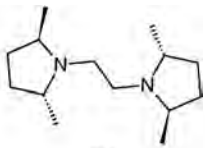


Figure 3.5 C_2-symmetric bidentate nitrogen ligands designed by Pfaltz *et al.*[31]

There are other classes of C_2-symmetric bidentate ligands, which apparently do not interact with the nucleophile or sterically hinder its approach to one of the allylic termini. Bidentate nitrogen ligands **58**[32] and **59**[33] for instance, have demonstrated good stereocontrol in palladium-catalysed allylic substitution, respectively leading to enantioselectivities of 85% and 91% e.e. (Figure 3.6). These ligands were assumed to induce enantioselectivity *via* distortion of the allyl group.



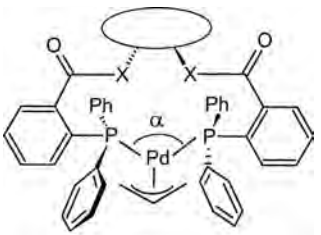
58



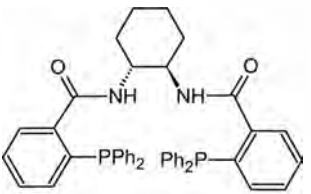
59

Figure 3.6 Bidentate C_2-symmetric nitrogen-based ligands used in asymmetric allylic substitution.

Another successful class of C_2-symmetric bidentate ligands in asymmetric allylic substitution was designed by Trost *et al.*[34,35] The idea of Trost was to increase the ligand chelating angle α in ligands of type **60**, and create a chiral cavity or "pocket" in which the allyl group would be embedded (Figure 3.7). The chirality of the cavity in **60**, arises from the chiral arrangement of the four phenyl substituents at the phosphine atoms imposed by the chiral backbone (e.g. *trans*-1,2-diaminocyclohexanone in **61**) (Figure 3.7). The resulting unequal allyl termini are likely to undergo nucleophilic substitution at different rates, and lead to two different enantiomers. The structure of the η^3-allyl palladium (II) complex bearing **61** was elucidated by X-ray analysis. As expected, a greater chelation angle α of 111° was found rather than the usual 90° (Figure 3.7).[35]



60

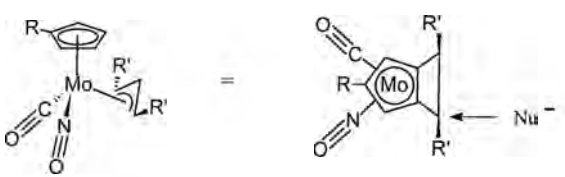


61

Figure 3.7 C_2-symmetric bidentate phosphine ligands designed by Trost.[35]

Trost's ligands were derived from chiral diols, diamines or dicarboxylates. The numerous combinations possible between the backbone constituents, and the donor made this class of ligands one of the most versatile for use in allylic substitution.

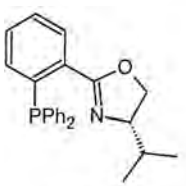
The concept known as "electronic differentiation" was initially observed and reported by Faller *et al.* in stoichiometric allylic substitution *via* allyl-molybdenum intermediate **62** (Figure 3.8).[36] Nucleophilic addition preferentially occurred *trans* to the donor featuring the strongest *trans* influence (CO).



62

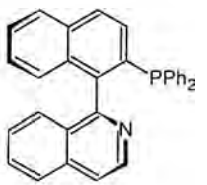
Figure 3.8 Electronic differentiation at η^3-allyl-Mo complex characterised by Faller *et al.*[36]

Chiral bidentate mixed-donor C_1-symmetric ligands, such as imino-phosphine ligands **63** and **64** have been successfully applied to palladium-catalysed allylic substitution (Figure 3.9).[37-40] The excellent e.e.s have been attributed to electronic differentiation.



63

up to 99% e.e.



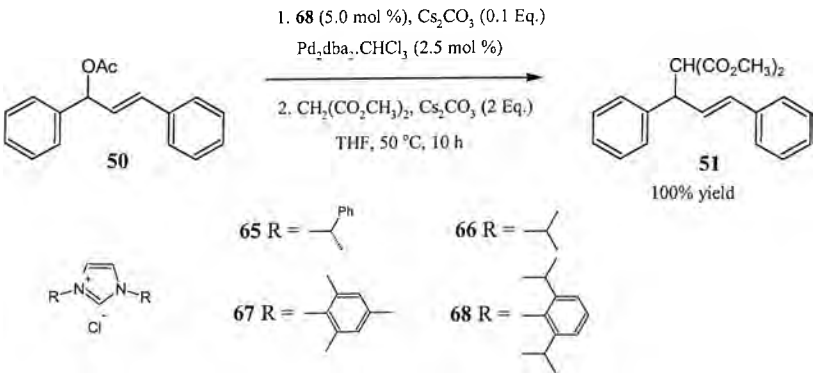
64

up to 98% e.e.

Figure 3.9 Chiral bidentate mixed-donor iminophosphine ligands used in Pd-catalysed asymmetric allylic substitution.

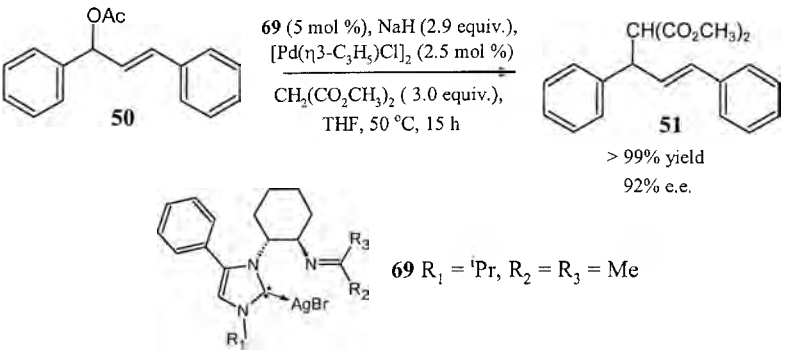
3.1.6 *N*-Heterocyclic carbene ligands

Only a few very successful applications of NHCs in asymmetric catalysis have been reported.[41] The use of *N*-heterocyclic carbene ligands in palladium-catalysed allylic substitution was first reported by Mori *et al.*[42] A range of imidazol-2-ylidene ligands **65** – **68** featuring different *N,N'*-alkyl and *N,N'*-aryl substituents was tested (Scheme 3.13). Different experimental conditions were used involving Cs_2CO_3 and NaH as bases, $PdCl_2$ and $Pd_2dba_3.CHCl_3$ as palladium sources, and various linear and cyclic allyl acetates as substrates. The best results were obtained using the sterically bulky ligand precursor **68**. The free carbene was formed after deprotonating the imidazolium salt **68** (5.0 mol%) using Cs_2CO_3 (0.1 equiv.). The active catalyst was subsequently generated *in situ*, after addition of $Pd_2dba_3.CHCl_3$ (2.5 mol%).



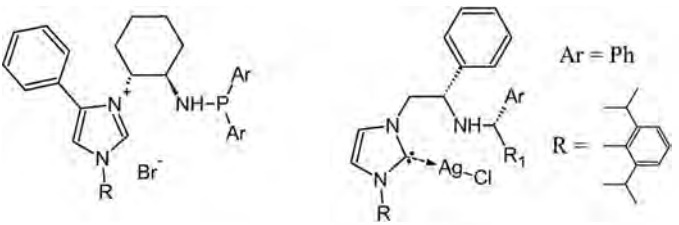
Scheme 3.13 The first example of Pd-catalysed allylic substitution using *N*-heterocyclic carbenes.

Soon after, Douthwaite *et al.* reported the first application of imino-NHC ligands, derived from *trans*-1,2-diaminocyclohexane, to asymmetric palladium-catalysed allylic substitution.[43] These C_1-symmetric bidentate mixed-donor ligands are among the most successful chiral imidazolylidene ligands used in asymmetric catalysis today. Enantioselectivities, up to 92% e.e., were attained using ligand precursor **69** (Scheme 3.14). The active catalyst was generated by addition of the silver NHC complex to $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$.



Scheme 3.14 Imino-NHC ligands in Pd-catalysed asymmetric allylic substitution.[43]

Recently, Douthwaite *et al.* reported the synthesis and evaluation of chiral imidazolium-phosphine compounds, derived from *trans*-(1*R*,2*R*)-diaminocyclohexane, in palladium-catalysed enantioselective allylic substitution. Moderate asymmetric inductions were generally observed (e.e.s up to 45%) using **70** (Figure 3.10).[44] Roland *et al.* recently reported the synthesis and application of bidentate amino-NHC ligands to Pd-catalyzed asymmetric allylic substitution. Good enantioselectivities were obtained (e.e. = 80%) using **71** (Figure 3.10).[45]



70 R = ^{i}Pr, Ar = Ph — 45 % e.e.

71a R_1 = Me — 80% e.e.

71b R_1 = Et

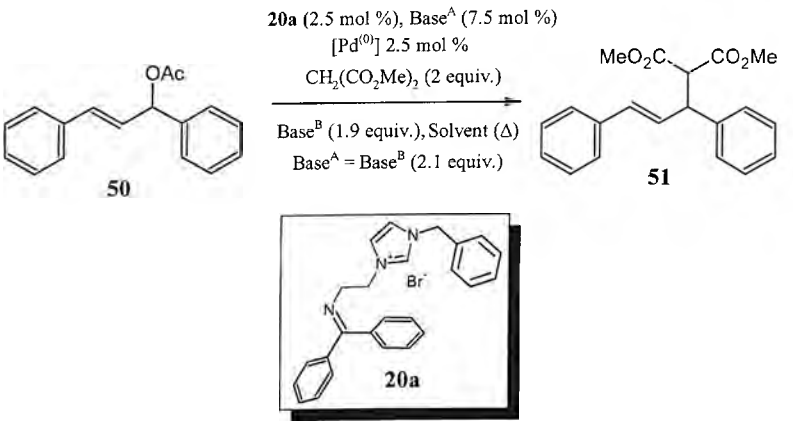
Figure 3.10 C_1-symmetric bidentate *N*, *C*-mixed-donor ligands

3.2 Results and discussion

In this chapter, mixed-donor ligands bearing a very strong σ-donor (NHC) and a weak σ-donor (imine group) were evaluated in asymmetric allylic substitution. It was envisaged that the different donor properties would induce electronic differentiation. The modular approach adopted in the synthesis was expected to enable optimisation of catalytic performance, *via* fine tuning of the ligand structure.

3.2.1 Testing of an achiral imidazolium salt as a ligand precursor for palladium-catalysed allylic substitution

Preliminary tests were carried out, using the achiral imidazolium salt **20a** (Scheme 3.15). The initial experimental conditions employed were similar to those used by Mori *et al.*[42] A range of standard bases for imidazolium salt and dimethyl malonate deprotonation were tested.



Scheme 3.15 Palladium-catalysed allylic substitution using **20a**.

A mixture of imidazolium salt **20a** (2.5 mol %) and base^{A} (7.5 mol %) in THF or CH_2Cl_2, was stirred at room temperature for 1 h to produce the free carbene. The palladium source, $Pd_2(dba)_3$ (2.5 mol %) was then added to the solution, and stirred at room temperature for 2 h to generate the active $Pd^{(0)}$ catalyst. Solutions of substrate (*E*)-1,3-diphenylprop-2-en-1-ylacetate **50**, and dimethyl malonate anion formed by the deprotonation of dimethyl malonate using base^{B}, were successively added to the catalyst. The reaction mixture was stirred for 18 h to give the substitution product **51**. Yields of **51** obtained under different experimental conditions are shown in Table 3.1. If a common base was used (Entries 1 – 4), 2.1 equivalents of base were added in the first step, and the dimethyl malonate solution was added in the final step. Each test was performed in duplicate. A preliminary calibration curve of product **51**, isolated by flash chromatography, was made in the presence of dodecane as internal standard

using gas chromatography (GC). Yields of **51** were obtained by GC analysis of the extracts after work-up.

Table 3.1 Palladium-catalysed allylic substitution using achiral iminoalkyl benzylimidazol-2-ylidene **20a**.

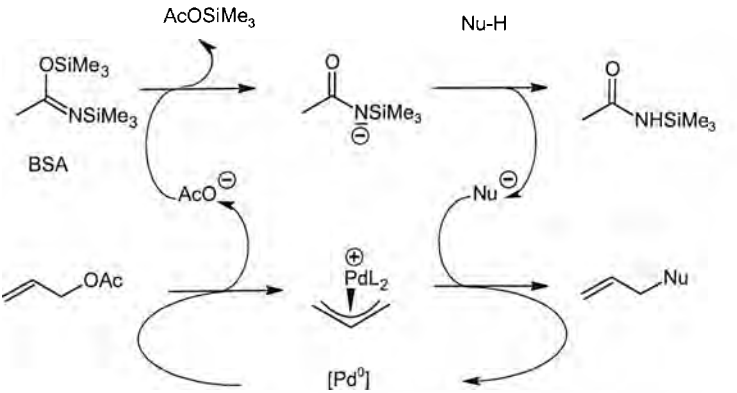
Entry	Base[A]	Base[B]	Solvent	Time (h)	Yield (%)[a]
1	Cs_2CO_3	Cs_2CO_3	CH_2Cl_2	18	5
2	Cs_2CO_3	Cs_2CO_3	THF	18	18
3	KO^{t}Bu	KO^{t}Bu	CH_2Cl_2	18	36
4	KO^{t}Bu	KO^{t}Bu	THF	18	7
5	Cs_2CO_3	NaH	CH_2Cl_2	18	18
6	Cs_2CO_3	NaH	THF	18	95
7	KO^{t}Bu	NaH	THF	18	77

[a] Determined by GC analysis using dodecane as internal standard.

NaH was the base of choice for deprotonation of dimethyl malonate. Unlike in the work of Mori, sodium hydride was not used to deprotonate the imidazolium salt in order to avoid imine reduction, which had been observed previously.[45,46] Cs_2CO_3 was the best base for generating the carbene ligand. THF was the solvent of choice.

Attempts to enhance activity were made by using BSA (*N,O*-bis(trimethylsilyl)acetamide)/KOAc as base[B], and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a palladium source. Mechanisms of nucleophile formation and BSA regeneration are depicted in Scheme 3.16.[47-50] The use of BSA/KOAc presents practical advantages such as: it can be used in catalytic amounts and does not require polar solvents. The neutral nucleophile precursor, which readily dissolves in non-polar solvents, unlike the

sodium malonate salt, is progressively deprotonated and converted to the active nucleophile.



Scheme 3.16 Formation of the nucleophile using BSA/AcO^-.

The same experimental conditions were used. BSA and KOAc were added to the active catalyst solution, followed by addition of dimethyl malonate in THF. The results are summarised in Table 3.2.

Table 3.2 Palladium-catalysed allylic substitution using achiral iminoalkyl benzylimidazol-2-ylidene **20a**.

Entry	$[Pd^{(0)}]$	Base[A]	Base[B]	Solvent	Time (h)	Yield (%)[a]
1	Pd_2dba_3	KO^tBu	NaH	THF	18	77
2	Pd_2dba_3	Cs_2CO_3	NaH	THF	18	95
3	Pd_2dba_3	KO^tBu	BSA/KOAc	THF	18	6
4	Pd_2dba_3	Cs_2CO_3	BSA/KOAc	THF	18	16
5	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	Cs_2CO_3	NaH	THF	18	18

[a] Determined by GC analysis using dodecane as internal standard.

Unfortunately, the use of BSA/KOAc did not bring the expected improvements. Comparisons between entries 1 and 3, and entries 2 and 4, show that lower activities were achieved. The comparison of the results in entries 2 and 5, also reveals unexpected loss of activity when $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was used. The work of Jutand *et al.* on structural and kinetic effects of chloride ions in the palladium-catalysed allylic substitutions, suggests that chloride ions may affect the reactivity of the allyl palladium (II) intermediate.[51] It was found that chloride ions can induce the formation of a neutral η^1-allyl-$PdClL_2$ complex over the requisite cationic $[\eta^3$-allyl-$PdL_2]^+$ species (L = $P(Ar)_3$). Kinetic studies show that the rate constant of nucleophilic attack is inversely proportional to the concentration of chloride ions. Similar catalytic behaviour is expected in the presence of bromide ions.[51]

3.2.2 Testing of a chiral imidazolium salt as a ligand precursor for palladium-catalysed allylic substitution

The optimised conditions, involving $Pd_2(dba)_3$ as palladium source, Cs_2CO_3 as base[A] to deprotonate the imidazolium salt, NaH as base[B] to deprotonate dimethyl malonate, and THF as solvent, were applied with the chiral ligand **25b**. The poor results obtained (Y = 32%) were attributed to active catalyst being sparingly generated (Figure 3.11).

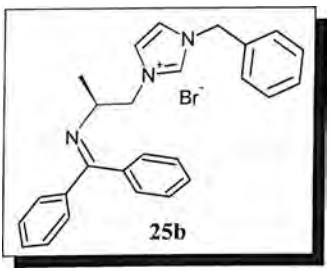


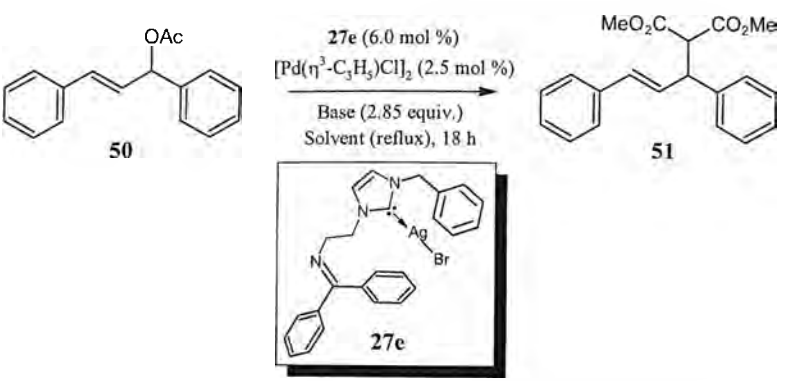
Figure 3.11

However, it is possible to generate the palladium active catalyst using mild conditions, and avoid problems related to the free carbene preparation. The synthesis of silver carbene complexes, obtained after deprotonation of azolium salts using silver (I) oxide (Ag_2O), and their ability to act as ligand transfer agents for the generation of palladium carbene complexes as reported for the first time by Wang and Lin.[52] This overcomes the necessity of strong bases to deprotonate imidazolium salts. This method also avoids problems related to the presence of halide ions. As suggested by Jutand *et al.*,[51] halide ions can affect the regioselectivity and the rate of nucleophilic attack in palladium-catalysed allylic substitution. Danopoulos *et al.*[53] and Douthwaite *et al.*[43] have reported a convenient and efficient way to prepare monodentate iminoalkyl *N*-functionalised imidazol-2-ylidene silver complexes. Douthwaite *et al.* reported their application in palladium-catalysed enantioselective allylic substitution.[43] During the preparation of the active catalyst, a white precipitate of AgBr is formed and filtered off. This prevents problems related to silver halides during the catalytic process. Some researchers suggest that the presence of silver ions

can reduce the reaction e.e.s.[45] The synthesis and application of silver carbene complexes to palladium-catalysed allylic substitution were investigated.

3.2.3 Use of achiral silver imidazol-2-ylidene complex as ligand precursor

Preliminary activity tests were carried out using an achiral silver imidazol-2-ylidene complex **27e** (Scheme 3.17). NaH and BSA/KOAc were assessed as bases for deprotonation of dimethyl malonate. $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ was employed as a source of palladium. CH_2Cl_2 and THF were tested as solvents. A solution of silver complex **27e** (6.0 mol%) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%) in THF or CH_2Cl_2, was treated under reflux for 30 minutes in the absence of light, to generate the palladium active catalyst *in situ*. The nucleophile was prepared separately in THF or CH_2Cl_2, by deprotonation of dimethyl malonate (3.0 equiv.) with NaH or BSA/KOAc (2.85 equiv.). A solution of substrate **50** was added, followed by addition of nucleophile in THF or CH_2Cl_2. The reaction mixture was stirred for 18 h affording the product **51**, Table 3.3.



Scheme 3.17 Palladium-catalysed allylic substitution using **27e**.

Table 3.3 Palladium-catalysed allylic substitution using achiral iminoalkyl benzylimidazol-2-ylidene **27e**.

Entry	$[Pd^{(0)}]$	Base	Solvent	Time (h)	Yield (%)[a]
1	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	NaH	THF	18	100
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	NaH	CH_2Cl_2	18	0
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	BSA/KOAc	THF	18	20
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	BSA/KOAc	CH_2Cl_2	18	2

[a] Determined by GC analysis using dodecane as internal standard.

The combination of NaH and THF gave the best results. The loss of activity observed between entries 1 and 2, and entries 3 and 4, was attributed to the poor solubility of the palladium (II) intermediate in CH_2Cl_2 and to a lower temperature at reflux.

3.2.4 Use of chiral silver imidazol-2-ylidene complexes as ligand precursors

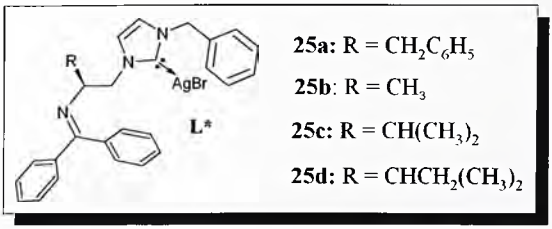
Having established the optimum conditions for the use of achiral silver iminoalkyl imidazol-2-ylidene **20a**, chiral silver NHC complexes were evaluated for enantioselective allylic substitution, using similar conditions.

3.2.4.1 Chiral *N*-benzylhydrylideneaminoalkyl *N'*-benzylimidazol-2-ylidene ligands

The influence of the alkyl substituent at the stereogenic centre on the backbone of *N*-iminoalkyl *N'*-benzylimidazol-2-ylidenes, **25a-d**, on enantioselectivity was evaluated at room temperature (Table 3.4). For each catalyst, the reaction was carried in duplicate. The mixture of enantiomers was isolated by flash chromatography.

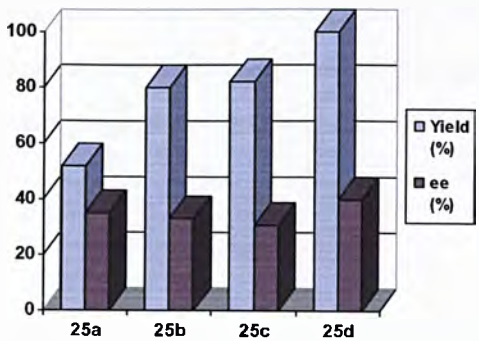
Enantiomeric excesses were measured by ^1H NMR analysis in $CDCl_3$, using enantiomerically pure chiral shift reagent $Eu(hfc)_3$ (15 mol%), Figure 3.12. Optical rotation measurements of the mixture in $CHCl_3$, were compared with literature values to determine the absolute configuration of the enantiomer in excess.[54]

Table 3.4 Palladium-catalysed asymmetric allylic substitution using chiral *N'*-benzylimidazol-2-ylidene ligands



Entry	Ligand	R	Time	Yield (%)[a]	Ee (%)[b,c]
1	**25a**	$CH_2C_6H_5$	18 h	52	35 (*R*)
2	**25b**	CH_3	18 h	80	33 (*R*)
3	**25c**	$CH(CH_3)_2$	18 h	82	31 (*R*)
4	**25d**	$CHCH_2(CH_3)_2$	18 h	100	40 (*R*)

[a] Determined by GC analysis using dodecane as internal standard.
[b] Determined by ^1H NMR using chiral shift reagent $Eu(hfc)_3$ (15 mol %).
[c] Determined by optical rotation measurement.[54]



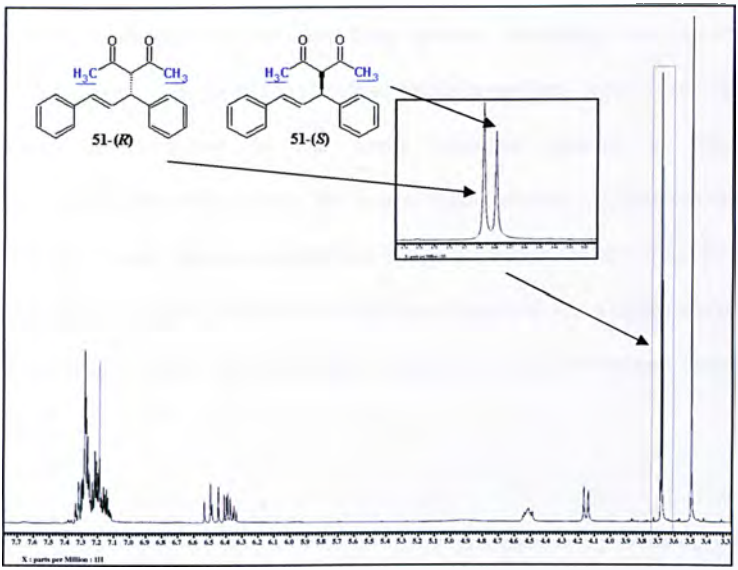


Figure 3.12 ^{1}H NMR spectrum of **51** using Eu(hfc)$_3$.

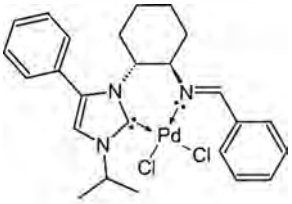
Modest e.e.s between 30% and 40% were obtained. It appears that variation of the alkyl group at the stereogenic centre of the ligand backbone has little effect on enantioselectivity. This suggests that the group at the stereogenic centre was too removed from the π-allyl unit to effectively transfer the chiral information.

The low enantioselectivity may be due to weak coordination of the imine group to the palladium centre resulting in a significant concentration of monodentate iminoalkyl imidazol-2-ylidene palladium species. HRMS of the product mixture from the

reaction of $Pd(PhCN)_2Cl_2$ with **25d** indicated the presence of a bis monodentate iminoalkyl imidazol-2-ylidene palladium species, indicating that non-chelating species are likely to be formed in the above catalytic reaction. Imine dissociation may in part be attributed to the steric hindrance created by the large diphenylmethylideneamine group. The loss of ligand chelation in the palladium allyl intermediate would disable any electronic differentiation of the ally group termini by the mixed donor ligand. Douthwaite *et al.* also rationalised a loss of enantiocontrol in allylic alkylation due to the hemi-labile nature of a sterically hindered imine donor group.[43]

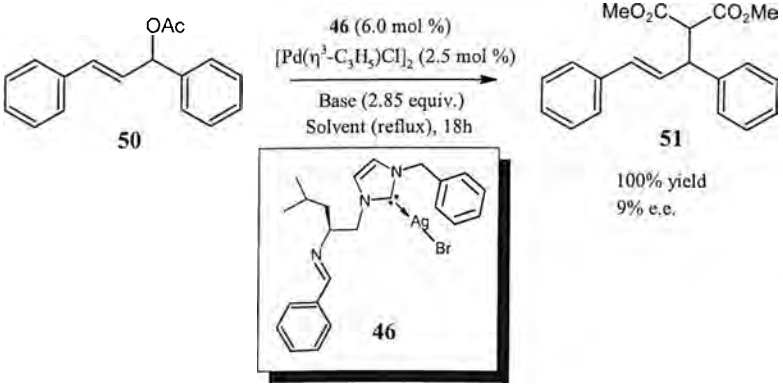
3.2.4.2 Chiral *N*-benzylideneaminoalkyl *N'*-benzylimidazol-2-ylidene ligands

The best enantioselectivity obtained by Douthwaite *et al.* was with a ligand precursor featuring a small dimethylmethylideneamine group. Attempts to prepare dimethylmethylideneamine functionalised imidazolium salts using the synthetic methods reported in this thesis were unsuccessful. The sterically undemanding benzylideneamine derivative **46** was prepared and tested. The X-ray structure of a chiral chelating $Pd^{(+II)}$(imino-carbene)Cl_2 complex **72**, containing benzylideneamine group, was reported by Douthwaite (Figure 3.13).[43] The X-ray structure suggests that the intermediate η^3-π-allyl $Pd^{(+II)}$ complexes derived from **46**, are more likely to have the ligand chelating. The results obtained using **46** are shown in Scheme 3.18 and indicate a much lower e.e. In this case, the low enantioselectivity may be due to hydrolysis of the benzylideneamine function. The resulting aminoalkyl imidazol-2-ylidene is unlikely to chelate.



72

Figure 3.13 $Pd^{(+II)}$(imino-carbene)Cl_2 complex prepared by Douthwaite.[43]



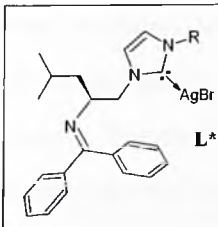
Scheme 3.18 Palladium-catalysed allylic substitution using **46**.

3.2.4.3 The influence of *N*-aryl and *N*-alkyl imidazol-2-ylidene substituents

In light of these stability issues, the use of ligands with diphenylmethylideneamine groups was further explored. Attempts to enhance asymmetric induction were made by varying the nature of the *N*-substituent on the imidazol-2-ylidene. The influence of the *N*-substituent on enantioselectivity was evaluated for a small range of ligands derived from leucine, Table 3.5. The data reveal that changing the *N*-substituent has a

significant effect on the e.e.. The *N*-methyl derivative has a similar e.e. to the benzyl derivative, which would be expected, given their similar steric bulks. The *N*-phenyl derivative gave a very modest result. In contrast the bulkier *N*-mesityl derivative gave the best result of them all.

Table 3.5 Palladium-catalysed asymmetric allylic substitution using chiral *N'*-substituted imidazol-2-ylidene ligands derived from leucine.



L*

25d: R = $CH_2C_6H_5$

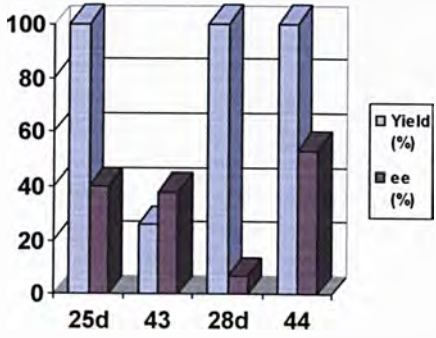
43: R = CH_3

28d: R = C_6H_5

44: R = 1,3,5-$(CH_3)_3C_6H_2$

Entry	Ligands	R	Time	Yield (%)[a]	Ee (%)[b,c]
1	**25d**	$CH_2C_6H_5$	18 h	100	40 (*R*)
2	**43**	CH_3	18 h	26	38 (*R*)
3	**28d**	C_6H_5	18 h	100	7 (*R*)
4	**44**	1,3,6-$(CH_3)_3$-C_6H_2	18 h	100	53 (*R*)

[a] Determined by GC analysis.
[b] Determined by ^1H NMR using chiral shift reagent $Eu(hfc)_3$ (15 mol %).
[c] Determined by optical rotation measurement.[54]



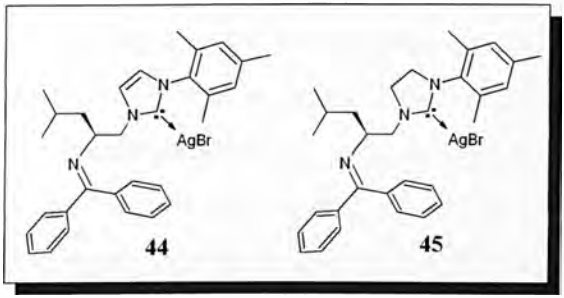
A number of studies estimating the steric and electronic properties of NHCs have been undertaken.[55-60] Nolan *et al.*, in one of the more detailed studies, demonstrated that *N*-aryl imidazol-2-ylidenes have similar σ-donor properties to *N*-alkyl imidazol-2-ylidenes. This was determined by measuring the carbonyl stretching frequencies of a range of $Ni(CO)_3(NHC)$ complexes. It was found that varying the *N*-substituent had little effect on the carbonyl stretching frequencies, compared to the effect seen in phosphine complexes when moving from alkyl- to aryl-substituted phosphines. As a result a change in catalytic activity or enantioselectivity in allylic alkylation is unlikely to be due to electronic factors related to the σ-donor abilities of different imidazol-2-ylidenes. Thus the differences in enantioselectivity may be attributed to the different steric bulk of *N*-substituent. Douthwaite *et al.* also noted that bulkier *N*-aryl imidazol-2-ylidenes gave higher e.e.s.[43] Similar effects of steric bulk enhancing enantioselectivity have been reported for phosphine based ligands. For example Helmchen *et al.* suggested that steric interaction between the allyl group and a phenyl substituent on the phosphine favoured the formation of the *exo* isomer over the *endo* isomer, leading to enantioselectivity.[24] In our case, it is possible that the bulkier mesityl group shifts the exo/endo equilibrium to a greater extent than the other ligands, to give a higher e.e. Preferential formation of the (*R*) isomer requires nucleophilic attack at the allyl terminus *trans* to the carbene of the *exo* intermediate (Scheme 3.10).

