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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8914–8917

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

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Received 15 February 2007; revised 28 September 2007; accepted 10 October 2007
Available online 14 October 2007

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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doi:10.1016/j.tetlet.2007.10.049

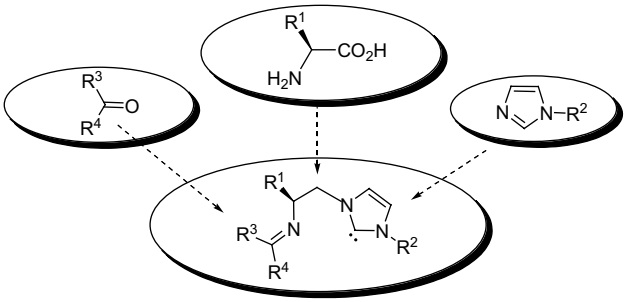


Figure 1. Modular design of ligands.

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

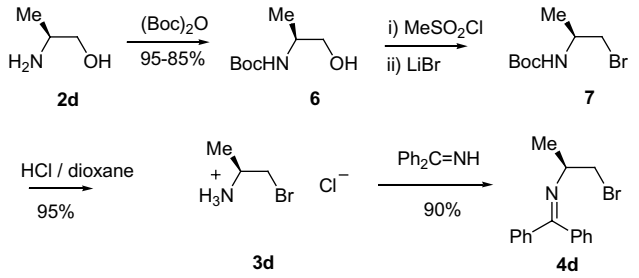
Amino acids **1** were reduced with sodium borohydride in the presence of iodine to give amino alcohols **2**. The aminoalkyl bromide hydrobromide salts **3** were prepared in high yields by stirring with thionyl bromide and DMF in cyclohexane for 16 h, according to the method of Jung (Scheme 1, Table 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

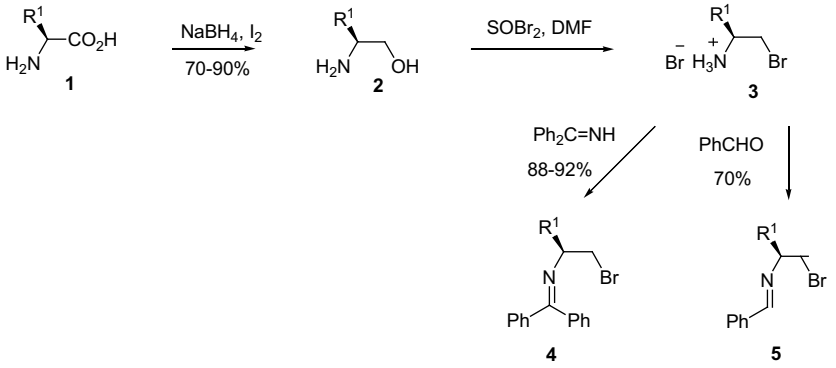
Table 1. Iminoalkyl bromides synthesised

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



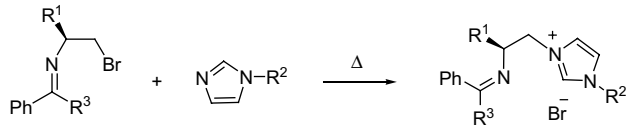
Scheme 2. Preparation of an iminoalkyl halide derived from alaninol.

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.

Table 2. Synthesis of iminoalkyl imidazolium salts



4 or 5 **8** **9**

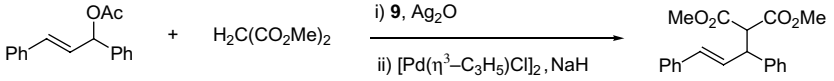
R^1	R^2	R^3	Yield %
Bn	Bn	Ph	**9a** 44
i-Pr	Bn	Ph	**9b** 57
i-Bu	Bn	Ph	**9c** 79
Me	Bn	Ph	**9d** 66
i-Bu	Me	Ph	**9e** 63
i-Bu	Mesityl	Ph	**9f** 46
i-Bu	Ph	Ph	**9g** 25
i-Bu	Bn	H	**9h** 70

alkylation;[16] however, attempts to make dimethylmethylideneamine functionalised imidazolium salts were unsuccessful.

Mori and co-workers reported the first example of palladium-catalysed allylic alkylation using *N*-heterocyclic carbene ligands.[17] Around the same time, Douthwaite reported the first asymmetric allylic alkylation using NHC–imine ligands derived from *trans*-1,2-diaminocyclohexane.[16] These ligands gave ees of up to 92% and represent one of the most successful examples of asymmetric catalysis using chiral imidazol-2-ylidenes to date. Related chiral NHC–phosphine ligands gave poorer results.[18] Hoveyda has reported copper catalysed enantioselective allylic alkylation with bidentate imidazolidin-2-ylidene ligands.[19] Wang and Lin first demonstrated that silver carbene complexes can be obtained easily by treating azolium salts with Ag_2O and that they are efficient ligand transfer agents for generating palladium carbene species.[20] This mild approach to the formation of imidazol-2-ylidenes obviates the need for strong bases. Danopoulos[21] and Douthwaite[22] have shown that the use of silver oxide is a convenient method for the generation of monodentate imino functionalised imidazol-2-ylidene complexes. Therefore, Ag_2O was used to deprotonate imidazolium salts **9** in the presence of 4 Å molecular sieves. After filtering the solution through Celite and removing the solvent, the silver carbene complex was added to a solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ in THF and stirred for 30 min before the addition of 1,3-diphenylpropenyl acetate (1 equiv), dimethyl malonate (3 equiv) and NaH (2.9 equiv). Conversions were measured by GC and ees were determined by ^{1}H NMR analysis using Eu(hfc) as a chiral shift reagent.

