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Review

Metal-mediated asymmetric alkylation using chiral *N*-heterocyclic carbenes derived from chiral amines

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Contents

Abstract

The significant advances in achiral catalysis using *N*-heterocyclic carbene (NHC) metal complexes have prompted intense investigation of chiral NHC derivatives for use in asymmetric catalysis in recent years. Discovery of new chiral NHC catalysts is supported by the development of synthetic routes to chiral NHC ligands and their metal complexes. Here routes to chiral NHC ligands derived principally from chiral diamines will be outlined and metal complex structures described in the context of application to asymmetric catalysis. Emphasis will be placed on palladium and copper catalysed asymmetric alkylations that serve to illustrate the potential and some limitations of NHC-based asymmetric catalysts.

Keywords: *N*-Heterocyclic carbenes; Catalysis; Chirality; Alkylation; Palladium; Copper

1. Introduction

Since the resurgence of metal *N*-heterocyclic carbene (NHC) chemistry prompted by the isolation of a free NHC by Arduengo et al. [1], arguably the most common application of NHCs and their relatives are as ancillary ligands for achiral metal-mediated catalysis [2,3]. Early work was largely driven by the similarities in electronic structure of NHCs and tertiary phosphines that have been broadly verified by empirical and theoretical investigations, although ideas on the extent of π-backbonding have been refined in recent years [4]. Notwithstanding the debate of the exact nature of NHC metal [4], or NHC-coligand bonding [5], significant progress has occurred over the last decade with respect to catalyst activity, selectivity and stability. Reactions incorporating NHC metal complexes represent some of the most significant advances in homogeneous catalysis particularly for late metal catalysed C–C and C–X coupling, and alkene metathesis polymerisation.

Once metal-mediated catalysis was demonstrated, and given the increasing demand for enantiopure compounds and challenge derived from developing enantioselective processes, it was evident that NHCs would also be applied to asymmetric synthesis. Indeed over the last 5 years the number of compounds, complexes and reactions exploring the synthesis, coordination

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chemistry and application of NHCs to enantioselective reactions has increased dramatically.

Although electronic and steric parameters can rarely be separated unambiguously, evidently the shape of a chiral catalyst is responsible for imparting significant enantioselectivity in a reaction. Therefore, the synthesis of NHC compounds that contain chiral elements, or impart chirality to a metal complex due to atropisomerism, has become of significant interest. Clearly the structure of NHCs is distinct from tertiary phosphines and as highlighted by Burgess and Gade in recent reviews [6,7], in comparison to relatively highly developed phosphine ligands, there is currently a paucity of data elucidating critical geometries and ligand–ligand, ligand–substrate interactions that can guide the design of chiral NHC catalysts. More generally, theory is currently not developed to the stage where it is possible to predict with confidence the stereochemical outcome of the vast majority of reactions, or identify the metal–ligand combination that will give useful activity, selectivity and longevity. Therefore, because of the large number of reaction parameters, which present a formidable challenge to predictive theoretical chemistry, the discovery of useful catalysts currently remains largely an empirical endeavour.

Nonetheless impressive advances in several classes of asymmetric reactions have occurred over the last 5 years. Reactions catalysed by metal-NHC complexes that exhibit significant enantioselectivity include hydrogenations, hydrosilylation, phenylation, ring closing metathesis, and alkylation, with undoubtedly more to follow. Reviews [6,7] on work prior to 2004 are available outlining enantioselective and stereoselective reactions catalysed by NHC compounds and complexes, and this issue contains the chemistry of oxazoline-NHCs as stereo directing ligands.

An initial challenge to developing NHC catalytic reactions is of course the synthesis of chiral NHC ligands and their derivatives. Chiral NHC complexes were prepared over a decade before the current resurgence in interest by Lappert and coworkers in the early 1980s [8,9]. Several rhodium and cobalt complexes were reported using electron rich chiral olefins (Fig. 1) as NHC precursors. Electron rich olefins can be used as a source of NHC to many catalytically active metals, however the main constraint, certainly with respect to asymmetric catalysis, is that modification of the N-substituents is limited to primary alkyl and small aryl groups.

Great effort has therefore been expended on the synthesis of a range of chiral NHC-based ligands and developing routes that allow modification of ligand substituents for the discovery of efficient catalysts. To restrict the number of accessible transition states that may determine the stereochemical outcome of a reaction, chelating ancillary ligands are commonly used, and therefore the synthesis of chelating chiral NHC has been of particular interest. However, it should be noted that chiral monodentate ligands such as phosphoramidates are very effective for some enantioselective reactions [10,11] and there are also now several examples of chiral mono-NHCs (vide infra) that give very respectable enantioselectivity.

Given the now significant number of new chiral ligand sets based on NHC that have been reported, the principal focus of this article will mainly be restricted to the use of chiral diamines for the synthesis of chiral NHC and their application to enantioselective alkylation. Although this is a restricted topic there is evidence present in the studies published to date that indicate some possible guiding principles with respect to ligand–ligand interactions and activities that may deserve more general consideration in asymmetric NHC metal-mediated catalysis.

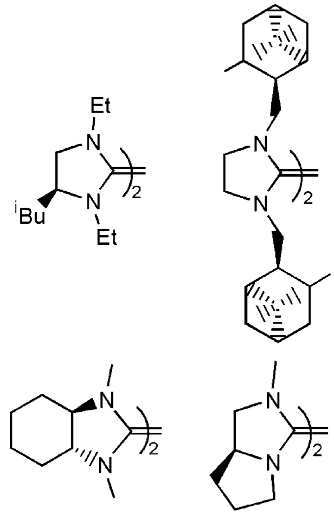
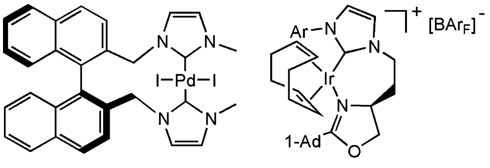


Fig. 1. Chiral electron rich olefins first described by Lappert and coworkers [8,9].

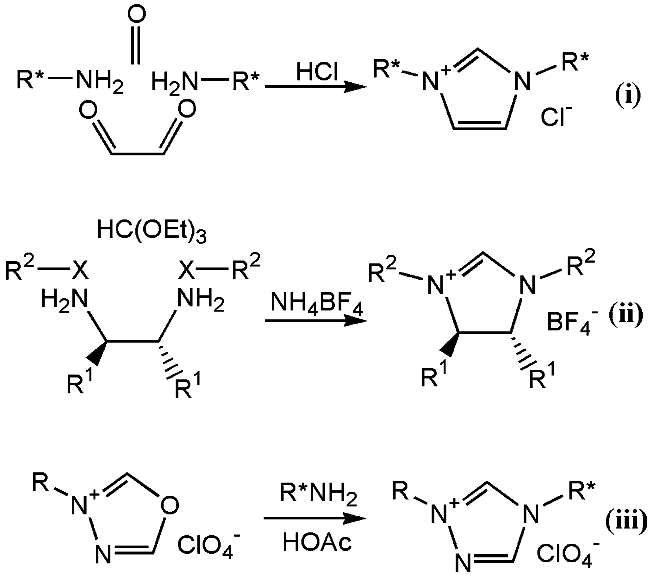
2. Synthesis of chiral NHC ligands: some strategies

Perhaps the simplest method to prepare a chelating NHC containing ligand is from reaction between an achiral imidazole and a chiral moiety that may also be capable of metal coordination. This method has been used to synthesise several ligand sets including the first example of a chelating di-NHC complex **1** by Rajanbabu and coworkers (Fig. 2) [12]. Unfortunately **1** has not resulted in high enantioselectivity, presumably due to ligand flexibility that results in the availability of *cis*/*trans* isomers in palladium complexes. However, the first example of significant enantioselectivity induced by an NHC ligand was using an NHC-oxazoline hybrid **2** reported by Burgess. This class of ligand is derived from achiral imidazoles, and was applied to asymmetric hydrogenation of non-functionalised aryl substituted alkenes [13]. More recently Gade has developed a similar strategy for related chiral NHC-oxazolines for the asymmetric hydrosilylation of alkyl ketones [14].



1 **2**

Fig. 2. Two examples of chiral chelating NHC ligand complexes derived from achiral imidazoles [13,14].



Scheme 1. Typical precursors for synthesis of (i) imidazolium, (ii) imidazolinium and (iii) triazolium salts.

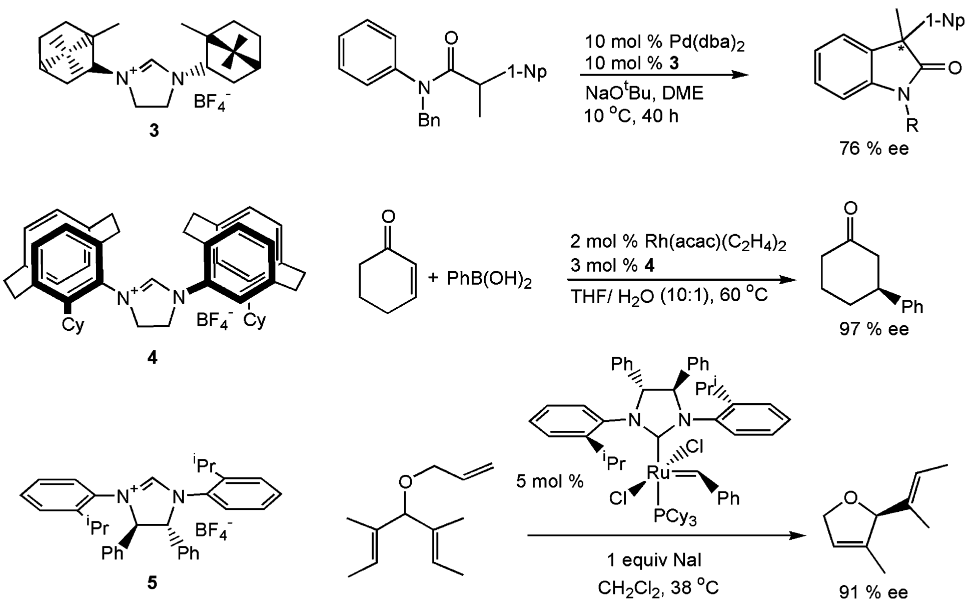
Alternatively chiral NHC can be constructed by incorporating chiral compounds into the *N*-heterocycle synthesis, most commonly using chiral mono- and diamines. Unsaturated and saturated mono-NHC derived from imidazolium and imidazolinium salts, respectively, have been prepared containing chirality at the N-substituents and at the C4 and C5 positions. Related chiral triazolium salts can also be synthesised from chiral monoamines (Scheme 1).