3.2.4.4 The use of a iminoalkyl imidazolin-2-ylidene ligand

The low e.e. observed for the phenyl derivative, **28d**, is difficult to explain. The planar nature of this substituent may result in it having a smaller steric interaction with the palladium centre.

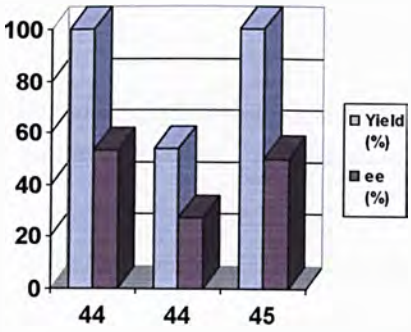
Additional attempts to improve the e.e. were made by changing the solvent and by substituting the unsaturated imidazol-2-ylidene group with a saturated imidazolin-2-ylidene group. It was initially thought that a saturated imidazolin-2-ylidene would be a stronger σ-donor than an unsaturated imidazol-2-ylidene. However, **45** gave a similar e.e. to that obtained with **44**. Later work by Nolan *et al.* suggested that in fact imidazolidin-2-ylidenes were slightly less electron-donating than their unsaturated analogues.[55] The slightly reduced e.e. obtained with **45** would be consistent with this observation. The reaction in less polar solvent toluene resulted in inferior activity and selectivity. This is probably due it being less effective in stabilising the cationic palladium allyl intermediates.

Table 3.6 The use of chiral *N'*-substituted imidazol-2-ylidene and imidazolin-2-ylidene ligands derived from leucine.



Entry	Ligand	Solvent	Time	Yield (%)[a]	Ee (%)[b,c]
1	**44**	THF	18 h	100	53 (*R*)
2	**44**	Toluene	18 h	54	27 (*R*)
3	**45**	THF	18 h	100	50 (*R*)

[a] Determined by GC analysis.
[b] Determined by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$ (15 mol %).
[c] Determined by optical rotation measurement.[54]



3.3 Conclusion and Future work

The work in this chapter demonstrates that chiral iminoalkyl imidazol-2-ylidenes exhibit modest enantioselectivity towards palladium catalysed allylic alkylation. The results indicate that changing the nature of the alkyl group at the stereogenic centre on the ligand backbone has little effect on enantioselectivity. In contrast increasing the steric bulk of the *N*-substituent on the imidazol-2-ylidene improved the e.e. of the reaction significantly. Douthwaite *et al.* observed high e.e.s for ligands containing dimethylmethylideneamine and *N*-imidazol-2-ylidene donor groups linked by a cyclohexane backbone. In light of this future work with the ligand set reported here would be aimed at synthesising and testing ligands with smaller imino donor groups. In addition, bulkier *N*-aryl or *N*-alkyl substituents, such as diisopropylphenyl, have been demonstrated to give greater activity in a range of catalytic reactions and they may realise improved performance with this ligand set. It would also be interesting to see if the introduction of an additional stereogenic centre on the backbone of an imidazolin-2-ylidene group would have a beneficial effect on enantioselectivity.

3.4 Typical procedure for palladium-catalysed allylic substitution using silver imidazolylidene and imidazolin-2-ylidene complexes in THF at room temperature

A dry Schlenk tube was charged with silver imidazole-2-ylidene complex (0.008 g, 0.012 mmol, 6 mol%), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.002 g, 0.005 mmol, 2.5 mol%) and THF (1 ml). The mixture was stirred for 1 h at room temperature in absence of light to generate the active catalyst. The solid deposit formed was filtered off under nitrogen

atmosphere. In the meantime, the nucleophile was prepared by deprotonation of dimethylmalonate (0.079 g, 0.594 mmol, 3 equiv.) using NaH (0.014 g, 0.564 mmol, 2.85 equiv.) in THF (1 ml). The internal standard dodecane (50 μL) was added to the active catalyst solution. A solution of substrate (*E*)-1,3-diphenylprop-3-en-1-ylacetate (0.050 g, 0.198 mmol, 1 equiv.) in THF (0.5 mL) was also added, followed by addition of the sodium dimethylmalonate solution. The reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then quenched with water and extracted with CH_2Cl_2 (2 x 20 mL). The yield of product was determined by GC analysis: HP-5 (Crosslinked 5% Ph Me silicone) 25 m x 0.32 mm x 0.52 μm. Subsequently, the residue was purified by flash chromatography (Hexane: EtOAc, 4:1). Enantiomeric excesses were then measured by ^1H NMR ($CDCl_3$) analysis using enantiomerically pure chiral shift reagent $Eu(hfc)_3$ (15 mol%). The absolute configuration was determined by optical activity measurement using an AA-10 automatic polarimeter (Optical Activity Ltd).[54]

2.5 References

1. B. M. Trost, T. J. Fullerton, *J. Am. Chem. Soc.*, 1973, **95**, 292.
2. B. M. Trost, T. J. Dietsche, *J. Am. Chem. Soc.*, 1973, **95**, 8200.
3. B. M. Trost, P. E. Strege, *J. Am. Chem. Soc.*, 1977, **99**, 1649.
4. B. M. Trost, T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435.
5. J. Tsuji, T. Yamakawa, *Tetrahedron Lett.*, 1976, 613.
6. B. M. Trost, C. Lee (2000) In: I. Oijima, (eds) *Catalytic Asymmetric Synthesis*. Wiley-VCH, Weinheim, Germany, Chapter 8E.
7. a) T. Yamamoto, M. Akimoto, O. Saito, A. Yamamoto, *Organometallics*, 1986, **5**, 1559; b) H. Kurosawa, *J. Organomet. Chem.*, 1987, **334**, 243.

8. C. Moberg, U. Bremberg, K. Hallman, M. Svensson, P. Norrby, H. Hallberg, M. Larhed, I. Csoregh, *Pure Appl. Chem.*, 1999, **71**, 1477.
9. N. Sauthier, J. Fornies, L. Toupet, R. Reau, *Organometallics*, 2000, **19**, 553.
10. P. S. Pregosin, H. Ruegger, R. Salzmann, A. Albinati, F. Lianza, R. W. Kunz, *Organometallics*, 1994, **13**, 83.
11. B. Åkermark, S. Hansson, B. Krakenberger, A. Vitagliano, K. Zetterberg, *Organometallics*, 1984, **3**, 679.
12. C. Amatore, A. Jutand, G. Meyer, L. Mottier, *Chem. Eur. J.*, 1995, **5**, 466.
13. a) B. M. Trost, D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; b) B. M. Trost, C. Lee, I. Ojima, (eds) *Catalytic Asymmetric Synthesis*, 2nd Ed, Wiley: New York, 2000, p153; c) B. M. Trost, *J. Org. Chem.*, 2004, **69**, 5813.
14. J. Sprinz, M. Kiefer, G. Helmchen, G. Huttner, O. Walter, L. Zsolnai, M Reggelin, *Tetrahedron Lett.*, 1994, **35**, 1523.
15. S. Hansson, P. O. Norrby, M. P. T. Sjögren, B. Åkermark, M. E. Cucciolito, F. Giordano, A. Vitagliano, *Organometallics*, 1993, **12**, 4940.
16. A. Gogoll, J. Örnebro, H. Grennberg, J. E. Bäckvall, *J. Am. Chem. Soc.*, 1994, **116**, 3631.
17. a) P. B. Mackenzie, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2046; b) K. L. Granberg, J. E. Bäckvall, *J. Am. Chem. Soc.*, 1992, **114**, 6858.
18. S. A. Godleski (1991) In: B. M. Trost, I. Fleming, M. F. Semmelhack (eds) *Comprehensive Organic Synthesis*. Pergamon, Oxford, vol. 4, chap. 3.3.
19. G. Consiglio, R. M. Waymouth, *Chem. Rev.*, 1989, **89**, 257.
20. B. Bosnich, P. B. Mackenzie, *Pure Appl. Chem.*, 1982, **54**, 189.
21. G. S. Hammond, *J. Am. Chem. Soc.*, 1955, **4**, 334.
22. a) J. Sprinz, M. Kiefer, G. Helmchen, M. Reggelin, G. Huttner, O. Walter, L. Zsolnai, *Tetrahedron Lett.*, 1994, **35**, 1523; b) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.*, 2000, **33**, 336.
23. H. Steinhagen, M. Reggelin, G. Helmchen, *Angew. Chem., Int. Ed. Eng.*, 1997, **36**, 2108.
24. a) G. Helmchen, S. Kudis, P. Sennhenn, H. Steinhagen, *Pure Appl. Chem.*, 1997, **69**, 513; b) B. Wiese, G. Helmchen, *Tetrahedron Lett.*, 1988, **39**, 5727.

25. S. Lui, J. F. K. Müller, M. Neuburger, S. Schaffner, S. Zehnder, *J. Organomet. Chem.*, 1997, **549**, 283.

26. P. E. Blöchl, A. Togni, *Organometallics*, 1996, **15**, 4125.

27. T. R. Ward, *Organometallics*, 1996, **15**, 2836.

28. B. M. Trost, D. J. Murphy, *Organometallics*, 1985, **4**, 1143.

29. a) T. Hayashi (1993), I Ojima (eds) *Catalytic Asymmetric Synthesis*. VCH, New York, chap. 7.1; b) T. Hayashi, A. Yamamoto, T. Hagihara, Y. Ito, *Tetrahedron Lett,* 2000, **27**, 191; c) T. Hayashi, *Pure Appl. Chem.*, 1988, **60**, 7.

30. A. Pfaltz, *Acc. Chem. Rev.*, 1993, **26**, 339.

31. V. Leutenegger, G. Umbricht, C. Fahrni, P. Von Matt, A. Pfaltz, *Tetrahedron*, 1992, **48**, 2143.

32. a) A. Togni, *Tetrahedron: Asymmetry*, 1991, **2**, 683; b) A. Togni, G. Rihs, P. S. Pregosin, C. Ammann, *Helv. Chem. Acta*, 1990, **73**, 723.

33. H. Kubota, M. Nakajima, K. Koga, *Tetrahedron Lett.*, 1993, **34**, 8135.

34. B. M. Trost, D. L, Van Vranken, *Chem. Rev.*, 1996, **89**, 257.

35. B. M. Trost, *Acc. Chem. Res.*, 1996, **29**, 355.

36. a) R. D. Adams, D. F. Chodosh, J. W. Faller, A. M. Rosan, *J. Am. Chem. Soc.*, 1979, **101**, 2570; b) K.-H. Chao, J. W. Faller, *J. Am. Chem. Soc.*, 1983, **105**, 3893; c) J. W. Faller, K.-H. Chao, H. H. Murray, *Organometallics*, 1984, **3**, 1231.

37. J. Spring, G. Helmchen, *Tetrahedron Lett.*, 1993, **34**, 1769.

38. P. von Matt, A. Pfaltz, *Angew. Chem., Int. Ed. Eng.*, 1993, **32**, 566.

39. a) G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.*, 1993, **334**, 3149; b) S. J. Coote, G. J. Dawson, C. G. Frost, J. M. J. Williams, *Synlett*, 1993, 509.

40. J. M. Brown, D. I. Hulmes, P. J. Guiry, *Tetrahedron*, 1994, **50**, 4493.

41. M. C. Perry, K. Burgess, *Tetrahedron: Asymmetry*, 2003, **14**, 951.

42. Y. Sato, T. Yoshino, M. Mori, *Org. Lett.*, 2003, **5**, 31.

43. L. G. Bonnet, R. E. Douthwaite, B. M. Kariuki, *Organometallics*, 2003, **22**, 4187.

44. R. Hodgson, R. E. Douthwaite, *J. Organomet. Chem.*, 2005, **690**, 5820.

45. A. Flahaut, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry*, 2007, **18**, 229.

46. a) M. A. Fox, J. K. Whitesell, *Organic Chemistry*, ISBN: 0 76 372197 2, Jones and Bartlett Publishers: Stadbury, MA, 2004, pp 849; b) J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, ISBN: 0 19 850346 6, Oxford University Press Inc.: New York, 2001, pp354 – 356.

47. U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron*, 1992, **48**, 2143.

48. a) B. M. Trost, S. J. Brickner, *J. Am. Chem. Soc.*, 1983, 105, 568; b) B. M. Trost, D. J. Murphy, *Organometallics*, 1985, **4**, 1143.

49. A Pfaltz (1994) In: E. Ottow, S. Schöllkopf, B.-G. Schulz (eds) *Stereoselective Synthesis*. Springer, Berlin Heidelberg, New York, pp. 15.

50. M. T. El Gihani, H. Heaney, *Synthesis*, 1998, 357.

51. T. Cantat, E. Génin, C. Giroud, G. Meyer, A. Jutand, *J. Organomet. Chem.*, 2003, **687**, 365.

52. H. M. J. Wang, I. J. B. Lin, *Organometallics*, 1998, **17**, 972.

53. A. A. D. Tulloch, A. A. Danopoulos, S. Winston, S. Kleinhenz, G. Eastham, *J. Chem. Soc., Dalton Trans.*, 2000, 4499.

54. a) T. Mino, T. Ogawa, M. Yamashita, *J. Organomet. Chem.*, 2003, **665**, 122; b) T. Fukuda, A. Takehara, M. Iwao, *Tetrahedron: Asymmetry*, 2001, **12**, 2793.

55. R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff, S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 2485.

56. X. Hu, Y. Tang, P. Gantzel, K. Meyer, *Organometallics*, 2003, **22**, 612.

57. X. Hu, I. Castro-Rodriguez, K. Olsen, K. Meyer, *Organometallics*, 2004, **23**, 755.

58. A. C. Hiller, W. J. Sommer, B. S. Yong, J. L. Petersen, L. Cavallo, S. P. Nolan, *Organometallics*, 2003, **22**, 4322.

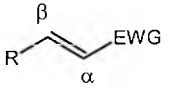
59. M. S. Viciu, O. Navarro, R. F. Germaneau, R. A. Kelly III, W. Sommer, N. Marion, E. D. Stevens, L. Cavallo, S. P. Nolan, *Organometallics*, 2004, **23**, 1629.

60. N. M. Scott, R. Dorta, E. D. Stevens, A. Correa, L. Cavallo, S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 3516.

4. Enantioselective copper-catalysed conjugate addition

4.1 Introduction to copper-catalysed 1,4-conjugate addition reaction.

Numerous α,β-unsaturated systems, which are conjugated with an electron-withdrawing group (EWG), Figure 4.1, give a 1,4 addition product after nucleophilic attack. Under different conditions 1,2-addition may be favourable.



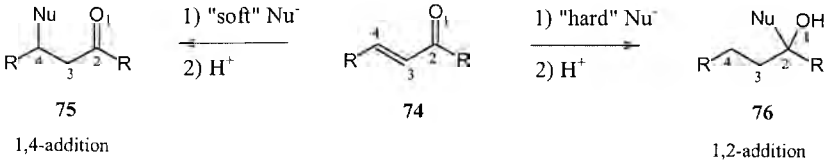
73

EWG = CHO, COR, CO_2R, $CONR_2$, CN, SOR_2, NO_2, etc.

Figure 4.1 α,β-unsaturated systems conjugated to an EWG.

4.1.1 Soft and hard nucleophiles

In general, "soft" nucleophiles, such as carbanions, attack at the 4-position to give the 1,4-addition product **75**, whereas "hard" nucleophiles, such as Grignard reagents, attack at the 2-position to afford the 1,2 addition product **76** (Scheme 4.1). The reaction conditions and the nature of the α,β-unsaturated carbonyl compound also play a role in determining the position of attack.



75

1,4-addition

74

76

1,2-addition

Scheme 4.1 Regioselectivity of nucleophilic addition.

4.1.2 Carbon nucleophiles

The use of carbon nucleophiles in the conjugate addition to α,β-unsaturated electrophiles is a very useful method for forming carbon-carbon bonds.[1] Organometallic reagents such as alkylzinc, Grignard and alkyllithium reagents present a wide range of carbon nucleophiles for application to conjugate addition.[2]

The nature of the carbon nucleophile in organometallic reagents is directly related to the metal-carbon bond polarisation, which in turn controls the regioselectivity of the conjugate addition.

"Hard" carbon nucleophiles are present in strongly polarised metal-carbon bond organometallics (LiR, NaR, MgR_2, etc.).[3] Unlike "soft" carbon nucleophiles, which are characterised by weakly polarised metal-carbon bonds, "hard" carbon nucleophiles are too reactive to exclusively attack at the 4-position. In fact, they undergo the competing addition at the 2-position. "Hard" carbon nucleophiles need the presence of a transition metal to generate "soft" carbon nucleophiles. Transition metal alkyl species can be generated *in situ* from organolithium, Grignard and organozinc reagents.

4.1.3 Copper-catalysed conjugate addition

In 1941, Kharash was the first to report copper-catalysed conjugate addition.[4] After the synthesis of methylcopper by Gilman and Woods in 1943 [5], Gilman *et al.* reported further organocuprates (Gilman reagents).[6] Over the past few years copper-catalysed conjugate addition with organolithium and Grignard reagents, has been widely used in organic synthesis.[7] The use of organocopper reagents in stoichiometric amounts, was extended to asymmetric conjugate addition. A major breakthrough was realised by Leyendecker in 1983 with the application of hydroxyprolinol-derived sulphide ligand complexes as chiral auxiliaries in asymmetric conjugate addition.[8] The conjugate addition to chalcone using dimethylcopper lithium gave the addition product in 94% e.e.. Unfortunately, catalytic procedures involving organolithium reagents were unsuccessful.

The first catalytic developments were carried out using organocuprate reagents prepared by transmetallation of Grignard reagents.[9] Recent procedures involving dialkylzinc reagents have dominated the field since their first application by Alexakis in 1993.[10] The covalent character of the zinc-carbon bond enables zinc organometallic reagents to undergo transmetallation with various transition metal salts.[11] The moderate activity of zinc organometallics prevents transmetallation of several groups to the same metal centre. As a result, decomposition of the copper-zinc organometallic intermediate is avoided during the catalytic process. The compatibility of alkyl zinc reagents with various functional groups, which prevents side reactions such as 1,2-addition, makes them desirable. The higher asymmetric induction they

exhibit made them prevail over Grignard reagents in asymmetric copper-catalysed conjugate addition.

4.1.4 Cyclic enones

2-cyclohexenone **77** is a widely used substrate because it has the advantage of remaining in a fixed *s-trans* conformation (Figure 4.2, (1)), compared to acyclic enones, which can exist in the *s-cis* **78** and *s-trans* **79** isomers (Figure 4.2, (2)).

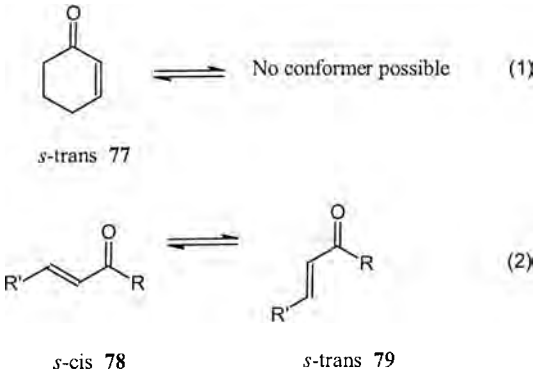
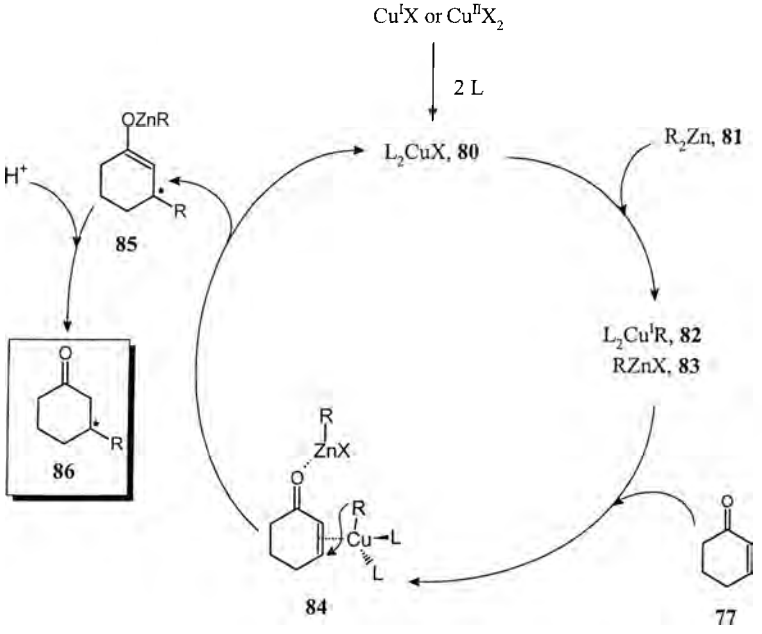


Figure 4.2 Fixed *s*-trans conformation for cyclic enone.

4.1.5 Enantioselective copper-catalysed 1,4-conjugate addition

A mechanism has been proposed for copper-catalysed conjugate addition of a dialkylzinc reagent to 2-cyclohexenone (Scheme 4.2).[12] Cu(I) or Cu(II) catalysts can be used, since Cu(II) may be reduced *in situ* to the corresponding Cu(I) complex.[12] After formation of the chiral complex **80** *via* ligand coordination to Cu(I), an alkyl

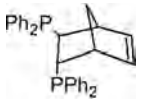
group is transferred from the dialkylzinc reagent **81** to generate the nucleophilic copper complex **82** and the organozinc species **83**. The organometallic compounds **82** and **83** then coordinate to cyclohexenone 77 to form the bimetallic complex **84**. The bimetallic complex **84** results from π-complexation of the carbon double bond to the copper species, and carbonyl group complexation to the Lewis acid Zn(II). The chiral ligands occupying the remaining sites of the copper tetrahedral coordination sphere provide the stereocontrol of the alkyl transfer. The zinc Lewis acid species activates the electrophile towards addition to give the zinc enolate **85**, which is then protonated to afford the final product **86**.



Scheme 4.2 A catalytic cycle suggested for copper catalysed asymmetric conjugate addition of dialkylzinc to 2-cyclohexenone.[12]

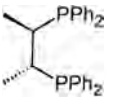
4.1.6 Chiral homo- and heterobidentate ligands

Chiral phosphine ligands have been widely used in asymmetric conjugate addition; chiral phosphoramidite ligands were particularly successful in the conjugate addition of diethylzinc to 2-cyclohexenone (Y = 94%, e.e. > 98%).[12] Low enantioselectivities were observed with most of the well known chiral diphosphines, for example Norphos **87** (e.e. = 44%)[13] and Chiraphos **88** (e.e. = 44%) gave modest e.e.s.[13] Very good results were observed using Miniphos **89-91** (e.e. up to 97% with cycloheptenone)[14] (Figure 4.3).



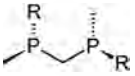
(R)-Norphos **87**

ee = 44%



(S,S)-Chiraphos **88**

ee = 44%



(R)-Minophos

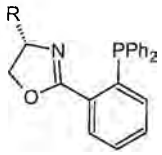
89 R = ^{t}Bu

90 R = c-C_6H_{11} *ee up to 97%*

91 R = ^{i}Pr

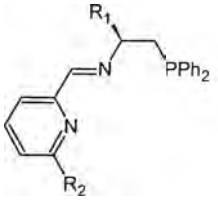
Figure 4.3 Chiral diphosphines used in copper-catalysed conjugate addition.

Bidentate *P*, *N* arylphosphine ligands bearing functional groups as oxazoline **92-94**, imidazolidine **95**, or pyridine **96-101**, have demonstrated high efficiency in enantioselective conjugate addition (Figure 4.4).[15]



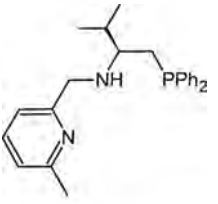
92 R = ^{t}Bu [16]
93 R = ^{i}Pr [17, 18]
94 R = Ph [17]

95 [19]



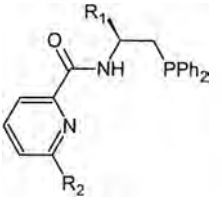
96 R_1 = ^{i}Pr, R_2 = H [20]
97 R_1 = ^{i}Pr, R_2 = Me [20]
98 R_1 = Me, R_2 = Me [20]

ee up to 91%



99 [20]

ee up to 30%



100 R_1 = ^{i}Pr, R_2 = H [20]
101 R_1 = ^{i}Pr, R_2 = Me [20]

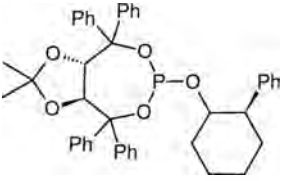
ee up to 52%

Figure 4.4 *P*, *N* ligands used in asymmetric conjugate addition.

Success in enantioselective conjugate addition relies on tight spatial control near the reaction site. For instance, chelating diphosphines ligands **89-91** (Figure 4.3) are able to stabilise the monoalkylcopper key intermediate and formed a fixed chiral pocket. The chirality information being very close to the copper atom, in turn allows greater stereocontrol. Recently, ligands bearing heteroatoms directly bonded to the phosphorous atom centre, such as TADDOL-phosphite **102** and BINOL-phosphoramidites **103**, have displayed very high enantioselectivities (Figure 4.5).

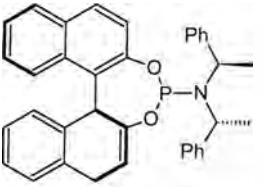
Phosphoramidite ligands derived from 2,2-binaphthol demonstrated versatility in copper-catalysed conjugate addition of $ZnEt_2$ to chalcone and 2-cyclohexenone.[21] Better enantioselectivities were obtained with ligands comprised of the sterically more demanding diisopropylamine moiety. Additional improvements were achieved using $Cu(OTf)_2$ instead of CuOTf due to better stability. The greatest advance in asymmetric induction using phosphoramidite ligands was accomplished after introduction of a stereogenic centre on the amine moiety. The presence of two additional stereogenic centres resulted in a matched (*S*, *R*, *R*; e.e. > 98%) and a mismatched (*S*, *S*, *S*; e.e. = 91%) combination. The absolute configuration of the product is mainly determined by the BINOL moiety, while the amine moiety fine-tunes enantioselectivity. An X-ray structure of copper iodide complex of the ligand provided insight into the ligand coordination, and hence, the mechanism controlling the addition stereochemistry. A bimetallic intermediate was suggested, that involves amine coordination to the zinc. This gives a better explanation of the role played by the amine in the addition stereocontrol.

TADDOL (α, α, α', α'-tetraaryl-1,3-dioxolane-4,5-dimethanol)-based ligands are substantial alternatives to BINOL-phosphoramidites for copper-catalysed asymmetric 1,4-addition. Very good e.e.s were obtained (96%) using TADDOL-phosphite **102**. As for the BINOL-based ligands, the TADDOL moiety is the main source of stereocontrol in copper-catalysed conjugate addition.



102[22]

Cyclohexenone 96% *ee*



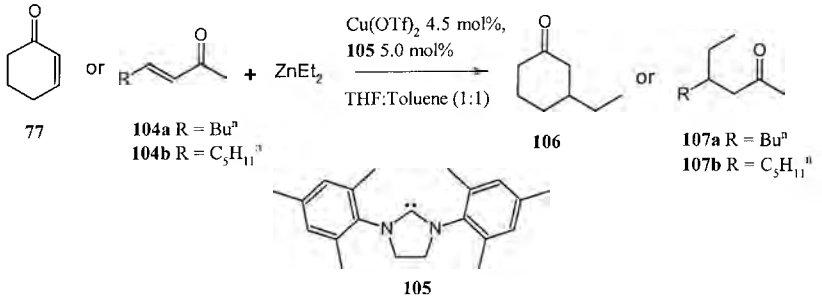
103[23, 24]

Cyclopentenone 10% *ee*
Cyclohexenone 98% *ee* (R)
Cycloheptenone 98% *ee*
Cyclooctenone 97% *ee*

Figure 4.5 TADDOL-phosphite **102** and BINOL-phosphoramidite **103** ligands in asymmetric conjugate addition of diethylzinc to cycloenones.

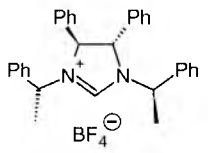
4.1.7 Chiral *N*-heterocyclic carbene ligands

Despite the great interest in *N*-heterocyclic carbenes (NHCs), there are still few applications to asymmetric conjugate addition. In 2001, Woodward *et al.* showed that Arduengo-type carbenes clearly accelerated the copper-catalysed conjugate addition of the diethylzinc to a range of enone substrates **77**, **104a** and **104b** (Scheme 4.3).[25] For example, the yield of **107a** was increased from 2% to 62% on addition of the carbene. The yield of **106** was increased from 14% to 82%.

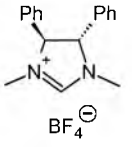


Scheme 4.3 Ligand and enones used in Woodward's LAC effect study.[25]

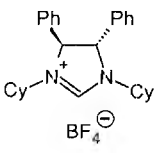
Soon after, Alexakis inspired by Woodward, synthesised a range of new chiral imidazolinium salts **108-112** (Figure 4.6), and was the first to use chiral carbene ligands in copper-catalysed 1,4-conjugate addition of diethylzinc to enones. Modest enantioselectivities were initially observed (e.e. = 0 – 27%).[26] Ligand precursors with stereogenic centres only on the imidazolinium salt carbon backbone gave the lowest e.e.s, presumably due to the stereogenic centres being removed from the metal centre. Better e.e.s were observed for ligand precursors with chiral *N*-substituents. The highest enantioselectivities were realised by **108**, which contained both types of stereogenic centre and displayed matched-pair behaviour. Changing the ring size of the carbene had no effect on the enantioselectivity, suggesting the ring size does not significantly change the conformation of the stereogenic centres. Also of interest is that **108** gives the (*R*) product whereas **111** gives the opposite absolute configuration. The ligand **108** gave the best results in dichloromethane (e.e. = 27%), whereas poor results (e.e. = 3%) were obtained in THF as expected for a Lewis base solvent.



