Novel Chiral N-Heterocyclic Carbene Ligands for Copper-Catalysed Conjugate Addition

Neil A. Williams and Mahboub Merzouk
School of Chemical and Pharmaceutical Sciences, Kingston University,
Kingston upon Thames, KT1 2EE, United Kingdom

Introduction

Woodward *et al* reported the first catalysed conjugate addition reaction using *N*-heterocyclic carbene ligands.[1] This was soon followed by examples of enantioselective conjugate addition of diethyl zinc to cyclohexenone using chiral *N*-heterocyclic carbenes from the groups of Alexakis and Roland.[2,3] The initial modest e.es were subsequently improved up to 69% by the lowering the temperature to -78 ^{0}C and using copper carboxylates as the copper source.[4]

The above examples employed monodentate *N*-heterocyclic carbene ligands. However, some of the best results for enantioselective conjugate addition reactions have been obtained with bidentate ligands such as oxazoline–phosphine ligands of Pfaltz.[5] 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%.[6] Maudit recently reported e.e.s of 93% for bidentate alkoxy-NHC ligands.[7] We have recently developed chiral imine-NHC ligands accessible from α-amino acids, the synthesis of which is reported here. Given the the success of imine-phosphine and alkoxy-NHC ligands in conjugate addition of diethyl zinc to cyclohexenone we have carried out some preliminary screening. The modular design of the ligands means that a large library of ligands can be prepared, allowing optimisation of the ligand structure for specific substrates.

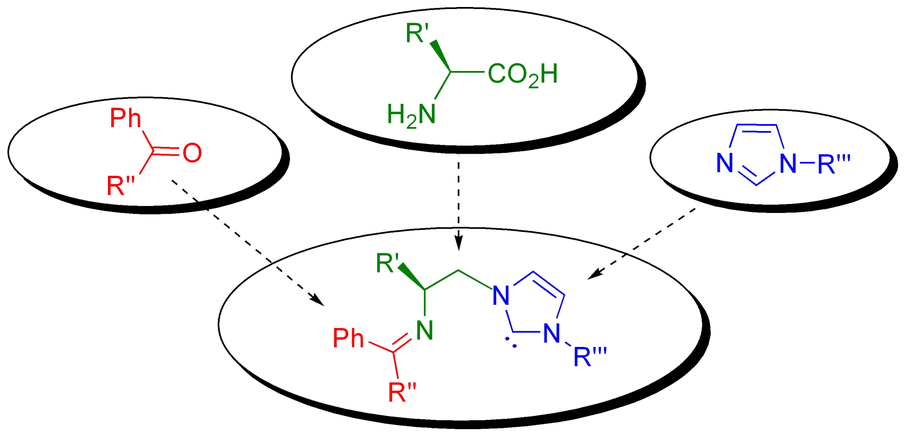
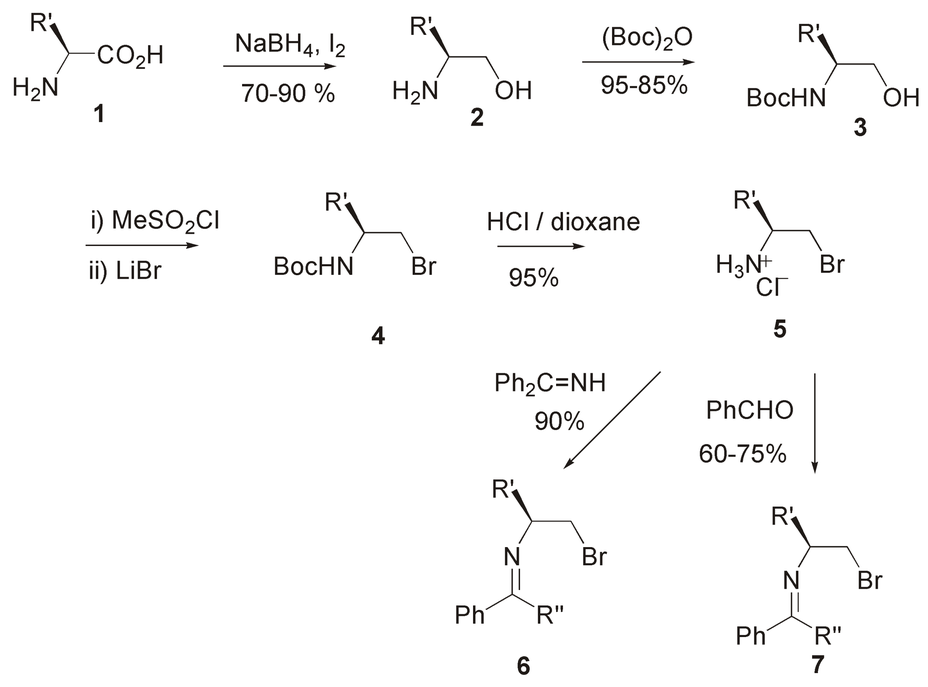