These classes of compounds have been applied to several catalytic reactions and in some cases have resulted in excellent stereoselectivity (Scheme 2). For example Hartwig reported a C–C coupling reaction using the α-pinene derived NHC from **3** that gives the highest enantioselectivity amongst the ligands tested, that included a wide range of phosphines [15]. Andrus synthesised a paracyclophane containing salt **4** that gives excellent enantioselectivity for rhodium catalysed arylation of enones [16] and Grubbs prepared **5** and a ruthenium precatalyst derivative for desymmetrisation via ring closing metathesis [17] (see Section 3.3 for additional examples).

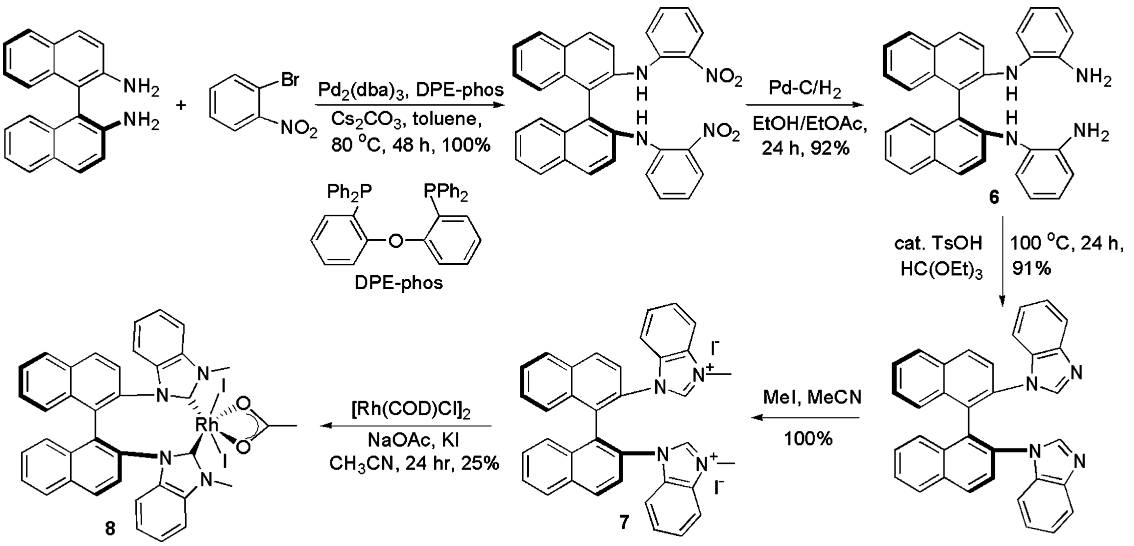
Perhaps more challenging with respect to ligand synthesis is the use of diamines to prepare chelating NHC and hybrids where a resulting NHC incorporates a single amine moiety. Routes have been developed for the synthesis of unsaturated and saturated NHC, and NHC containing C4 and C5 as part of an aromatic ring. Shi prepared chelating di-NHC derived from BINAM using palladium catalysed coupling and reduction to obtain the amine **6** that can be cleanly converted to a dibenzimidazole and dibenzimidazolium salt **7** [18]. The rhodium complex **8** of this ligand was applied to hydrosilylation of methyl ketones giving ee up to 98% (Scheme 3).

Di-NHC and NHC-imine have been prepared from *trans*-1,2-diaminocyclohexane (Scheme 4) [19–21]. The key reaction is a base-induced 1,3-cyclisation reaction between a diimine and tosylmethylisocyanide to give mono- and di-imidazoles where substitution at the imine largely determines if single or double ring formation occurs. A phenyl substituent gives exclusively mono-imidazole formation whereas mono- and di-imidazoles can be prepared from alkyl-substituted imines. Imidazolium salts can be prepared using standard alkylation procedures to give NHC precursor diimidazolium **9** or imidazolium-imine **10** salts. These ligands and their derivatives have been applied to palladium catalysed allylic alkylation as will be discussed in more detail in Section 3.1.

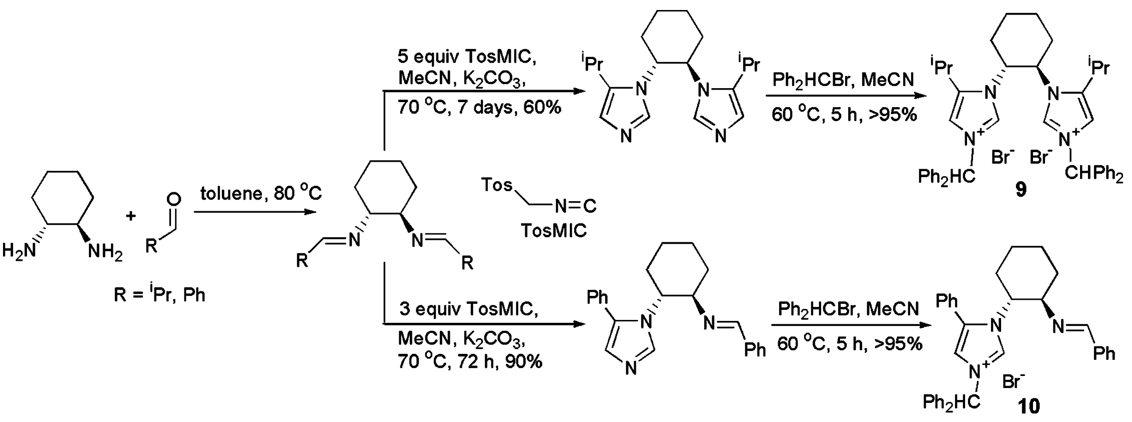
Desymmetrisation of diamines has also been achieved using palladium catalysed C–N coupling reactions to give NHC-hybrid ligands. Helmchen described the synthesis of an NHC–phosphine precursor **11** (Scheme 5) that exhibits axial chirality [22]. The observation of two species in solution NMR



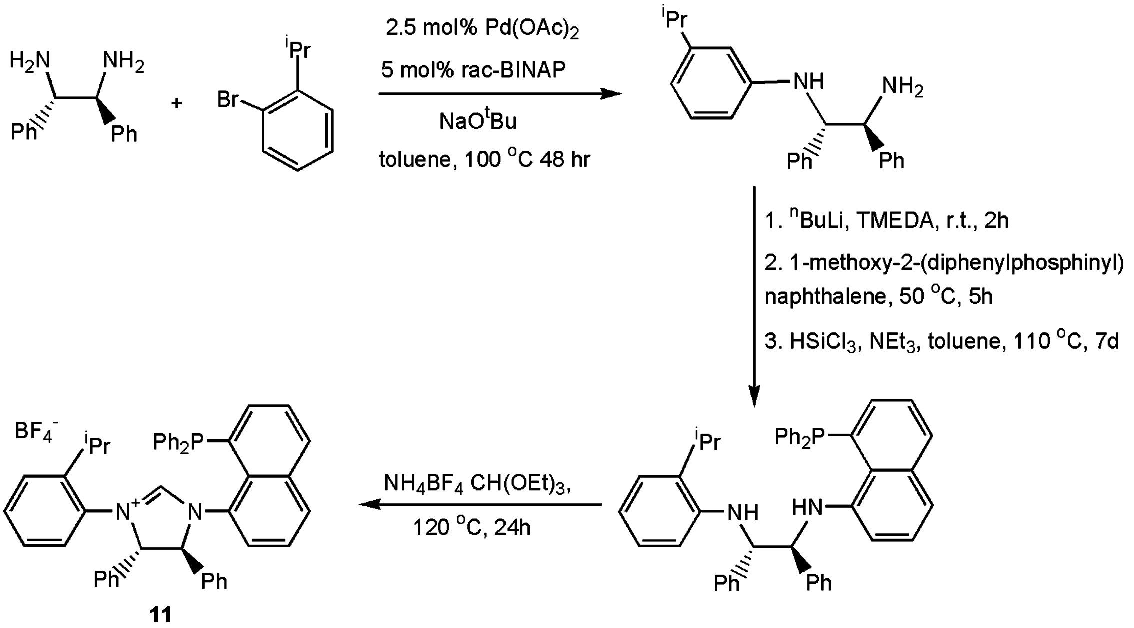
Scheme 2. Examples of chiral mono-NHC precursor salts derived from chiral amines that lead to high levels of enantioselectivity [15–17].



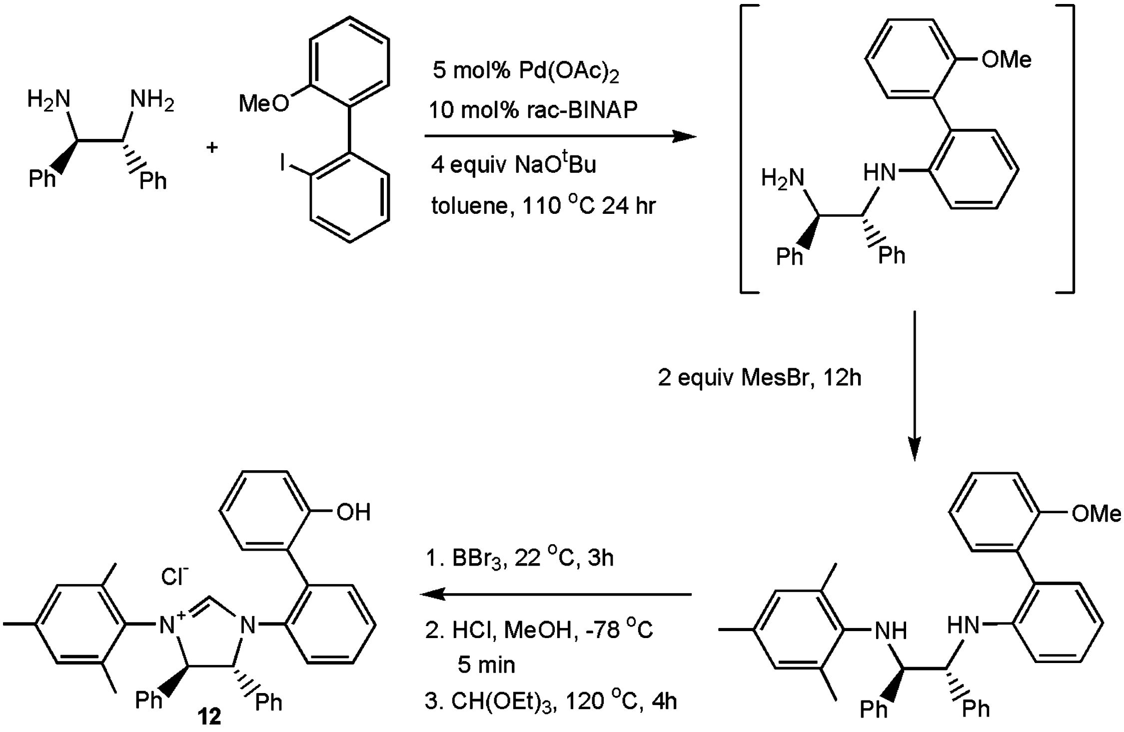
Scheme 3. Synthesis of chiral di-NHC rhodium complex derived from BINAM [18].