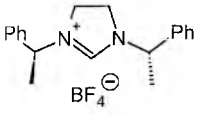
108



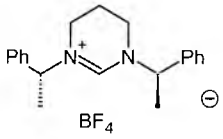
109



110



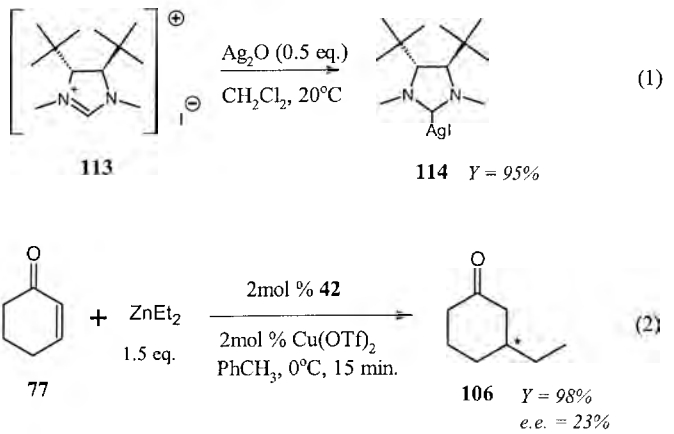
111



112

Figure 4.6 Imidazolinium salts containing multiple stereogenic centres.

In the meantime, Roland *et al.* reported the synthesis of a new chiral silver imidazolin-2-ylidene complex **114** and its application to copper-catalysed asymmetric conjugate addition (Scheme 4.4, (1)).[27] The chiral silver imidazolin-2-ylidenes complex **114** was obtained after deprotonation of the imidazolinium salt **113**, using silver (I) oxide (Ag_2O). The silver carbene complex was used to transfer the carbene ligand to the copper *in situ*, avoiding the need for addition of a strong base to deprotonate the imidazolinium salt (Scheme 4.4, (2)).

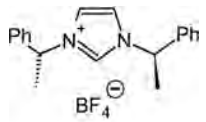


Scheme 4.4 Synthesis of chiral silver (I) carbene complex **114**, and its application to copper catalysed conjugate addition.

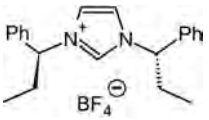
Excellent yields were obtained using toluene, hexane and diethyl ether. However, poor yields were obtained when dichloromethane and THF were used at room temperature. Similar results have been reported for phosphine- and amine-based ligands, where the usual trend is the deceleration of the reaction in the presence of coordinating solvents.[28,29] Only very modest e.e.s were observed, the best being 23%. Unexpectedly e.e.s were reduced when reactions were carried out at lower temperatures (-40 °C and -78 °C).

Alexakis *et al.* found that chiral imidazolium salts gave better e.e.s than chiral imidazolinium salts. The initial belief was that asymmetric induction in conjugate addition using imidazolinium salts **108** – **112** (Figure 4.6) would be higher than imidazolium salts due to their nucleophilicity and their ring distortion from planarity.

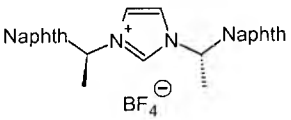
Changes in reaction conditions that improved e.e.s with phosphorous-based ligands, were tested on chiral imidazolium salt **115** (Figure 4.7).[30] The results revealed some improvement in enantioselectivity (from 39% e.e. to 54% e.e.) at lower temperature (-78°C) using Et_2O and different copper sources ($Cu(OAc)_2$ and or CuTC = copper thiophenecarboxylate).[31] Additional chiral imidazolium salts **116** – **118** were synthesised and tested giving similar e.e.s to **115** (up to 54% e.e.) (Figure 4.7).



115



116



117 = 1-Naphth
118 = 2-Naphth

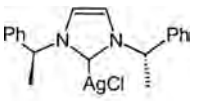
Figure 4.7 Chiral imidazolium salts

Alexakis also found that employing silver carbene complexes as ligand transfer reagents instead of generating the ligand *in situ* by deprotonation of the imidazolium salts, was more convenient.

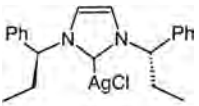
Chiral silver imidazolin-2-ylidenes and imidazol-2-ylidenes complexes **119** – **123**, were tested and evaluated in asymmetric copper-catalysed conjugate addition of diethylzinc to 2-cyclohexenone (Figure 4.8). The comparison was made between chiral imidazolium salts **115** – **117** and the corresponding chiral imidazol-2-ylidene complexes **119** – **121**. Better activities and enantioselectivities were realised with the

silver complexes. The best e.e. = 62% was attained using **119**. Chiral silver imidazolin-2-ylidene complexes **122** and **123** with stereogenic centres exclusively on the *N*-heterocycle at C^4 and C^5 positions were also synthesised and tested. The highest enantioselectivity was realised using **123** (e.e. = 69%) in diethyl ether at -78 °C with 2-cyclohexenone as substrate and CuTC as copper source. These improved results may be explained by an interaction between the zinc and the methoxy substituent.

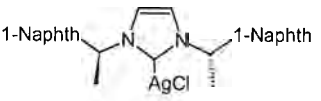
The chiral silver carbene complexes were also evaluated using different substrates. Higher enantioselectivities were observed using 2-cycloheptenone. An e.e. of 93% was obtained for addition to 2-cycloheptenone catalysed by $Cu(OAc)_2$/**121** in Et_2O at -78 °C.



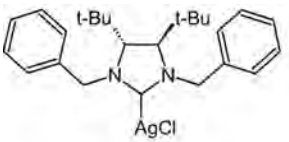
119



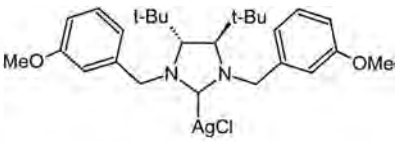
120



121



122



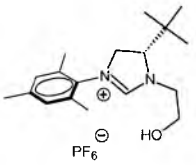
123

Figure 4.8 Range of chiral silver carbene complexes used in asymmetric conjugate addition.

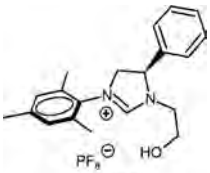
4.1.8 Mixed donor bidentate ligands containing a carbene donor group

Mauduit *et al.* have synthesised a range of bidentate chiral hydroxyalkyl imidazolin-2-ylidene ligands and evaluated their performance in asymmetric copper-catalysed conjugate addition of diethylzinc to 2-cyclohexenone (Figure 4.9).[32] The first generation of ligands **124** – **125** contain a single stereogenic centre on the ring backbone and gave e.e.s as high as 66%.[33] Use of chiral amino alcohols in the synthesis of hydroxyalkyl imidazolin-2-ylidene allowed the introduction of additional stereogenic centres to the ligand structure. It was observed that ligands **126** and **131** – **135** in which the stereogenic centre is α to the ring nitrogen gave the highest e.e.s. Surprisingly, ligands with stereogenic centres β to the ring nitrogen such as **127**, hence presumably close to the copper when the ligand is chelating, gave poorer results. *N*-mesityl derivative **131** gave higher enantioselectivities than the less sterically hindered phenyl derivative **128**, and the bulkier diisopropylphenyl **129** and *tert*-butyl **130** derivatives.

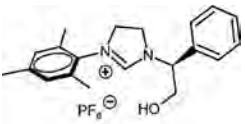
Chiral *N*-mesityl derivatives **131**, **134** and **135**, identified as the most efficient ligand precursors, were tested with a range of enones and dialkylzinc reagents (Table 4.2).[33b] Enantioselectivities, as high as 94%, were obtained for **135**.



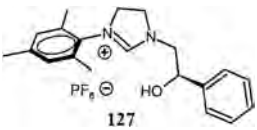
124
e.e. = 66%



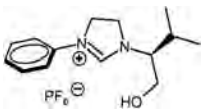
125
e.e. = 47%



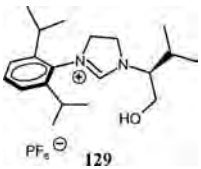
126
e.e. = 86%



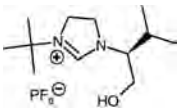
127
e.e. = 17%



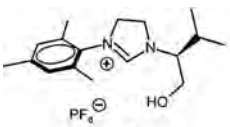
128
e.e. = 54%



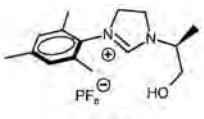
129
e.e. = 29%



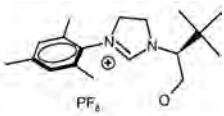
130
e.e. = 73%



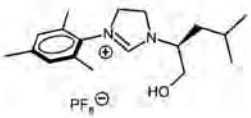
131
e.e. = 85%



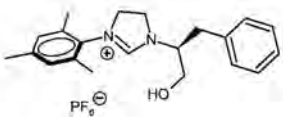
132
e.e. = 79%



133
e.e. = 87%



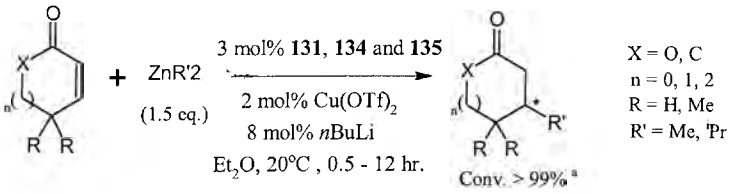
134
e.e. = 86%



135
e.e. = 83%

Figure 4.9 Chiral bidentate alkoxy-NHC ligands used by Mauduit in asymmetric conjugate addition of Et_2Zn to 2-cyclohexenone.[32,33]

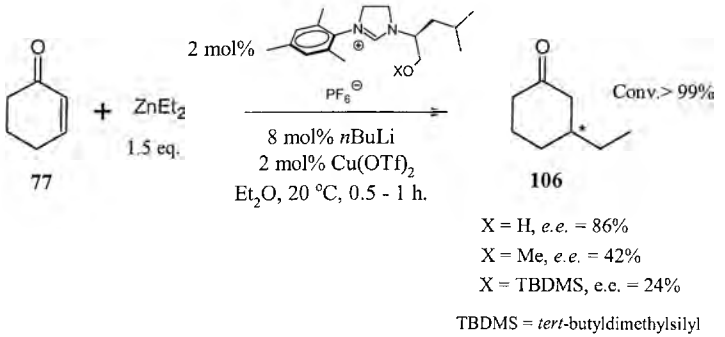
Table 4.2 Enantioselective copper-catalysed conjugate addition of dialkylzinc to cyclic enones



Entry	Ligand	Substrate			Alkylzinc	Time	E.e.
		X	n	R	ZnR'_2	(h)	(%)[b]
1	**131**	C	1	Me	$ZnEt_2$	2	85
2	**131**	C	2	H	$ZnEt_2$	2	86
3	**134**	C	1	H	$ZnMe_2$	3	88[c]
4	**134**	C	1	H	Zn^iPr_2	1	79
5	**134**	C	1	Me	$ZnEt_2$	12	93
6	**134**	C	2	H	$ZnEt_2$	0.5	90
7	**134**	O	1	H	$ZnEt_2$	1	72
8	**134**	C	0	H	Zn^iPr_2	1	53
9	**135**	C	1	Me	$ZnEt_2$	2	94

[a] Determined by GC analysis.
[b] Determined by chiral GC (Lipodex E).
[c] Determined by chiral GC (BTA).

Mauduit *et al.* investigated the importance of the hydroxymethylene side chain in the enantiocontrol of the conjugate addition (Scheme 4.5).[33b] Chiral alkoxy imidazolin-2-ylidene ligands with the hydroxyl function protected to prevent the covalent O-metal bonding, were synthesised and tested in enantioselective conjugate addition. The results indicated that chelation of alkoxy imidazolinylidene ligands to the metal was crucial for the enantiocontrol of the reaction since e.e.s were reduced from 86% for X = H to 24% for X = TBDMS (Scheme 4.6).



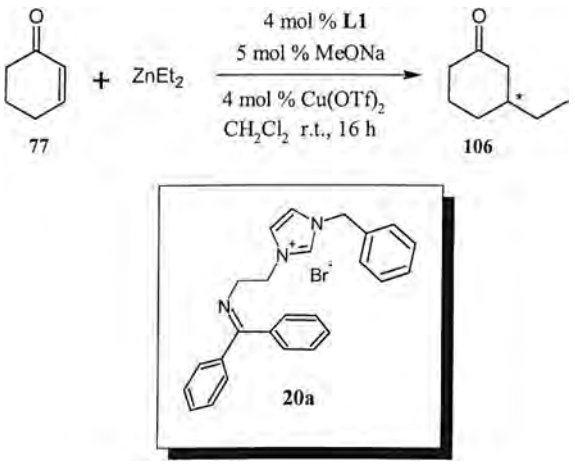
Scheme 4.6 Influence of hydroxyalkyl side chain in the enantiocontrol of asymmetric copper-catalysed conjugate addition.

4.2 Results

Structural and electronic similarities between our chiral bidentate iminoalkyl imidazol-2-ylidenes **20a**, **25a-d**, **26a**, **26b**, **26d** and **38 – 40** and the successful iminoalkyl phosphines **96 – 98** (Figure 4.4) in asymmetric copper-catalysed addition, suggested that **20a**, **25a-d**, **26a**, **26b**, **26d** and **38 – 40** may have the potential to induce enantioselection.[20] It is well documented that imidazol-2-ylidenes present the same strong σ-donation behaviour as phosphines and they had also demonstrated similar ligand accelerated catalyst effect in copper-catalysed conjugate addition. Furthermore, the similar chelating and donor properties of the hydroxyalkyl imidazolin-2-ylidenes reported by Mauduit *et al.* gave us encouragement.[33] However Mauduit's results suggested that the latent dative nitrogen coordination of an imino donor group may not be as effective as the covalent *O*-metal bonding that is expected from the hydroxyalkyl imidazolin-2-ylidenes.

4.2.1 Copper-catalysed 1,4-conjugate addition using an achiral imidazolium salt as ligand precursor.

Preliminary tests were carried out using the achiral imidazolium salt **20a** in order to determine activity towards conjugate addition and to maximise the yield (Scheme 4.7). Alexakis *et al.* found that non-polar solvent such as toluene and Et_2O higher e.e.s than polar solvents.[31] However, **20a** was poorly soluble in toluene and Et_2O, so was used instead.



Scheme 4.7 Conjugate addition catalysed by $Cu(OTf)_2$/**20a**.

The imidazolium salt **20a** (4 mol%) was deprotonated *in situ* using sodium methoxide (5 mol%) in CH_2Cl_2 to generate the corresponding free carbene. The use of NaOMe as a base is convenient, because the methanol formed after deprotonation of an imidazolium salt, is expected to have low effect on the catalytic process. A solution of copper (II) triflate (4 mol%) was added to the free carbene solution. The mixture was

stirred to generate the corresponding active catalyst. After 2 h of stirring to ensure maximum carbene complexation to the copper, the substrate 2-cyclohexenone **77** (1 equiv.) and diethylzinc (1.5 equiv.) were added. The reaction was then stirred overnight for 16 h at room temperature, and finally quenched using 2 M HCl solution. The 1,4-addition product **106** was obtained in 98% yield. Yields were determined by GC analysis using *n*-dodecane as internal standard.

4.2.2 Enantioselective copper-catalysed 1,4-conjugate addition using chiral imidazolium salts as ligand precursors.

Having established the optimum conditions for the use of iminoalkyl imidazolium salts as ligand precursors, chiral iminoalkyl imidazolium salts were tested for enantioselective conjugate addition. Firstly, the influence of the alkyl substituent at the stereogenic centre in the iminoalkyl side-chain derived from amino acids, for *N*-benzyl substituted imidazolium salts **25** was evaluated at room temperature (Table 4.5). As for the achiral imidazolium salt **20a**, yields were determined by GC analysis using *n*-dodecane as internal standard. Enantiomeric excesses were determined by chiral GC using an Alpha Dex™ 225 capillary column with the following temperature programme T_1 = 60 °C: 15 min; T_1 = 60 °C → T_2 = 120 °C: 10 °C/min; T_2 = 120 °C (Figure 4.10). The absolute configuration for each peak was deduced from comparison with experimental data reported by Arnold, obtained under the same conditions.[34] For each catalyst, the reaction was carried in duplicate.

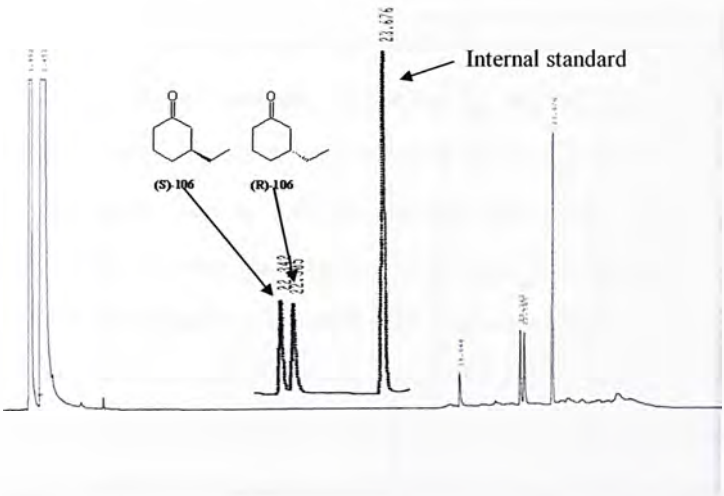
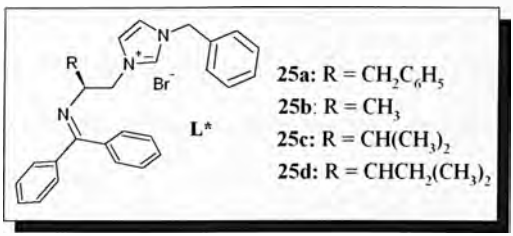


Figure 4.10 Chiral GC Chromatogram of conjugate addition product **106**.

Table 4.5 Copper-catalysed asymmetric 1,4-conjugate addition of Et_2Zn to 2-cyclohexenone using chiral *N'*-benzylimidazol-2-ylidene ligands



Entry	Ligand	R	Time	Yield (%)[a]	ee (%)[b]
1	**25a**	$CH_2C_6H_5$	15 h	92	2
2	**25b**	CH_3	15 h	78	7
3	**25c**	$CH(CH_3)_2$	15 h	91	3
4	**25d**	$CHCH_2(CH_3)_2$	15 h	88	1

[a] Determined by GC analysis
[b] Determined by chiral GC analysis

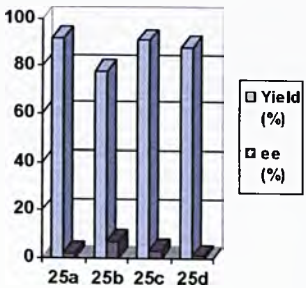
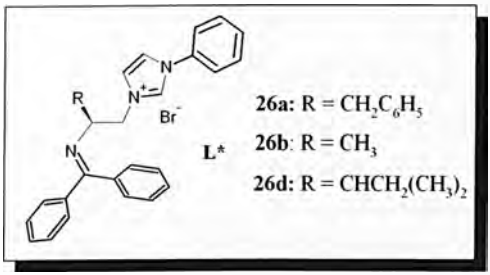
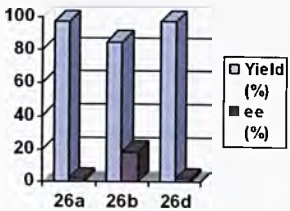


Table 4.6 Copper-catalysed asymmetric 1,4-conjugate addition of Et_2Zn to 2-cyclohexenone using chiral *N'*-phenylimidazol-2-ylidene ligands



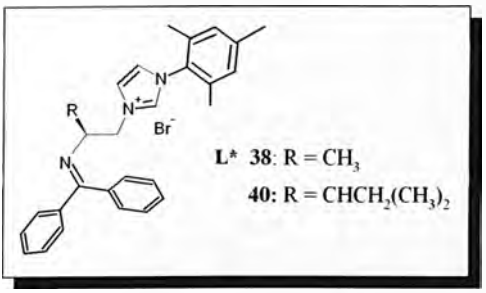
Entry	Ligand	R	Time	Yield (%)[a]	ee (%)[b]
1	**26a**	$CH_2C_6H_5$	15 h	97	2
2	**26b**	CH_3	15 h	85	18
3	**26d**	$CHCH_2(CH_3)_2$	15 h	97	2



[a] Determined by GC analysis
[b] Determined by chiral GC analysis

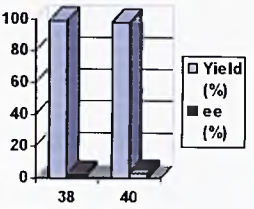
Indeed a significant increase in enantioselectivity for the *N*-phenyl substituted iminoalkyl imidazolylidene derived from alanine was seen compared to the *N*-benzyl derivative, up from 7% to 18%. However, the e.e. is still very low. Again steric bulk at the stereogenic centre appears to prevent enantiocontrol and e.e.s of just 2% were observed for **26a** and **26d**. It was hoped that *N*-mesityl substituted ligands would give further improvement, as seen by Mauduit *et al.* with alkoxy imidazolinylidenes.[33] Thus, the iminoalkyl *N*-mesityl imidazolium salts derived from alanine and leucinol were synthesised and tested (Table 4.7).

Table 4.7 Copper-catalysed asymmetric 1,4-conjugate addition of Et_2Zn to 2-cyclohexenone using chiral *N'*-mesitylimidazol-2-ylidene ligands



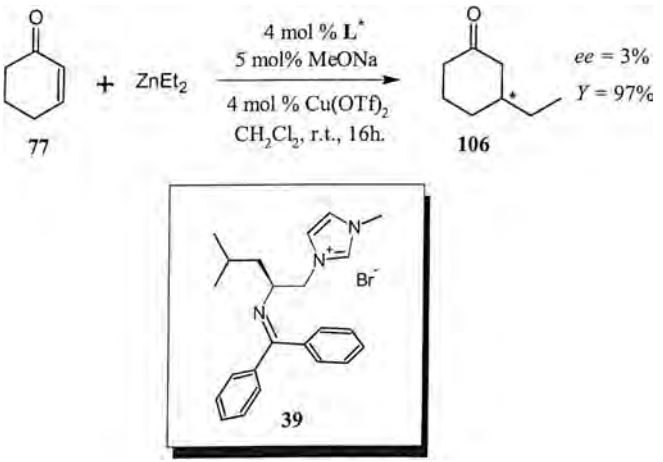
Entry	Ligand	R	Time	Yield (%)[a]	ee (%)[b]
1	**38**	CH_3	16h	99	2
2	**40**	$CHCH_2(CH_3)_2$	16h	98	3

[a] Determined by GC analysis
[b] Determined by chiral GC analysis



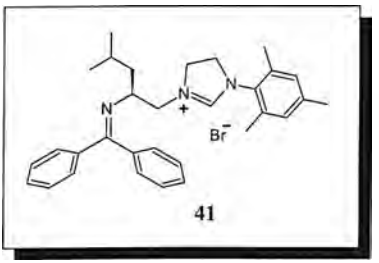
Surprisingly **38** and **40** gave near negligible e.e.s; for **38** the e.e. was significantly lower than the phenyl derivative. As the *N*-substituent obviously plays a role in achieving enantioselectivity, an iminoalkyl *N*-methyl imidazolium salt **39** was tested, this also gave low enantioselectivity (e.e. = 3%) (Scheme 4.8).

In all cases good conversions and high yields were obtained. However, the only ligand that showed any significant enantioselectivity was **25b** in which the alkyl substituent is methyl, however even for this ligand the e.e. was extremely low (7%). Other alkyl group such as isobutyl, isopropyl and benzyl gave negligible enantioselectivity. This suggests that steric bulk at the stereogenic centre may induce a hindrance to enantiocontrol of the addition. To explore this effect further, ligand sets that exhibit greater enantioselectivity were needed. The work of Mauduit *et al.* on the use of bidentate alkoxy imidazolinylidenes for enantioselective addition indicated that ligands with an *N*-aryl substituents gave very good e.e.s and variation of the alkyl substituent at the stereogenic centre only had a small effect on the enantioselectivity.[32] They found that the ligands with an *N*-mesityl substituent gave a higher e.e. than those with the less hindered phenyl group. The bulkier 2,6-diisopropyl aryl group gave a lower e.e. than either phenyl or mesityl. Hoveyda *et al.* has seen similar effects for allylic substitution.[35] Therefore, the performance of *N*-phenyl substituted iminoalkyl imidazolylidenes **26a**, **26b** and **26d**, derived from alanine, phenylalanine and leucinol, was evaluated (Table 4.6).



Scheme 4.8 Conjugate addition catalysed by $Cu(OTf)_2$/**39**.

The highest asymmetric inductions reported by Mauduit in conjugate addition, were realised using hydroxylalkyl *N*-mesitylimidazolinium salts. Hence the iminoalkyl *N*-mesitylimidazolinium salt **41** was tested (Figure 4.11). Despite good activity (99% yield), an e.e. of only 2% was observed unfortunately, compound **41** initially designed for allylic substitution presents two main differences with Mauduit's best ligand. **41** presents weak imine coordination to copper compared to the strong O-copper covalent bond. The other difference is the position of the stereogenic centre. Mauduit's best results were realised for ligands featuring a stereogenic centre on the alkyl chain α to the *N*-heterocycle, **41** whereas has a stereogenic centre β- to the *N*-heterocycle.

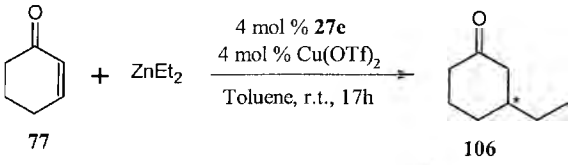


41

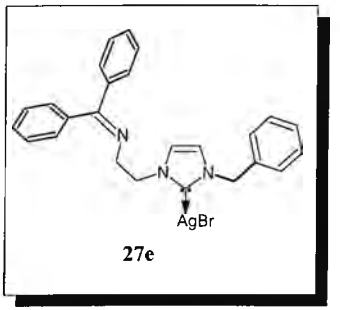
Figure 4.11 Ligand precursor **41** used in copper-catalysed conjugate addition.

4.2.3 Enantioselective copper-catalysed 1,4-conjugate addition using imidazolylidene silver complexes as ligand precursors.

As Alexakis realised improved results with silver imidazolin-2-ylidene complexes as carbene transfer reagents for this reaction,[31] the activity of achiral silver imidazol-2-ylidene **27e** in conjugate addition was tested. The copper catalyst was generated by mixing $Cu(OTf)_2$ and the silver imidazol-2-ylidene complex **27e** in 1:1 ratio for 1 h in toluene or dichloromethane. The internal standard *n*-dodecane was added followed by addition of cyclohexenone and diethylzinc. The reaction was carried in duplicate. After 17 h the conversions obtained were 32% in dichloromethane and 73% in toluene (Scheme 4.9). The results were consistent with those reported by Roland.[27]



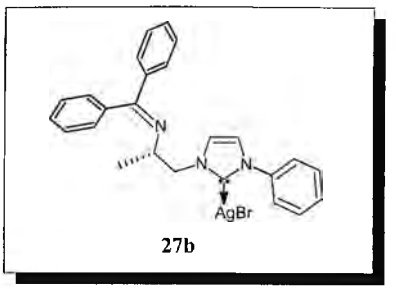
77 106



27e

Scheme 4.9 Ligand precursor **27e** used in copper-catalysed conjugate addition.

As the use of silver imidazolylidene complex **27e** as a carbene transfer reagent in toluene proved to be successful in copper-catalysed conjugate addition, the chiral silver imidazolylidene **27b** was tested for enantioselective addition (Figure 4.12). The reaction was carried out in toluene at room temperature for 17 h. The product was obtained in 99% yield with an e.e. of 18%.



27b

Figure 4.12 Ligand precursor **27b** used in copper-catalysed conjugate addition

Unfortunately, no significant improvements were achieved with the silver complex **27b** compared to the imidazolium salts **26b**. Although some improvements observed in activity, similar enantioselectivity was attained. This could be attributed to not using the hygroscopic imidazolium salt.

4.3 Discussion

The mechanism of the copper-catalysed conjugate addition of diethylzinc to 2-cyclohexenone has not been fully elucidated. A likely key intermediate is a monoalkyl copper (I) complex. A general catalytic cycle has been presented in scheme 4.2. In this work $Cu^{II}(OTf)_2$ has been used as the copper source, because this has been demonstrated to give better results than copper halide salts. $Cu^{II}(OTf)_2$ was preferred over $Cu^{I}(OTf)$ due to its greater stability. To generate the ligated copper species **80**, the free imidazol-2-ylidene is generated by deprotonating the imidazolium salt with sodium methoxide followed by addition of $Cu^{II}(OTf)_2$ to give a yellow solution of **80**. It is thought that the zinc reagent reduces the copper (II) species to the active copper (I) catalyst.

The exact role of the potential bidentate ligand is not clear. High selectivities have been observed for monodentate ligands such as the phosphoramidite **103** (Figure 4.5) and also for bidentate *P*, *N* arylphosphines (Figure 4.4). The very modest e.e.s observed here are comparable to those observed in the first reports of enantioselective addition using monodentate chiral imidazolinylidene ligands.[26,27] In these cases the best e.e.s were observed for ligands with a chiral nitrogen substituent rather than ligands derived from imidazolinium salts with the stereogenic centre on the

imidazolinylidene backbone (Figures 4.6 & 4.7). Chelating hydroxyalkyl imidazolylidenes reported by Mauduit *et al.*[33] and Arnold *et al.*[36] gave much better results than those of our iminoalkyl imidazolylidenes. The work of Hoveyda *et al.* indicates that the bidentate nature of the hydroxybinaphtalene imidazolin-2-ylidene ligand is critical for copper-catalysed enantioselective allylic alkylation.[35] An air stable copper complex of the chiral imidazol-2-ylidene was structurally characterised by Hoveyda *et al.*[35], demonstrating the bidentate nature of the hydroxybinaphtalene imidazolinylidene ligand. Secondly the hydroxyalkyl imidazolin-2-ylidene demonstrated much greater activity than the methoxy derivative. This suggests that a covalent metal oxygen bond rather than a dative methoxy-metal bond is critical for high enantioselectivity.

The low e.e.s observed for our ligands, suggest that a dative imino-metal may not be sufficient to ensure chelation of the ligand in the transition state and hence facilitate enantiocontrol. In fact, as our results are comparable to those seen for monodentate ligands[26], it is possible that the ligand is not chelated (Figure 4.13).

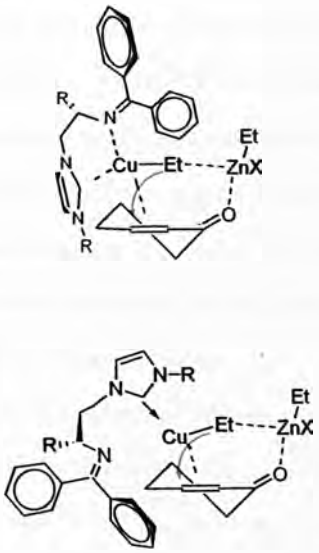


Figure 4.13 Possible chelating and non-chelating structures of copper intermediate **80**.

One other possibility for potential bidentate ligands is that the oxygen or nitrogen could interact with the Lewis acid zinc species. However, this is thought to be less likely for cyclohexenone than for acyclic enones, which can adopt a *cis* configuration. Mauduit's results suggest that the *N*-mesityl group played a key role in hindering one side of the ligand, and blocking the approach of the substrate from that direction, and also that the nature of the stereogenic centre was not significant for enantioselectivity. The results presented here differ in that *N*-phenyl derivatives gave better results than the mesityl analogue. The nature of the stereogenic centre seems to play a key role given that significant enantioselectivities are only achieved when R = Me, bulkier substituents give much poorer results.

