Synthesis of chiral nitrogen-imidazolylidene ligands and their application to asymmetric conjugate addition and asymmetric Suzuki coupling.

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Introduction

A modular approach to the synthesis of mixed donor nitrogen-imidazolylidene ligands has been developed. The modular design means that a library of ligands can be easily prepared from small libraries of starting materials. It also allows easy optimisation of the ligand structure for specific substrates. We are interested in testing them for enantioselectivity in a variety of asymmetric processes in which related nitrogen phosphine mixed donor ligands have shown exciting potential. These include copper catalysed conjugate addition of dialkyl zinc reagents and the asymmetric Suzuki reaction. A library of imino alkyl imidazolylidene ligands have been synthesised and tested for conjugate addition. In addition a programme to synthesise amino alkyl imidazolylidene ligands has been started.

Synthesis of imino alkyl imidazolylidene ligands

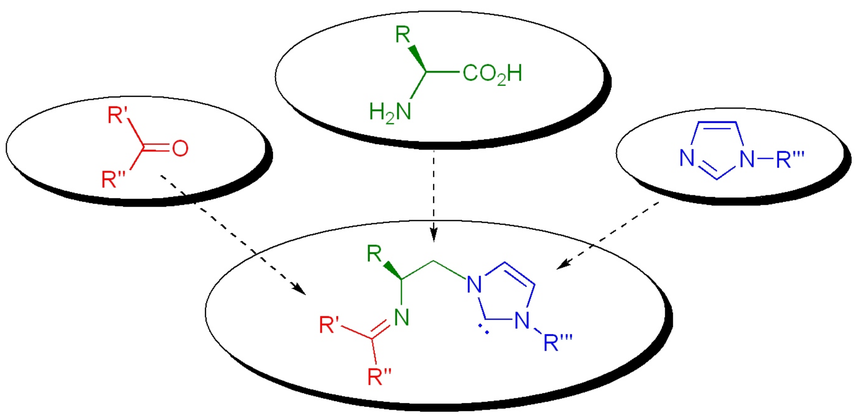
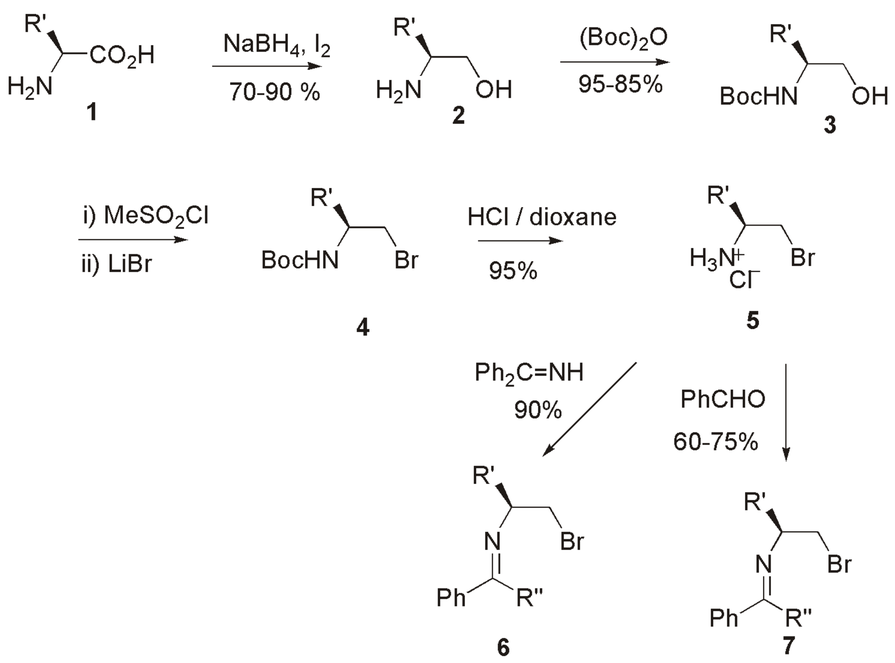