Figure 1 Modular design of iminoalkyl imidazolylidene ligands

Ligand Synthesis

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

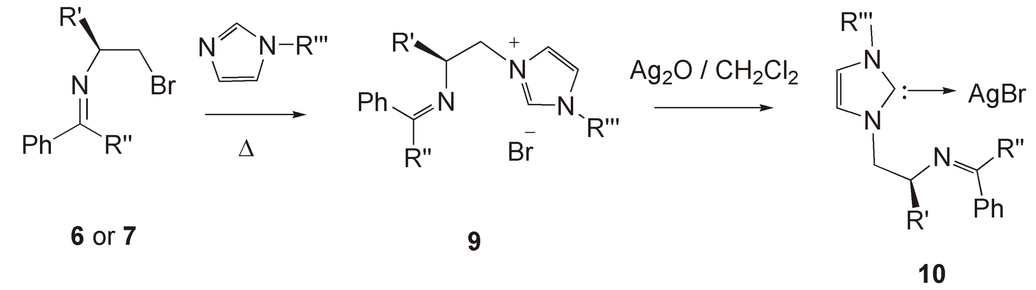
Table 1 Synthesis of iminoalkyl bromides

R'	R''	Yield of 4	Yield of 6 or 7
Me	Ph	47%	93%
i-Pr	Ph	38%	68%
i-Bu	Ph	47%	75%
Bn	Ph	42%	67%
i-Bu	H	47%	70%
H	Ph		64%

Imidazolium salts have proved useful precursors to NHCs 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, Scheme 2. Silver carbene complexes have proved efficient ligand transfer agents for generating catalytic species.

Table 2 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%



Scheme 2 Synthesis of silver carbene complexes

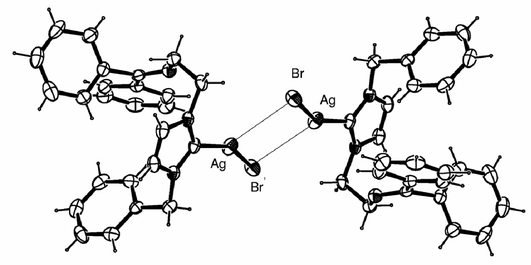
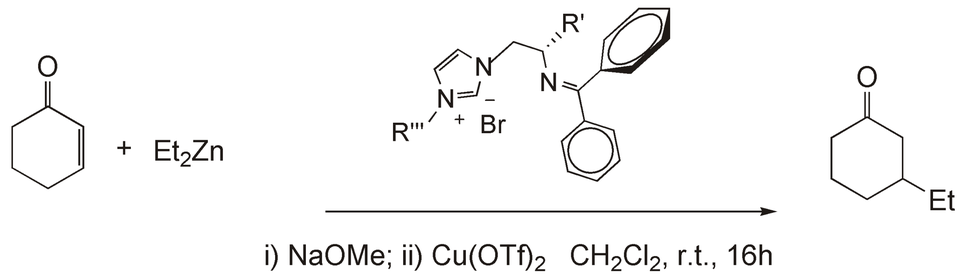


Figure 2 X-ray crystal structure of silver NHC complex 10a

The molecular structure of **10a** was determined by single crystal X-ray diffraction, indicating the monodentate co-ordination of the (imino-alkyl)imidazolylidene ligand. There are weak interactions between monomers across an inversion centre.

Copper Catalysed Enantioselective Conjugate Addition of Diethylzinc

The chiral (imino-alkyl)imidazolylidene ligands were tested on copper catalysed enantioselective conjugate addition using copper(I) triflate. It was envisaged that selectivity could be achieved via the formation of bimetallic intermediate involving a (imino-alkyl)imidazolylidene alkylcopper species in which the cyclohexenone is held in a fixed co-ordination due to the interaction of zinc with the carbonyl group and the alkyl group transferred to the copper, Figure 3, as suggested by Ferringa for phosphoramidites.



Scheme 3 Enantioselective copper catalysed conjugate addition

Table 3 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

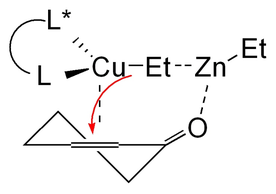


Figure 3 Posssible bimetallic intermediate in conjugate addition

Conclusion and Future Work

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. This work is ongoing. In addition, future work will be directed at testing aminoalkyl imidazolylidene ligand and some tridentate ligands

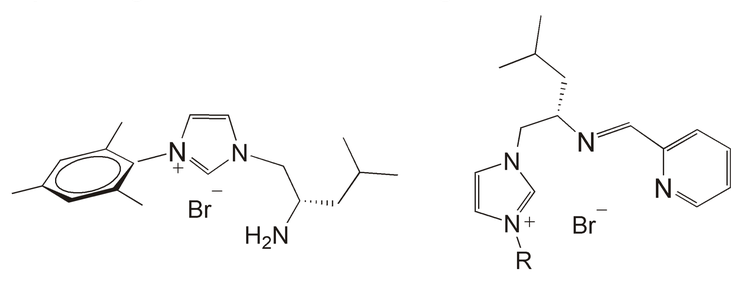


Figure 4 Future ligand targets for enantioselective conjugate addition

Acknowledgments

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