4.4 Conclusion and future work

Iminoalkyl imidazolylidenes have shown disappointing selectivities in asymmetric conjugate addition. This is likely to be due to a lack of bidentate coordination of the ligand in the enantiodetermining step. The success of hydroxyalkyl NHC suggests that aminoalkyl imidazol-2-ylidenes should also be active ligands in asymmetric conjugate addition. Their matched pair behaviour seen by Alexakis suggests that replacing the imidazolylidene function with an imidazolin-2-ylidene, containing stereogenic centres on the ring backbone would give improved results.

Information on the structure of the transition state species in asymmetric conjugate addition to 2-cyclohexenone is very limited. A number of models have been suggested, such as **131** in Figure 4.13 where the ligand controls which face of the substrate coordinates to the copper, which in return sets up the delivery of the alkyl group. The only structure of an imino-carbene copper complex showed that imino-carbene did not chelate.[37] In fact, the ligand bridges two copper centres. The ^{13}C NMR spectrum of the imino-carbene copper complex displayed significant change in chemical shifts for the C(=N)O carbon (152.5 ppm) compared to that of the ligand precursor (148.8 ppm) which may indicate weak oxazoline coordination.

The synthesis of achiral aminoalkyl *N*-phenyl imidazolium hydrobromide salts **12** has already been achieved in good yields, *via* N-alkylation of 1-phenyl and 1-methyl imidazoles using achiral 2-bromoethylamine hydrobromide. A wider variety of chiral aminoalkyl N-substituted imidazolium bromide hydrobromide salts should be easily synthesised using the same procedure. Deprotonation of the amino group and the imidazolium salt in the presence of copper salt could generate aminoalkyl imidazol-2-ylidene copper species, which may prove better catalysts.

4.5 Typical procedures

Typical procedure for conjugate addition using imidazolium salt in CH_2Cl_2 at room temperature

A dry Schlenk tube was charged with imidazolium salt (0.04 mmol, 4 mol%), NaOMe (0.0027 g, 0.05 mmol, 5 mol%) and CH_2Cl_2 (3 ml). The mixture was stirred for 1 h at room temperature to generate the free carbene. A solution of $Cu(OTf)_2$ (0.014 g, 0.04 mmol, 4 mol%) in CH_2Cl_2 (1 ml) was then added. The mixture was stirred for 1h at room temperature to form the active catalyst. The internal standard dodecane (50 μl) was added followed by addition of the substrate 2-cyclohexenone (0.096 g, 1 mmol, 1 equiv.) and 1.0 M solution of $ZnEt_2$ in hexane (1.5 mol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 15 – 16 h. The mixture was then quenched using a solution of HCl (2.0 M, 2 ml). The resulting mixture was stirred for 1 h and extracted with Et_2O (3 x 10 ml). The yield was obtained by GC analysis: HP-5 (Crosslimked 5% Ph Me silicone) 25 m x 0.32 mm x 0.52 μm. The e.e was obtained by chiral GC analysis: Alpha Dex™ 225 capillary column 30 m x 0.25 mm, 0.25 μm.

Typical procedure for conjugate addition using silver imidazolylidene complexes in toluene at room temperature

A dry Schlenk tube was charged with silver imidazolylidene complex (0.04 mmol, 4 mol%), $Cu(OTf)_2$ (0.014 g, 0.04 mmol, 4 mol%) and toluene (3 ml). The mixture was stirred for 1 h at room temperature protected from light to form the active catalyst. The internal standard dodecane (50 μl) was added followed by addition of the

substrate 2-cyclohexenone (0.096 g, 1 mmol, 1 equiv.) and 1.0 M solution of $ZnEt_2$ in hexane (1.5 mol, 1.5 equiv.). The reaction mixture was stirred at room temperature for 17 h. The mixture was then quenched using a solution of HCl (2.0 M, 4 ml). The resulting mixture was stirred for 1 h and extracted with Et_2O (3 x 10ml). The yield and e.e. were determined as above.

4.6 References

1. N. Krause, E. Hoffmann-Roder, *Synthesis*, 2001, **2**, 171.
2. H.-G. Schmalz, *In Comprehensive Organic Synthesis*, Eds: B. M. Trost, I. Fleming, Oxford, Pergamon Press, 1991, Vol . **4**, Chapter 1.5.
3. For Li see: a) J. L. Wardell, *Comprehensive Organometallic Chemistry*, G. Wilkinson, F. G. A. Stone, E. W. Abel, Eds; Pergamon: Oxford, 1982, Vol. **1**; b) M. A. Beswick, D. S. Wright, *Comprehensive Organometallic Chemistry II*, G. Wilkinson, F. G. A. Stone, E. W. Abel, Eds.; Pergamon; Oxford, 1995, Vol. 1.
4. M. S. Karash, P. O. Tawney, *J. Am. Chem. Soc.*, 1941, **63**, 2308.
5. H. Gilman, L. A. Woods, *J. Am. Chem. Soc.*, 1943, **65**, 435.
6. H. Gilman, R. G. Jones, L. A. Woods, *J. Org. Chem.*, 1952, **17**, 1630.
7. J. A. Kozlowski, *In Comprehensive Organic Synthesis*, Eds: B. M. Trost, I. Fleming, Oxford, Pergamon Press, 1991, Vol . **4**, 169.
8. F. Leyendecker, D. Laucher, *Tetrahedron Lett.*, 1983, **24**, 3517.
9. G. M. Villacorta, C. P. Rao, S. J. Lippard, *J. Am. Chem. Soc.*, 1988, 110, 3175.
10. A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry*, 1993, **4**, 2427.
11. P. Knochel, J. J. Perea, P. Jones, *Tetrahedron*, 1998, **54**, 8275.
12. B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, H. M. de Vries, *Angew. Chem. Int. Ed. Engl.*, 1997, **36**, 2620.
13. A. Alexakis, J. Burton, J. Vastra, P. Mangeney, *Tetrahedron: Asymmetry*, 1997, **8**, 3987.
14. Y. Yamanoi, T. Imamoto, *J. Org. Chem.*, 1999, **64**, 2988.
15. A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.*, 2002, 3221.

16. C. Benhaim, Ph.D. Thesis, *Univ. Geneva*, 2002.

17. E. L. Stangeland, T. Sammakia, *Tetrahedron*, 1997, **53**, 16503.

18. a) Y. Takemoto, S. Kuraoka, N. Hamaue, K. Aoe, H. Hiramatsu, C. Iwata, *Tetrahedron*, 1996, 52, 14177; b) Y. Takemoto, S. Kuraoka, N. Hamaue, C. Iwata, *Tetrahedron: Asymmetry*, 1996, **7**, 993.

19. C. Benhaim, A. Tomassini, A. Alexakis, unpublished results.

20. T. Morimoto, Y. Yamaguchi, M. Suzuki, A. Saitoh, *Tetrahedron Lett.*, 2000, **41**, 10025.

21. A.H.M. De Vries, A. Meetsma, B. L. Feringa, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2374.

22. A. Alexakis, J. Vastra, J. Burton, C. Benhaim, P. Mangeney, *Tetrahedron Lett.*, 1998, **39**, 7869.

23. B. L. Feringa, M. Peneschi, L. A. Arnold, R. Imbos, A. H. M. De Vries, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620.

24. R. Naasz, L. A. Arnold, M. Pineschi, E. Keller, B. L. Feringa, *J. Am. Chem. Soc.*, 1999, **121**, 1104.

25. P. K. Fraser, S. Woodward, *Tetrahedron Lett.*, 2001, **42**, 2747.

26. F. Guillen, C. L. Winn, A. Alexakis, *Tetrahedron: Asymmetry*, 2001, **12**, 2083.

27. J. Pytkowicz, S. Roland, P. Mangeney, *Tetrahedron: Asymmetry*, 2001, **12**, 2087.

28. A. Alexakis, J. Vastra, P. Mangeney, *Tetrahedron Lett.*, 1997, **38**, 7745.

29. A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.*, 2002, 3221.

30. A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.*, 2002, **124**, 5262.

31. A. Alexakis, F. Guillen, C. L. Winn, J. Pytkowicz, S. Roland, *Adv. Synth. Catal.*, 2003, **3**, 345.

32. H. Clavier, L. Boulanger, N. Audic, L. Toupet, J.-C. Guillemin, M. Mauduit, Chem. Commun., 2004, 1224.

33. a) H. Clavier, L. Coutable, J.-C. Guillemin, M. Mauduit, *Tetrahedron: Asymmetry*, 2005, **16**, 921; b) H. Clavier, L. Coutable, L. Toupet, J.-C. Guillemin, M. Mauduit, *J.Organomet. Chem.*, 2005, **690**, 5237.

34. A. E. Arnold, 2002, *Phosphoramidite as ligands for copper in catalytic asymmetric C-C bond formation reactions with organozinc reagents*, PhD Thesis, University of Groningen, Groningen, The Netherlands.

35. A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell, A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 11130.

36. a) P. L. Arnold, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.*, 2001, 2340; b) P. L. Arnold, M. Rodden, K. M. Davis, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.*, 2004, 1612.

37. N. Schneider, V. César, S. Bellemin-Laponnaz, L. H. Gade, *J.Organomet. Chem.*, 2005, **690**, 5556.

5. Experimental

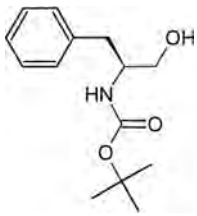
5.1 Reagents and instrumentation

Reactions were carried out under nitrogen using Schlenk tubes or round-bottom flasks. Toluene, diethyl ether and THF were dried over sodium in the presence of benzophenone as indicator. Dichloromethane was dried over anhydrous calcium chloride. Reagents and other dry solvents were purchased from Sigma-Aldrich. 1-mesitylimidazole[1], 1-mesitylimidazoline[2], (*E*)-1,3-diphenylprop-2-en-1-ylacetate[3], $Pd(PhCN)_2Cl_2$[4] and were prepared using literature procedures.

NMR spectra were recorded at 300 MHz (^1H) and 75 MHz (^{13}C) on a Brüker AM 300 spectrometer, or at 400 MHz (^1H) and 100 MHz (^{13}C) on a Jeol Eclipse$^+$ 400 NMR spectrometer using Jeol Delta version 4.3.6. control and processing software. Chemical shifts are reported in ppm, downfield from tetramethylsilane (TMS) internal reference. Proton and carbon NMR spectra were referenced to the chemical shift of the solvent residual proton signals. ^{13}C HetCor and ^{13}C DEPT 135 experiments were performed using default Jeol pulse sequences. FT-IR spectra were recorded on a Brüker Tensor27 FT-IR spectrometer using OPUS version 4.0 control and processing software. Melting points were measured using a Stuart Scientific SMP3 advance melting point apparatus and were uncorrected. GC analyses were implemented using Varian 3400 GC with flame ionisation detector. Chiral GC analyses were performed using a Carlo Erber HIGC 5160 GC with flame ionisation detector.

Absolute configurations were determined by optical activity measurement using an AA-10 automatic polarimeter (Optical Activity Ltd). Elemental analyses were carried out at the CHN Microanalysis service at the University of London. High resolution mass spectroscopy analyses were carried out either at King's College London or at the EPSRC National Mass Spectroscopy Service Centre. The crystallography was performed by Peter Hitchcock at Sussex University.

5.2 Procedures and analytical data

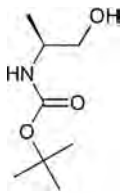


***(S)*-2-(*tert*-Butoxycarbonyl-amino)-3-phenyl-1-propanol (6a).**

6a was prepared according to the literature methods.[5]

Di-*tert*-butyl dicarbonate (2.21 g, 10.10 mmol) was added to an ice-cooled solution of L-phenylalaninol **2** (1.25 g, 8.55 mmol) and triethylamine (1.02 g, 10.10 mmol) in dichloromethane (30 ml). The reaction mixture was stirred at 0 °C for 1 h at room temperature overnight. The reaction mixture was then washed with brine (3 x 30 ml) and dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure affording **6a** as a white solid (1.76 g, quant); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 1.40 (s, 9H, C(CH_3)$_3$), 2.84 (d, 2H, CH_2-OH, J = 7.1 Hz), 3.06 – 3.14 (m, 1H, O*H*), 3.49 – 3.72 (m, 2H, CH_2-C_6H_5), 3.77 – 3.95 (m, 1H, N*H*), 4.82 (s, 1H, N*H*), 7.13 – 7.37 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C 28.4 (3C, C(CH_3)$_3$), 37.5 (1C, CH_2-C_6H_5), 53.6 (1C, *C*H-N), 63.9 (1C, CH_2-OH), 79.7 (1C,

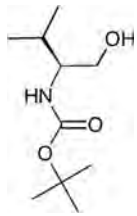
$C(CH_3)_3$), 126.5 (1C, *p*-C_6H_5), 128.5 (2C, *o*-C_6H_5), 129.3 (2C, *m*-C_6H_5), 138.0 (1C, *ipso*-C_6H_5), 156.2 (1C, *C*=O).



***(S)*-2-(*tert*-Butoxycarbonyl-amino)-1-propanol (6b).**

6b was prepared according to the literature methods.[6]

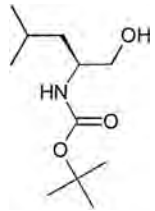
A solution of di-*tert*-butyl dicarbonate (27.66 g, 126.7 mmol) in dichloromethane (50 ml) was added dropwise to an ice-cooled solution of alaninol **3** (10.02 g, 133.4 mmol) in dichloromethane (150 ml). The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The solution was then washed with aqueous 20% citric acid (3 x 100 ml) and brine (200 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield **14a** as a white solid (18.29 g, 88%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.12 (d, 3H, C*H*$_3$, J = 6.8 Hz), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 2.79 (s, 1H, O*H*), 3.42-3.66 (m, 2H, C*H*$_2$-OH), 3.68 – 3.88 (m, 1H, C*H*-N), 4.68 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 17.1 (1C, *C*H$_3$), 28.3 (3C, C(*C*H$_3$)$_3$), 48.5 (1C, *C*H-N), 67.4 (1C, *C*H$_2$-OH), 79.5 (1C, *C*(CH$_3$)$_3$), 156.4 (1C, *C*=O).



***(S)*-2-(*tert*-Butoxycarbonyl-amino)-3-methyl-1-butanol (6c).**

6c was prepared according to the literature methods.[6]

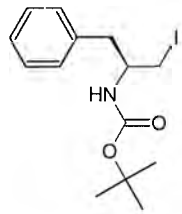
A solution of di-*tert*-butyl dicarbonate (20.10 g, 92.08 mmol) in dichloromethane (14 ml) was added dropwise to an ice-cooled solution of L-valinol **13b** (10.00 g, 96.93 mmol) in dichloromethane (36 ml). The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction was then washed with aqueous 20% citric acid (3 x 100 ml) and brine (200 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield **15a** as a colourless and translucent oil (20.65 g, quant.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (d, 3H, CH(CH_3)$_a$, J = 6.8 Hz), 0.90 (d, 3H, CH(CH_3)$_b$, J = 6.8 Hz), 1.40 (s, 9H, C(CH_3)$_3$), 1.71 – 1.88 (m, 1H, C*H*(CH_3)$_2$), 2.98 (br s, 1H, O*H*), 3.32 – 3.43 (m, 1H, C*H*-N), 3.55 (dd, 1H, CH_a-OH, J = 11.1 Hz, J = 6.3 Hz), 3.63 (dd, 1H, CH_b-OH, J = 11.1 Hz, J = 3.7 Hz), 4.81 (d, 1H, N*H*, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 18.4 (1C, CH(CH_3)$_a$), 19.4 (1C, CH(CH_3)$_b$), 28.3 (3C, C(CH_3)$_3$), 29.2 (1C, *C*H(CH_3)$_2$), 57.9 (1C, *C*H-N), 63.8 (1C, *C*H_2-OH), 79.4 (1C, *C*(CH_3)$_3$), 156.8 (1C, *C*=O).



***(S)*-2-(*tert*-Butoxycarbonyl-amino)-4-methyl-1-pentanol (6d).**

6d was prepared according to the literature methods.[6]

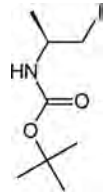
A solution of di-*tert*-butyl dicarbonate (17.69 g, 81.06 mmol) in dichloromethane (100 ml) was added dropwise to an ice-cooled solution of L-leucinol **5** (15.78 g, 134.65 mmol) in dichloromethane (250 ml). The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. The reaction was then washed with aqueous 20% citric acid (4 x 100 ml) and brine (2 x 200 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure to yield **6d** as a colourless and translucent oil (31.19 g, quant.); ^{1}H NMR ($CDCl_3$, 400MHz) δ_H 0.88 (d, 3H, $CH(CH_3)_a$, J = 1.5 Hz), 0.90 (d, 3H, $CH(CH_3)_b$, J = 1.5 Hz), 1.23 – 1.31 (m, 2H, CH_2-$CH(CH_3)_2$), 1.41 (s, 9H, $C(CH_3)_3$), 1.56 – 1.69 (m, 1H, $CH(CH_3)_2$), 2.89 (br s, 1H, OH), 3.46 (dd, 1H, CH_a-OH, J = 10.9 Hz, J = 5.8 Hz), 3.59 (dd, 1H, CH_b-OH, J = 10.9 Hz, J = 3.5 Hz), 3.62 – 3.73 (m, 1H, CH-N), 4.67 (d, 1H, NH, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100MHz) δ_C 22.2 (1C, $CH(CH_3)_a$), 23.0 (1C, $CH(CH_3)_b$), 24.7 (1C, $CH(CH_3)_2$), 28.3 (3C, $C(CH_3)_3$), 40.5 (1C, CH_2-$CH(CH_3)_2$), 50.9 (1C, CH-N), 66.3 (1C, CH_2-OH), 79.5 (1C, $C(CH_3)_3$), 156.5 (1C, C=O).



***(S)*-2-(*tert*-Butoxycarbonyl-amino)-1-iodo-3-phenylpropane (7a).**

7a was prepared according to the literature methods.[7]

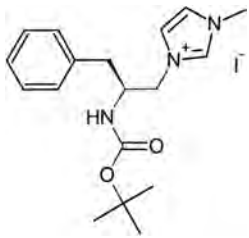
Iodine (16.66 g, 65.65 mmol) was slowly added to a solution of triphenylphosphine (15.65 g, 59.68 mmol) and imidazole (4.06 g, 59.68 mmol) in dichloromethane (130 ml). After five minutes, a solution of **6a** (15.00 g, 59.68 mmol) in dichloromethane (120 ml) was added. Stirring was maintained at room temperature until no starting material remained, as judged by TLC (hexane-EtOAc, 5:1). The solvent was removed and the residue was filtered through a short column of silica, eluting with diethyl ether. The solution was concentrated to give a dark oil. The crude product was then purified by flash chromatography (hexane-EtOAc, 5:1). The solvent was removed under reduced pressure affording **7a** as a white solid (3.55 g, 26%); ^{1}H NMR ($CDCl_3$, 300MHz) δ_H 1.44 (s, 9H, C(CH_3)$_3$), 2.77 (dd, 1H,CH_a-C_6H_5, J = 8.1 Hz, J = 13.5 Hz), 2.91 (dd, 1H, CH_b-C_6H_5, J = 5.8 Hz, J = 13.5 Hz), 3.17 (dd, 1H, CH_a-I, J = 3.8 Hz, J = 10.2 Hz), 3.40 (dd, 1H, CH_b-I, J = 3.8 Hz, J = 9.5 Hz), 3.51 – 3.71 (m, 1H, CH-N), 4.53 – 4.80 (m, 1H, NH), 7.17 – 7.39 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 75.5MHz) δ_C 28.3 (3C, C(CH_3)$_3$), 40.6 (2C, CH_2-C_6H_5 + CH_2-I), 51.0 (1C, CH-N), 79.9 (1C, C(CH_3)$_3$), 126.9 (1C, p-C_6H_5), 128.7 (2C, o-C_6H_5), 129.2 (2C, m-C_6H_5), 137.1 (1C, *ipso*-C_6H_5), 154.9 (1C, C=O).



***(S)*-2-(*tert*-Butoxycarbonyl-amino)-1-iodopropane (7b).**

7b was prepared according to the literature methods.[7]

Iodine (3.19 g, 65.65 mmol) was slowly added to a solution of triphenylphosphine (2.99 g, 11.4 mmol) and imidazole (0.78 g, 11.4 mmol) in dichloromethane (30 ml). After five minutes, a solution of **6b** (2.00 g, 11.4 mmol) in dichloromethane (20 ml) was added. Stirring was maintained at room temperature until no starting material remained, as judged by TLC (hexane/EtOAc, 5:1). The solvent was removed under reduced pressure and the residue was filtered through a short column of silica using diethyl ether as eluent. The filtrate was concentrated to give a dark oil. The crude product was then purified by flash column chromatography (hexane/EtOAc, 5:1). The solvent was removed under reduced pressure affording **7b** as a white solid (0.64 g, 20%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 0.90 (d, 3H, CH_3, J = 6.5 Hz), 1.24 (s, 9H, $C(CH_3)_3$), 3.28 (dd, 1H, CH_aI, J = 9.9 Hz, J = 3.7 Hz), 3.32 – 3.44 (m, 1H, CH_bI), 3.45 – 3.59 (m, 1H, C*H*-N), 4.62 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C 21.1 (1C, CH_3-CH), 28.4 (3C, $C(CH_3)_3$), (1C, CH_2-I), 45.9 (1C, CH-N), 79.8 (1C, $C(CH_3)_3$), 154.8 (1C, C=O).

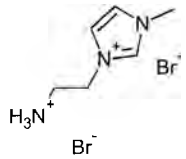


1-{*(S)*-2-(*tert*-Butoxycarbonyl-amino)-3-phenyl-propyl}-3-methylimidazolium iodide (8).

1-methylimidazole (0.52 g, 6.28 mmol) was added to a solution of **7a** (2.00 g, 5.54 mmol) in toluene (50 ml). The reaction mixture was refluxed until no starting material remained, as judged by TLC (hexane/EtOAc, 5:1). The solvent was removed to give a mixture of **8** and **9** as a dark oil. Attempts to purify the crude product by re-crystallisation failed to isolate the desired product. Only characteristic peaks of the N-*t*-Boc protected aminoalkyl imidazolium salt **8** have been reported; ^{1}H NMR (DMSO-d_6, 300 MHz) δ_H 1.27 (s, 9H, C(CH_3)$_3$), 2.70 – 2.90 (m, 2H, CH_2-NCH=CHN), 3.95 – 4.00 (m, 4H, CH_3-NCH=CHN + C*H*-N), 4.07 – 4.20 (m, 2H, CH_2-C_6H_5)), 7.15 – 7.35 (m, 5H, C_6H_5), 7.49 (s, 1H, NC*H*=CHN), 7.57 (s, 1H, NCH=C*H*N), 8.72 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ_C (1C, CH_3-NCH=CHN), 28.2 (3C, C(CH_3)$_3$), (1C, C(CH_3)$_3$), 41.2 (1C, CH_2-C_6H_5), 119.9 (1C, NCH=CHN), 120.8 (1C, NCH=CHN), 127.2 (1C, *p*-C_6H_5), 129.0 (2C, *m*-C_6H_5), 129.1 (2C, *o*-C_6H_5), 136.0 (1C, *ipso*-C_6H_5), 189.2 (1C, C=O) .

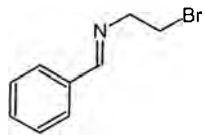
1-{2-amino-ethyl hydrobromide}-3-phenylimidazolium bromide (12).

1-Phenylimidazole (1.94 g, 13.5 mmol) was added to a solution of 2-bromoethylamine, hydrobromide **15** (2.76 g, 13.5 mmol) in acetonitrile (15 ml). The reaction mixture was stirred under reflux for 15 h. The solid precipitate formed was filtered and washed with Et_2O (2 x 10 ml). The solid was then recrystallised from hot ethanol and dried under vacuum, affording **12** as a white solid (4.42 g, 94%); ^1H NMR (CD_3OD, 300 MHz) δ_H 3.52 (t, 2H, CH_2-NCH=CHN, J = 5.5 Hz), 4.62 (t, 2H, CH_2-NH_3^+ J = 5.5 Hz), 7.55 – 7.90 (m, 5H, C_6H_5), 8.11 (s, 1H, NCH=CHN), 8.28 (s, 1H, NCH=CHN), 8.37 (br s, 3H, NH_3^+), 8.43 (s, 1H, NCH=CHN), 10.01 (s, 1H, NCHN); ^{13}C NMR (CD_3OD, 75.5 MHz) δ_C 40.3 (1C, CH_2-N), 46.7 (1C, CH_2-NCH=CHN), 121.1 (1C, p-C_6H_5), 121.7 (2C, o-C_6H_5), 123.5 (1C, NCH=CHN), 129.7 (1C, NCH=CHN), 130.1 (2C, m-C_6H_5), 134.6 (1C, NCHN).



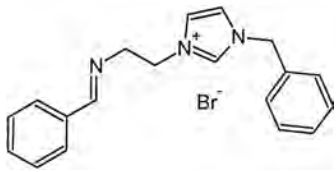
1-{2-amino-ethyl hydrobromide}-3-methylimidazolium bromide (13).

1-Methylimidazole (2.06 g, 24.4 mmol) was added to a solution of 2-bromoethylamine, hydrobromide **15** (2.76 g, 13.5 mmol) in acetonitrile (15 ml). The reaction mixture was stirred under reflux for 64 h. The precipitate was filtered and washed with Et_2O (2 x 10 ml). The solid was then recrystallised from hot ethanol and dried under vacuum, affording **13** as a white solid (0.47 g, 2.27 mmol); ^{1}H NMR (CD_3OD, 300 MHz) δ_H 3.88 (t, 2H, C*H*$_2$-NCH=CHN, J = 5.7 Hz), 4.08 (s, 3H, C*H*$_3$-NCH=CHN), 4.88 (t, 2H, C*H*$_2$-NH_3^+, J = 5.7 Hz), 4.96 (br s, 3H, N*H*$_3^+$), 7.75 (s, 1H, NC*H*=CHN), 7.91 (s, 1H, NCH=C*H*N), 9.29 (s, 1H, NC*H*N); ^{13}C NMR (CD_3OD, 75.5 MHz) δ_C 37.1 (1C, *C*H$_3$-NCH=CHN), 40.7 (1C, *C*H$_2$-N), 47.8 (1C, *C*H$_2$-NCH=CHN), 124.0 (1C, NC*H*=CHN), 129.7 (1C, NCH=*C*HN), 139.0 (1C, NCHN).



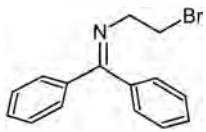
2-(Benzylidene-amino)-1-bromoethane (17).

A solution of 2-bromoethylamine hydrobromide **15** (5.00 g, 24.40 mmol) in dichloromethane (60 ml) was successively treated with triethylamine (2.47 g, 24.40 mmol) and benzaldehyde (2.59 g, 24.40 mmol) in the presence of activated 4 Å molecular sieves (10.00 g). The reaction mixture was stirred for 6 h. The drying agent was filtered off and the filtrate was concentrated. The residue was then treated with diethyl ether (40 ml). The precipitate formed was filtered off and washed with diethyl ether (2 x 20 ml). The solvent was removed under reduced pressure to give **9** as a clear yellow oil (4.29 g, 83%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 3.78 (t, 2H, C*H*$_2$-N, J = 5.7 Hz), 3.98 (t, 2H, C*H*$_2$-Br, J = 5.7 Hz), 7.45 – 7.50 (m, 3H, *m/p*-C$_6$*H*$_5$), 7.76 – 7.84 (m, 2H, *o*-C$_6$*H*$_5$), 8.33 (s, 1H, N=C*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ_C 34.3 (1C, *C*H$_2$-N=), 61.6 (1C, *C*H$_2$-Br), 128.0 (2C, *m*-*C*$_6$H$_5$), 128.5 (2C, *o*-*C*$_6$H$_5$), 130.8 (1C, *p*-*C*$_6$H$_5$), 135.6 (1C, *ipso*-*C*$_6$H$_5$), 162.7 (1C, N=*C*HC$_6$H$_5$).



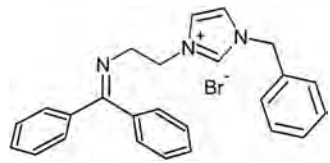
1-{2-(Benzylidene-amino)-ethyl}-3-benzyl imidazolium bromide (18).

1-benzylimidazole (1.62 g, 10.23 mmol) was added to a solution of **17** (2.17 g, 10.23 mmol) in THF (25 ml). The mixture was stirred under reflux for 50 minutes, in the presence of activated 4 Å molecular sieves (1.0 g). After filtration and solvent removal under vacuum, the residue was triturated and washed with dry diethyl ether (3 x 20 ml). The solid was recrystallised from dry CH_2Cl_2/Et_2O, filtered under nitrogen, and dried under vacuum to give **18** as a hygroscopic yellow solid (3.14 g, 83%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 3.98 (t, 2H, CH_2-N=, J = 5.2 Hz), 4.56 (t, 2H, CH_2-NCH=CHN, J = 5.2 Hz), 5.45 (s, 2H, CH_2-C_6H_5), 7.07 – 7.73 (m, 10H, N=CHC$_6H_5$ + CH_2-C$_6H_5$), 7.83 (s, 1H, NC*H*=CHN), 7.86 (s, 1H, NCH=C*H*N), 8.31 (s, 1H, N=C*H*), 9.42 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 49.8 (1C, *C*H_2-N=), 51.6 (1C, *C*H_2-NCH=CHN), 58.5 (1C, *C*H_2-C_6H_5), 122.4 (1C, NC*H*=CHN), 123.0 (1C, NCH=C*H*N), 127.6 (1C, Ar*C*), 128.0 (4C, Ar*C*), 128.5 (1C, Ar*C*), 128.6 (2C, Ar*C*), 128.8 (2C, Ar*C*), 131.0 (1C, NCHN), 134.8 (1C, N=C(*ipso*-C_6H_5)), 136.4 (1C, CH_2-(*ipso*-C_6H_5)), 163.5 (1C, N=*C*H).



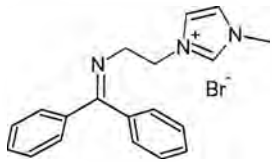
2-(Benzylhydrylidene-amino)-1-bromoethane (19).