Scheme 4. Synthetic of chiral di-NHC and NHC-imine precursors derived from *trans*-1,2-diaminocyclohexane [19–21].



Scheme 5. Synthesis of chiral NHC-P ligand precursor via desymmetrisation of *trans*-1,2-diphenylethylenediamine [22].



Scheme 6. Synthesis of chiral NHC-O ligand precursor via desymmetrisation of *trans*-1,2-diphenylethylenediamine [24].

spectra of the corresponding silver and rhodium complexes is attributed to atropisomers due to restricted rotation about the ^{i}PrC$_6$H$_4$–N bond. Nonetheless excellent enantioselectivities (up to 99%) are observed for both rhodium catalysed hydrogenation of functionalised alkenes [22] and addition of phenyl boronic acid to enones (up to 94%) [23].

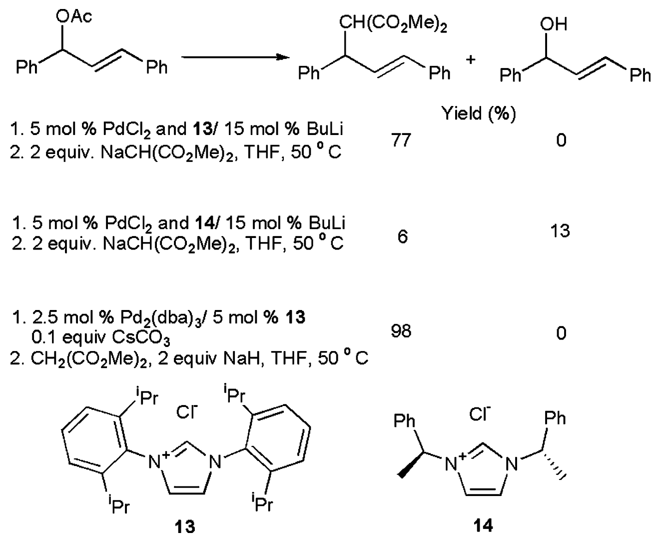
Hoveyda and coworkers prepared the structurally similar NHC-phenoxide precursor **12** (Scheme 6) again using palladium catalysed C–N bond formation that has recently been applied to copper catalysed alkylations [24]. This and related ligand sets are discussed in more detail in Section 3.2.

3. Metal catalysed allylic alkylation

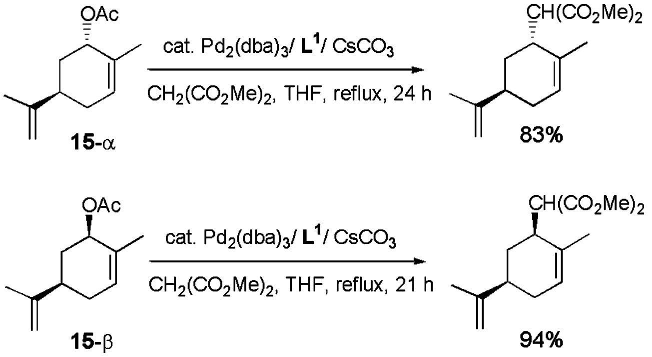
Metal catalysed allylic alkylation and its asymmetric variant is one of the most important carbon–carbon bond forming reactions for the synthesis of organic molecules. Concomitant with its undoubted use there is also a rich chemistry with respect to mechanism and the variety of metal and ligand systems that allow regio- and stereo-control. Palladium and to a lesser extent molybdenum catalysed reactions have been developed widely, largely for use with soft nucleophiles (typically p$K_a < 25$) such as malonates and subsequently applied to problems in total synthesis [25]. Harder nucleophiles including metal alkyls can be incorporated into asymmetric allylic alkylation catalysis using copper chemistry although in comparison these reactions are less developed than palladium analogues and mechanistically are less well understood [26]. Both palladium and copper catalysed reactions have been investigated using a diversity of ligand sets including chiral phosphorus donors as ancillary ligands. Therefore it is not surprising that NHC ligands and their hybrids have also been investigated for application to metal catalysed alkylation reactions including the development of enantioselective protocols.

3.1. Palladium catalysed allylic alkylation

Mori and coworkers first described the use of mono-NHC ligands for palladium catalysed allylic alkylation (Scheme 7) [27]. Reactions between (*E*)-1,3-diphenylprop-3-en-1-ylacetate



Scheme 7. Initial attempts at palladium catalysed allylic alkylation using mono-NHC ligands [27].



Scheme 8. Reactions to determine substitution stereochemistry of palladium catalysed alkylation using mono-NHC ligands [27].

and dimethylmalonate were performed using palladium-NHC catalysts prepared in situ. NHC containing bulky aromatic N-substituents such as **13** gave the greatest yield and Pd_2dba_3. $CHCl_3$ was superior to $PdCl_2$ as the palladium source. No enantioselectivity was reported for reactions using chiral NHC precursor **14**.

The stereochemistry of substitution was examined using the diastereoisomers **15**-α and **15**-β that showed reaction proceeded mainly with retention of configuration as is observed for phosphine based catalysts (Scheme 8). However, with respect to activity the NHC catalysts are much less active than phosphine systems. Typically palladium phosphine catalysed reactions occur at room temperature whereas the NHC reactions required heating at 50 °C for several hours.

In a subsequent report this work was extended to examine other nucleophiles and allylic substrates [28]. It was found that reaction between nitrogen nucleophiles derived from benzylamine or *N*-methyltosylamide and (*E*)-1,3-diphenylprop-3-en-l-ylacetate did not give substitution products at 50 °C using NaH or $CsCO_3$ as base. The only isolated products were stereoisomers derived from deacetylation. The use of acyclic and cyclic β-ketoesters **16** and **17** did give substitution products (Scheme 9) including the formation of a quaternary carbon centre in **18**, however again reactions required quite forcing conditions relative to known phosphine protocols.

Palladium complexes were not prepared and used as precatalysts although all reactions were conducted with 1:1 Pd:L ratio implying a mono-NHC Pd complex is the catalytic species.

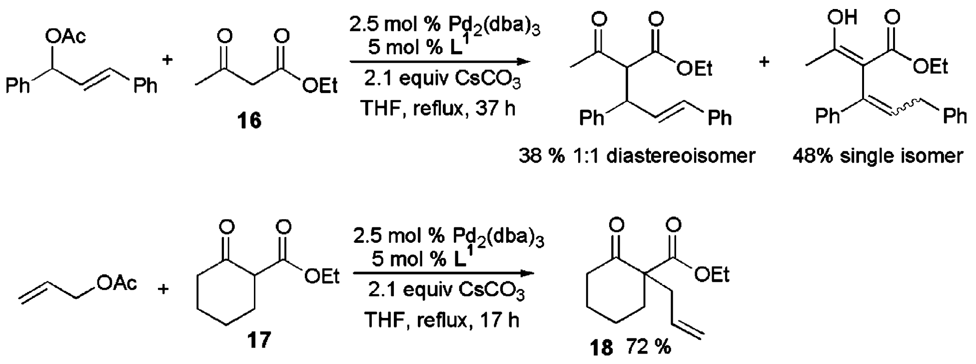
Asymmetric allylic alkylation has been examined using a range of chiral chelating NHC ligands derived from **9** and **10** (Scheme 4) including the use of isolated palladium NHC complexes as precatalysts. Synthesis of these new ligands was prompted by the proven track record of 1,2-diaminocyclohexane as a chiral motif on which to base ligand sets for application to a range of asymmetric reactions including allylic alkylation [19–21,29]. Further modification of NHC-imine ligands can be achieved via hydrolysis of imidazole-imine or imidazolium-imine compounds giving the corresponding primary amine that serve as precursors to a range of derivatives **19**–**25** (Scheme 10). In practise reactivity of the amine moiety of the imidazole-amine is significantly greater than the imidazolium salt analogue although the reason for this is not clear.

Representative palladium complexes of all these ligands were prepared and where possible, structurally characterised. Synthesis is most conveniently achieved via the silver(I) complex analogues [30] that are air and moisture stable except for the NHC–phosphines where silver complexes could not be prepared. However, free NHC–phosphines could easily be generated from the imidazolium salts using a range of bases [21].