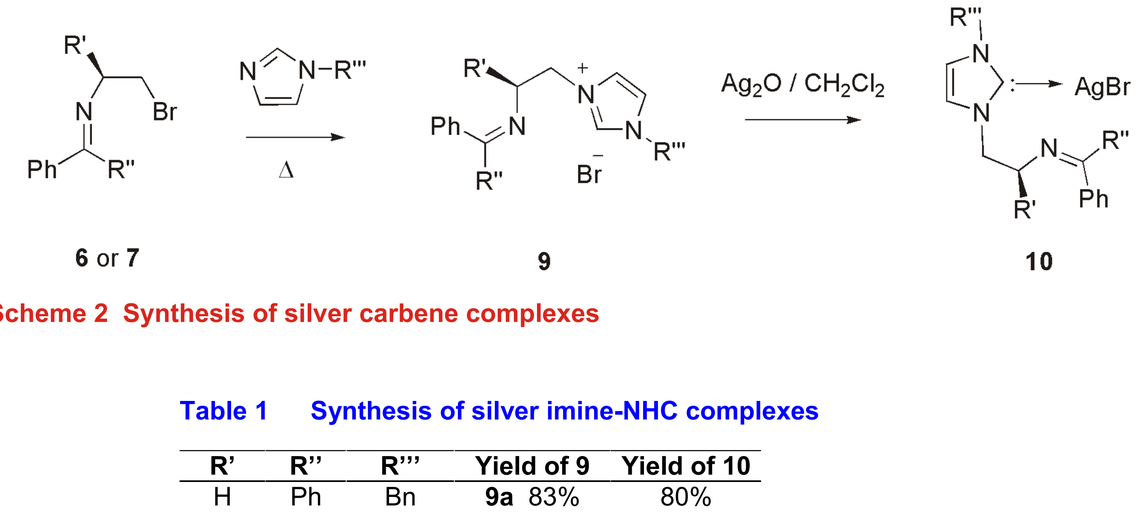
Figure 1 Modular design of iminoalkyl imidazolylidene ligands

Amino acids **1** were reduced to amino alcohols using $NaBH_4$ and I_2, N-protected and converted to the alkyl bromides **4** *via* the methane sulfonates. Deprotection with HCl in dioxane followed by condensation with benzophenone imine yields the iminoalkyl bromides **6**. Further imine derivative are accessible by condensation with aldehydes eg **7**.



Scheme 1 Synthesis of chiral iminoalkyl bromides from amino acids

Imidazolium salts have proved useful precursors to imidazolylidenes and in this case were most conveniently prepared by heating a mixture of the iminoalkyl bromide and an *N*-substituted imidazole in the absence of solvent. The crude product was triturated with diethyl ether and then recrystallised from dichloromethane and diethyl ether. Lower yields were obtained with *N*-aryl imidazoles than with *N*-alkyl imidazoles. The NHCs were prepared by deprotonation of the imidazolium salt with Ag_2O to give silver carbene complexes. Silver carbene complexes have proved efficient ligand transfer agents for generating catalytic species.



Scheme 2 Synthesis of silver carbene complexes

Table 1 Synthesis of silver imine-NHC complexes

R'	R''	R'''	Yield of 9	Yield of 10
H	Ph	Bn	**9a** 83%	80%
H	Ph	Ph	**9b** 59%	78%
i-Bu	Ph	Me	**9c** 63%	93%
i-Bu	Ph	Bn	**9d** 79%	68%
i-Bu	Ph	Ph	**9e** 25%	75%
i-Bu	Ph	Mesityl	**9f** 46%	67%
i-Bu	H	Bn	**9g** 70%	64%

Acknowledgments

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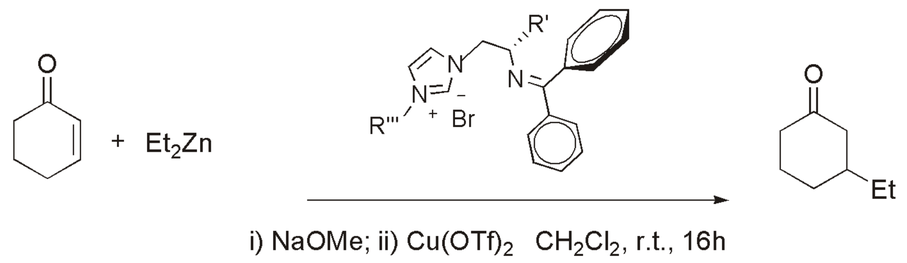
Copper Catalysed Enantioselective Conjugate Addition of Diethylzinc

The chiral iminoalkyl imidazolylidene ligands were tested oncopper catalysed enantioselective conjugate addition using copper(I) triflate. Woodward *et al* reported the first catalysed conjugate addition reaction using *N*-heterocyclic carbene(NHC) ligands.[1] This was soon followed by examples of enantioselective conjugate addition of diethyl zinc to cyclohexenone using chiral NHC ligands from the groups of Alexakis and Roland.[2,3] Some of the best results for enantioselective conjugate addition reactions have been obtained with bidentate ligands such as oxazoline–phosphine ligands of Pfaltz.[4] Arnold *et al* reported the use of chelating alkoxy-NHC ligands in copper catalysed conjugate addition and obtained e.e.s of up to 51%.[5] Maudit recently reported e.e.s of 93% for bidentate alkoxy-NHC ligands.[6]