2-Bromoethylamine hydrobromide **15** (10.00 g, 48.80 mmol) was added to a solution of benzophenone imine (8.85 g, 48.80 mmol) in dichloromethane (200 ml). The reaction mixture was stirred at room temperature for 74 h. The ammonium chloride precipitate was filtered off and aqueous 10% $NaHCO_3$ (200 ml) was added to the filtrate. The mixture was stirred for 15 minutes. The resulting emulsion was filtered through a celite layer. The organic layer was decanted and the aqueous phase was extracted with dichloromethane (2 x 100 ml). The combined organic layers were washed with water (200 ml) and dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent removed under reduced pressure affording **19** as a white solid (13.59 g, 97%); mp 65.5 – 67.5 °C; HRMS (ESI): M+Na$^+$ m/z = 310.02698 ($C_{15}H_{14}NBrNa$ requires 310.0202); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 3.71 (t, 2H, CH_2-N=, J = 6.0 Hz), 3.81 (t, 2H, CH_2-Br, J = 6.0 Hz), 7.16 – 7.74 (m, 10H, N=C(C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 33.3 (1C, CH_2-N), 55.0 (1C, CH_2-Br), 127.5 (2C, Ar*C*), 128.0 (2C, Ar*C*), 128.4 (4C, Ar*C*), 130.1 (2C, Ar*C*), 136.2 (1C, N=C(*ipso*-(C_6H_5)$_a$)), 139.3 (1C, N=C(*ipso*-(C_6H_5)$_b$)), 169.7 (1C, *C*=N); Anal. found: C 62.79%, H 4.86%, N 4.80% ($C_{15}H_{14}NBr$ requires C 62.52%, H 4.90%, N 4.86%). Some ^{13}C NMR signals are due to multiple carbon atoms.



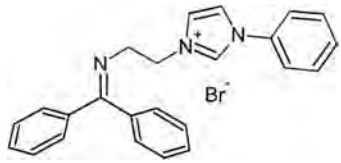
1-{2-(Benzylhydrylidene-amino)-ethyl}-3-benzylimidazolium bromide (20a).

A mixture of **19** (2.00 g, 6.94 mmol) and 1-benzylimidazole (1.10 g, 6.94 mmol) was heated at 90 °C for 50 minutes. The solid formed was triturated and washed with dry diethyl ether (3 x 60 ml). The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **20a** as a clear white/yellow solid (2.56 g, 83%); mp 129.6 – 131.9 °C; HRMS (ESI): $[C_{19}H_{23}N]^+$ m/z = 366.19295 ($[C_{19}H_{23}N_3]^+$ requires); $\upsilon_{(C=N)}$: 1631 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ_H 3.66 (t, 2H, CH_2-N=, J = 5.5 Hz), 4.59 (t, 2H, CH_2-NCH=CHN, J = 5.5 Hz), 5.59 (s, 2H, CH_2-C_6H_5), 6.93 – 6.99 (m, 2H, N=C(C_6H_5)$_a$), 7.26 - 7.60 (m, 15H, CH_2-C_6H_5 + NC*H*=C*H*N + N=C(C_6H_5)$_2$), 10.37 (s, 1H, NC*H*N); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ_C 51.3 (1C, CH_2-N=), 53.8 (1C, CH_2-NCH=CHN), 54.2 (1C, CH_2-C_6H_5), 122.9 (1C, NCH=CHN), 124.1 (1C, NCH=CHN), 127.4 (1C, Ar*C*), 129.3 (1C, Ar*C*), 129.6 (1C, Ar*C*), 130.0 (1C, Ar*C*), 130.4 (1C, Ar*C*), 131.0 (1C, Ar*C*), 131.7 (2C, N=C(*p*-C_6H_5)$_2$), 134.8 (1C, N=C(*ipso*-C_6H_5)$_a$), 137.0 (1C, N=C(*ipso*-C_6H_5)$_b$), 138.2 (1C, NCHN), 140.0 (1C, CH_2-(*ipso*-C_6H_5)), 172.2 (1C, *C*=N); Anal. found: C 64.53%, H 5.53%, N 8.98% ($C_{25}H_{24}N_3Br$ requires C 67.27%, H 5.42%, N 9.41%). Some ^{13}C NMR signals are due to multiple carbon atoms.



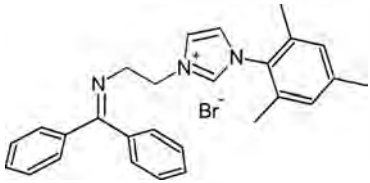
1-{2-(Benzylhydrylidene-amino)-ethyl}-3-methylimidazolium bromide (20b).

A mixture of **19** (1.00 g, 3.47 mmol) and 1-methylimidazole (0.28 g, 3.47 mmol) was heated at 85 °C for 1.5 h. The sticky solid formed was triturated and washed with dry diethyl ether (3 x 60 ml) under nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **20b** as a clear white/yellow solid (1.04 g, 81%); mp 45.7 – 47.7 °C; HRMS (ESI): $[C_{19}H_{23}N\text{-}Br]^+$ m/z = 290.1656 ($[C_{19}H_{23}N_3\text{-}Br]^+$ requires 290.1652); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 3.65 (t, 2H, CH_2-N=, J = 5.3 Hz), 3.90 (s, 3H, CH_3-NCH=CHN), 4.49 (t, 2H, CH_2-NCH=CHN, J = 5.3 Hz), 7.10 (s, 1H, N=C(C_6H_5)$_a$), 7.12 (s, 1H, N=C(C_6H_5)$_a$), 7.33 – 7.62 (m, 8H, N=C(C_6H_5)$_2$), 7.70 (s, 1H, NCHCHN), 7.79 (s, 1H, NCH=CHN), 9.26 (s, 1H, NCHN); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 39.5 (1C, CH_3-NCH=CHN), 53.9 (1C, CH_2-N=), 56.2 (1C, CH_2-NCH=CHN), 126.4 (1C, NCH=CHN), 127.1 (1C, NCH=CHN), 130.9 (2C, ArC), 131.8 (4C, ArC), 132.5 (2C, ArC), 134.1 (2C, ArC), 139.4 (1C, N=C(*ipso*-(C_6H_5)$_a$)), 140.4 (1C, NCHN), 142.4 (1C, N=C(*ipso*-(C_6H_5)$_b$)), 173.1 (1C, C=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



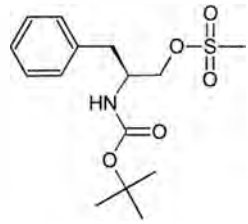
1-{2-(Benzylhydrylidene-amino)-ethyl}-3-phenylimidazolium bromide (20c).

A mixture of **19** (1.91 g, 6.63 mmol) and 1-phenylimidazole (0.96 g, 6.63 mmol) was heated at 85 °C for 1 h. The sticky solid formed was triturated and washed with dry diethyl ether (3 x 60 ml) under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **20c** as a clear white/yellow solid (1.68 g, 59%); mp 121.1 – 123.4 °C; HRMS (ESI): $[C_{24}H_{22}N_3Br\text{-}Br]^+$ m/z = 352.1804 ($[C_{24}H_{22}N_3Br\text{-}Br]^+$ requires 352.1808); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 3.77 (t, 2H, CH_2-N=, J = 5.5 Hz), 4.60 (t, 2H, CH_2-NCH=CHN, J = 5.5 Hz), 7.13 (d, 1H, N=C(C_6H_5)$_a$, J = 1.1 Hz), 7.14 (d, 1H, N=C(C_6H_5)$_a$, J = 1.1 Hz), 7.32 – 7.90 (m, 13H, NCH=CHN-(*o*-C_6H_5)$_2$ + N=C(C_6H_5)$_2$), 8.09 (s, 1H, NC*H*=CHN), 8.36 (s, 1H, NCH=C*H*N), 10.05 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 51.3 (1C, *C*H$_2$-N=), 52.8 (1C, *C*H$_2$-NCH=CHN), 121.6 (1C, N*C*H=CHN), 122.4 (2C, NCH=CHN-(*o*-C_6H_5)), 124.4 (1C, NCH=*C*HN), 127.9 (Ar*C*), 128.7 (Ar*C*), 129.4 (Ar*C*), 130.4 (Ar*C*), 130.9 (Ar*C*), 135.3 (1C, N=C(*ipso*-C_6H_5)$_a$), 136.3 (2C, N*C*HN + N=C(*ipso*-C_6H_5)$_b$), 139.4 (1C, NCH=CHN-(*ipso*-C_6H_5)), 170.1 (1C, *C*=N); Anal. found: C 64.67%, H 5.09%, N 9.64% ($C_{24}H_{22}N_3Br$ requires C 66.67%, H 5.13%, N 9.72%). Some ^{13}C NMR signals are due to multiple carbon atoms.



1-{2-(Benzylhydrylidene-amino)-ethyl}-3-mesitylimidazolium bromide (20d).

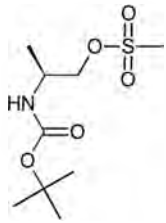
A mixture of **19** (0.80 g, 2.78 mmol) and 1-mesitylimidazole (0.52 g, 2.78 mmol) was heated at 85 °C for 50 minutes. The sticky solid formed was triturated and washed with dry diethyl ether (3 x 50 ml) under nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **20d** as a clear white/yellow solid (0.67 g, 51%); mp 207.6 – 209.4 °C; HRMS (ESI): $[C_{27}H_{28}N_3Br\text{-}Br]^+$ m/z = 394.2281 ($[C_{27}H_{28}N_3Br\text{-}Br]^+$ requires 394.2278); ^1H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 1.94 (s, 6H, *2,6*-$(CH_3)_3$-C_6H_2), 2.32 (s, 3H, *4*-$(CH_3)_3$-C_6H_2), 3.76 (t, 2H, CH_2-N=, J = 4.9 Hz), 4.64 (t, 2H, CH_2-NCH=CHN, J = 4.9 Hz), 7.08 – 7.61 (m, 12H, 2,4,6-$(CH_3)_3$-(*3,5*-C_6H_2) + N=C(C_6H_5)$_2$), 7.95 (s, 1H, NC*H*=CHN), 8.14 (s, 1H, NCH=C*H*N), 9.69 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 16.6 (2C, *2,6*-$(CH_3)_3C_6H_2$), 20.4 (1C, *4*-$(CH_3)_3C_6H_2$), 50.6 (1C, CH_2-N=), 51.9 (1C, CH_2-NCH=CHN), 123.0 (1C, NCH=CHN), 123.8 (1C, NCH=CHN), 127.1 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.7 (Ar*C*), 129.1 (Ar*C*), 130.4 (2C, 2,4,6-$(CH_3)_3$-(*3,5*-C_6H_2)), 131.0 (1C, 2,4,6-$(CH_3)_3$-(*ipso*-C_6H_2)), 134.1 (2C, 2,4,6-$(CH_3)_3$-(*2,6*-C_6H_2)), 135.5 (1C, N=C(*ipso*-$C_6H_5)_a$), 137.7 (1C, N=C(*ipso*-$C_6H_5)_b$), 138.5(1C, NCHN), 140.1 (1C, 2,4,6-$(CH_3)_3$-(*4*-C_6H_2), 169.5 (1C, *C*=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



(*S*)-2-(*tert*-Butoxycarbonyl-amino)-3-phenyl-1-propylmethane sulfonate (21a).

21a was prepared according to the literature methods.[8]

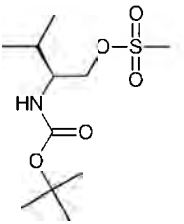
A solution of methane sulfonyl chloride (2.64 g, 23.03 mmol) in dichloromethane (50 ml) was added dropwise to an ice-cooled solution of **6a** (5.00 g, 20.14 mmol) and triethylamine (2.24 g, 22.15 mmol) in dichloromethane (100 ml) over a period of 30 minutes. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ (150 ml) and brine (150 ml). The organic layer was then dried over anhydrous $MgSO_4$. The drying agent was filtered off and washed with ethyl acetate (3 x 20 ml). The solvent was removed under reduced pressure affording **21a** as a clear white solid (6.07 g, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.40 (s, 9H, C(CH_3)$_3$), 2.79 – 2.95 (m, 2H, CH_2-C_6H_5), 3.00 (s, 3H, CH_3-SO_2), 4.02 – 4.29 (m, 2H, CH_2-O), 4.17 - 4.30 (m, 1H, C*H*-N), 4.77 (br s, 1H, N*H*), 7.18 – 7.33 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 28.2 (3C, C(CH_3)$_3$), 37.1 (1C, CH_2-C_6H_5), 37.2 (1C, CH_3-SO_2), 50.8 (1C, *C*H-N), 69.8 (1C, CH_2-O), 79.9 (1C, *C*(CH_3)$_3$), 126.9 (1C, *p*-C_6H_5), 128.7 (2C, *o*-C_6H_5), 129.2 (2C, *m*-C_6H_5), 136.6 (1C, *ipso*-C_6H_5), 155.0 (1C, *C*=O).



(*S*)-2-(*tert*-Butoxycarbonyl-amino)-1-propylmethane sulfonate (21b).

21b was prepared according to the literature methods.[8]

A solution of methane sulfonyl chloride (3.46 g, 30.19 mmol) in dichloromethane (50 ml) was added dropwise to an ice-cooled solution of **6b** (5.00 g, 29.03 mmol) and triethylamine (3.39 g, 33.21 mmol) in dichloromethane (100 ml) over a period of 30 minutes. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ (150 ml) and brine (150 ml). The organic layer was then dried over anhydrous $MgSO_4$. The drying agent was filtered off and washed with ethyl acetate (3 x 20 ml). The solvent was removed under reduced pressure affording **21b** as a clear white solid (6.32 g, 88%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.20 (d, 3H, CH_3-CH, J = 7.0 Hz), 1.41 (s, 9H, C(CH_3)$_3$), 3.00 (s, 3H, SO_2-CH_3), 3.94 (br s, 1H, CH-N), 4.12 (dd, 1H, CH_b-O, J = 4.4 Hz, J = 9.9 Hz), 4.15 – 4.25 (m, 1H, CH_a-O), 4.66 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 17.1 (1C, CH_3-CH), 27.6 (1C, CH_3-SO_2), 28.3 (3C, C(CH_3)$_3$), 37.2 (1C, CH-NH), 72.0 (1C, CH_2-O), 79.8 (1C, C(CH_3)$_3$), 155.0 (1C, C=O).

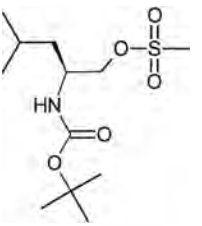


(*S*)-2-(*tert*-Butoxycarbonyl-amino)-3-methyl-1-butylmethane sulfonate (21c).

21c was prepared according to the literature methods.[8]

A solution of methane sulfonyl chloride (6.42 g, 56.08 mmol) in dichloromethane (50 ml) was added dropwise to an ice-cooled solution of **6c** (10.80 g, 53.92 mmol) and triethylamine (6.29 g, 61.69 mmol) in dichloromethane (130 ml) over a period of 30 minutes. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ (200ml) and brine (2 x 150 ml). The organic layer was then dried over anhydrous $MgSO_4$. The drying agent was filtered off and washed with ethyl acetate (3 x 20 ml). The solvent was removed under reduced pressure affording **21c** as a clear white solid (12.75 g, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.93 (d, 3H, CH(C*H*$_3$)$_a$, J = 6.8 Hz), 0.96 (d, 3H, CH(C*H*$_3$)$_b$, J = 6.8 Hz), 1.42 (s, 9H, C(C*H*$_3$)$_3$), 1.77 – 1.91 (m, 1H, C*H*(CH$_3$)$_2$), 3.00 (s, 3H, C*H*$_3$-SO$_2$), 3.50 - 3.70 (m, 1H, C*H*-N), 4.24 (d, 2H, C*H*$_2$-O, J = 4.4 Hz), 4.65 (d, 1H, N*H*, J = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 18.4 (1C, CH(*C*H$_3$)$_a$), 19.3 (1C, CH(*C*H$_3$)$_b$), 28.3 (3C, C(*C*H$_3$)$_3$), 29.0 (1C, *C*H(CH$_3$)$_2$), 37.3

(1C, CH_3-SO_2), 54.8 (1C, *C*H-N), 69.7 (1C, CH_2-O), 79.7 (1C, $C(CH_3)_3$), 155.6 (1C, *C*=O).

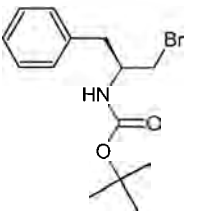


(*S*)-2-(*tert*-Butoxycarbonyl-amino)-4-methyl-pentylmethane sulfonate (21d).

21d was prepared according to the literature methods.[8]

A solution of methane sulfonyl chloride (5.20 g, 45.37 mmol) in dichloromethane (50 ml) was added dropwise to an ice-cooled solution of **6d** (5.50 g, 39.66 mmol) and triethylamine (4.41 g, 43.63 mmol) in dichloromethane (130 ml) over a period of 30 minutes. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ (200 ml) and brine (2 x 150 ml). The organic layer was then dried over anhydrous $MgSO_4$. The drying agent was filtered off and washed with ethyl acetate (3 x 20 ml). The solvent was removed under reduced pressure affording **21d** as a clear white solid (10.00 g, 86%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.90 (d, 3H, CH(CH_3)$_a$, J = 6.8 Hz), 0.92 (d, 3H, CH(CH_3)$_b$, J = 6.8 Hz), 1.31 – 1.47 (m, 11H, C(CH_3)$_3$ + CH_2-

$CH(CH_3)_2$), 1.58 – 1.73 (m, 1H, $CH(CH_3)_2$), 3.00 (s, 3H, CH_3-SO_2), 3.82 – 3.95 (m, 1H, CH-N), 4.05 – 4.30 (m, 2H, CH_2-O), 4.81 (d, 1H, NH, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 21.9 (1C, $CH(CH_3)_a$), 22.9 (1C, $CH(CH_3)_b$), 24.5 (1C, $CH(CH_3)_2$), 28.3 (3C, $C(CH_3)_3$), 37.2 (1C, CH_3-SO_2), 40.0 (1C, CH_2-$CH(CH_3)_2$), 47.8 (1C, CH-N), 71.6 (1C, CH_2-O), 79.7 (1C, $C(CH_3)_3$), 155.2 (1C, C=O).

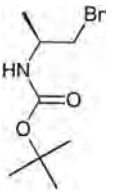


(*S*)-2-(*tert*-Butoxycarbonyl-amino)-3-phenyl-1-bromopropane (22a).

22a was prepared according to the literature methods.[8]

Lithium bromide (4.32 g, 49.74 mmol) was added to a solution of **21a** (5.77 g, 17.76 mmol) in acetone (60 ml) in the presence of activated 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 42 h. The solution was concentrated under reduced pressure to give a yellow solid/oil mixture. The residue was dissolved in ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ (150 ml) and brine (150 ml). The solvent was removed under reduced pressure to give a clear yellow solid. The crude product was then purified by flash column

chromatography (hexane/EtOAc, 9:1) affording **22a** as a white solid (2.51 g, 45%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.43 (s, 9H, C(CH_3)$_3$), 2.85 (dd, 1H, CH_a-C_6H_5, J = 8.4 Hz, J = 13.5 Hz), 2.93 (dd, 1H, CH_b-C_6H_5, J = 5.7 Hz, J = 13.5 Hz), 3.35 (m, 1H, CH_a-Br, J = 3.5 Hz, J = 10.2 Hz), 3.52 (m, 1H, CH_b-Br, J = 3.5 Hz, J = 10.2 Hz), 4.05 (br s, 1H, C*H*-N), 4.82 (d, 1H, N*H*, J = 7.0 Hz), 7.21 – 7.34 (m, 5H, ArH_5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 28.3 (3C, C(CH_3)$_3$), 37.4 (1C, CH_2-Br), 38.8 (1C, CH_2-C_6H_5), 51.4 (1C, *C*H-N), 79.8 (1C, $C(CH_3)_3$), 126.8 (1C, *p*-C_6H_5), 128.7 (2C, *o*-C_6H_5), 129.2 (2C, *m*-C_6H_5), 137.0 (1C, *ipso*-C_6H_5), 154.9 (1C, *C*=O).

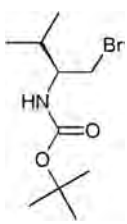


***(S)*-2-(*tert*-Butoxycarbonyl-amino)-1-bromopropane (22b).**

22b was prepared according to the literature methods.[8]

Lithium bromide (6.32 g, 72.73 mmol) was added to a solution of **21b** (6.45 g, 25.97 mmol) in acetone (60 ml) in the presence of activated 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 63 h. The solution was concentrated under reduced pressure to give a yellow solid/oil mixture. The residue was dissolved in ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$

(150 ml) and brine (150 ml). The solvent was removed under reduced pressure to give a clear yellow solid. The crude product was then purified by flash column chromatography (hexane/EtOAc, 9:1) affording **22b** as a white solid (3.19 g, 52%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.21 (d, 3H, C*H*$_3$, J = 6.6 Hz), 1.42 (s, 9H, C(C*H*$_3$)$_3$), 3.38 – 3.60 (m, 2H, C*H*$_2$-Br), 3.92 (br s, 1H, C*H*-N), 4.69 (br s, 1H, N*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 19.2 (1C, *C*H$_3$), 28.3 (3C, C(*C*H$_3$)$_3$), 39.7 (1C, *C*H$_2$-Br), 46.2 (1C, *C*H-N), 79.6 (1C, *C*(CH$_3$)$_3$), 154.8 (1C, *C*=O).

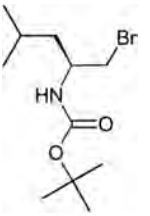


(*S*)-2-(*tert*-Butoxycarbonyl-amino)-3-methyl-1-bromobutane (22c).

22c was prepared according to the literature methods.[8]

Lithium bromide (5.28 g, 60.79 mmol) was added to a solution of **21c** (6.00 g, 21.71 mmol) in acetone (60 ml) in the presence of activated 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 63 h. The solution was concentrated under reduced pressure to give a yellow solid/oil mixture. The residue was dissolved in ethyl acetate (100 ml) and water (100 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$

(150 ml) and brine (150 ml). The solvent was removed under reduced pressure to give a clear yellow solid. The crude product was then purified by flash column chromatography (hexane/EtOAc, 9:1) affording **22c** as a white solid (2.51 g, 44%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.93 (d, 3H, $CH(CH_3)_a$, J = 2.2 Hz), 0.94 (d, 3H, $CH(CH_3)_b$, J = 2.2 Hz), 1.43 (s, 9H, $C(CH_3)_3$), 1.78 – 1.92 (m, 1H, $CH(CH_3)_2$), 3.45 – 3.60 (m, 3H, CH_2-Br + CH-N), 4.64 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 18.4 (1C, $CH(CH_3)_a$), 19.4 (1C, $CH(CH_3)_b$), 28.3 (3C, $C(CH_3)_3$), 30.5 (1C, $CH(CH_3)_2$), 37.2 (1C, CH_2-Br), 55.9 (1C, CH-N), 79.5 (1C, $C(CH_3)_3$), 155.5 (1C, C=O).

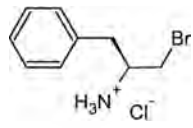


(*S*)-2-(*tert*-Butoxycarbonyl-amino)-4-methyl-1-bromopentane (22d).

22d was prepared according to the literature methods.[8]

Lithium bromide (8.23 g, 94.71 mmol) was added to a solution of **21d** (9.87 g, 33.83 mmol) in acetone (80 ml) in the presence of activated 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 63 h. The solution was concentrated under reduced pressure to give a yellow solid/oil mixture. The residue was dissolved in ethyl acetate (100 ml) and water (100 ml). The organic layer was

separated and the aqueous layer was extracted with ethyl acetate (100 ml). The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ (150 ml) and brine (150 ml). The solvent was removed under reduced pressure to give a clear yellow solid. The crude product was then purified by flash column chromatography (hexane-EtOAc, 9:1) affording **22d** as a white solid (5.18 g, 55%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.86 (d, 3H, $CH(CH_3)_a$, J = 1.8 Hz), 0.87 (d, 3H, $CH(CH_3)_b$, J = 1.8 Hz), 1.31 – 1.43 (m, 11H, $C(CH_3)_3$ + CH_2-$CH(CH_3)_2$), 1.52 – 1.63 (m, 1H, $CH(CH_3)_2$), 3.39 (dd, 1H, CH_a-Br, J = 2.9 Hz, J = 10.1 Hz), 3.52 (dd, 1H, CH_b-Br, J = 3.8 Hz, J = 10.1 Hz), 3.75 – 3.89 (m, 1H, C*H*-N), 4.69 (d, 1H, N*H*, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 22.2 (1C, $CH(CH_3)_a$), 22.6 (1C, $CH(CH_3)_b$), 24.6 (1C, $CH(CH_3)_2$), 28.2 (3C, $C(CH_3)_3$), 39.1 (1C, CH_2-$CH(CH_3)_2$), 42.0 (1C, CH_2-Br), 48.2 (1C, C*H*-N), 79.3 (1C, $C(CH_3)_3$), 155.0 (1C, *C*=O).

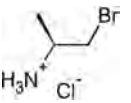


(*S*)-2-amino-1-bromo-3-phenylpropane hydrochloride (23a).

23a was prepared according to the literature methods.[8]

N-*t*-Boc protected amino alkyl bromide **22a** (1.50 g, 5.32 mmol) was treated with 4 M hydrogen chloride in dioxane (18 ml) with stirring for 2 h at room temperature. The solvent was removed under reduced pressure and the crude product was washed with diethyl ether (15 ml) and then purified by recrystallisation from EtOH/Et_2O (1 : 3).

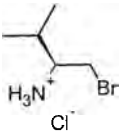
The precipitate formed was filtered and dried under reduced pressure to give **23a** as white crystals (1.15 g, 86%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.78 – 3.20 (m, 2H, CH_2-C_6H_5), 3.40 – 4.00 (m, 3H, C*H*-N + CH_2-Br), 7.15 – 7.48 (m, 5H, C_6H_5), 8.53 (br s, 3H, NH_3^+); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 38.4 (1C, CH_2-C_6H_5), 39.5 (1C, CH_2-Br), 55.2 (1C, *C*H-N), 130.1 (1C, *p*-C_6H_5), 131.7 (2C, *o*-C_6H_5), 132.2 (2C, *m*-C_6H_5), 138.5 (1C, *ipso*-C_6H_5).



***(S)*-2-amino-1-bromopropane hydrochloride (23b).**

23b was prepared according to the literature methods.[8]

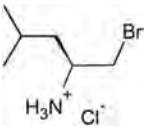
N-*t*-Boc protected amino alkyl bromide **22b** (6.75 g, 28.57 mmol) was treated with 4 M hydrogen chloride in dioxane (100 ml) with stirring for 2 h at room temperature. The solvent was removed under reduced pressure and the crude product was washed with diethyl ether (30 ml) and then purified by recrystallisation from EtOH/Et_2O (1 : 10). The precipitate formed was filtered and dried under reduced pressure to give **23b** as white crystals (4.74 g, 95%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 1.25 – 1.33 (m, 3H, CH_3), 3.72 (d, 2H, CH_2-Br, J = 5.1 Hz), 3.79 – 3.92 (m, 1H, C*H*-N), 8.46 (br s, 3H, NH_3^+); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 17.1 (1C, CH_3), 35.4 (1C, CH_2-Br), 47.2 (1C, *C*H-N).



(*S*)-2-amino-1-bromo-3-methylbutane hydrochloride (23c).

23c was prepared according to the literature methods.[8]

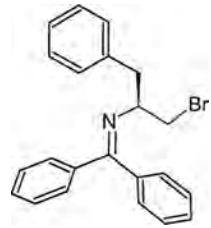
N-*t*-Boc protected amino alkyl bromide **22c** (2.73 g, 10.33 mmol) was treated with 4 M hydrogen chloride in dioxane (36 ml) with stirring for 2 h at room temperature. The solvent was removed under reduced pressure and the crude product was washed with diethyl ether (20 ml) and then purified by recrystallisation from EtOH/Et_2O (2 : 15). The precipitate was filtered and dried under reduced pressure to give **23c** as white crystals (1.84 g, 88%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 0.93 (dd, 3H, CH(CH_3)$_a$, J = 4.1 Hz, J = 6.6 Hz), 0.98 (d, 3H, CH(CH_3)$_b$, J = 6.6 Hz), 1.91 – 2.07 (m, 1H, CH(CH$_3$)$_2$), 3.23 (m , 1H, CH-N), 3.70 – 4.03 (m, 2H, CH_2-Br), 8.36 (br s, 3H, NH_3^+); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 17.9 (1C, CH(*C*H$_3$)$_a$), 18.4 (1C, CH(*C*H$_3$)$_b$), 28.3 (1C, *C*H(CH$_3$)$_2$), 33.6 (1C, *C*H$_2$-Br), 56.2 (1C, *C*H-N).



(*S*)-2-amino-1-bromo-4-methyl-pentane hydrochloride (23d).

23d was prepared according to the literature methods.[8]

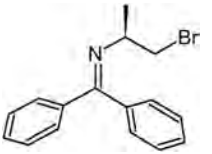
N-*t*-Boc protected amino alkyl bromide **22d** (4.92 g, 17.56 mmol) was treated with 4 M hydrogen chloride in dioxane (62 ml) with stirring for 2 h at room temperature. The solvent was removed under reduced pressure and the crude product was washed with diethyl ether (20 ml) and then purified by recrystallisation from $EtOH/Et_2O$ (2 : 15). The precipitate formed was filtered and dried under reduced pressure to give **23d** as white crystals (3.56 g, 93%); ^1H NMR (DMSO-d_6, 400 MHz) δ_H 0.87 (d, 3H, $CH(CH_3)_a$, J = 4.1 Hz), 0.89 (d, 3H, $CH(CH_3)_b$, J = 4.1 Hz), 1.41 – 1.57 (m, 2H, CH_2-$CH(CH_3)_2$), 1.65 – 1.77 (m, 1H, $CH(CH_3)_2$), 3.42 – 3.58 (m, 1H, CH-N), 3.68 – 4.01 (m, 2H, CH_2-Br), 8.32 (br s, 3H, NH_3^+); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 22.2 (1C, $CH(CH_3)_a$), 22.6 (1C, $CH(CH_3)_b$), 23.4 (1C, $CH(CH_3)_a$), 35.3 (1C, CH_2-$CH(CH_3)_2$), 49.9 (1C, CH_2-Br), 48.8 (1C, CH-N).



***(S)*-2-(Benzylhydrylidene-amino)-1-bromo-3-phenylpropane (24a).**

Benzophenone imine (1.05 g, 5.80 mmol) was added to a solution of **23a** (1.45 g, 5.80 mmol) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 8 days. The ammonium chloride deposit was filtered off and aqueous 10% $NaHCO_3$ (200 ml) was added to the filtrate. The mixture was stirred for 30 minutes and the resulting emulsion was filtered through a celite layer. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 100 ml). The combined organic layers were then washed with water (200 ml) and dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed. The residue was recrystallised from hot hexane and the crystals were dried under reduced pressure affording **24a** as a white solid (1.97 g, 90%); mp 108.6 – 110.4 °C; $[\alpha]_D^{20°C}$ = - 103.3 (*c* = 1.04, $CHCl_3$); HRMS (ESI): M^+ m/z = 378.0831 ($C_{22}H_{21}N^{79}Br$ requires 378.0852); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 2.90 (dd, 1H, C*H*$_a$-C_6H_5, *J* = 7.7 Hz, *J* = 13.1 Hz), 2.98 (dd, 1H, C*H*$_b$-C_6H_5, *J* = 5.1 Hz, *J* = 13.1 Hz), 3.54 (dd, 1H, C*H*$_a$-Br, *J* = 4.8 Hz, *J* = 9.9 Hz), 3.60 (dd, 1H, C*H*$_b$-Br, *J* = 7.7 Hz, *J* = 9.9 Hz), 3.70 – 3.87 (m, 1H, C*H*-N=), 6.50 – 7.70 (m, 15H, N=C(C_6H_5)$_2$ + CH_2-C_6H_5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 37.6 (1C, *C*H_2-Br), 41.7 (1C, *C*H_2-C_6H_5),

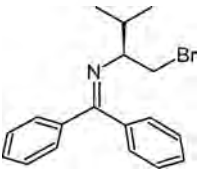
64.6 (1C, *C*H-N=), 126.3 (1C, Ar*C*), 127.7 (2C, Ar*C*), 128.03 (2C, Ar*C*), 128.05 (2C, Ar*C*), 128.1 (1C, Ar*C*), 128.3 (2C, Ar*C*), 128.5 (2C, Ar*C*), 129.8 (2C, Ar*C*) 130.1 (1C, Ar*C*), 136.4 (1C, N=C(*ipso*-$C_6H_5)_a$), 138.0 (1C, CH_2-C(*ipso*-C_6H_5)), 139.6 (1C, N=C(*ipso*-$C_6H_5)_b$), 166.4 (1C, *C*=N); Anal. found: C 69.90%, H 5.42%, N 3.61% ($C_{22}H_{21}NBr$ requires C 69.66%, H 5.58%, N 3.69%).