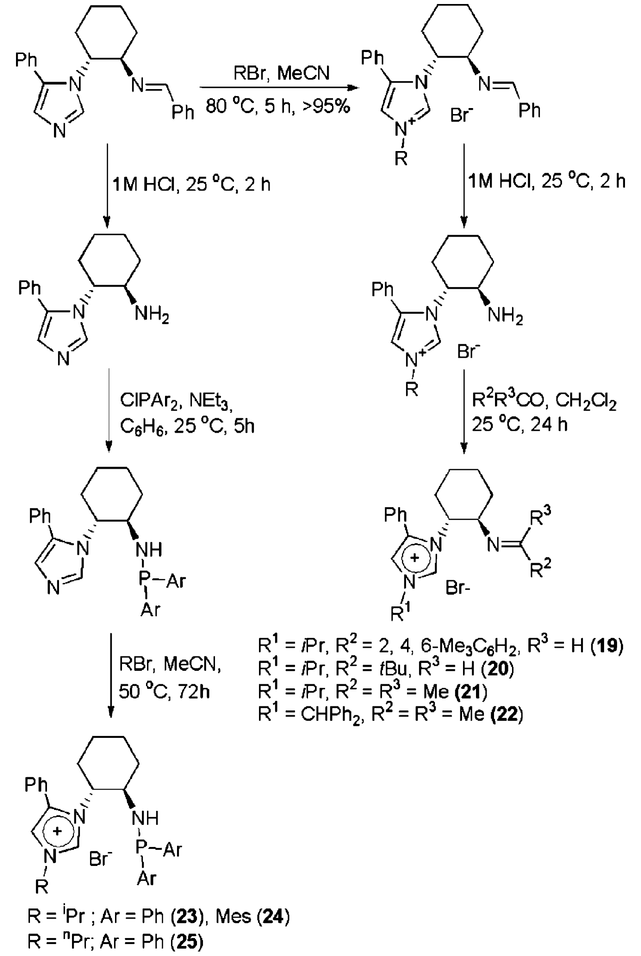
Catalytic reactions were conducted using either preformed palladium complexes or precatalysts prepared in situ from palladium precursors and silver NHC complexes, or in the case of the NHC–phosphines in situ generated free carbene.

Reactions containing preformed $PdCl_2$(di-NHC) complexes or catalysts derived in situ from silver(I) adducts (Fig. 3) of the di-NHC derivatives and $[Pd(allyl)Cl]_2$ gave no appreciable product at temperatures up to 80 °C employing a range of bases and solvents. In related work attempts at asymmetric hydrogenation using $[Rh(di\text{-}NHC)(norbornadiene)][SbF_6]$ complexes also showed extremely poor activities. These observations are largely reflected in the literature where di-NHC complexes, particularly chelating derivatives tend to exhibit lower catalytic activities than mono-NHC or phosphine analogues particularly for reactions where a change in the formal oxidation state of the metal occurs [31,32].

However, NHC-hybrid ligands exhibit a range of more promising activities than di-NHC counterparts, with NHC-P compounds giving comparable rates to bis-phosphines [21]. Therefore it was possible to try and examine the effect of ligand structure on activity and stereoselectivity [19,21].

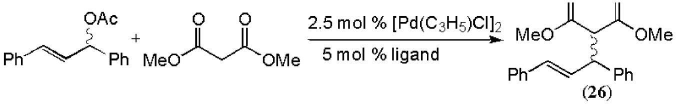


Scheme 9. Allylic alkylation using β-keto ester derived nucleophiles [28].



Scheme 10. Synthesis of NHC-P and NHC-imine precursors derived from an imidazole-imine [20,21].

Table 1
Asymmetric alkylation using NHC-P and NHC-imine ligands **19**–**25** (ligands **19**–**22** were added as silver(I) complexes and ligands **23**–**25** added as free carbene [20,21])



Ligand	Base	T (°C):t (h)	Yield (%)	ee (%)
19	NaH	50:15	69	36 (S)
20	NaH	50:15	60	12 (S)
21	NaH	50:15	>99	92 (S)
22	NaH	50:15	>99	90 (S)
23	BSA/K_2CO_3	25:5	98	38 (S)
24	BSA/K_2CO_3	25:5	70	17 (S)
25	BSA/K_2CO_3	25:5	98	24 (S)

A selection of results is shown in Table 1 for reaction between (E)-1,3-diphenylprop-3-en-l-ylacetate and dimethylmalonate using a range of NHC-N and NHC-P ligands. High yields of **26** could be obtained under a number of conditions although THF gave the greatest rates primarily for reasons of base solubility. It was also clear that NHC-P ligands gave by far the greatest rates allowing reaction to occur at room temperature in less than an hour compared to several hours at 50 °C for NHC-imines. Within the NHC-imine ligands it was shown that generally bulkier groups on the NHC N-substituent and smaller groups on the imine give the highest yield but all could be taken to completion if given sufficient time. At no stage was there any indication of palladium precipitation indicating reaction was inherently slow and the yield is not limited by catalyst decomposition. In addition, enantioselectivity did not vary during the course of the reaction.

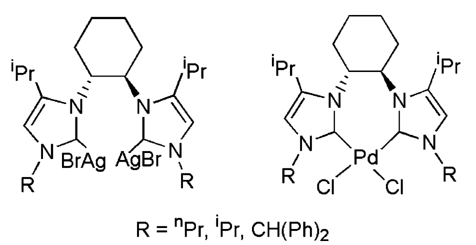


Fig. 3. Examples of chiral di-NHC silver(I) and palladium(II) complexes incorporating *trans*-1,2-diaminocyclohexane as the chiral motif [19].

For NHC-imine ligands all but one reaction showed some enantioselectivity, with ligand **21** giving the highest ee of 92%. Ligands derived from (1*R*, 2*R*)-diaminocyclohexane always gave *S*-**26** whereas *ent*-**21** gave *R*-**26**. Within the limited number of derivatives investigated, enantioselectivity was clearly more sensitive to the imine substituent than the NHC N-moiety. Analogous to the activity, the greatest enantioselectivity was found for relatively small groups at the imine position. Synthetic limitations prevented examination of some desired ligand derivatives. For example bulky aryl substituents that are widely applied in mono-NHC chemistry are not accessible using this route and attempts to prepare imines derived from aryl ketones were also unsuccessful.

The structure of a palladium dichloride derivative of an NHC-imine ligand was obtained in an attempt to rationalise catalytic data (Fig. 4). Relevant structural features are the Pd–Cl bond lengths that clearly reflect the strong *trans*-influence exerted by the NHC moiety relative to the imine (Pdl–Cll = 2.3185(7) Å and Pdl–Cl2 = 2.3695(7) Å). Furthermore, a six-atom palladacycle was observed that exhibits a boat-like conformation that variable NMR spectroscopy indicates is retained in solution up to at least 100 °C.

Previous studies have provided evidence for nucleophilic attack occurring *trans* to the group exhibiting the greatest *trans*-influence in palladium catalysed allylic alkylation [33–35]. Catalytic data were subsequently interpreted based on an allyl intermediate (Fig. 5) where nucleophilic attack occurs *trans* to the NHC moiety. Increasing the bulk of the NHC substituent and imine directs coordination of the allyl. However, larger imine substituents would likely reduce the relative rate of nucleophilic attack *trans* to the NHC moiety due to steric congestion, negating an electronic preference. Therefore a relatively large group at the NHC-N and small group at the imine position promote high enantioselectivity. Selectivity in palladium catalysis determined by electronic differentiation due to relative *trans*-influences/effects has also previously been used to

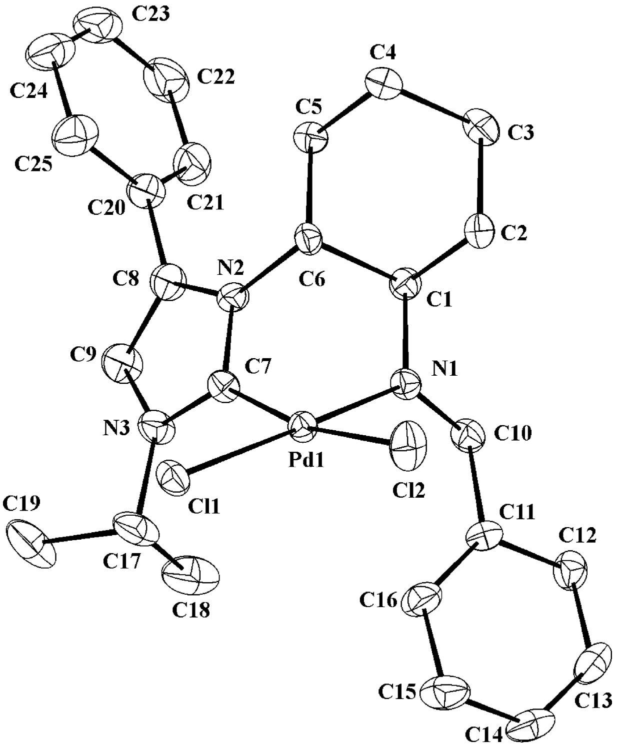


Fig. 4. Molecular structure of a palladium(II) complex of an NHC-imine ligand derived from *trans*-1,2-diaminocyclohexane [20].

explain asymmetric chemistry using C_1 symmetric P–N ligands [36].

For **21** that exhibits the highest enantioselectivity, it was initially suspected that the actual catalyst was a primary amine analogue resulting from in situ hydrolysis of the imine. However control experiments using the isolated primary amine ligand gave poor enantioselectivity and very poor conversion. One potential reason for this apparently anomalous result was provided by hydrolysis of the palladium dichloride complex **27** that gives an insoluble precipitate. Controlled hydrolysis of **27** using an ammonium chloride solution was sufficiently slow to allow precipitation of single crystals of the primary amine analogue **28** (Scheme 11) [29].

The very poor solubility is due to the formation of Pd–Cl···H–N hydrogen bonds that result in a 1D polymer (Fig. 6). Therefore the possibility exists that use of $[PdCl(C_3H_5)]_2$ in catalytic reactions also results in Pd–C1···H–N bonding arising from either free or metal bound ligand thus reducing the activity.

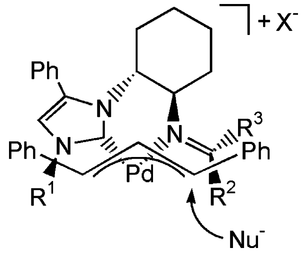
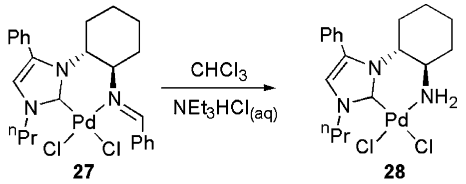


Fig. 5. Proposed structure of ally intermediate that determines stereoselectivity using NHC-imine ligands [20].



Scheme 11. Synthesis of a palladium NHC-amine complex via hydrolysis of an NHC-imine [29].