Scheme 3 Enantioselective copper catalysed conjugate addition

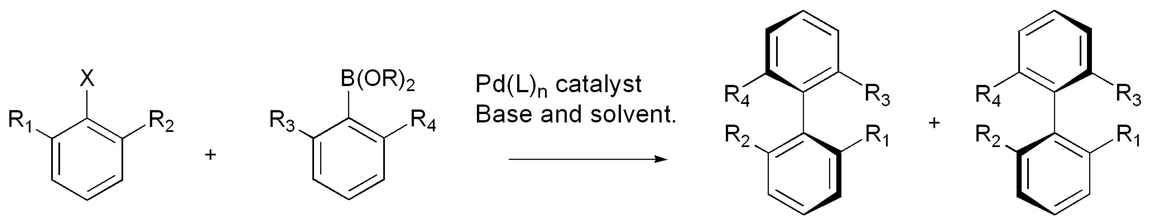
Table 2 Enantioselective copper catalysed conjugate addition

Entry	R'	R'''	Yield	ee
9h	Me	Bn	85	7
9i	Me	Ph	85	18
9j	Me	Mesityl		3
9e	i-Bu	Ph	97	3

The initial results were disappointing, with ees < 20%. However, by comparison with the work of Alexakis improved ees may be obtained at -78 C using copper carboxylates as a source of copper instead of copper triflate.[7] This work is ongoing. In addition, future work will be directed at testing aminoalkyl imidazolylidene ligand and some tridentate ligands.

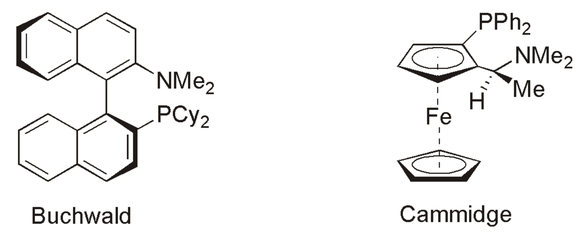
Asymmetric Suzuki Reaction

Atropisomerism in biaryls (or axial chirality) requires restricted rotation around a single bond (usually between two aryl rings with bulky ortho-substituents). Chiral biaryls are a common structural motif in many natural products and hence the interest in their synthesis. The asymmetric Suzuki is a convenient route to enantiomerically enriched biaryl units.



Scheme 4 Asymmetric Suzuki Coupling

Examples of Asymmetric Suzuki couplings have been published by both Buchwald[8] and Cammidge.[9] These studies both used phosphine ligands, the most successful of which shared one main design feature, the presence of an NMe_2 group in addition to the phosphine donor. It is thought this NMe_2 group aids the transmetallaion step in the catalytic cycle by co-ordinating to the boron on the boron reagent.



Buchwald Cammidge

Figure 2 Ligands for asymmetric Suzuki Coupling

With this in mind a design for new amine-carbene ligands related to our imine-carbene ligands has been conceived. Our aim is to synthesise amino and dialkylamino functionalised imidazolylidenes

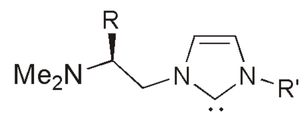
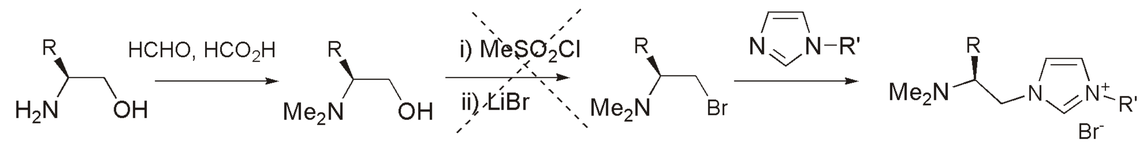


Figure 3 Ligand Targets for asymmetric Suzuki Coupling

Our initial route to dialkylaminoalkyl bromides, Scheme 5, was unsuccessful at the bromination step due to neighbouring group interference from the amine, which is not sufficiently protected. We are now exploring alternative routes to the dialkylamino carbene ligands. The aminoalkyl imidazolium salts can be easily prepared by alkylation of imidazoles with aminoalkyl halides **5**



Scheme 5 Synthesis of dialkylamino imidazolium salts

References

1. S. Woodward, P. K. Fraser, *Tetrahedron Lett.* **2001**, *47*, 2747. **2**. F. Guillen, C. L.Winn, A. Alexakis *Tetrahedron: Asymmetry* **2001**, *12,* 2083. **3.** J. Pytkowicz, S. Roland, P. Mangeney,*Tetrahedron: Asymmetry* **2001**, *12,* 2087**. 4**. G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33,* 336-345. **5.** P. L. Arnold, M. Rodden, K. M. Davis, A. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.* **2004**, 1612-1613. **6.** H. Clavier, L. Coutable, J-C. Guillemin, M. Maudit, *Tetrahedron: Asymmetry* **2005**, *16*, 921-924. **7.** A. Alexakis, C. L. Winn, F. Guillen. J. Pytkowicz, S. Roland, P. Mangeney, *Adv. Synth. Catal.* **2003**, *345*, 345-348. **8**. J. Yin, S.L Buchwald, *J. Am. Chem. Soc.* **2000**, 12051. **9.** A. N. Cammidge, K. V. L. Crépy, *Tetrahedron*, **2004**, *60*, 4377-4386.