***(S)*-2-(Benzylhydrylidene-amino)-1-bromopropane (24b).**

Benzophenone imine (4.86 g, 26.83 mmol) was added to a solution of **23b** (4.68 g, 26.83 mmol) in dichloromethane (200 ml). The reaction mixture was stirred at room temperature for 6 days. The ammonium chloride deposit was filtered off, and aqueous 10% $NaHCO_3$ (300 ml) was added to the filtrate. The mixture was stirred for 30 minutes and the resulting emulsion was filtered through a layer of celite. The organic layer was separated and the aqueous layer was extracted with dichloromethane (300 ml). The combined organic layers were then washed with water (400 ml) and dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed. The residue was recrystallised from hot hexane and the crystals were dried under reduced pressure affording **24b** as a white solid (7.44 g, 92%); mp 68.8 – 71.0 °C; $[\alpha]_D^{20°C} = +93.3$ ($c = 2.45$, $CHCl_3$); HRMS (ESI): M^+ m/z = 302.0526

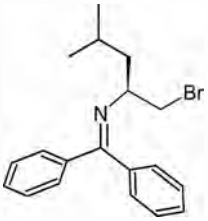
($C_{16}H_{17}N^{79}Br$ requires 302.0539); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 1.25 (d, 3H, CH_3, J = 6.2 Hz), 3.45 (dd, 1H, CH_a-Br, J = 4.8 Hz, J = 9.6 Hz), 3.55 (dd, 1H, CH_b-Br, J = 7.9 Hz, J = 9.6 Hz), 3.67 – 3.78 (m, 1H, CH-N=), 7.13 – 7.70 (m, 10H, N=C(C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 20.9 (1C, CH_3), 39.2 (1C, CH_2-Br), 58.4 (1C, CH-N=), 127.7 (2C, ArC), 128.0 (2C, ArC), 128.3 (1C, ArC), 128.4 (2C, ArC), 128.5 (2C, ArC), 130.1 (1C, ArC), 136.7 (1C, N=C(*ipso*-C_6H_5)$_a$), 139.7 (1C, N=C(*ipso*-C_6H_5)$_b$), 168.4 (1C, C=N); Anal. found: C 63.76%, H 5.48%, N 4.60% ($C_{24}H_{22}N_3Br$ requires C 63.42%, H 5.66%, N 4.62%).



(*S*)-2-(Benzylhydrylidene-amino)-1-bromo-3-methylbutane (24c).

Benzophenone imine (1.58 g, 8.74 mmol) was added to a solution of **23c** (1.77 g, 8.74 mmol) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 7 days. The ammonium chloride deposit was filtered off and aqueous 10% $NaHCO_3$ (200 ml) was added to the filtrate. The mixture was stirred for 30 minutes and the resulting emulsion was filtered through a layer of celite. The organic layer was separated and the aqueous layer was extracted with dichloromethane (200 ml). The combined organic layers were then washed with water (200 ml) and dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was

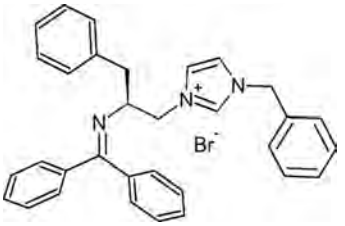
removed. The residue was recrystallised from hot hexane and the crystals were dried under reduced pressure affording **24c** as a white solid (2.55 g, 88%); mp 52.5 – 54.5 °C; $[\alpha]_D^{20°C}$ = - 37.2 (*c* = 1.16, $CHCl_3$); HRMS (ESI): M+Na$^+$ m/z = 352.0635 ($C_{18}H_{20}N^{79}BrNa$ requires 352.0671); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.90 (d, 3H, $CH(CH_3)_a$, *J* = 7.0 Hz), 0.99 (d, 3H, $CH(CH_3)_b$, *J* = 7.0 Hz), 1.92 – 2.08 (m, 1H, $CH(CH_3)_2$), 3.42 – 3.51 (m, 1H, C*H*-N=), 3.57 – 3.67 (m, 2H, CH_2-Br), 7.18 – 7.88 (m, 10H, N=C(C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 18.3 (1C, $CH(CH_3)_a$), 19.3 (1C, $CH(CH_3)_b$), 32.8 (1C, $CH(CH_3)_2$), 36.7 (1C, CH_2-Br), 67.2 (1C, *C*H-N=), 128.0 (2C, Ar*C*), 128.16 (2C, Ar*C*), 128.20 (2C, Ar*C*), 128.25 (1C, Ar*C*), 129.9 (2C, Ar*C*), 130.0 (1C, Ar*C*), 136.7 (1C, N=C(*ipso*-C_6H_5)$_a$), 140.0 (1C, N=C(*ipso*-C_6H_5)$_b$), 168.5 (1C, *C*=N); Anal. found: C 65.78%, H 6.05%, N 4.24% ($C_{18}H_{20}NBr$ requires C 65.46%, H 6.10%, N 4.24%).



***(S)*-2-(Benzylhydrylidene-amino)-1-bromo-4-methylpentane (24d).**

Benzophenone imine (2.93 g, 16.16 mmol) was added to a solution of **23d** (3.50 g, 16.16 mmol) in dichloromethane (200 ml). The reaction mixture was stirred at room temperature for 7 days. The ammonium chloride deposit was filtered off and aqueous 10% $NaHCO_3$ (400 ml) was added to the filtrate. The mixture was stirred for 30 minutes and the resulting emulsion was filtered through a celite layer. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 150 ml). The combined organic layers were then washed with water (2 x 200 ml) and dried over anhydrous $MgSO_4$. The drying agent was filtered off and the solvent was removed. The residue was recrystallised from hot hexane and the crystals were dried under reduced pressure affording **24d** as a white solid (4.82 g, 87%); mp 53.8 –56.8 °C; $[\alpha]_D^{20°C}$ = - 2.8 (*c* = 1.04, $CHCl_3$); HRMS (ESI): M^+ m/z = 344.1007 ($C_{19}H_{22}N^{79}Br$ requires 344.1009); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.74 –0.83 (m, 3H, $CH(CH_3)_a$), 0.60 – 0.69 (m, 3H, $CH(CH_3)_b$), 1.44 – 1.58 (m, 3H, $CH(CH_3)_2$ + CH_2-$CH(CH_3)_2$), 3.48 – 3.56 (m, 2H, CH_2-Br), 3.61 – 3.76 (m, 1H, CH-N=), 7.20 – 7.70 (m, 10H, N=C(C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 22.6 (1C, $CH(CH_3)_a$), 23.1 (1C, $CH(CH_3)_b$), 24.8 (1C, $CH(CH_3)_2$), 38.3 (1C, CH_2-Br), 44.6 (1C, CH_2-$CH(CH_3)_2$),

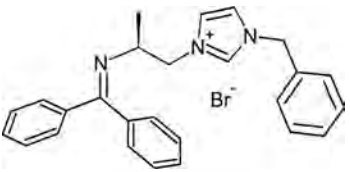
60.8 (1C, *C*H-N=), 128.0 (2C, Ar*C*), 128.1 (2C, Ar*C*), 128.3 (2C, Ar*C*), 128.4 (1C, Ar*C*), 128.6 (2C, Ar*C*), 130.0 (1C, Ar*C*), 136.7 (1C, N=C(*ipso*-$C_6H_5)_a$), 139.9 (1C, N=C(*ipso*-$C_6H_5)_b$), 168.6 (1C, *C*=N); Anal. found: C 66.33%, H 6.15%, N 8.31% ($C_{19}H_{22}NBr$ requires C 68.71%, H 6.38%, N 8.58%).



1-{*(S)*-2-(Benzylhydrylidene-amino)-4-phenyl-propyl}-3-benzylimidazolium bromide (25a).

A mixture of **24a** (0.70 g, 1.85 mmol) and 1-benzylimidazole (0.29 g, 1.85 mmol) was heated at 85 °C for 21 h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **25a** as a white solid (0.44 g, 44%); mp 43.7 – 46.9 °C; $[\alpha]_D^{20°C}$ = - 36.2 (*c* = 1.05, $CHCl_3$); HRMS (ESI): $[C_{32}H_{30}N_3]^+$ m/z = 456.2437 ($[C_{32}H_{30}N_3]^+$ requires 456.2434); ^{1}H NMR (CD_2Cl_2, 400 MHz) δ_H 2.83 (dd, 1H, CH-C*H*$_a$-C_6H_5, *J* = 8.8 Hz, *J* = 13.2 Hz), 2.99 (dd, 1H, CH-C*H*$_b$-C_6H_5, *J* = 4.4 Hz, *J* = 13.2 Hz), 3.72 – 3.82 (m, 1H, C*H*-N=), 4.55 (m, 2H, CH-C*H*$_2$-NCH=CHN), 5.55 (m, 1H, NCH=CHN-C*H*$_a$-C_6H_5, *J* =

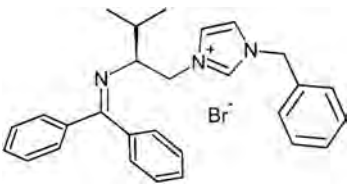
14.3 Hz), 5.61 (d, 1H, NCH=CHN-CH_b-C_6H_5, J = 14.3 Hz), 5.78 (d, 1H, N=C(C_6H_5)$_a$, J = 1.9 Hz), 5.80 (d, 1H, N=C(C_6H_5)$_a$, J = 1.9 Hz), 6.94 – 7.62 (m, 20H, NCH=CHN-CH_2-C_6H_5 + CH-CH_2-C_6H_5 + N=C(C_6H_5)$_2$), 10.07 (s, 1H, NCHN); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ_C 38.8 (1C, CH-CH_2-C_6H_5), 52.0 (1C, CH-CH_2-NCH=CHN), 53.8 (1C, NCH=CHN-CH_2-C_6H_5), 62.3 (1C, CH-N=), 120.9 (1C, NCH=CHN), 121.9 (1C, NCH=CHN), 125.7 (ArC), 127.2 (ArC), 127.6 (ArC), 127.8 (ArC), 128.2 (ArC), 128.9 (ArC), 129.7 (ArC), 132.6 (1C, N=C(*ipso*-C_6H_5)$_a$), 134.3 (1C, NCH=CHN-CH_2-(*ipso*-C_6H_5)), 136.0 (1C, NCHN), 136.3 (1C, CH-CH_2-(*ipso*-C_6H_5)), 137.5 (1C, N=C(*ipso*-C_6H_5)$_b$), 169.7 (1C, C=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



1-{*(S)*-2-(Benzylhydrylidene-amino)-propyl}-3-benzylimidazolium bromide (25b).

A mixture of **24b** (0.70 g, 2.98 mmol) and 1-benzylimidazole (0.47 g, 2.98 mmol) was heated at 85 °C for 44 h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **25b** as a white solid (0.91 g, 66%); mp 140.2 – 142.9 °C; $[\alpha]_D^{20°C}$ = + 67.0 (c = 1.11,

$CHCl_3$); HRMS (ESI): $[C_{26}H_{26}N_3]^+$ m/z = 380.2136 ($[C_{26}H_{26}N_3]^+$ requires 380.2121); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 1.15 (d, 3H, C*H*$_3$, *J* = 6.2 Hz), 3.51 – 3.64 (m, 1H, C*H*-N=), 4.31 – 4.45 (m, 2H, C*H*$_2$-NCH=CHN), 5.47 (d, 1H, C*H*$_a$-C_6H_5, *J* = 14.3 Hz), 5.50 (d, 1H, C*H*$_b$-C_6H_5, *J* = 14.3 Hz), 6.61 (s, 1H, N=C(C_6H_5)$_a$), 6.63 (s, 1H, N=C(C_6H_5)$_a$), 7.15 – 7.60 (m, 13H, CH_2-C_6H_5 + N=C(C_6H_5)$_2$), 7.64 (s, 1H, NC*H*=CHN), 7.88 (s, 1H, NCH=C*H*N), 9.43 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 18.8 (1C, *C*H$_3$), 51.7 (1C, *C*H$_2$-C_6H_5), 55.0 (1C, *C*H$_2$-NCH=CHN), 57.1 (1C, *C*H-N=), 122.4 (1C, N*C*H=CHN), 123.1 (1C, NCH=*C*HN), 126.6 (2C, Ar*C*), 128.2 (4C, Ar*C*), 128.5 (3C, Ar*C*), 128.6 (2C, Ar*C*), 128.8 (2C, Ar*C*), 130.5 (2C, Ar*C*), 135.4 (1C, N=C(*ipso*-C_6H_5)$_a$), 136.0 (1C, CH_2-(*ipso*-C_6H_5)), 136.7 (1C, N*C*HN), 139.1 (1C, N=C(*ipso*-C_6H_5)$_b$), 168.6 (1C, *C*=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



1-{*(S)*-2-(Benzylhydrylidene-amino)-3-methyl-butyl}-3-benzylimidazolium bromide (25c).

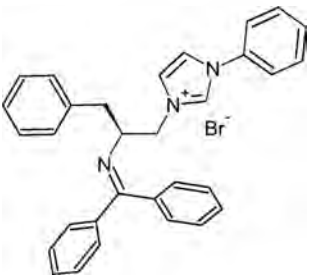
A mixture of **24c** (0.70 g, 2.12 mmol) and 1-benzylimidazole (0.34 g, 2.12 mmol) was heated at 85 °C for 64 h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was

recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **25c** as a white solid (0.59 g, 57%); mp 156.0 – 157.6 °C; $[\alpha]_D^{20°C} = +27.4$ (c = 1.13, $CHCl_3$); HRMS (ESI): $[C_{28}H_{30}N_3]^+$ m/z = 408.2445 ($[C_{28}H_{30}N_3]^+$ requires 408.2434); ^{1}H NMR (CD_2Cl_2, 400 MHz,) δ_H 0.92 (d, 3H, CH(CH_3)$_a$, J = 6.8 Hz), 0.95 (d, 3H, CH(CH_3)$_b$, J = 6.8 Hz), 1.78 – 1.96 (m, 1H, CH(CH$_3$)$_2$), 3.33 – 3.43 (m, 1H, CH-N=), 4.46 (dd, 1H, CH-CH_a-NCH=CHN, J = 8.8 Hz, J = 13.6 Hz), 4.57 (dd, 1H, CH-CH_b-NCH=CHN, J = 2.9 Hz, J = 13.6 Hz), 5.57 (d, 1H, CH_a-C$_6$H$_5$, J = 14.3 Hz), 5.62 (d, 1H, CH_b-C$_6$H$_5$, J = 14.3 Hz), 6.39 (s, 1H, N=C(C$_6H_5$)$_a$), 6.41 (s, 1H, N=C(C$_6H_5$)$_a$), 7.13 – 7.60 (m, 15H, CH$_2$-C$_6H_5$ + NCH=CHN + N=C(C$_6H_5$)$_2$), 10.12 (s, 1H, NCHN); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ_C 18.9 (2C, CH(CH_3)$_2$), 32.2 (1C, CH(CH$_3$)$_2$), 53.2 (2C, CH_2-C$_6$H$_5$ + CH-CH_2-NCH=CHN), 66.6 (1C, CH-N=), 122.0 (1C, NCH=CHN), 123.1 (1C, NCH=CHN), 127.2 (2C, ArC), 128.3 (4C, ArC), 128.6 (3C, ArC), 129.1 (2C, ArC), 129.3 (2C, ArC), 130.7 (2C, ArC), 133.8 (1C, N=C(*ipso*-C_6H$_5$)$_a$), 135.7 (1C, CH$_2$-(*ipso*-C_6H$_5$)), 137.0 (1C, NCHN), 139.0 (1C, N=C(*ipso*-C_6H$_5$)$_b$), 170.1 (1C, C=N).

1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-pentyl}-3-benzylimidazolium bromide (25d).

A mixture of **24d** (0.70 g, 2.03 mmol) and 1-benzylimidazole (0.32 g, 2.03 mmol) was heated at 85 °C for 17 h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **25d** as a white solid (0.81 g, 79%); mp 149.4 – 151.5 °C; $[\alpha]_D^{20°C}$ = + 30.8 (*c* = 1.74, CH_2Cl_2); HRMS (ESI): $[C_{29}H_{32}N_3]^+$ m/z = 422.2593 ($[C_{29}H_{32}N_3]^+$ requires 422.2591); ^{1}H NMR (CD_2Cl_2, 400 MHz) δ_H 0.65 (d, 3H, CH(C*H*$_3$)$_a$, *J* = 6.4 Hz), 0.73 (d, 3H, CH(C*H*$_3$)$_b$, *J* = 6.4 Hz), 1.30 – 1.60 (m, 3H, C*H*$_2$-C*H*(CH$_3$)$_2$), 3.66 – 3.77 (m, 1H, C*H*-N=), 4.43 – 4.50 (m, 2H, C*H*$_2$-NCH=CHN), 5.57 (d, 1H, C*H*$_a$-C$_6$H$_5$, *J* = 14.3 Hz), 5.62 (d, 1H, C*H*$_b$-C$_6$H$_5$, *J* = 14.3 Hz), 6.58 (s, 1H, N=C(C$_6$H$_5$)$_a$), 6.60 (s, 1H, N=C(C$_6$H$_5$)$_a$), 7.20 – 7.60 (m, 15H, CH$_2$-C$_6$*H*$_5$ + NC*H*=C*H*N + N=C(C$_6$H$_5$)$_2$), 10.22 (s, 1H, NC*H*N); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ_C 21.4 (2C, CH(*C*H$_3$)$_2$), 23.3 (1C, *C*H(CH$_3$)$_2$), 41.4 (1C, *C*H$_2$-CH(CH$_3$)$_2$), 51.9 (1C, *C*H$_2$-C$_6$H$_5$), 53.8 (1C, *C*H$_2$-NCH=CHN), 58.2 (1C, *C*H-N=), 120.7 (1C, NCH=CHN), 121.9 (1C, NCH=*C*HN), 126.1 (2C, Ar*C*), 127.1 (4C, Ar*C*), 127.5 (3C, Ar*C*), 127.7 (2C, Ar*C*), 128.1 (2C,

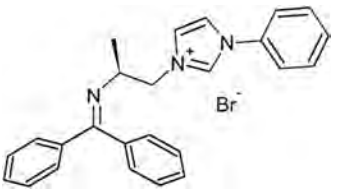
Ar*C*), 129.5 (2C, Ar*C*), 132.6 (1C, N=C(*ipso*-$C_6H_5)_a$), 134.5 (1C, CH_2-(*ipso*-C_6H_5)), 136.0 (1C, N*C*HN), 137.7 (1C, N=C(*ipso*-$C_6H_5)_b$), 168.7 (1C, *C*=N); Anal. found: C 66.33%, H 6.15%, N 8.31% ($C_{28}H_{31}N_3Br$ requires C 68.71%, H 6.38%, N 8.58%).



(1-{*(S)*-2-(Benzylhydrylidene-amino)-4-phenyl-propyl}-3-phenylimidazolium bromide (26a).

A mixture of **24a** (0.60 g, 1.59 mmol) and 1-phenylimidazole (0.23 g, 1.59 mmol) was heated at 95 °C for 19 h. The crude product was triturated, washed with dry diethyl ether (3 x 30 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **26a** as a clear white solid (0.36 g, 43%); mp 127.3 – 129.1 °C; $[\alpha]_D^{20°C}$ = + 67.0 (*c* = 1.05, $CHCl_3$); HRMS (ESI): $[C_{31}H_{28}N_3]^+$ m/z = 442.2240 ($[C_{31}H_{28}N_3]^+$ requires 442.2278); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 2.94 (dd, 1H, CH_a-NCH=CHN, *J* = 8.4 Hz, *J* = 13.1 Hz), 3.07 (dd, 1H, CH_b-NCH=CHN, *J* = 4.2 Hz, *J* = 13.1 Hz),

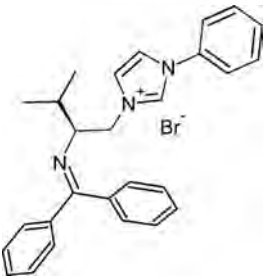
3.75 – 3.90 (m, 1H, C*H*-N=), 4.56 (d, 2H, C*H*$_2$-C_6H_5, J = 5.9 Hz), 6.05 (s, 1H, N=C(C_6H_5)$_a$), 6.07 (s, 1H, N=C(C_6H_5)$_a$), 7.02 – 7.74 (m, 18H, NCH=CHN-C_6H_5 + CH_2-C_6H_5 + N=C(C_6H_5)$_2$), 7.91 (s, 1H, NC*H*=CHN), 8.32 (s, 1H, NCH=C*H*N), 9.88 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 39.5 (1C, *C*H$_2$-C_6H_5), 54.2 (1C, *C*H$_2$-NCH=CHN), 63.5 (1C, *C*H-N=), 120.9 (1C, N*C*H=CHN), 121.6 (2C, NCH=CHN-(o-*C*$_6$H$_5$)), 124.2 (1C, NCH=*C*HN), 126.4 (Ar*C*), 126.5 (Ar*C*), 128.1 (Ar*C*), 128.2 (Ar*C*), 128.5 (Ar*C*), 129.7 (Ar*C*), 129.9 (Ar*C*), 130.2 (Ar*C*), 130.6 (Ar*C*), 134.5 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_a$), 135.2 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_b$), 135.5 (1C, N*C*HN), 137.5 (1C, CH$_2$-(*ipso*-*C*$_6$H$_5$)), 138.5 (1C, NCH=*C*HN-(*ipso*-*C*$_6$H$_5$)), 169.3 (1C, *C*=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



1-{*(S)*-2-(Benzylhydrylidene-amino)-propyl}-3-phenylimidazolium bromide (26b).

A mixture of **24b** (0.70 g, 2.32 mmol) and 1-phenylimidazole (0.33 g, 2.32 mmol) was heated at 85 °C for 47 h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give

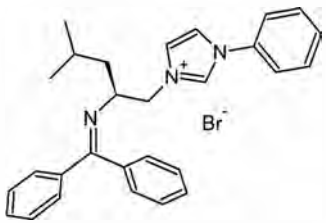
26b as a clear white solid (0.29 g, 28%); mp 192.1 – 194.3 °C; $[\alpha]_D^{20°C}$ = + 51.5 (*c* = 1.11, CH_3OH); HRMS (ESI): $[C_{25}H_{24}N_3]^+$ m/z = 366.1956 ($[C_{25}H_{24}N_3]^+$ requires 366.1965); ^1H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 1.23 (d, 3H, C*H*$_3$, *J* = 6.2 Hz), 3.68 –3.85 (m, 1H, C*H*-N=), 4.43 (dd, 1H, C*H*$_a$-NCH=CHN, *J* = 8.1 Hz, *J* = 13.2 Hz,), 4.48 (dd, 1H, C*H*$_b$-NCH=CHN, *J* = 3.7 Hz, *J* = 13.2 Hz,), 6.91 (d, 1H, N=C(C$_6$*H*$_5$)$_a$, *J* = 2.2 Hz), 6.93 (d, 1H, N=C(C$_6$*H*$_5$)$_a$, *J* = 2.2 Hz), 7.30 – 7.78 (m, 13H, NCH=CHN-C$_6$*H*$_5$ + N=C(C$_6$*H*$_5$)$_2$), 7.91 (s, 1H, NC*H*=CHN), 8.31 (s, 1H, NCH=C*H*N), 9.92 (s, 1H, NC*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 18.7 (1C, *C*H$_3$), 55.2 (1C, *C*H$_2$-NCH=CHN), 56.8 (1C, *C*H-N=), 121.0 (1C, NCH=CHN), 121.6 (2C, NCH=CHN-(*o*-*C*$_6$H$_5$)), 123.8 (1C, NCH=*C*HN), 126.8 (Ar*C*), 128.0 (Ar*C*) , 128.1 (Ar*C*), 128.6 (Ar*C*), 129.8 (Ar*C*), 130.1 (Ar*C*), 130.4 (Ar*C*), 134.4 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_a$), 135.4 (2C, N*C*HN + N=C(*ipso*-*C*$_6$H$_5$)$_b$), 138.5 (1C, NCH=CHN-(*ipso*-*C*$_6$H$_5$)), 168.5 (1C, *C*=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



(1-{*(S)*-2-(Benzylhydrylidene-amino)-3-methyl-butyl}-3-phenylimidazolium bromide (26c)

A mixture of **24c** (0.56 g, 1.70 mmol) and 1-phenylimidazole (0.24 g, 1.70 mmol) was heated at 85 °C for 40h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2/Et_2O, filtered and dried under reduced pressure to give **26c** as a clear white solid (0.17 g, 21%); mp 161.8 – 164.2 °C; $[\alpha]_D^{20°C} = +47.7$ ($c = 1.11$, CH_3OH); HRMS (ESI): $[C_{27}H_{28}N_3]^+$ m/z = 394.2253 ($[C_{27}H_{28}N_3]^+$ requires 394.2278); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 0.99 (d, 3H, CH(CH_3)$_a$, $J = 3.6$ Hz), 1.01 (d, 3H, CH(CH_3)$_b$, $J = 3.6$ Hz), 1.90 – 2.40 (m, 1H, CH(CH$_3$)$_2$), 3.42 – 3.54 (m, 1H, CH-N=), 4.50 (dd, 1H, CH_a-NCH=CHN, $J = 9.2$ Hz, $J = 13.4$ Hz), 4.58 (dd, 1H, CH_b-NCH=CHN, $J = 3.0$ Hz, $J = 13.4$ Hz), 6.66 (d, 2H, N=C(C$_6H_5$)$_2$), 7.28 – 7.76 (m, 13H, NCH=CHN-C$_6H_5$ + N=C(C$_6H_5$)$_2$), 7.88 (s, 1H, NCH=CHN), 8.31 (s, 1H, NCH=CHN), 9.84 (s, 1H, NCHN); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 18.7 (1C, CH(CH_3)$_a$), 18.9 (1C, CH(CH_3)$_b$), 31.4 (1C, CH(CH$_3$)$_2$), 52.4 (1C, CH_2-NCH=CHN), 66.5 (1C, CH-N=), 121.0 (1C, NCH=CHN), 121.5 (2C, NCH=CHN-

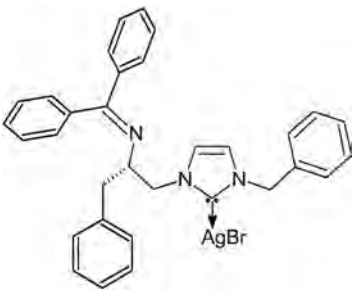
(*o*-C_6H_5)), 124.2 (1C, NCH=*C*HN), 126.8 (Ar*C*), 128.08 (Ar*C*), 128.12 (Ar*C*), 128.4 (Ar*C*), 128.5 (Ar*C*), 130.2 (Ar*C*), 130.4 (Ar*C*), 134.2 (1C, N=C(*ipso*-$C_6H_5)_a$), 135.0 (2C, N*C*HN + N=C(*ipso*-$C_6H_5)_b$), 139.0 (1C, NCH=CHN-(*ipso*-C_6H_5)), 168.9 (1C, *C*=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



(1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-pentyl}-3-phenylimidazolium bromide (26d).

A mixture of **24d** (0.70 g, 2.03 mmol) and 1-methylimidazole (0.29 g, 2.03 mmol) was heated at 85 °C for 47h. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was recrystallised from CH_2Cl_2 / Et_2O, filtered and dried reduced pressure to give **26d** as a clear white solid (0.25 g, 25%); mp 176.9 – 178.4; $[\alpha]_D^{20°C}$ = + 13.8 (*c* = 1.74, CH_2Cl_2); HRMS (ESI): $[C_{28}H_{30}N_3]^+$ m/z = 408.2416 ($[C_{28}H_{30}N_3]^+$ requires 408.2434); ^1H NMR ($CDCl_3$, 400 MHz) δ_H 0.58 (d, 3H, CH(C*H*$_3)_a$, *J* = 6.2 Hz), 0.70 (d, 3H, CH(C*H*$_3)_b$, *J* = 6.2 Hz), 1.28 – 1.58 (m, 3H, C*H*$_2$-C*H*(CH$_3)_2$), 3.75 – 3.87 (m, 1H, C*H*-N=), 4.64 (dd, 1H, C*H*$_a$-NCH=CHN, *J* = 7.3 Hz, *J* = 13.6 Hz), 4.77 (dd, 1H, C*H*$_b$-NCH=CHN, *J* = 2.9 Hz, *J* = 13.6 Hz), 6.72 – 6.82 (m, 2H, N=C(C$_6$*H*$_5)_2$), 7.20 –

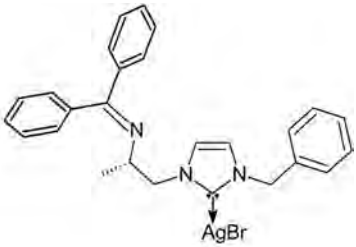
7.58 (m, 12H, ArH_{11} + NC*H*=CHN), 7.63 – 7.73 (m, 2H, ArH_2), 7.86 (s, 1H, NCH=C*H*N), 10.53 (s, 1H, NC*H*N); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 22.7 (1C, CH(CH_3)$_a$), 23.2 (1C, CH(CH_3)$_b$), 24.5 (1C, *C*H(CH_3)$_2$), 42.5 (1C, *C*H_2-CH(CH_3)$_2$), 55.5 (1C, *C*H_2-NCH=CHN), 59.3 (1C, *C*H-N=), 120.3 (1C, NCH=CHN), 121.8 (2C, Ar*C*), 124.2 (1C, NCH=*C*HN), 127.2 (2C, Ar*C*), 128.4 (2C, ArC), 128.5 (2C, Ar*C*), 128.9 (2C, Ar*C*), 129.0 (1C, Ar*C*), 130.3 (1C, Ar*C*), 130.7 (2C, Ar*C*), 130.8 (1C, Ar*C*), 134.4 (1C, N=C(*ipso*-C_6H_5)$_a$), 135.8 (1C, N=C(*ipso*-C_6H_5)$_b$), 136.2 (1C, NCH), 138.8 (1C, NCH=CHN-(*ipso*-C_6H_5)), 169.7 (1C, *C*=N). Some ^{13}C NMR signals are due to multiple carbon atoms.



[$(C_6H_5)_2$C=NCH(CH_2CH(CH_3)$_2$)CH_2-NCN-Bn]AgBr (27a).