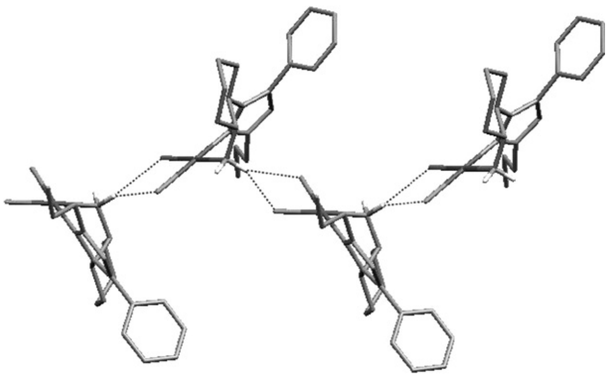


Fig. 6. Hydrogen bonding motif in the structure of **28** that results in a 1D insoluble polymer [29].

Furthermore it was also shown that if palladium NHC catalysts are prepared in situ it is important to maintain a Pd:ligand ratio of 1:1. Catalytic reactions conducted using Pd:ligand ratios of 1:1 and 1:2 clearly show that both activity and enantioselectivity decrease if excess ligand was used. Reaction between $PdCl_2(MeCN)_2$ and 2 equiv. of a silver salt gave *trans*-$PdCl_2(NHC)_2$. A representative structure **29** (Fig. 7) shows the imine moieties are not coordinated to the palladium atom that was also evident in solution as judged by NMR spectroscopy. The implication is that chelation of the ligand is required to give high enantioselectivity although hemilability has not been discounted. In agreement with earlier work the implication is that a palladium di-NHC complex exhibits lower activity than a mono-NHC analogue [31,32].

As stated NHC-P ligands were by far the most active of the ligands investigated, however enantioselectivities were not generally an improvement on those observed for NHC-imine ligand derivatives. In addition to NHC-aminophosphine ligands **23–25**

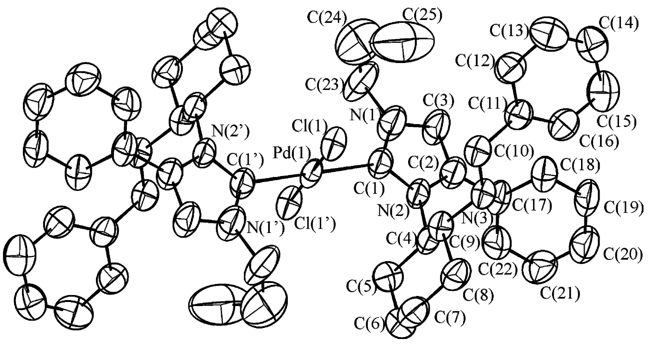
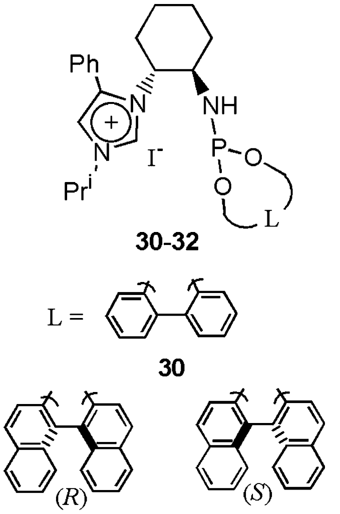


Fig. 7. Molecular structure of a palladium di-NHC complex **29** that gives lower activity and enantioselectivity than the corresponding mono-NHC complexes [19].



30-32

30

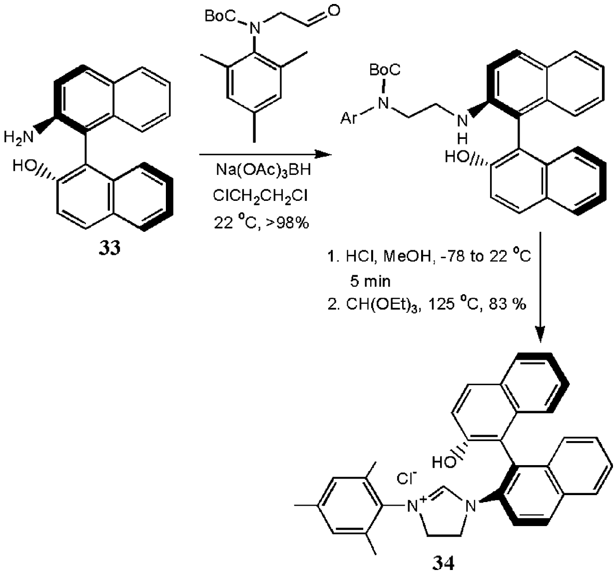
31 **32**

Fig. 8. NHC–phosphoramidate ligand salt precursors [21].

achiral and chiral phosphoramidate derivatives **30–32** (Fig. 8) were examined in an attempt to probe the affect of additional chirality. In common with observations using NHC-imine ligands it was found that bulkier substituents on the P-atom tend to give lower enantioselectivity, and in all cases *S*-**26** predominated where additional chirality on the ligand is not present. Chiral phosphoramidates derived from *R*- and *S*-binaphthol did significantly affect enantioselectivity. Use of *S*-binaphthol enhanced the ee from 17 to 42% (*S*) relative to biphenol whereas *R*-binaphthol gave 11% (*R*).

Although work presented here are the first attempts to apply NHC ligands to palladium catalysed allylic substitution, clearly the results are inferior to those obtained for a range of more highly developed phosphine ligands. Perhaps the most important observation to be made is with respect to the relative activity of NHC and phosphine based catalysts. It is clear that di-NHC palladium complexes are very poor catalysts and the presence of a phosphine moiety dramatically increases the rate of reaction with respect to an imine in hybrid ligand derivatives. The mechanism of palladium catalysed allylic alkylation occurs via Pd(0) and Pd(II) intermediates with a number of potential rate limiting steps [25]. As strong σ-donors, NHC can increase the rate of oxidative addition relative to many phosphines and therefore in reactions where an oxidative addition is the rate limiting step the rate of catalysis *may* increase. However, the inability of NHC ligands to accept significant electron density will slow steps that result in charge build-up at the metal. Substrate addition in palladium catalysed allylic alkylation is usually considered facile and therefore the implication is that the lack of significant π-back donation from palladium to NHC ligand either lowers the electrophilicity of the palladium(II) allyl cation therefore reducing the rate of reaction with the malonate nucleophile, or product alkene binds strongly to a palladium(0) NHC reducing the rate of substrate alkene addition.

In an attempt to be positive, whilst the activities of NHC-based ligands are inferior to phosphine systems, respectable enantioselectivity has been observed in one case, and NHC-P ligands do exhibit good activity. If an immediate outcome of this work is only to serve as a warning to others, there is of course the potential to apply new NHC ligand sets to asymmetric reactions where formal redox chemistry is perhaps less important than observed here.



Scheme 12. Synthesis of NHC-O ligand precursor derived from an aminoalcohol binaphthyl derivative [38].

Further comments comparing the rates of palladium and copper catalysed alkylations are provided in Section 4.

3.2. Copper catalysed allylic alkylation

With respect to copper catalysed alkylations recent work has demonstrated the potential of NHC-based ligands to challenge and arguably out perform known ligand systems with respect to scope, activity and selectivity.

Hoveyda and coworkers have reported two classes of NHC-oxy hybrid ligands initially derived from an axially chiral amino alcohol [37] and subsequently a second generation from a chiral diamine [24].

The first generation ligand was prepared (Scheme 12) from the binaphthyl derivative **33** to give **34** and initially applied to ruthenium catalysed asymmetric ring-opening/cross-metathesis [38]. Excellent results were obtained for ring-opening metathesis and ruthenium complexes were stable enough to be recycled without significant loss in activity.

Ligand **34** and related derivatives (Fig. 9) were also subsequently applied to copper catalysed allylic alkylation and it has been demonstrated that these ligands exhibit improved performance and ease of use that is superior to known processes [26].

Enantioselectivity and conversion are sensitive to a range of ligand structural and electronic parameters exemplifying the general difficulty in identifying an efficient catalyst for a particular substrate. An initial screen (Table 2) using an air sensitive copper(I) source $(CuOTf)_2 \cdot C_6H_6$ showed that substitution on the NHC nitrogen atom significantly affects both conversion and enantioselectivity (mesityl **34** > 2,6-$^iPr_2C_6H_3$ **36** > adamantyl

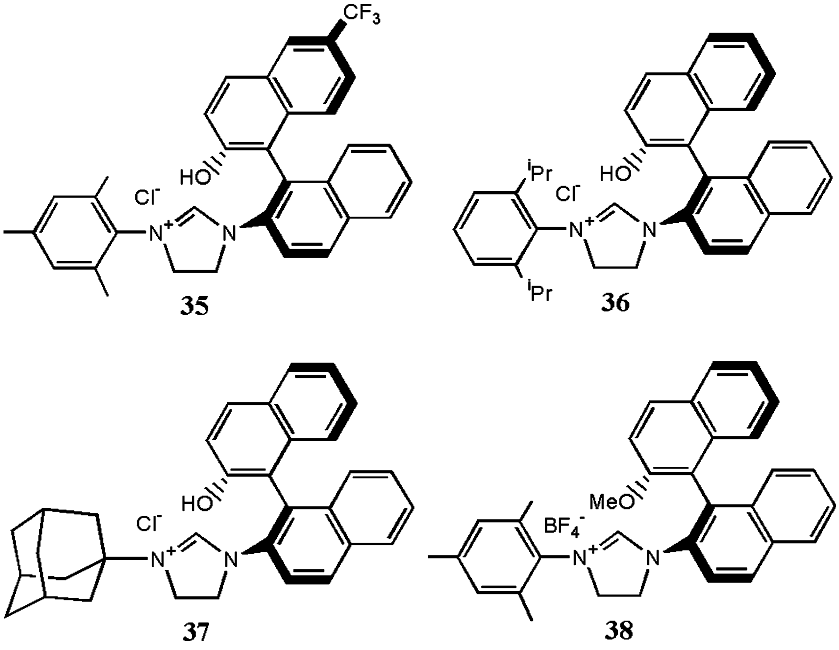


Fig. 9. NHC-O ligand precursor derivatives [38].

37), and introduction of an electron-withdrawing group on the O-containing naphthyl moiety in **35** reduced the catalytic rate. All reactions that resulted in product gave a selectivity of >98:2 for S_N2':S_N2. Importantly, methylation of the naphthol oxide **38** gave significantly inferior conversion and enantioselectivity, strongly indicating that coordination of the aryloxide moiety is necessary. In one case, and in common with many copper catalysed reactions, it was found that enantioselectivity is greater (ee 82% versus 65%) at higher catalyst concentration (10 mol% versus 1 mol%) indicating that monomer/dimer/cluster equilibria could play an important role in determining enantioselectivity.

