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Synthesis of chiral iminoalkyl functionalised *N*-heterocyclic carbenes and their use in asymmetric catalysis

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Abstract—A library of new chiral iminoalkyl imidazolium salts has been synthesised from amino acids using a modular design approach. Deprotonation with silver oxide yields silver carbene transfer reagents, which can be used as ligand sources in asymmetric catalysis. Preliminary testing has shown that the ligands induce enantioselectivity in the palladium-catalysed allylic alkylation of 1,3-diphenylprop-3-enyl acetate with dimethyl malonate.

The design of new classes of chiral ligands is of great importance to extend the substrate scope, activity and enantioselectivity of asymmetric catalysis. To date, most research has focused on phosphine and amine ligands due to the large variation of electronic and steric properties that is possible and their relative ease of synthesis.[1] Stable *N*-heterocyclic carbenes (NHCs), first isolated by Arduengo,[2] are recognised as being valuable alternatives to phosphines displaying stronger σ-donor and poorer π-acceptor properties.[3] *N*-Heterocyclic carbenes have been shown to be superior to phosphine ligands in a number of metal-catalysed reactions, including palladium-catalysed Suzuki–Miyaura cross coupling of sterically hindered aryl chlorides[4] and ruthenium-catalysed ring-opening and closing metathesis.[5] Progress in the synthesis and application of chiral *N*-heterocyclic carbene catalysts was initially slow; most of the early examples were monodentate with chiral N-substituents, which were presumably too flexible to yield a catalyst with a fixed conformation conducive to enantioselectivity.[6] More recently, excellent enantiomeric excesses have been reported for hydrogenation[7] and alkylation reactions[8] using chiral bidentate ligands containing NHCs. In each case the chirality is located in the backbone of the ligand and the constrained geometry of the ligand is critical to the excellent enantioselectivity. The work described here highlights a novel route to chiral NHC ligands using amino acids and a modular design approach.

Chiral mixed donor imine phosphine ligands display high ees for a wide range of asymmetric catalysed reactions, such as alkene hydrogenation,[9] allylic alkylation[10] and conjugate addition.[11] Our aim was to replace the phosphine donor group with a NHC donor group in such ligand structures. We were particularly interested in allylic alkylation where the much stronger σ-donor ability of the carbene compared to the imine would allow significant electronic differentiation of the terminal carbons of the meso allyl intermediate. We anticipated that the chiral backbone of our bidentate ligands, derived from a chiral amino acid, would create a suitable fixed-geometry chiral pocket to induce enantioselection. Without detailed mechanistic information for our ligands it would be difficult to predict which combination of alkyl and aryl substituents would give the optimum performance. Therefore, we adopted a modular approach to the design of the ligands that would allow the synthesis of a large library of ligands from small libraries of amino acids, carbonyl compounds and N-substituted imidazoles Figure 1. The use of cheap amino acids, available from the chiral pool, was an attractive feature of the design.

One of the attractions of NHCs is that they can be readily prepared by the deprotonation of imidazolium salts, which are air stable, unlike trialkylphosphines. The imidazolium salts were synthesised by alkylation of N-substituted imidazoles with chiral iminoalkyl halides.

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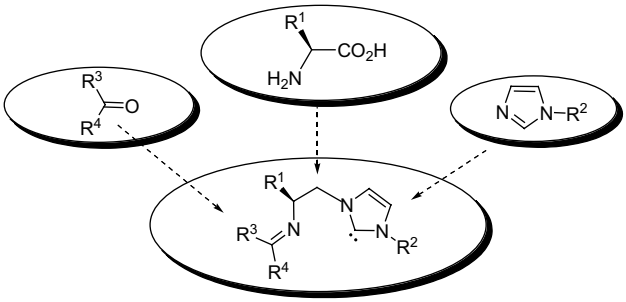


Figure 1. Modular design of ligands.

The chiral iminoalkyl halides were prepared from commercially available amino acids or amino alcohols.