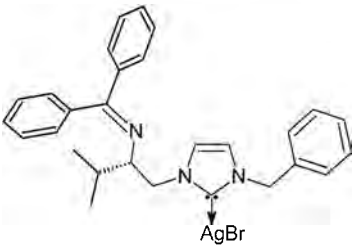
Silver oxide (I) (0.08 g, 0.36 mmol) was added to a solution of **25a** (0.35 g, 0.65 mmol) in dichloromethane (25 ml) in the presence 4 Å activated molecular sieves (1 g). The reaction mixture was protected from light and was refluxed for 3 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **27a** as a white solid (0.21 g, 50%); ^{1}H NMR (DMSO-d_6, 400

MHz, 35 °C) δ_H 2.89 (dd, 1H, CH-CH_a-C_6H_5, J = 8.8 Hz, J = 13.0 Hz), 2.95 (dd, 1H, CH-CH_b-C_6H_5, J = 4.4 Hz, J = 13.0 Hz), 3.60 – 3.75 (m, 1H, C*H*-N=), 4.31 (dd, 1H, CH-CH_a-NCH=CHN, J = 2.6 Hz, J = 13.3 Hz), 4.49 (dd, 1H, CH-CH_b-NCH=CHN, J = 9.9 Hz, J = 13.3 Hz), 5.05 – 5.25 (m, 2H, NCH=CHN-CH_2-C_6H_5), 5.66 (s, 1H, N=C(C_6H_5)$_a$), 5.68 (s, 1H, N=C(C_6H_5)$_a$), 6.90 – 7.52 (m, 20H, NC*H*=C*H*N-CH_2-C_6H_5 + CH-CH_2-C_6H_5 + N=C(C_6H_5)$_a$); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 49.4 (1C, CH-*C*H_2-C_6H_5), 54.2 (1C, CH-*C*H_2-NCH=CHN), 56.4 (1C, NCH=CHN-*C*H_2-C_6H_5), 64.8 (1C, *C*H-N=), 121.7 (1C, N*C*H=CHN), 122.9 (1, NCH=*C*HN), 126.2 (Ar*C*), 126.4 (Ar*C*), 127.4 (Ar*C*), 127.6 (Ar*C*), 127.8 (Ar*C*), 128.0 (Ar*C*), 128.09 (Ar*C*), 128.13 (Ar*C*), 128.6 (Ar*C*), 129.7 (2C, N=C(*p*-C_6H_5)$_2$), 130.2 (1C, CH-CH_2-(*p*-C_6H_5)), 132.6 (1C, N=C(*ipso*-C_6H_5)$_a$), 136.9 (1C, NCH=CHN-CH_2-(*ipso*-C_6H_5)), 137.9 (1C, CH-CH_2-(*ipso*-C_6H_5)), 138.4 (1C, N=C(*ipso*-C_6H_5)$_b$), 168.4 (1C, *C*=N), 179.8 (1C, *C*-Ag); Anal. found: C 59.98%, H 4.18%, N 6.31% ($C_{32}H_{29}N_3AgBr$ requires C 59.74%, H 4.54%, N 6.53%).



$[(C_6H_5)_2C{=}NCH(CH_3)CH_2\text{-}NCN\text{-}Bn]AgBr$ (27b).

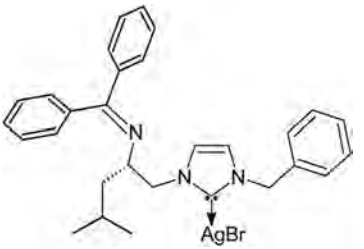
Silver oxide (I) (0.12 g, 0.54 mmol) was added to a solution of **25b** (0.45 g, 0.98 mmol) in dichloromethane (30 ml) in the presence 4 Å activated molecular sieves (1.5 g). The mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **27b** as a white solid (0.47 g, 84%); mp 85.5 – 88.2 °C; ^{1}H NMR (DMSO-d$_6$, 400 MHz, 35 °C) δ_H 1.12 (d, 3H, C*H*$_3$, *J* = 6.6 Hz), 3.57 – 3.69 (m, 1H, CH$_3$-C*H*-N=), 4.17 (dd, 1H, C*H*$_a$-NCH=CHN, *J* = 2.9 Hz, *J* = 13.2 Hz), 4.34 (dd, 1H, C*H*$_b$-NCH=CHN, *J* = 9.5 Hz, *J* = 13.2 Hz), 5.05 – 5.40 (m, 2H, C*H*$_2$-C$_6$H$_5$), 6.54 (s, 1H, N=C(C$_6$*H*$_5$)$_a$), 6.56 (s, 1H, N=C(C$_6$*H*$_5$)$_a$), 7.50 – 7.60 (m, 15H, CH$_2$-C$_6$*H*$_5$ + NC*H*=C*H*N + N=C(C$_6$*H*$_5$)$_2$); ^{13}C NMR (DMSO-d$_6$, 100 MHz, 35 °C) δ_C 19.2 (1C, *C*H$_3$), 54.1 (1C, *C*H$_2$-C$_6$H$_5$), 57.5 (1C, *C*H$_2$-NCH=CHN), 58.4 (1C, *C*H-N=), 121.8 (1C, NCH=CHN), 122.7 (1C, NCH=*C*HN), 126.7 (Ar*C*), 127.4 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.46 (Ar*C*), 128.53 (Ar*C*), 130.2 (Ar*C*), 135.6 (1C, CH$_2$-(*ipso*-*C*$_6$H$_5$),), 137.1 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_a$), 138.4 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_b$), 167.4 (1C, *C*=N), 179.6 (1C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.



$[(C_6H_5)_2C{=}NCH(CH(CH_3)_2)CH_2\text{-}NCN\text{-}Bn]AgBr$ (27c).

Silver oxide (I) (0.05 g, 0.22 mmol) was added to a solution of **25c** (0.20 g, 0.41 mmol) in dichloromethane (15 ml) in the presence 4 Å activated molecular sieves (1 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **27c** as a white solid (0.11 g, 45%); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 0.88 (d, 3H, CH(C*H*$_3$)$_a$, *J* = 6.6 Hz), 0.94 (d, 3H, CH(C*H*$_3$)$_b$, *J* = 6.6 Hz), 1.79 – 1.93 (m, 1H, C*H*(CH$_3$)$_2$), 3.40 – 3.50 (m, 1H, C*H*-N=), 4.34 (dd, 1H, CH-C*H*$_a$-NCH=CHN, *J* = 2.7 Hz, *J* = 13.4 Hz), 4.43 (dd, 1H, CH-C*H*$_b$-NCH=CHN, *J* = 9.3 Hz, *J* = 13.4 Hz), 5.00 – 5.25 (m, 2H, C*H*$_2$-C$_6$H$_5$, *J* = 7.0 Hz), 6.29 (s, 2H, N=C(C$_6$*H*$_5$)$_2$), 7.13 – 7.60 (m, 15H, CH$_2$-C$_6$*H*$_5$ + NC*H*=C*H*N + N=C(C$_6$*H*$_5$)$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 18.6 (1C, CH(*C*H$_3$)$_a$), 19.4 (1C, CH(*C*H$_3$)$_b$), 31.8 (1C, *C*H(CH$_3$)$_2$), 54.2 (1C, *C*H$_2$-C$_6$H$_5$), 54.7 (1C, CH-*C*H$_2$-NCH=CHN), 67.6 (1C, *C*H-N=), 121.7 (1C, NCH=CHN), 123.1 (1C, NCH=*C*HN), 127.0 (Ar*C*), 127.6 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.6 (Ar*C*), 130.1 (Ar*C*), 135.5 (1C, CH$_2$-(*ipso*-*C*$_6$H$_5$), 136.8 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_a$), 138.7 (1C, N=C(*ipso*-*C*$_6$H$_5$)$_b$),

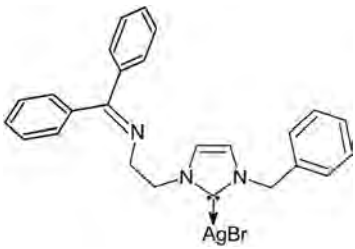
168.0 (1C, *C*=N), 179.9 (1C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.



[$(C_6H_5)_2$C=NCH(CH_2CH$(CH_3)_2$)CH_2-NCN-Bn]AgBr (27d).

Silver oxide (I) (0.13 g, 0.55 mmol) was added to a solution of **25d** (0.50 g, 1.00 mmol) in dichloromethane (30 ml) in the presence 4 Å activated molecular sieves (1.5 g). The reaction mixture was protected from light and was refluxed for 3 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **27d** as a white solid (0.25 g, 68%); ^1H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 0.63 (d, 3H, CH(CH_3)$_a$, J = 6.4 Hz), 0.76 (d, 3H, CH(CH_3)$_b$, J = 6.4 Hz), 1.37 – 1.59 (m, 3H, CH_2-CH(CH_3)$_2$), 3.55 – 3.68 (m, 1H, CH-N=), 4.22 – 4.50 (m, 2H, CH_2-NCH=CHN), 5.07 – 5.27 (m, 2H, CH_2-C_6H_5), 6.39 (s, 2H, N=C(C_6H_5)$_2$), 7.09 – 7.55 (m, 15H, CH_2-C_6H_5 + NCH=CHN + N=C(C_6H_5)$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 22.6 (1C, CH(CH_3)$_a$), 23.0 (1C, CH(CH_3)$_b$), 23.9 (1C, CH(CH_3)$_2$), 42.8 (1C, CH_2-CH(CH_3)$_2$), 54.1 (1C, CH_2-C_6H_5), 56.4 (1C, CH_2-N_{im}), 60.8 (1C, CH-N=), 121.7 (1C, NCH=CHN), 122.9 (1C, NCH=CHN),

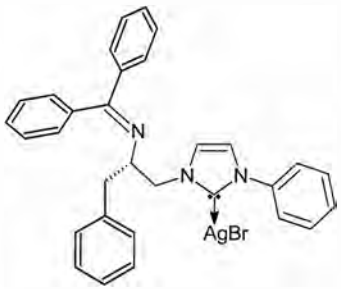
126.9 (2C, Ar*C*), 130.0 (2C, Ar*C*), 127.4 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.2 (Ar*C*), 128.5 (Ar*C*), 135.5 (1C, N=C(*ipso*-C_6H_5)$_a$), 136.8 (1C, CH_2-(*ipso*-C_6H_5)), 138.6 (1C, N=C(*ipso*-C_6H_5)$_b$), 167.7 (1C, *C*=N), 179.9 (1C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.



[$(C_6H_5)_2C$=NCH_2CH_2-NCN-Bn]AgBr (27e).

Silver oxide (I) (0.45 g, 1.93 mmol) was added to a solution of **20a** (1.50 g, 3.36 mmol) in dichloromethane (100 ml) in the presence 4Å activated molecular sieves (4 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **27e** as a white solid (1.47 g, 79%); mp 157.5 – 162.1 °C; $\upsilon_{(C=N)}$: 1623 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 3.63 (t, 2H, CH_2-N=C(C_6H_5)$_2$, J = 5.3 Hz), 4.39 (t, 2H, CH_2CH_2-NCH=CHN, J = 5.3 Hz), 5.26 (s, 2H, CH_2-C_6H_5), 6.79 – 6.86 (m, 2H, N=C(C_6H_5)$_2$), 7.15 – 7.60 (m, 15H, CH_2-C_6H_5 + NC*H*=C*H*N + N=C(C_6H_5)$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 52.1 (1C, CH_2-N=C(C_6H_5)$_2$), 53.9 (2C, CH_2-NCH=CHN + CH_2-C_6H_5), 121.8 (1C,

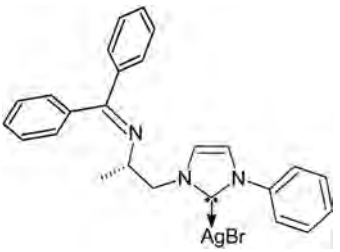
NCH=CHN), 122.4 (1C, NCH=*C*HN), 127.0 (Ar*C*), 127.3 (Ar*C*), 127.9 (Ar*C*), 128.5 (Ar*C*), 130.1 (Ar*C*), 135.6 (1C, N=C(*ipso*-$C_6H_5)_a$), 137.1 (1C, N=C(*ipso*-$C_6H_5)_b$), 138.6 (1C, CH_2-(*ipso*-C_6H_5), 168.7 (1C, *C*=N), 179.8 (1C, *C*-Ag); Anal. found: C 54.26%, H 4.00%, N 7.64% ($C_{25}H_{23}N_3AgBr$ requires C 54.27%, H 4.19%, N 7.60%). Some ^{13}C NMR signals are due to multiple carbon atoms.



[$(C_6H_5)_2$C=NCH($CH_2C_6H_5$)CH_2-NCN-Ph]AgBr (28a).

Silver oxide (I) (0.05 g, 0.21 mmol) was added to a solution of **26a** (0.20 g, 0.38 mmol) in dichloromethane (15 ml) in the presence 4 Å activated molecular sieves (1.0 g). The reaction mixture was protected from light and was refluxed for 47 h. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **28a** as a white solid (0.16 g, 66%); ^1H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 3.20 – 3.35 (m, 2H, CH_2-NCH=CHN), 3.60 – 3.80 (m, 1H, C*H*-N=), 4.10 – 4.25 (m, 1H, CH_a-C_6H_5), 4.30 – 4.45 (m, 1H, CH_b-C_6H_5), 6.69 (s, 2H,

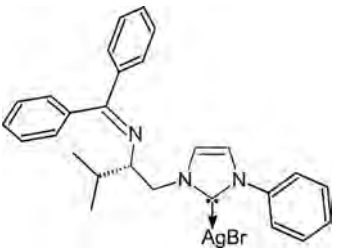
N=C(C_6H_5)$_2$), 7.10 – 7.90 (m, 20H, NC*H*=C*H*N-C_6H_5 + CH_2-C_6H_5 + N=C(C_6H_5)$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 57.6 (2C, *C*H_2-NCH=CHN + *C*H_2-C_6H_5), 58.4 (1C, *C*H-N=), 121.6 (1C, N*C*H=CHN), 123.5 (3C, NCH=CHN-(*o*-C_6H_5) + NCH=*C*HN), 126.6 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.3 (Ar*C*) 128.5 (Ar*C*), 129.6 (Ar*C*), 129.9 (Ar*C*), 130.1 (Ar*C*), 135.7 (2C, CH_2-(*ipso*-C_6H_5) + N=C(*ipso*-C_6H_5)$_a$), 138.5 (1C, N=C(*ipso*-C_6H_5)$_b$), 139.7 (1C, NCH=CHN-(*ipso*-C_6H_5)), 167.4 (1C, *C*=N), not vis. (1C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.



[(C_6H_5)$_2$C=NCH(CH_3)CH_2-NCN-Ph]AgBr (28b).

Silver oxide (I) (0.028 g, 0.12 mmol) was added to a solution of **26b** (0.100 g, 0.22 mmol) in dichloromethane (15 ml) in the presence 4 Å activated molecular sieves (1.0 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **28b** as a white solid (0.111 g, 91%); mp 85.0 – 87.4 °C; ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 1.20 (d, 3H, CH_3, J = 5.9 Hz), 3.68 –3.85 (m,

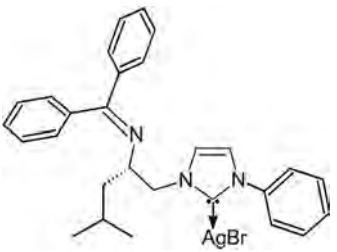
1H, C*H*-N=), 4.17 – 4.33 (m, 1H, CH_a-NCH=CHN), 4.40 (dd, 1H, CH_b-NCH=CHN, J = 9.3 Hz, J = 13.4 Hz), 6.75 (s, 2H, N=C(C_6H_5)$_2$), 7.25 – 7.62 (m, 14H, NCH=CHN-C_6H_5 + NC*H*=CHN + N=C(C_6H_5)$_2$), 7.83 (s, 1H, NCH=C*H*N); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 19.3 (1C, *C*H$_3$), 57.7 (1C, *C*H$_2$-NCH=CHN), 58.5 (1C, *C*H-N=), 121.9 (1C, NCH=CHN-(*o*-C_6H_5)), 123.5 (1C, NCH=CHN), 123.6 (1C, NCH=*C*HN), 126.6 (Ar*C*), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.6 (Ar*C*), 129.7 (Ar*C*), 130.3 (Ar*C*), 135.7 (1C, N=C(*ipso*-C_6H_5)$_a$), 138.5 (1C, N=C(*ipso*-C_6H_5)$_b$), 139.6 (1C, NCH=CHN-(*ipso*-C_6H_5)), 168.5 (1C, *C*=N), Not vis. (1C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.



[(C_6H_5)$_2$C=NCH(CH(CH$_3$)$_2$)CH$_2$-NCN-Ph]AgBr (28c).

Silver oxide (I) (0.04 g, 0.18 mmol) was added to a solution of **26c** (0.15 g, 0.41 mmol) in dichloromethane (10 ml) in the presence 4 Å activated molecular sieves (0.5 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under

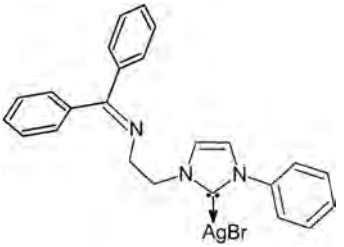
reduced pressure to give **28c** as a white solid (0.12 g, 64%); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 0.87 (d, 3H, CH(C*H*$_3$)$_a$, *J* = 6.9 Hz), 0.95 (d, 3H, CH(C*H*$_3$)$_b$, *J* = 6.9 Hz), 0.95 (d, 1H, C*H*(CH$_3$)$_2$), 3.63 – 3.81 (m, 1H, C*H*-N=), 4.30 – 4.60 (m, 2H, C*H*$_2$-NCH=CHN), 6.30 – 6.70 (m, 2H, N=C(C$_6$*H*$_5$)$_2$), 7.10 – 7.90 (m, 15H, NCH=CHN-C$_6$*H*$_5$ + NC*H*=C*H*N + N=C(C$_6$*H*$_5$)$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 19.2 (2C, CH(*C*H$_3$)$_2$), 32.1 (1C, C*H*(CH$_3$)$_2$), 55.0 (1C, *C*H$_2$-NCH=CHN), 68.9 (1C, *C*H-N), 120.2 (1C, NCH=CHN-(*o*-*C*$_6$H$_5$)), 121.6 (1C, N*C*H=CHN), 123.9 (1C, NCH=*C*HN), 126.8 (Ar*C*), 128.1 (Ar*C*), 128.2 (Ar*C*), 128.3 (Ar*C*), 128.4 (Ar*C*), 128.6 (Ar*C*), 129.6 (Ar*C*), 130.2 (Ar*C*), 132.7 (Ar*C*), 135.6 (3C, N=C(*ipso*-*C*$_6$H$_5$)$_2$ + NCH=CHN-(*ipso*-*C*$_6$H$_5$)), not vis (1C, *C*=N), not vis. (1C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.



[(C$_6$H$_5$)$_2$C=NCH(CH$_2$CH(CH$_3$)$_2$)CH$_2$-NCN-C$_6$H$_5$]AgBr (28d).

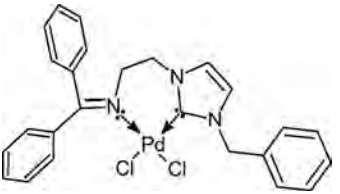
Silver (I) oxide (0.04 g, 0.18 mmol) was added to a solution of **26d** (0.099 g, 0.20 mmol) in dichloromethane (10 ml) in the presence 4 Å activated molecular sieves (0.5 g). The reaction mixture was protected from light and was refluxed for 2 days. The

mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **28d** as a white solid (0.071 g, 60%); mp 68.2 – 70.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.70 (d, 3H, $CH(CH_3)_a$, J = 6.4 Hz), 0.82 (d, 3H, $CH(CH_3)_b$, J = 6.4 Hz), 1.40 – 1.63 (m, 3H, $CH(CH_3)_2$ + $CH_2CH(CH_3)_2$), 3.73 – 3.87 (m, 1H, CH-N=), 4.22 – 4.45 (m, 2H, CH_2-NCH=CHN), 6.57 (s, 1H, N=C(C_6H_5)$_2$), 6.59 (s, 1H, N=C(C_6H_5)$_2$), 7.10 – 7.65 (m, 15H, NCH=CHN-C_6H_5 + NCH=CHN + N=C(C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 22.8 (1C, $CH(CH_3)_a$), 23.2 (1C, $CH(CH_3)_b$), 24.6 (1C, $CH(CH_3)_2$), 43.1 (1C, CH_2-NCH=CHN), 57.7 (1C, CH_2-$CH(CH_3)_2$), 61.2 (1C, CH-N=), 121.0 (1C, NCH=CHN), 123.2 (1C, NCH=CHN), 123.6 (2C, ArC), 126.9 (2C, ArC), 128.1 (2C, ArC), 128.38 (2C, ArC), 128.41 (2C, ArC), 128.7 (1C, ArC), 128.9 (1C, ArC), 129.8 (2C, ArC), 130.3 (1C, ArC), 135.9 (1C, N=C(*ipso*-C_6H_5)$_a$), 138.9 (1C, N=C(*ipso*-C_6H_5)$_b$), 139.6 (1C, NCH=CHN-(*ipso*-C_6H_5)), 168.8 (1C, C=N), 180.7 (1C, C-Ag).



[$(C_6H_5)_2$C=NCH_2CH_2-NCN-Ph]AgBr (28e).

Silver (I) oxide (0.10 g, 0.44 mmol) was added to a solution of **20c** (0.35 g, 0.81 mmol) in dichloromethane (35 ml) in the presence 4Å activated molecular sieves (1.0 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **28e** as a clear white/orange solid (0.34 g, 78%); ^{1}H NMR (DMSO-d_6, 400 MHz, 35 °C) δ_H 3.67 (t, 4H, C*H*$_2$-N=C(C_6H_5)$_2$, *J* = 5.4 Hz), 4.45 (t, 4H, C*H*$_2$-N$_{im}$, *J* = 5.4 Hz), 6.29 (s, 2H, N=C(C_6H_5)$_a$), 7.10 – 7.53 (m, 15H, N=C(C_6H_5)$_2$ + NC*H*=C*H*N-C_6H_5); ^{13}C NMR (DMSO-d_6, 100 MHz, 35 °C) δ_C 52.5 (1C, *C*H$_2$-N=C(C_6H_5)$_2$), 53.9 (1C, *C*H$_2$-NCH=CHN), 121.8 (1C, NC*H*=CHN), 123.4 (1C, NCH=C*H*N), 123.5 (Ar*C*), 126.9 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*), 128.39 (Ar*C*), 128.43 (Ar*C*), 128.6 (Ar*C*), 129.4 (Ar*C*), 129.5 (Ar*C*), 130.1 (Ar*C*), 135.6 (2C, N=C(*ipso*-C_6H_5)$_a$), 138.6 (2C, N=C(*ipso*-C_6H_5)$_b$), 139.6 (2C, N$_{im}$-(*ipso*-C_6H_5)), 170.1 (2C, *C*=N), 168.9 (2C, *C*-Ag). Some ^{13}C NMR signals are due to multiple carbon atoms.

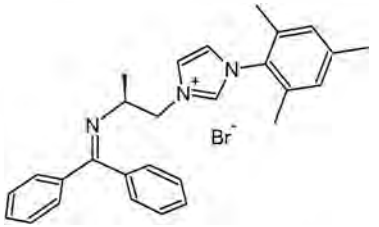


Pd[$(C_6H_5)_2$C=NCH_2CH_2-NCN-Bn]Cl_2 (33b).

Bis(benzonitrile) dichloropalladium (II) (0.21 g, 0.54 mmol) was added to a solution of **27e** (0.30 g, 0.27 mmol) in dichloromethane (20 ml). The reaction mixture protected from light was stirred for 28 h. The mixture was reduced and layered with hexane. The clear precipitate formed was filtered and washed with hexane (40 ml). The precipitate was then dried under reduced pressure to give **33b** as a clear yellow solid (0.29 g, quant.); $\upsilon_{(C=N)}$: 1615 cm^{-1}; ^{1}H NMR (Pyridine-d_5, 400 MHz) δ_H 4.28 (t, 2H, CH_2-N=, J = 5.7 Hz), 5.23 (t, 2H, CH_2-NCH=CHN, J = 5.7 Hz), 6.09 (s, 2H, N=C(C_6H_5)$_a$), 7.20 – 7.58 (m, 12H, ArH_{12}), 7.70 – 7.88 (m, 5H, ArH_3 + NCH=CHN); ^{13}C NMR (Pyridine-d_5, 100 MHz) δ_C 47.6 (1C, CH_2-N=C(C_6H_5)$_2$), 49.4 (1C, CH_2-C_6H_5), 49.7 (1C, CH_2-NCH=CHN), 116.6 (1C, NCH=CHN), 119.4 (1C, NCH=CHN), 122.9 (ArC), 123.5 (ArC), 123.5 (ArC), 123.7 (ArC), 123.9 (ArC), 124.1 (ArC), 124.2 (ArC), 124.3 (ArC), 125.3 (ArC), 125.5 (ArC), 127.7 (ArC), 130.8 (ArC), 131.8 (1C, N=C(*ipso*-C_6H_5)$_a$), 131.9 (1C, N=C(*ipso*-C_6H_5)$_b$), 133.0 (ArC), 135.0 (1C, CH_2-(*ipso*-C_6H_5)), 145.2 (1C, C-Pd), 164.7 (1C, C=N). Some ^{13}C NMR signals are due to multiple carbon atoms.

***(S)*-2-(Benzylhydrylidene-amino)-4-methyl-bromopentane (37).**

A solution of **23d** (0.148 g, 0.68 mmol) in dichloromethane (10 ml) was successively treated with triethylamine (0.069 g, 0.68 mmol, 95 µl) and benzaldehyde (0.073 g, 0.68 mmol, 70 µl) in the presence of activated 4 Å molecular sieves (2.00 g). The reaction mixture was stirred for 19 h. The drying agent was filtered and the filtrate was concentrated. The residue was then treated with diethyl ether (10 ml). The precipitate formed was filtered off and washed with diethyl ether (2 x 10 ml). The solvent was removed under reduced pressure to give **37** as a clear yellow oil (0.138 g, 76%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (d, 3H, $CH(CH_3)_a$, J = 6.6 Hz), 0.92 (d, 3H, $CH(CH_3)_b$, J = 6.6 Hz), 1.38 – 1.48 (m, 1H, CH_a-$CH(CH_3)_2$), 1.49 – 1.62 (m, 1H, $CH(CH_3)_2$), 1.63 – 1.74 (m, 1H, CH_b-$CH(CH_3)_2$), 3.40 – 3.51 (m, 1H, CH-N=), 3.55 – 3.70 (m, 2H, CH_2-Br), 7.35 – 7.45 (m, 3H, N=CH(*o*,*p*-C_6H_5), 7.72 – 7.80 (m, 2H, N=CH(*m*-C_6H_5), 8.28 (s, 1H, N=CH-C_6H_5); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 21.5 (1C, $CH(CH_3)_a$), 23.8 (1C, $CH(CH_3)_a$), 24.7 (1C, $CH(CH_3)_2$), 42.8 (1C, CH_2-$CH(CH_3)_2$), 48.9 (1C, CH_2-Br), 70.5 (1C, CH-N=), 128.5 (2C, N=CH(*m*-C_6H_5)), 128.7 (2C, N=CH(*o*-C_6H_5)), 131.0 (1C, N=CH(*p*-C_6H_5)), 136.0 (1C, N=CH-(*ipso*-C_6H_5)), 161.9 (1C, N=CH-C_6H_5).



1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-propyl}-3-(2,4,6-trimethylphenyl)-imidazolium bromide (38).

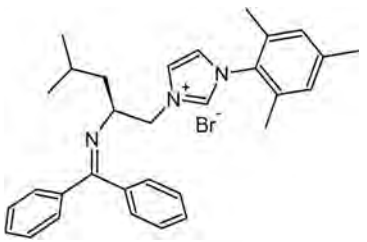
A mixture of **24b** (0.500 g, 1.73 mmol) and 1-mesitylimidazole (0.323 g, 1.73 mmol) was heated in toluene (0.3 ml) at 85 °C for 17 h. The crude product was triturated, washed with dry diethyl ether (2 x 30 ml) and recrystallised from CH_2Cl_2/Et_2O. The off-white crystals were filtered and washed with Et_2O. The solid was then dried under reduced pressure to give **38** as a clear white solid (0.149 g, 18 %); mp 64.3 – 66.4 °C; HRMS (ESI): $[C_{28}H_{30}N_3]^+$ m/z = 408.2438 ($[C_{28}H_{30}N_3]^+$ requires 408.2434); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 1.18 (d, 3H, CH_3CH-N=, J = 6.4 Hz), 1.90 (s, 3H, *2*-(CH_3)$_3$-C_6H_2), 2.04 (s, 3H, *6*-(CH_3)$_3$-C_6H_2), 2.30 (s, 3H, *4*-(CH_3)$_3$-C_6H_2), 3.85 – 3.97 (m, 1H, C*H*-N=), 4.87 – 5.05 (m, 2H, CH_2-NCH=CHN), 6.88 – 702 (m, 4H, N=C(C_6H_5)$_2$ + 2,4,6-(CH_3)$_3$-*3,5*-C_6H_2), 7.11 (s, 1H, NC*H*=CHN), 7.26 – 7.34 (m, 2H, N=C(C_6H_5)$_2$), 7.35 – 7.45 (m, 4H, N=C(C_6H_5)$_2$), 7.52 – 7.59 (m, 2H, N=C(C_6H_5)$_2$), 7.83 (s, 1H, NCH=C*H*N), 10.09 (s, 1H, NC*H*N); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 17.5 (1C, *2*-(CH_3)$_3$-C_6H_2), 17.8 (1C, *6*-(CH_3)$_3$-C_6H_2), 18.8 (1C, CH_3CH-N=), 21.2 (1C, *4*-(CH_3)$_3$-C_6H_2), 56.3 (1C, CH_2-NCH=CHN), 56.8 (1C, CH-N=), 122.4 (1C, NCH=CHN), 124.0 (1C, NCH=CHN), 127.0 (2C, Ar*C*), 128.4

(4C, N=C(*o,m,p*-C_6H_5)$_2$), 129.0 (2C, N=C(*o,m,p*-C_6H_5)$_2$), 129.1 (1C, Ar*C*), 129.9 (2C, ArC), 130.7 (1C, 2,4,6-(CH_3)$_3$-(*ipso*-C_6H_2)), 130.8 (1C, N=C(*o,m,p*-C_6H_5)$_2$), 134.2 (1C, N=C(*ipso*-C_6H_5)$_2$), 134.3 (1C, N=C(*ipso*-C_6H_5)$_2$), 135.8 (1C, 2,4,6-(CH_3)$_3$-(*2*-C_6H_2)), 138.4 (1C, N*C*HN), 138.9 (1C, 2,4,6-(CH_3)$_3$-(*6*-C_6H_2)), 141.5 (1C, 2,4,6-(CH_3)$_3$-(*4*-C_6H_2)), 169.9 (1C, *C*=N).

(1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-pentyl}-3-methylimidazolium bromide (39).