Evidence to support aggregation of copper species was provided by single crystal diffraction studies of silver(I) **39** and copper(II) **40** complexes derived from **34** that reveal a dimer motif (Fig. 10) in each case. NMR spectroscopy studies also show that the dimer motif is retained in solution.

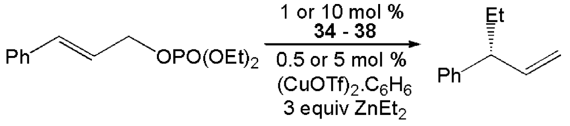
Catalytic reactions using **39** as a ligand transfer agent to copper precursors, examined the tolerance of reaction to a range of substrates, zinc alkylating agents, and use of an air stable copper source $CuCl_2{\cdot}2H_2O$ (Table 3). In addition, copper complex **40** was also used directly as a precatalyst (Table 3).

It was found that preformed silver and copper complexes allow lower catalyst loading in comparison to in situ catalyst generation from **34** to **38** and that enantioselectivity does not suffer from lower loadings. Importantly for practical application, air stable $CuCl_2{\cdot}2H_2O$ could be used and in comparative cases to Cu(I) sources, gave higher activity and enantioselectivity. Furthermore in contrast to other catalytic systems this new class of NHC-O ligand allows the formation of quaternary stereogenic centres, tolerates a greater diversity of zinc reagents and overall represents one of the most general methods for allylic alkylations using hard metal alkyls [26].

In a more recent development the synthesis of a second generation of chiral NHC-oxy ligand precursors (**12**, Scheme 6) has lead to even greater improvements with respect to ease of ligand synthesis, enantioselectivity and substrate generality

Table 2

Copper catalysed asymmetric allylic alkylation using ligands **34**–**38** [38]



Ligand (mol%)	*T* (°C):*t* (h)	Conv. (%)	ee (%)
34 (1)	−15:1	>98	65
34 (10)	−15:1	>98	82
35 (10)	−15:36	87	80
36 (10)	−15:24	18	64
37 (10)	−15:24	70	52
38 (10)	−15:10	20	21

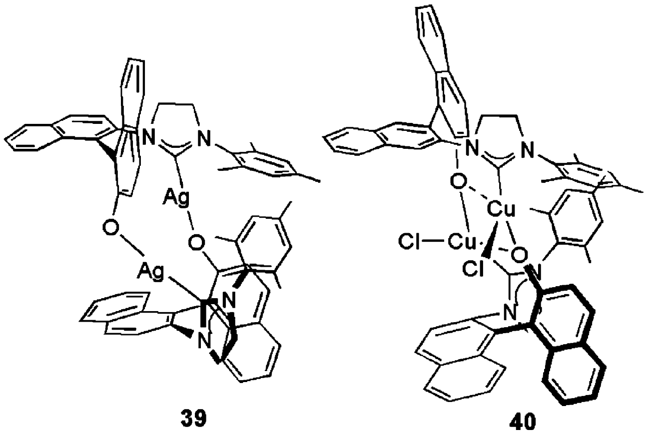
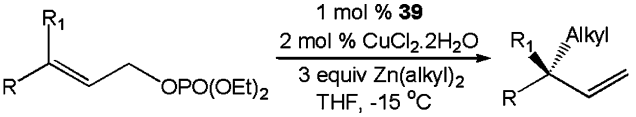


Fig. 10. Structures of silver(I) and copper(II) complexes of ligand **34** [38].

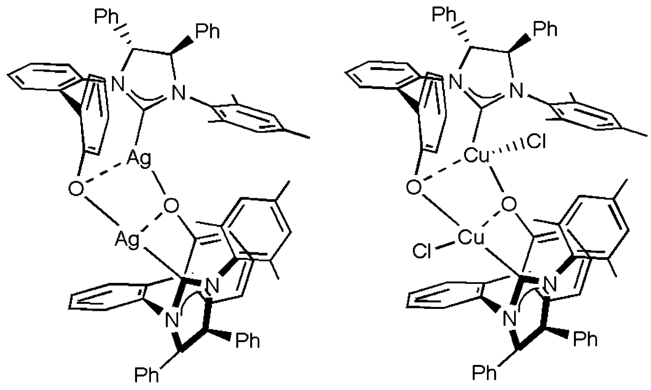
Table 3
Effect of variation of substrate and alkyl group on alkylation using ligand **34** [38]



R	R_1	$Zn(alkyl)_2$	*t* (h):conv. (%)	ee (%)
C_6H_5	H	$ZnEt_2$	4:>98	86
C_6H_5	H	$ZnMe_2$	24:>98	71
C_6H_5	H	$Zn(PivOCH_2)_2$	24:>98	76
p-$NO_2C_6H_4$	Me	$ZnEt_2$	4:>98	98
Cy	Me	$ZnEt_2$	12:>98	93
0.5 mol% (**40**)				
C_6H_5	Me	$ZnEt_2$	48:>98	92

[24]. Compound **12** can be readily synthesised in multigram quantities with very high enantiopurity (Scheme 6), which somewhat contrasts the tedious synthesis of aminoalcohol binaphthyl derivatives such as **33**. Chirality is derived from a chiral diamine that is incorporated into synthesis of the *N*-heterocycle and an achiral biphenol provides the aryloxide moiety. On coordination to a metal, steric interactions within the ligand, result in the *N*-heterocycle chirality being expressed as a single atropoisomer, which is supported by X-ray diffraction studies. Similar to the first generation examples, silver(I) **41** and copper(II) **42** complexes (Fig. 11) exhibit M_2L_2 dimers in the solid state that are also present in solution.

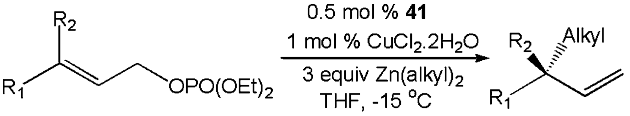
Enantioselective catalysis using ligand **12** has shown improved performance in comparison to the first generation catalysts in both ruthenium catalysed metathesis and copper catalysed allylic alkylation. With respect to the latter a greater range of substrates can be utilised with improved enantioselectivity and similar benefits are exhibited including use of air stable copper salts such as $CuCl_2{\cdot}2H_2O$ and relatively low catalyst loading (ca. 0.25–2 mol%). An additional feature is that a greater range of larger and less reactive zinc reagents other than $ZnEt_2$ can be utilized including Zn^nBu_2 and Zn^iPr_2 again giving excellent enantioselectivity. Representative examples include the alkylation of the disubstituted and trisubstituted olefins (Table 4) that result in excellent activity and the highest enantioselectivity for any allylic alkylation using hard nucleophiles. Using the silver complex **41** as ligand transfer agent or copper complex **42** gave essentially identical results (Table 4).



41 **42**

Fig. 11. Structures of silver(I) and copper(II) complexes of ligand **12** [24].

Table 4
Copper catalysed asymmetric allylic alkylation using complex **41** [24]

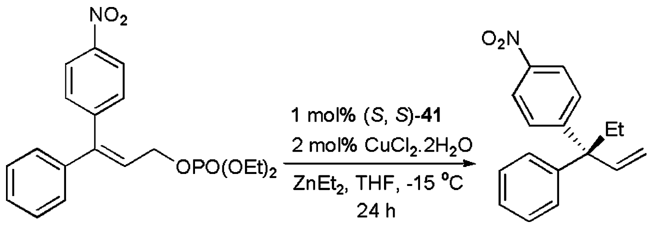


R_1	R_2	$Zn(alkyl)_2$	*t* (h):conv. (%)	ee (%)
C_6H_5	H	$ZnEt_2$	24:>98	90
C_6H_5	H	Zn^iPr_2	2:>98	86
o-$NO_2C_6H_4$	H	$ZnEt_2$	2:>98	90
Cy	H	Zn^iPr_2	24:>98	90
C_7H_{15}	H	$ZnEt_2$	15:>98	88
C_6H_5	Me	$ZnEt_2$	2:>98	97
C_6H_5	Me	Zn^iPr_2	12:>98	98
Cy	Me	$ZnEt_2$	24:>98	97
0.5 mol% (**42**)				
Cy	H	Zn^iPr_2	24:>98	90
C_6H_5	Me	Zn^iPr_2	12:>98	97

The reaction in Scheme 13 is a particularly interesting example because high enantioselectivity (85% ee) is observed in a substrate that contains two aryl groups that are structurally very similar, differing only in the presence of a nitro group on the periphery of the molecule. Enantioselectivity appears to be determined principally on electronic differentiation, although the mechanism has yet to be elucidated.

Copper catalysed allylic alkylation using achiral and chiral mono-NHC ligands has been described by Okamoto and coworkers [39]. The mono-NHC copper(I) compounds **43–46** (Fig. 12) were prepared and reactions utilised Grignard reagents as the hydrocarbyl source. No structural studies are presented but control reactions clearly showed that an NHC ligand precursor must be present for catalysis to occur. An initial screen of achiral reactions proceed very efficiently giving high yields for a range of alkyl, cyclic and aryl Grignard reagents with non-aryls and aryls exhibiting almost exclusively γ and α regioselective addition, respectively.

An asymmetric variant (Table 5) using ^{n}hexMgBr as the nucleophile was then examined that gave low to moderate enantioselectivities, with the highest ee of 70% observed for the bulkiest monoamine complex **44**. There was also a marked dependence on leaving group with carbonate **b** and chloride **c** giving ee's <10%, but a 2-pyridyl ether derivative **d** giving



Scheme 13. Enantioselectivity potentially determined by electronic difference between phenyl and nitrophenyl moieties [24].

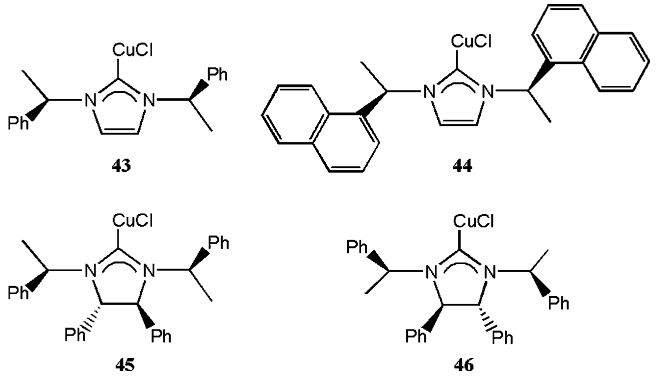


Fig. 12. Copper precatalysts for asymmetric alkylation using Grignard reagents [39].