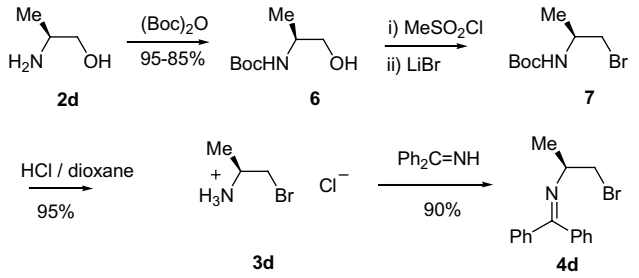
Amino acids **1** were reduced with sodium borohydride in the presence of iodine to give amino alcohols **2**. The aminoalkyl bromide hydrobromide salts **3** were prepared in high yields by stirring with thionyl bromide and DMF in cyclohexane for 16 h, according to the method of Jung (Scheme 1, Table 1).[12] The amino group enhances the rate of bromination and the reaction proceeds with retention of configuration. Diphenylmethylideneamine derivatives **4** were conveniently prepared by reaction of **3** with benzophenone imine. Benzylideneamine alkyl bromides **5** were prepared by condensation of **3** with benzaldehyde in the presence of molecular sieves.[13]

The aminoalkyl bromide derived from alaninol could not be made by bromination using thionyl bromide. An alternative method involving protection was used. Alaninol was treated with di-*tert*-butyl dicarbonate in CH_2Cl_2 at 0 °C followed by warming to room temperature to give the protected product in near quantitative yield.[14] The protected alaninol was mesylated in 80–95% yield by methanesulfonyl chloride and converted into bromide **7** by stirring with anhydrous lithium bromide in dry acetone.[15] Derivative **7** was deprotected by treatment with HCl in dioxane to give product **3d** (Scheme 2).

Imidazolium salts have proved very convenient precursors to imidazol-2-ylidene ligands. The iminoalkyl halides **4** or **5** were coupled to N-substituted imidazoles

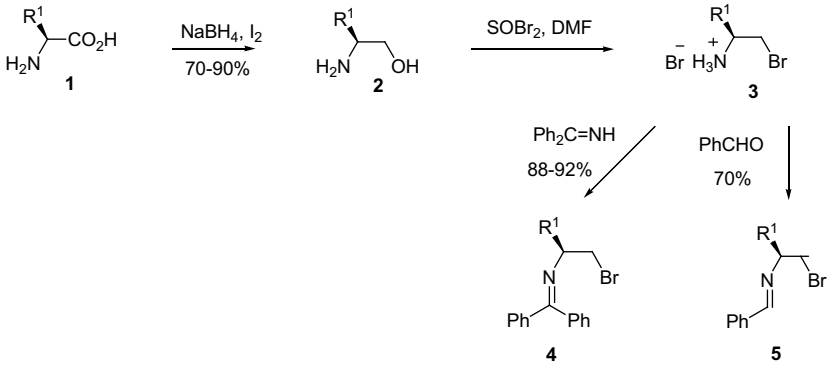
Table 1. Iminoalkyl bromides synthesised

1	Yield of 3	Yield of 4	Yield of 5
1a R^1 = Bn	55	90	
1b R^1 = *i*-Pr	90	88	
1c R^1 = *i*-Bu	85	87	70



Scheme 2. Preparation of an iminoalkyl halide derived from alaninol.

8 to give the imidazolium salt derivatives **9** that are convenient precursors to imidazolylidene ligands (Table 2). The salts were most conveniently obtained by heating the reactants at 85 °C in the absence of a solvent. After 12 h the reaction mixture was allowed to cool and the crude product formed was triturated and washed with dry diethyl ether, then dried under vacuum. The salts were purified by recrystallisation from dichloromethane and diethyl ether. Lower yields were obtained with *N*-aryl imidazoles (25–46%) than with *N*-alkyl imidazoles (44–79%). It is thought that sterically hindered alkyl halides can undergo elimination in competition with nucleophilic substitution when reacted with the bulkier *N*-aryl imidazoles. In addition, the aryl imidazoles produced more viscous melts during the reaction which impeded stirring. The ^{1}H NMR spectra display a signal between δ 10 and 11 characteristic of the C1 proton of the imidazolium cation. The diphenylmethylideneamine imidazolium derivatives are air stable white solids and were not hygroscopic. The benzylideneamine imidazolium derivatives were however moisture sensitive and prone to hydrolysis. The yields of imidazolium salts not used extensively in catalyst testing, such as **9d** and **9g**, were not optimised. Douthwaite and co-workers reported that dimethylmethylideneamino functionalised NHCs gave the best results for asymmetric allylic



Scheme 1. Preparation of iminoalkyl halides.