A mixture of **24d** (0.25 g, 0.73 mmol) and 1-methylimidazole (0.06 g, 0.73 mmol) was heated at 85 °C for 65 h. The crude product formed was triturated, washed with dry diethyl ether (3 x 40 ml) and recrystallised from CH_2Cl_2/Et_2O. The white crystals were filtered and washed with Et_2O and filtered under a nitrogen atmosphere. The solid was then dried reduced pressure to give **39** as a white solid (0.18 g, 63 %); mp 187.2 – 188.5 °C; $[\alpha]_D^{20°C}$ = + 38.7 (*c* = 1.19, $CHCl_3$); HRMS (ESI): $[C_{23}H_{28}N_3]^+$ m/z = 346.2278 ($[C_{23}H_{28}N_3]^+$ requires 346.2281); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.60 (d, 3H, CH(CH_3)$_a$, *J* = 6.2 Hz), 0.71 (d, 3H, CH(CH_3)$_b$, *J* = 6.2 Hz), 1.27 – 1.54 (m, 3H, CH_2-CH(CH_3)$_2$ + C*H*(CH_3)$_2$), 3.71 – 3.81 (m, 1H, C*H*-N=), 4.06 (s, 3H, CH_3-

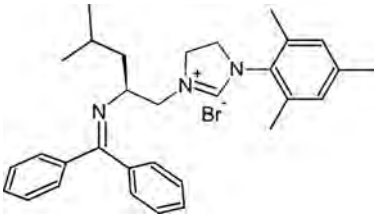
NCH=CHN), 4.42 – 4.50 (m, 2H, CH_2-NCH=CHN), 6.75 – 6.82 (m, 2H, N=C(C_6H_5)$_2$), 7.27 – 7.33 (m, 5H, N=C(C_6H_5)$_2$ + NC*H*=CHN), 7.35 – 7.43 (m, 2H, N=C(C_6H_5)$_2$), 7.50 – 7.60 (m, 3H, N=C(C_6H_5)$_2$ + NCH=C*H*N), 9.92 (s, 1H, NC*H*N); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 22.7 (1C, CH(CH_3)$_a$), 23.1 (1C, CH(CH_3)$_b$), 24.5 (1C, *C*H(CH_3)$_2$), 36.9 (1C, CH_3-N_{im}), 42.5 (1C, CH_2-CH(CH_3)$_2$), 55.2 (1C, CH_2-NCH=CHN), 59.3 (1C, *C*H-N=), 123.2 (2C, N*C*H=*C*HN), 127.3 (2C, 2,4,6-(CH_3)$_3$-(*3,5*-C_6H_2)), 128.4 (2C, N=C(*o,m,p*-C_6H_5)$_2$), 128.5 (2C, N=C(*o,m,p*-C_6H_5)$_2$), 128.9 (2C, N=C(*o,m,p*-C_6H_5)$_2$), 129.1 (1C, N=C(*o,m,p*-C_6H_5)$_2$), 130.8 (1C, N=C(*o,m,p*-C_6H_5)$_2$), 135.8 (1C, N=C(*ipso*-C_6H_5)$_a$), 137.9 (1C, NCH), 138.8 (1C, N=C(*ipso*-C_6H_5)$_b$), 169.8 (1C, *C*=N).



(1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-pentyl}-3-(2,4,6-trimethylphenyl)-imidazolium bromide (40).

A mixture of **24d** (0.197 g, 0.57 mmol) and 1-mesitylimidazole (0.107 g, 0.57 mmol) was heated at 85 °C for 4.5 days. The crude product was triturated, washed with dry diethyl ether (3 x 40 ml) and recrystallised from CH_2Cl_2/Et_2O. The white crystals were filtered and washed with Et_2O and filtered under a nitrogen atmosphere. The

solid was then dried reduced pressure to give **40** as a white solid (0.14 g, 46%); mp 191.6 – 193.8 °C; HRMS (ESI): $[C_{31}H_{36}N_3]^+$ m/z = 450.2905 ($[C_{31}H_{36}N_3]^+$ requires 450.2904); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.55 (d, 3H, $CH(CH_3)_a$, J = 6.1 Hz), 0.67 (d, 3H, $CH(CH_3)_b$, J = 6.1 Hz), 1.16 – 1.27 (m, 1H, CH_a-$CH(CH_3)_2$), 1.41 – 1.57 (m, 2H, $CH(CH_3)_2$ + CH_b-$CH(CH_3)_2$), 1.88 (s, 3H, 2-$(CH_3)_3$-(C_6H_2)), 2.06 (s, 3H, 6-$(CH_3)_3$-(C_6H_2)), 2.27 (s, 3H, 4-$(CH_3)_3$-(C_6H_2)), 3.84 – 3.95 (m, 1H, CH-N=), 4.82 (dd, 1H, CH_a-NCH=CHN, J = 2.9 Hz, J = 13.7 Hz), 5.00 (dd, 1H, CH_b-NCH=CHN, J = 6.6 Hz, J = 13.7 Hz), 6.86 – 6.96 (m, 4H, 2,4,6-$(CH_3)_3$-(3,5-C_6H_2) + N=C(C_6H_5)$_2$), 7.09 (t, 1H, NCH-CHN, J = 1.7 Hz), 7.24 – 7.42 (m, 6H, N=C(C_6H_5)$_2$), 7.50 – 7.56 (m, 2H, N=C(C_6H_5)$_2$), 7.78 (t, 1H, NCH=CHN, J = 1.7 Hz), 1.06 – 10.09 (m, 1H, NCHN); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 17.3 (1C, 2-$(CH_3)_3$-(C_6H_2)), 17.7 (1C, 6-$(CH_3)_3$-(C_6H_2)), 21.0 (1C, 4-$(CH_3)_3$-(C_6H_2)), 22.5 (1C, $CH(CH_3)_a$), 23.0 (1C, $CH(CH_3)_b$), 24.3 (1C, $CH(CH_3)_2$), 42.4 (1C, CH_2-$CH(CH_3)_2$), 55.4 (1C, CH_2-NCH=CHN), 58.6 (1C, CH-N=), 122.2 (1C, NCH=CHN), 124.2 (1C, NCH=CHN), 127.4 (2C, 2,4,6-$(CH_3)_3$-(3,5-C_6H_2)), 128.2 (2C, N=C(o,m,p-C_6H_5)$_2$), 128.4 (2C, N=C(o,m,p-C_6H_5)$_2$), 128.8 (2C, N=C(o,m,p-C_6H_5)$_2$), 129.0 (1C, N=C(o,m,p-C_6H_5)$_2$), 129.8 (2C, N=C(o,m,p-C_6H_5)$_2$), 130.6 (1C, 2,4,6-$(CH_3)_3$-(ipso-C_6H_2)), 130.6 (1C, N=C(o,m,p-C_6H_5)$_2$), 134.1 (1C, 2,4,6-$(CH_3)_3$-(2-C_6H_2)), 134.2 (1C, 2,4,6-$(CH_3)_3$-(6-C_6H_2)), 135.6 (1C, N=C(ipso-C_6H_5)$_a$), 138.6 (1C, NCHN), 138.9 (1C, N=C(ipso-C_6H_5)$_b$), 141.2 (1C, 2,4,6-$(CH_3)_3$-(4-C_6H_2), 169.5 (1C, C=N).



(1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-pentyl}-3-(2,4,6-trimethylphenyl)-imidazolinium bromide (41).

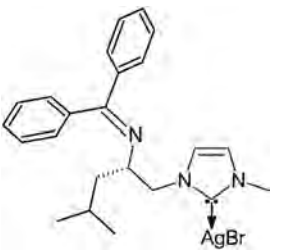
A mixture of **24d** (0.200 g, 0.58 mmol) and 1-mesitylimidazoline (0.109 g, 0.58 mmol) was heated at 85 °C for 64 h. The crude product formed was triturated, washed with dry diethyl ether (3 x 20 ml) and recrystallised from CH_2Cl_2/Et_2O. The off-white crystals were filtered and washed with Et_2O. The solid was then dried reduced pressure to give **41** as a white solid (0.094 g, 30%); mp 180.3 – 183.3 °C; $[\alpha]_D^{20°C}$ = -50.0 (*c* = 0.20, $CHCl_3$); HRMS (ESI): $[C_{31}H_{38}N_3]^+$ m/z = 452.3062 ($[C_{31}H_{38}N_3]^+$ requires 452.3060); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.64 (d, 3H, CH(C*H*$_3$)$_a$, *J* = 6.1 Hz), 0.73 (d, 3H, CH(C*H*$_3$)$_b$, *J* = 6.1 Hz), 1.37 – 1.57 (m, 3H, $(CH_3)_2CHCH_2$)), 2.21 (s, 6H, *2,6*-(C*H*$_3$)$_3$-(C_6H_2), 2.22 (s, 3H, *4*-(C*H*$_3$)$_3$-C_6H_2), 3.72 – 3.82 (m, 1H, C*H*-N=), 3.86 (dd, 1H, C*H*$_a$-NCH_2-CH_2N, *J* = 2.9 Hz, *J* = 13.9 Hz), 4.07 – 4.18 (m, 1H, NC*H*$_a$-CH_2N), 4.19 – 4.28 (m, 1H, NC*H*$_b$-CH_2N), 4.29 – 4.52 (m, 3H, CHC*H*$_b$-NCH_2-CH_2N + NCH_2-C*H*$_2$N), 6.85 (br s, 2H, N=C(*o,m,p*-C_6H_5)), 7.10 – 7.16 (m, 2H, 2,4,6-$(CH_3)_3$-(*3,5*-C_6H_2)), 7.28 – 7.34 (m, 2H, N=C(*o,m,p*-C_6H_5)), 7.36 – 7.42 (m, 1H, N=C(*o,m,p*-C_6H_5)), 7.43 – 7.53 (m, 3H, N=C(*o,m,p*-C_6H_5)), 7.54 – 7.60 (m, 2H, N=C(*o,m,p*-C_6H_5)), 9.06 (s, 1H, NC*H*N); ^{13}C NMR ($CDCl_3$, 100 MHz,) δ_C 17.9 (1C, *2*-(CH_3)$_3$-C_6H_2), 18.7 (1C, *6*-(CH_3)$_3$-C_6H_2), 21.1 (1C, *4*-(CH_3)$_3$-C_6H_2), 22.7

(1C, $(CH_3)_aCHCH_2$), 23.0 (1C, $(CH_3)_bCHCH_2$), 24.6 (1C, $(CH_3)_2CHCH_2$), 42.9 (1C, NCH_2-NCH_2), 51.2 (1C, NCH_2-NCH_2), 51.3 (1C, $CH_2CH(CH_3)_2$), 54.3 (1C, CH_2-NCH_2-CH_2N), 57.9 (1C, *C*H-N=), 127.6 (2C, 2,4,6-$(CH_3)_3$-(*3,5*-C_6H_2)), 128.3 (2C, N=C($C_6H_5)_2$), 129.0 (2C, N=C($C_6H_5)_2$), 129.1 (2C, N=C($C_6H_5)_2$), 129.5 (1C, N=C($C_6H_5)_2$), 130.0 (2C, N=C($C_6H_5)_2$), 130.6 (1C, 2,4,6-$(CH_3)_3$-(*ipso*-C_6H_2)), 130.7 (1C, N=C($C_6H_5)_2$), 132.4 (1C, 2,4,6-$(CH_3)_3$-(*2*-C_6H_2)), 135.5 (1C, 2,4,6-$(CH_3)_3$-(*6*-C_6H_2)), 136.0 (2C, N=C(*ipso*-$C_6H_5)_a$), 139.1 (2C, N=C(*ipso*-$C_6H_5)_b$), 140.3 (1C, 2,4,6-$(CH_3)_3$-(*4*-C_6H_2)), 159.6 (1C, NCHN), 169.2 (1C, *C*=N).

1-{*(S)*-2-(Benzylhydrylidene-amino)-4-methyl-pentyl}-3-benzylimidazolium bromide (42).

A mixture of **37** (0.24 g, 0.88 mmol) and 1-benzylimidazole (0.14 g, 0.88 mmol) was heated at 85 °C for 19 h. The crude product formed was triturated, washed with dry diethyl ether (3 x 40 ml) and filtered under a nitrogen atmosphere. The solid was then dried reduced pressure to give **42** as a clear white solid (0.26 g, 70 %); mp 110.1 – 113.5; $[\alpha]_D^{20°C} = +52.5$ ($c = 0.8$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.83 (d, 6H, $CH(CH_3)_2$, $J = 6.2$ Hz), 1.35 – 1.55 (m, 3H, $CH(CH_3)_2 + CH_2$-$CH(CH_3)_2$), 3.66 –

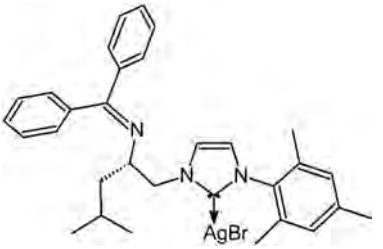
3.83 (m, 1H, C*H*-N=), 4.33 (dd, 1H, CHCH_a-NCH=CHN, J = 9.2 Hz, J = 13.6 Hz), 4.57 (dd, 1H, CHCH_a-NC*H*=CHN, J = 2.9 Hz, J = 13.6 Hz), 5.42 (d, 1H, CH_a-C_6H_5, J = 14.3 Hz), 5.52 (d, 1H, CH_b-C_6H_5, J = 14.3 Hz), 7.07 – 7.44 (m, 10H, NC*H*-C*H*N + ArH_8), 7.54 – 7.62 (m, 2H, ArH_2), 8.04 (s, 1H, N=C*H*-C_6H_5), 10.19 (s, 1H, NC*H*N); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 21.3 (1C, CH(CH_3)$_2$), 23.3 (1C, CH(CH_3)$_2$), 24.0 (1C, *C*H(CH_3)$_2$), 41.5 (1C, *C*H_2-CH(CH_3)$_2$), 53.0 (1C, *C*H_2-C_6H_5), 54.9 (1C, CH*C*H_2- NCH=CHN), 67.6 (1C, *C*H-N), 121.4 (1C, NC*H*=CHN), 123.0 (1C, NCH=*C*HN), 128.2 (2C, Ar*C*), 128.5 (2C, Ar*C*), 128.6 (2C, Ar*C*), 129.1 (1C, Ar*C*), 129.1 (2C, Ar*C*), 131.2 (1C, Ar*C*), 132.9 (1C, CH_2-(*ipso*-C_6H_5)), 134.9 (1C, N=CH-(*ipso*-C_6H_5)), 136.8 (1C, NCHN), 162.6 (1C, N=*C*H-C_6H_5).



[$(C_6H_5)_2$C=NCH(CH_2CH(CH_3)$_2$)CH_2-NCN-CH_3]AgBr (43).

Silver (I) oxide (0.03 g, 0.13 mmol) was added to a solution of **39** (0.09 g, 0.23 mmol) in dichloromethane (10 ml) in the presence 4 Å activated molecular sieves (1.0 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under

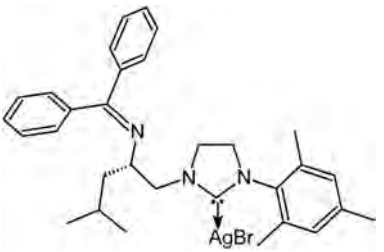
reduced pressure to give **43** as a white solid (0.11 g, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.70 (d, 3H, $CH(CH_3)_a$, J = 6.2 Hz), 0.81 (d, 3H, $CH(CH_3)_b$, J = 6.2 Hz), 1.44 (t, 2H, CH_2-$CH(CH_3)_2$, J = 6.2 Hz), 1.49 – 1.62 (m, 1H, $CH(CH_3)_2$), 3.74 – 3.83 (m, 4H, CH_3-NCH=CHN + CH-N=), 4.17 (dd, 1H, $CHCH_a$-NCH=CHN, J = 8.8 Hz, J = 13.6 Hz), 4.26 (dd, 1H, $CHCH_b$-NCH=CHN, J = 3.3 Hz, J = 13.6 Hz), 6.62 (s, 1H, N=C(C_6H_5)$_2$), 6.63 (s, 1H, N=C(C_6H_5)$_2$), 6.88 (d, 1H, NCH=CHN, J = 1.5 Hz), 6.93 (d, 1H, NCH=CHN, J = 1.5 Hz), 7.29 – 7.44 (m, 6H, N=C(C_6H_5)$_2$), 7.56 – 7.62 (m, 2H, N=C(C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 22.9 (1C, $CH(CH_3)_a$), 23.2 (1C, $CH(CH_3)_b$), 24.6 (1C, $CH(CH_3)_2$), 38.7 (1C, CH_3-NCH=CHN), 43.0 (1C, CH_2-$CH(CH_3)_2$), 57.2 (1C, CH_2-NCH=CHN), 61.1 (1C, CH-N), 121.3 (1C, NCH=CHN), 122.7 (1C, NCH=CHN), 127.1 (2C, N=C(*o,m,p*-C_6H_5)$_2$), 128.1 (2C, N=C(*o,m,p*-C_6H_5)$_2$), 128.5 (4C, N=C(*o,m,p*-C_6H_5)$_2$), 128.7 (1C, N=C(*o,m,p*-C_6H_5)$_2$), 130.3 (1C, N=C(*o,m,p*-C_6H_5)$_2$), 135.9 (1C, N=C(*ipso*-C_6H_5)$_a$), 139.1 (1C, N=C(*ipso*-C_6H_5)$_b$), 168.7 (1C, C=N), 181.7 (1C, C-Ag).



[$(C_6H_5)_2C$=NCH($CH_2CH(CH_3)_2$)CH_2-NCN-(2,4,6-$(CH_3)_3C_6H_2$)]AgBr (44).

Silver (I) oxide (0.016 g, 0.07 mmol) was added to a solution of **40** (0.073 g, 0.14 mmol) in dichloromethane (15 ml) in the presence 4 Å activated molecular sieves (1.0 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **44** as a white solid (0.06 g, 67%); mp 86.4 – 88.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.64 (d, 3H, CH(CH_3)$_a$, J = 6.6 Hz), 0.76 (d, 3H, CH(CH_3)$_b$, J = 6.6 Hz), 1.34 – 1.61 (m, 3H, $CH(CH_3)_2$ + CH_2-$CH(CH_3)_2$), 1.82 (s, 3H, *2*-(CH_3)$_3$-(C_6H_2)), 2.00 (s, 3H, *6*-(CH_3)$_3$-(C_6H_2)), 2.30 (s, 3H, *4*-(CH_3)$_3$-(C_6H_2)), 3.77 – 3.90 (m, 1H, CH-N=), 4.35 – 4.50 (m, 2H, CH_2-NCH=CHN), 6.81 – 7.02 (m, 5H, 2,4,6-$(CH_3)_3$-(*3,5*-C_6H_2) + NCH=CHN + N=C(*o,m,p*-C_6H_5)$_2$), 7.09 (d, 1H, NCH=CHN, J = 1.5 Hz), 7.27 – 7.51 (m, 6H, N=C(*o,m,p*-C_6H_5)$_2$), 7.55 – 7.70 (m, 2H, N=C(*o,m,p*-C_6H_5)$_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 17.6 (1C, *2*-(CH_3)$_3$-(C_6H_2)), 17.9 (1C, *6*-(CH_3)$_3$-(C_6H_2)), 21.1 (1C, *4*-(CH_3)$_3$-(C_6H_2)), 23.0 (1C, CH(CH_3)$_a$), 23.1 (1C, CH(CH_3)$_b$), 24.7 (1C, $CH(CH_3)_2$), 43.2 (1C, CH_2-$CH(CH_3)_2$), 57.6 (1C, CH_2-NCH=CHN), 60.7 (1C, CH-N=), 122.2 (1C, NCH=CHN), 122.4

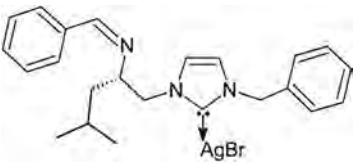
(1C, NCH=CHN), 127.6 (2C, 2,4,6-$(CH_3)_3$-(*3,5*-C_6H_2)), 128.4 (2C, N=C(*o,m,p*-$C_6H_5)_2$), 128.6 (2C, N=C(*o,m,p*-$C_6H_5)_2$), 128.7 (2C, N=C(*o,m,p*-$C_6H_5)_2$), 128.9 (1C, N=C(*o,m,p*-$C_6H_5)_2$), 129.5 (1C, N=C(*o,m,p*-$C_6H_5)_2$), 129.6 (1C, N=C(*o,m,p*-$C_6H_5)_2$), 130.2 (1C, 2,4,6-$(CH_3)_3$-(*ipso*-C_6H_2)), 130.5 (1C, N=C(*o,m,p*-$C_6H_5)_2$), 134.5 (1C, 2,4,6-$(CH_3)_3$-(*2*-$C_6H_2)_a$), 134.9 (1C, 2,4,6-$(CH_3)_3$-(*6*-$C_6H_2)_b$), 135.4 (1C, N=C(*ipso*-$C_6H_5)_a$), 136.1 (1C, N=C(*ipso*-$C_6H_5)_b$), 139.6 (1C, 2,4,6-$(CH_3)_3$-(*4*-C_6H_2)), 166.8 (1C, *C*=N), 182.6 (1C, *C*-Ag).



[$(C_6H_5)_2$C=NCH(CH$(CH_3)_2$)CH_2-NCN-(2,4,6-$(CH_3)_3C_6H_2$)]AgBr (45).

Silver (I) oxide (0.016 g, 0.07 mmol) was added to a solution of **41** (0.070 g, 0.13 mmol) in dichloromethane (10 ml) in the presence 4 Å activated molecular sieves (0.2 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solvent was then removed under reduced pressure to give **45** as a white solid (0.064 g, 77%); ^{1}H NMR (CD_2Cl_2, 400 MHz) δ_H 0.65 (d, 3H, CH($CH_3)_a$, J = 6.3 Hz), 0.72 (d, 3H, CH($CH_3)_b$, J = 6.3 Hz), 1.37 – 1.57 (m, 3H, $(CH_3)_2CHCH_2$)), 1.96 (s, 3H, *2*-($CH_3)_3$-(C_6H_2), 2.12 (s, 3H, *6*-

(CH_3)$_3$-(C_6H_2), 2.20 (s, 3H, *4*-(CH_3)$_3$-C_6H_2), 3.54 – 3.77 (m, 6H, =N-$CHCH_a$-NCH_2-CH_2N), 3.84 – 3.94 (m, 1H, =N-$CHCH_b$-NCH_2-CH_2N), 6.81 (s, 1H, N=C(C_6H_5)$_a$), 6.87 (s, 1H, N=C(C_6H_5)$_a$), 7.08 (s, 1H, 2,4,6-(CH_3)$_3$-(*3*-C_6H_2)), 7.10 (s, 1H, 2,4,6-(CH_3)$_3$-(*5*-C_6H_2)), 7.20 – 7.36 (m, 3H, N=C(C_6H_5)), 7.37 – 7.47 (m, 3H, N=C(C_6H_5)), 7.55 – 7.65 (m, 2H, N=C(C_6H_5)); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ_C 17.7 (1C, *2*-(CH_3)$_3$-C_6H_2), 17.8 (1C, *6*-(CH_3)$_3$-C_6H_2), 20.8 (1C, *4*-(CH_3)$_3$-C_6H_2), 22.77 (1C, (CH_3)$_a$$CHCH_2$), 22.83 (1C, ($CH_3$)$_b$$CHCH_2$), 24.8 (1C, ($CH_3$)$_2$$CHCH_2$), 43.2 (1C, NCH_2-NCH_2), 50.6 (1C, NCH_2-NCH_2), 51.2 (1C, $CH_2CH(CH_3)_2$), 56.9 (1C, CH_2-NCH_2-CH_2N), 58.9 (1C, *C*H-N=), 127.7 (2C, 2,4,6-(CH_3)$_3$-(*3,5*-C_6H_2)), 128.2 (2C, N=C(C_6H_5)$_2$), 128.7 (4C, N=C(C_6H_5)$_2$), 129.5 (3C, N=C(C_6H_5)$_2$), 130.3 (1C, N=C(C_6H_5)$_2$), 135.7 (1C, 2,4,6-(CH_3)$_3$-(*ipso*-C_6H_2)), 135.8 (1C, 2,4,6-(CH_3)$_3$-(*2*-C_6H_2)), 135.9 (1C, 2,4,6-(CH_3)$_3$-(*6*-C_6H_2)), 136.6 (1C, N=C(*ipso*-C_6H_5)$_a$), 138.6 (1C, N=C(*ipso*-C_6H_5)$_b$), 139.3 (1C, 2,4,6-(CH_3)$_3$-(*4*-C_6H_2)), 167.9 (1C, *C*=N), not vis. (1C, *C*-Ag)..



[C_6H_5CH=NCH($CH_2CH(CH_3)_2$)CH_2-NCN-Bn]AgBr (46).

Silver (I) oxide (0.077 g, 0.33 mmol) was added to a solution of **42** (0.262 g, 0.61 mmol) in dichloromethane (15 ml) in the presence 4 Å activated molecular sieves (1.0 g). The reaction mixture was protected from light and was refluxed for 2 days. The mixture was filtered through a layer of celite. The solid was then dried reduced pressure to give **46** as a clear white solid (0.27 g, 85%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 0.88 (d, 3H, CH(CH_3)$_a$, J = 6.6 Hz), 0.93 (d, 3H, CH(CH_3)$_b$, J = 6.6 Hz), 1.35 – 1.73 (m, 3H, CH(CH_3)$_2$ + CH_2-CH(CH_3)$_2$), 3.63 – 3.72 (m, 1H, CH-N=), 4.22 (dd, 1H, CHCH_a-NCH=CHN, J = 9.2 Hz, J = 13.6 Hz), 4.34 (dd, 1H, CHCH_b-NCH=CHN, J = 3.7 Hz, J = 13.6 Hz), 5.20 (d, 2H, CH_2-C_6H_5, J = 9.2 Hz), 7.07 – 7.44 (m, 9H, NCH=CHN + ArH_7), 7.54 – 7.62 (m, 2H, ArH_2), 8.04 (s, 1H, N=CH-C_6H_5), 10.19 (s, 1H, NCHN); ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C 21.6 (1C, CH(CH_3)$_2$), 23.5 (1C, CH(CH_3)$_2$), 24.4 (1C, CH(CH_3)$_2$), 42.1 (1C, CH_2-CH(CH_3)$_2$), 55.6 (1C, CH_2-C_6H_5), 57.2 (1C, CHCH_2-NCH=CHN), 70.1 (1C, CH-N=), 120.4 (1C, NCH=CHN), 122.9 (1C, NCH=CHN), 128.2 (2C, ArC), 128.5 (2C, ArC), 128.6 (2C, ArC), 129.1 (1C, ArC), 129.1 (2C, ArC), 131.2 (1C, ArC), 135.5 (1C, N=CH-(*ipso*-C_6H_5)), 137.4 (1C, CH_2-(*ipso*-C_6H_5)), 161.6 (1C, N=CH-C_6H_5), not vis. (1C, C-Ag).

5.3 References

1. M. G. Gardiner, Wolfgang A. Herrmann, C.-P. Reisinger, J. Schwarz, M. Spiegler, *J. Organomet. Chem.*, 1999, **572**, 239.
2. R. C. F. Jones, J. R. Nichols, *Tetrahedron Lett.*, 1990, **31**, 12, 1767
3. a) E. Ihara, K. Koyama, H. Yasuda, N. Kanehisa, Y. Kai, *J. Organomet. Chem.*, 1999, **574**, 40; b) P. R. Auburn, P. B. Mackenzie, B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2033.
4. a) M. S. Kharash, R. C. Seyler, F. R. Mayo, *J. Am. Chem. Soc.*, 1938, **60**, 882; b) J. R. Doyle, P. E. Slade, H. B. Jonassen, Inorg. Synth., 1960, **6**, 218.
5. A. Saitoh, K. Achiwa, K. Tanaka, T. Morimoto, *J. Org. Chem.*, 2000, **65**, 4227.
6. V. T. Myllymäki, M. K. Lindvall, A. M. P. Koskinen, *Tetrahedron*, 2001, **57**, 4629.
7. C. Hunter, R. F. W. Jackson, H. K. Rami, *J. Chem. Soc., Perkin Trans. 1*, 2000, 219.
8. H. Higashirua, H. Morino, H. Matsuura, Y. Toyomaki, K. Ienaga, *J. Chem. Soc., Perkin Trans. 1*, 1989, 1479.

X-ray structural data of silver carbene complex **27e**.

Angles (°)		Distances (Å)	
C(1)-Ag-Br	154.76(8)		
C(1)-Ag-Br'	109.20(7)	Ag-Br	2.4969(3)
Br-Ag-Br'	95.823(11)	Ag-Br'	3.0549(4)
Ag-Br-Ag'	84.177(11)	N(1)-C(1)	1.353(4)
C(1)-N(1)-C(2)	111.1(2)	N(1)-C(2)	1.382(4)
C(1)-N(1)-C(4)	124.7(2)	N(1)-C(4)	1.460(4)
C(2)-N(1)-C(4)	124.0(3)	N(2)-C(1)	1.350(4)
C(1)-N(2)-C(3)	111.0(2)	N(2)-C(3)	1.392(4)
C(1)-N(2)-C(11)	125.1(2)	N(2)-C(11)	1.462(4)
C(3)-N(2)-C(11)	123.5(2)	N(3)-C(13)	1.278(4)
C(13)-N(3)-C(12)	121.3(2)	N(3)-C(12)	1.455(4)
N(2)-C(1)-N(1)	104.3(2)	C(2)-C(3)	1.330(5)
N(2)-C(1)-Ag	129.5(2)	C(4)-C(5)	1.511(4)
N(1)-C(1)-Ag	126.19(19)	C(5)-C(10)	1.381(4)
C(3)-C(2)-N(1)	107.1(3)	C(5)-C(6)	1.392(4)
C(2)-C(3)-N(2)	106.6(3)	C(6)-C(7)	1.379(4)
N(1)-C(4)-C(5)	112.1(2)	C(7)-C(8)	1.382(5)
C(10)-C(5)-C(6)	118.7(3)	C(8)-C(9)	1.371(5)
C(10)-C(5)-C(4)	120.9(3)	C(9)-C(10)	1.387(5)
C(6)-C(5)-C(4)	120.3(3)	C(11)-C(12)	1.518(4)
C(7)-C(6)-C(5)	121.0(3)	C(13)-C(14)	1.497(4)
C(6)-C(7)-C(8)	119.7(3)	C(13)-C(20)	1.507(4)
C(9)-C(8)-C(7)	119.7(3)	C(14)-C(15)	1.391(4)
C(8)-C(9)-C(10)	120.8(3)	C(14)-C(19)	1.394(4)
C(5)-C(10)-C(9)	120.0(3)	C(15)-C(16)	1.391(4)
N(2)-C(11)-C(12)	110.6(2)	C(16)-C(17)	1.370(5)
N(3)-C(12)-C(11)	109.4(2)	C(17)-C(18)	1.377(5)
N(3)-C(13)-C(14)	117.5(2)	C(18)-C(19)	1.378(4)
N(3)-C(13)-C(20)	125.0(2)	C(20)-C(25)	1.383(4)
C(14)-C(13)-C(20)	117.4(2)	C(20)-C(21)	1.385(4)
C(15)-C(14)-C(19)	118.4(3)	C(21)-C(22)	1.383(5)
C(15)-C(14)-C(13)	121.5(3)	C(22)-C(23)	1.363(5)
C(19)-C(14)-C(13)	120.0(3)	C(23)-C(24)	1.375(5)
C(16)-C(15)-C(14)	120.6(3)		
C(17)-C(16)-C(15)	120.1(3)		

Synthesis of chiral iminoalkyl functionalised N-heterocyclic carbenes and their use in asymmetric catalysis. M. Merzouk, T. Moore, N. A. Williams, *Tetrahedron Letters*, 2007, **48**, 50, 8914.

Synthesis of amidoalkyl imidazol-2-ylidene ligands and their application to enantioselective copper-catalysed conjugate addition. T. Moore, M. Merzouk, N. A. Williams, *Synlett*, 2008, **19** (1), 21.