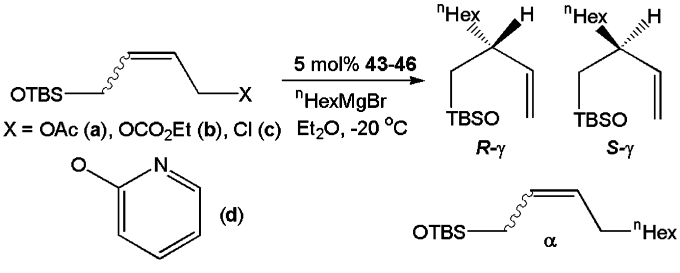
70% potentially due to coordination of the pyridine moiety to magnesium. Additional chirality in the NHC backbone derived from a chiral diamine did not result in improved enantioselectivity. However, comparing reactions using NHC complexes **45** and **46** showed that chirality at C4 and C5 detrimentally affect enantioselectivity. This observation will be discussed in more detail in Section 4.

3.3. Copper catalysed conjugate addition

Conjugate addition to enones is a related reaction to allylic alkylation and was one of the first reported applications of chiral NHC copper complexes to asymmetric catalysis. Several examples of mono- [40–43] and more recently chelating NHC [44–46] have been investigated with both classes of ligand now exhibiting very good levels of enantioselectivity in select cases.

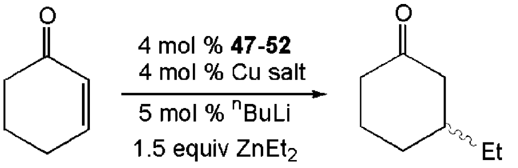
Drawing on earlier studies Alexakis, Mangeney and Roland have examined a number of chiral mono-NHC for conjugate addition of diethyl zinc to a variety of cyclic and acyclic Michael acceptors [40]. Several classes of chiral NHC were screened including saturated, unsaturated, six- and five-member heterocycles with chiral centres at the N-substituents and within the ring (Fig. 13). NHC were added to the reaction as either the organic salt or via NHC silver(I) complexes.

Table 5
Regio- and enantio-selectivity for asymmetric alkylation using complexes **43**–**46** [39]



Allylic substrate	Cat.	γ:α	γ-ee (%)
(*Z*)-**a**	**43**	87:13	40 (*R*)
	44	95:5	60 (*R*)
	45	88:12	38 (*S*)
	46	84:16	6 (*R*)
(*E*)-**a**	**44**	97:3	38 (*S*)
(*Z*)-**d**	**44**	98:2	70 (*R*)
(*E*)-**d**	**44**	86:14	60 (*S*)

Table 6
Copper catalysed conjugate addition of cyclohexanone using complexes **47**–**52** [40]



Ligand	Cu salt	*T* (°C):*t* (h)	Yield (%)	ee (%)
47	Cu(OTf)$_2$	−20:2	99	13 (*S*)
48	Cu(OTf)$_2$	−20:2	60	39 (*R*)
48	Cu(OAc)$_2$	−78:16	75	54 (*R*)
49	Cu(TC)	−78:16	76	38 (*S*)
50	Cu(OTf)$_2$	−20:2	99	4 (*S*)
51	Cu(OTf)$_2$	−20:2	97	7 (*S*)
52	Cu(OTf)$_2$	−20:2	92	22 (*S*)

As may be expected, in addition to ligand structure, the enantioselectivity is strongly dependent on temperature, solvent, substrate and copper source, however it is possible to identify some interesting features with respect to the ligand (Table 6). Initial catalytic reactions were conducted using NHC precursor salts including **47**–**52**, that require in situ deprotonation and complexation of NHC to copper. Reactions were all conducted with a 1:1 Cu:ligand ratio and variation of several reaction parameters resulted in a maximum ee of 54% (Table 6). It was found that for salts containing only chiral N-substituents including **47** and **48**, compounds derived from (*S*)-amines gave (*S*)-product and vice versa. There was also limited enantioselectivity for salts such as **50** and **51** that contain chirality at the C4 and C5 positions and relatively symmetric N-substituents. However, it is interesting to compare **48** and **52** that are both derived from a mono-(*S*)-amine, but where **52** contains additional chiral stereogenic centres at the C4 and C5 positions. Compound **52** gives product with the opposite configuration to **48** indicating that the backbone substituents control how the chirality of the ligand is expressed at the metal. Subsequent synthesis of C4/C5 stereoisomers derived from *ent*- and *meso*-diamine showed that **52** is the matched pair, exhibiting the highest enantioselectivity of the three stereoisomers.

Application of NHC silver(I) halide complexes gave improved results potentially because transfer of the NHC moiety to copper is cleaner and catalytic reactions using hygroscopic *N*-heterocycle salts are avoided. A diverse range of chiral motifs were investigated including **53**–**56** (Fig. 13) and applied mainly to alkylation of cyclohexenone and cycloheptenone (Table 7). Comparison of results for complex **53** and compound **49** under identical conditions showed an increase in enantioselectivity to 54 (*S*) from 38 (*S*), respectively. A maximum ee of 93% for addition to cycloheptenone was observed for **53** reflecting that a larger ring tended to give higher ee's. Again the influence of C4/C5 chirality was evident in reactions using **54**–**56** (Table 7). Compounds **54** and **55** incorporate achiral N-substituents that

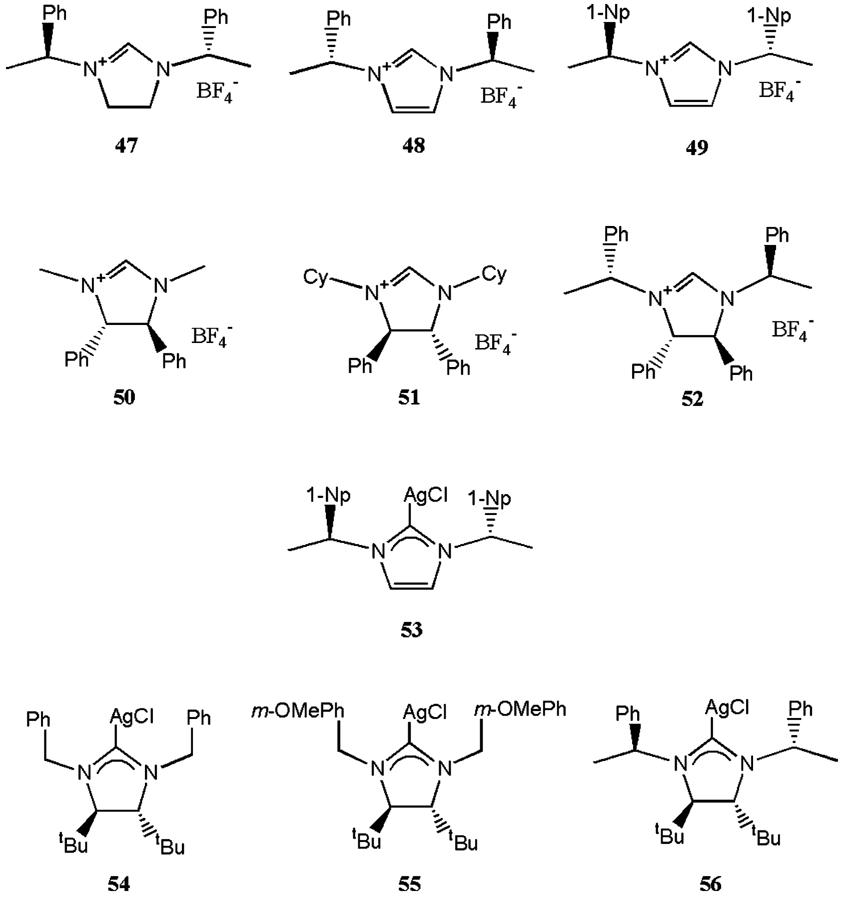
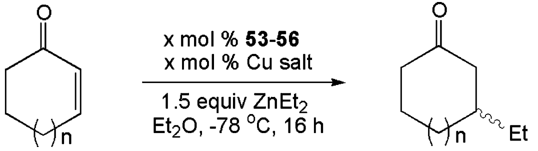


Fig. 13. Silver complexes used as ligand transfer agents in copper catalysed allylic alkylations [40].

express the chirality at the metal centre resulting in respectable enantioselectivity, in contrast to **56**, which contains chiral N-substituents and exhibits the poorest ee. However, it should also be noted that **52** and **56** both give (*S*)-product although they are derived from (*S*, *S*) and (*R*, *R*) diamines, respectively.

Conjugate additions have also recently been described in a thorough study by Mauduit and coworkers for a series of chelating chiral NHC-alkoxides [46]. Initially structures incorporating chirality in the N-heterocycle backbone (Fig. 14) were examined and a maximum ee of 66% was obtained for ethyl addition to cyclohexenone [45].

Table 7
Copper catalysed conjugate addition of cyclohexanone and cycloheptanone using complexes **53**–**56** [40]



Ligand (mol%)	Cu salt (mol%)	Substrate (*n*)	Yield (%)	ee (%)
53(2)	Cu(TC) (2)	1	79	54 (*S*)
53(2)	$Cu(OAc)_2$(2)	2	95	93 (*S*)
53(2)	Cu(TC) (2)	2	95	89 (*S*)
54(4)	Cu(TC) (4)	1	100	58 (*S*)
55(4)	Cu(TC) (4)	1	99	69 (*S*)
55(4)	Cu(OTf) (4)	2	100	88 (*S*)
56(4)	Cu(TC) (4)	1	98	29 (5)

More recently chiral elements have been introduced on to the alkoxy substituents via aminoalcohols, which permits significant diversity (Scheme 14, Fig. 15). In addition to strong dependence on temperature, substrate, copper source, base, solvent, and Cu:ligand ratio, several features of the ligand structure also have a significant influence on enantioselectivity. Ligands including **58** and **59** derived from 2-substituted β-aminoalcohols contain a single chiral centre adjacent to the *N*-heterocycle and generally exhibit higher values (max. 94% ee for **58**) than those derived from bulkier 1,2-disubstituted β-aminoalcohols such as **60**. As may be anticipated, ligands such as **61** give the lowest ee, but also structures including **62** that position chirality closer to the metal than **58** and **59** also perform poorly. This observation is also in accord with an earlier study by Arnold et al. showing that chiral elements on the carbon adjacent to the alkoxide do not give high levels of enantioselectivity [44].