Table 3 summarises conversions and enantiomeric excesses for a screen of some representative ligands from our library in the palladium catalysed asymmetric allylic alkylation of 1,3-diphenylprop-3-enyl acetate with dimethyl malonate. In the work of Douthwaite and co-workers[16] the catalyst mixture was filtered to remove any precipitated silver bromide. In our work, we found that filtration had little effect on the yield or ee of the reaction. Entries 1–5 indicate that the alkyl substituent on the ligand backbone has only a minor effect on the ee of the reaction. The data reveal that changing the imidazol-2-ylidene substituent has a more dramatic effect. The *N*-methyl imidazol-2-ylidene derivative (entry 6) has a similar ee to entries 1–5 but the activity is severely diminished compared to the *N*-benzyl imidazolylidene derivatives. The *N*-phenyl derivative (entry 8) gave modest results. In contrast, entry 7, involving the bulkier *N*-mesityl derivative displayed a greater activity and also gave the best ee (53%). Greater steric bulk on the imidazol-2-ylidene N-substituent is effective in increasing activity and selectivity. In the work of Douthwaite, reducing the steric bulk around the imine nitrogen, by employing imines derived from acetone, increased the enantioselectivity.[16,18] However, dimethylmethylideneamine derivatives were not accessible using our synthetic method. Here the less sterically demanding benzylideneamine derivative was tested (entry 9), however, a lower ee was observed. This may well be due to

Table 3. Asymmetric allylic alkylations



Entry	Imidazolium salt			Time (h)	Conversion[a] (%)	ee[b] (%)
	R^1	R^2	R^3			
1 **9a**	Bn	Bn	Ph	18	52	35
2 **9b**	*i*-Pr	Bn	Ph	18	83	31
3 **9c**	*i*-Bu	Bn	Ph	18	60	30
4 **9c**	*i*-Bu	Bn	Ph	87	99	40
5 **9d**	Me	Bn	Ph	18	80	33
6 **9e**	*i*-Bu	Me	Ph	18	26	38
7 **9f**	*i*-Bu	Mesityl	Ph	18	99	53
8 **9g**	*i*-Bu	Ph	Ph	18	99	7
9 **9h**	*i*-Bu	Bn	H	18	99	9

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol %), silver carbene complex (6 mol %) generated from **9** and Ag_2O were stirred for 30 min in THF and then 1,3-diphenylpropenyl acetate (1 equiv), dimethyl malonate (3 equiv) and NaH (2.9 equiv) were added.

[a] Measured by GC.

[b] Measured by ^{1}H NMR using Eu(hfc)$_3$ as a chiral shift reagent.

hydrolysis of the benzylideneamine function, the resulting aminoalkyl imidazol-2-ylidene is unlikely to chelate resulting in a loss of enantioselectivity in the reaction. The ees of our reactions are modest: it is possible that the imine nitrogen is only weakly co-ordinating and may in fact be hemi-labile. Evidence to support this comes from an attempt to synthesise palladium complexes containing a chelating ligand. Mass spectral analysis of the reaction product indicates the presence of a bis(imidazol-2-ylidene)palladium species. Related bis(iminocarbene) palladium complexes containing two bulky, C-bonded iminocarbene moieties have been isolated and characterised by Tilset and co-workers[23] This group has also demonstrated the hemi-labile nature of bulky iminocarbene ligands in DMSO by ^{1}H NMR.[24]

In conclusion, we have synthesised a small library of chiral imidazol-2-ylidene ligands by adopting a modular approach with readily available amino acids as the chiral building blocks. The ligands have shown enantioselectivity for allylic alkylation, but further modification of the ligand structure to give smaller imino-substituents and bulkier *N*-imidazol-2-ylidene substituents is likely to be required to enhance the enantioselectivity. Given the highly successful application of related imino-phosphine ligands to a wide range of catalytic asymmetric syntheses, we aim to test ligands from our library on other reactions, such as copper-catalysed conjugate addition and iridium-catalysed hydrogenation of arylalkenes.

Acknowledgements

Financial support from EPSRC is gratefully acknowledged (M.M.). The service provided by the EPRSC mass spectrometry service centre (Swansea) is also gratefully acknowledged.

Supplementary data

Supplementary data including synthetic procedures and spectroscopic characterisation are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.049.

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