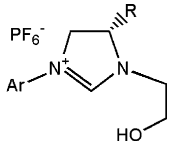
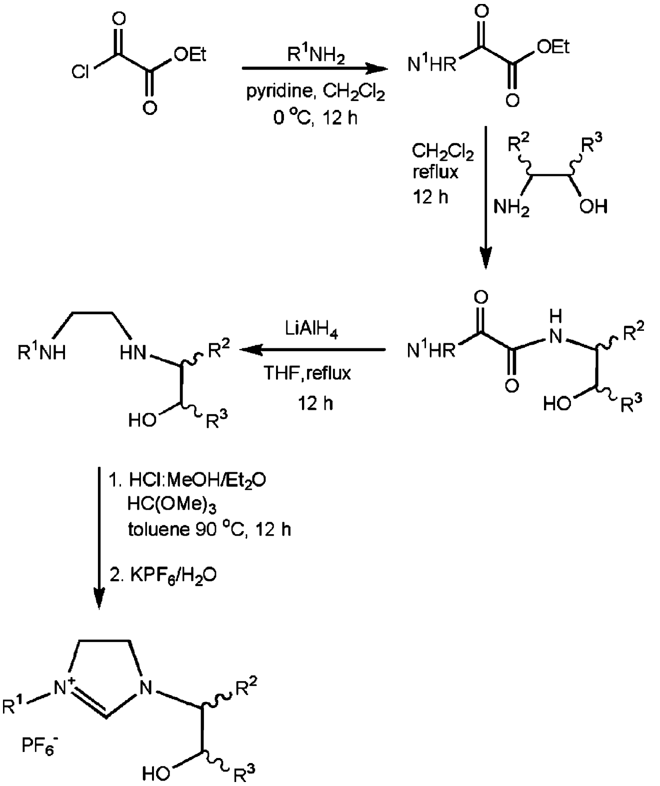


Fig. 14. First generation of chelating NHC-O ligands used for asymmetric conjugate addition [45].



Scheme 14. Synthesis of second generation NHC-O ligand precursors derived from β-aminoalcohols [46].

For derivatives of **57** dependence is also observed with respect to the N-substituent where mesityl gives the greatest enantioselectivity (85%) in comparison to phenyl (54), 2,6-^{i}Pr$_2$C$_6$H$_3$ (29) and *tert*-butyl (73) amongst others. Given these observations it may be interesting to develop a synthetic route to compounds similar to that shown in Fig. 14, or **57** and **58**, that are derived from a diamine to introduce chirality at the C4 and C5 positions of the heterocycle.

Unfortunately structures of relevant copper complexes that may help to interpret the catalytic data are very limited, which in any event may not represent the structure of the true catalytic species. An indication of the complexity of this class of reaction is given by the variation in enantioselectivity with temperature and copper source observed for ligand **57**. Cu(OTf)$_2$ exhibited ee values of 15, 86, and 84% for temperatures −78, 25, and 45 °C, respectively, whereas copper(II)ethylacetoacetate showed comparatively little temperature dependence. It was also shown that the optimum Cu:ligand ratio is a slight excess of ligand, and that greater quantities severely reduced the selectivity. The implication is that in common with many copper catalysed alkylation reactions metal/ligand/anion equilibria are operative that significantly influence the resulting enantioselectivity.

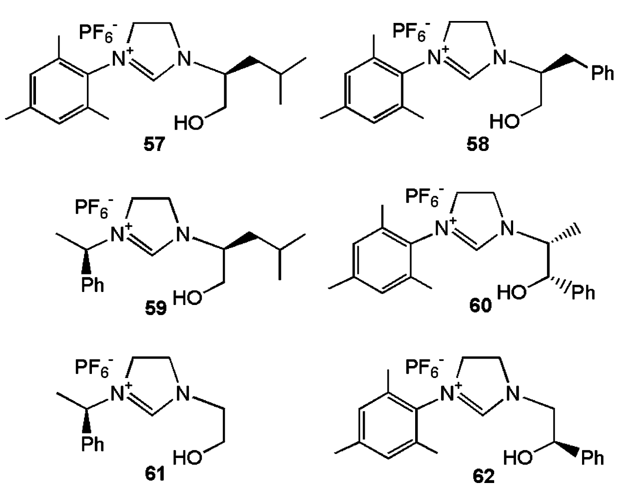


Fig. 15. Diversity of ligand structures derived from β-aminoalcohols [46].

4. Influence of NHC ligands on activity and enantioselectivity

The mechanism of copper catalysed allylic alkylations and related reactions are arguably much less developed than complementary palladium chemistry [26,47,48]. Two commonly proposed mechanisms proceed via carbocupration where the copper oxidation state formally remains constant or alternatively via a formal copper(III) transition state. Of course both are formalisms that try to describe the redistribution of electron density along the reaction coordinate during bond forming/cleavage processes. Theoretical work has suggested that in copper catalysed alkylations the copper atom does not experience large charge density build-up and that electron distribution is largely ligand centred [47].

Woodward first described copper catalysed conjugate addition using achiral NHC ligands and stated that the strong σ-donation of NHC could stabilise a putative Cu(III) transition state [49]. Copper catalysed alkylation is closely related to conjugate addition and similar arguments are also applicable. Many studies describe the sensitivity of regio- and stereo-selective alkylation to various parameters including temperature, solvent, catalyst/substrate concentration, substrate structure and hard metal alkyl source as indicated by the work described here. This diversity is reflective of aggregate formation between copper and metal alkyls and the potential for several mechanistic possibilities, which renders study difficult [47].

Notwithstanding the mechanistic nuances, the changes in charge density at the metal on intermediates and transition states will be less for copper catalysed reactions in comparison to palladium analogues, where discrete Pd(0) and Pd(II) species can be detected and in many cases isolated. Therefore in addition to potential rate increases for copper catalysed reactions, as a consequence of strong σ-donation, the absence of significant π-accepting ability of NHC ligands will not be as significant for copper as for palladium catalysed alkylations.

More generally, for palladium catalysed processes such as coupling reactions, strong σ-donating NHCs increase the rate of oxidative addition that is commonly the rate limiting step. As poor π-acceptors the use of NHC will reduce the rate of transmetallation and reductive elimination, however the latter can be accelerated by using NHC that contain bulky groups on the N-substituents. In comparison to di-NHC and other chelating ligand systems mono-NHC also allow reaction to proceed more rapidly via mono-coordinated Pd(0) and three coordinate

Pd(II) species as observed for some phosphine based systems [50]. It is evident from the literature that in comparison to bisphosphines, palladium complexes of chelating di-NHC ligands are less active, although are thermally more robust allowing reaction at higher temperature.

With respect to enantioselectivity it is of course extremely difficult, if not currently impossible, to predict with any certainty the ligand composition and structure that will give optimum results for most asymmetric catalytic reactions. However, regarding NHC ligand design there are now several examples where chiral diamines have been incorporated into NHC ligands and provided a basis for the development of new ligands. A strategy that perhaps has been applied most successfully to the widest range of reaction, is the incorporation of chiral diamines at the C4 and C5 positions of an imidazolinium salt as part of mono- and chelating NHC ligands. Although the chiral information is at the periphery of the ligand with respect to the metal-coordinating C2 carbene atom, the chiral information is expressed via the N-substituents that exert steric influence at the metal. This principle has previously been used in other ligand systems [50] and was first demonstrated successfully for NHC ligands by Grubbs using compound **5** (Scheme 2). The phenyl groups on the stereogenic C4 and C5 atoms restrict rotation about the $N–C_6H_4{}^{i}Pr$ bond inducing enantioselective reaction. Copper catalysed alkylation reactions using ligands **45** and **46** (Table 5) exhibit enantioselectivity that demonstrate competitive interactions between ligand substituents resulting in mismatched pairs and low selectivity. Complexes **54** and **55** show how achiral N-substituents can be coerced into generating chirality at the metal via interaction with C4 and C5 stereogenic centres.

However, the catalysts exhibiting the greatest enantioselectivity for the widest range of substrates and reactions (copper catalysed alkylation, ruthenium catalysed ring closing metathesis, rhodium catalysed hydrogenation and rhodium catalysed phenylation) are those derived from chelating compounds where conformation is directed by chiral centres on the C4/C5 positions. The examples shown here, **11** and particularly **34**, are extremely impressive and will doubtless provide inspiration for the development of new chiral chelating NHC ligand sets.

5. Concluding remarks and outlook

Given the relatively short period of time dedicated to intensively exploring the synthesis and application of chiral NHC ligands to asymmetric catalysis significant progress has been achieved. With respect to any catalytic process, ideally a reaction will proceed quickly with high selectivity. Structurally there is now ample evidence, including that cited here, demonstrating that NHC ligands can be used to direct reactions with very high levels of stereoselectivity. In particular the development of chelating NHC ligands containing chiral centres that direct coordination of N-substituent moieties appears to be a generally successful strategy. There is also evidence to suggest that in an analogous manner to chelating hybrid phosphines, the electronic characteristics of an NHC moiety can also be used to help direct stereoselective bond formation in hybrid chelating NHC ligands (e.g. Fig. 5 and perhaps Scheme 13).

One potential drawback to the general utility of NHC ligands is with respect to activity exemplified by the contrast between palladium and copper catalysed alkylation chemistry described here. Although strong σ-donation will promote oxidative addition and stabilise formally high oxidation state transition states/intermediates, within any catalytic cycle the complementary reductive elimination or reactions involving an electrophilic intermediate (e.g. transmetallation, nucleophilic attack) will be slowed. In cases where oxidative addition may not be rate limiting, such as palladium catalysed allylic alkylations, the lack of appreciable π-acidity of NHC ligands can result in slower rates in comparison to phosphines. Notwithstanding this limitation, the early indication regarding application of chiral NHC ligands to asymmetric catalysis is very positive, and a bright future seems assured [51].

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