Synthesis of Amidoalkyl Imidazol-2-ylidene Ligands and Their Application to Enantioselective Copper-Catalysed Conjugate Addition

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Abstract: A small library of precursors to chiral amidoalkyl imidazol-2-ylidene ligand was synthesised via a two-step procedure starting from commercially available amino alcohols. Preliminary screening of these bidentate ligands for the enantioselective copper-catalysed conjugate addition of diethyl zinc to cyclohexenone revealed some moderate ee values. Related chiral iminoalkyl imidazole-2-ylidene ligands demonstrated much poorer enantioselectivity. The results indicate that chelation involving a covalent copper–nitrogen bond gives better selectivity than that arising from a dative copper–nitrogen co-ordination.

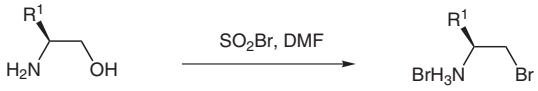
Key words: asymmetric catalysis, carbenes, copper, Michael additions

Despite the great interest in the use of N-heterocyclic carbenes (NHCs) as ligands in homogeneous catalysis,[1] their use in asymmetric catalysis, and more specifically conjugate addition, is limited compared to that of nitrogen- and phosphorus-based ligands.[2] Excellent enantioselectivities have been reported for a number of reactions using NHCs as ligands, such as hydrogenation[3], olefin metathesis,[4] and allylic alkylation.[5] Woodward et al. first showed that NHCs accelerated the rate of copper-catalysed conjugate addition.[6] This was soon followed by the first reports of the use of monodentate chiral NHCs in asymmetric copper-catalysed conjugate addition to cyclohexenone by Alexakis[7] and Roland.[8] The best results (54% ee) were obtained with a matched pair imidazolidin-2-ylidene containing exocyclic and endocyclic stereogenic centres. Improved results were obtained by using silver–carbene complexes as ligand-transfer reagents; ee as high as 93% were obtained for the addition of diethylzinc to cycloheptenone.[9] Further developments involved the synthesis of chiral, chelating hydroxyalkyl imidazolidin-2-ylidenes via a five-step procedure from commercially available β-amino alcohols.[10] These chelating ligands, containing a single exocyclic stereogenic centre, gave the best results yet seen for conjugate addition to cyclohexenone using NHCs (89% ee). Screening of the alkoxide ligands, which contain a stereogenic centre on the NHC ring backbone, produced modest levels of enantioselectivity.[11] Silver(I) complexes of heterobidentate ligands, containing an NHC group coupled and an alcohol or amine moiety have been structurally characterised.[11] Copper–NHC complexes have been successfully applied to the catalysis of other organic reactions.[12]

In light of these results, we report the synthesis of amidoalkyl imidazol-2-ylidene ligand precursors in two steps from commercially available β-amino alcohols and a preliminary evaluation of their performance in copper-catalysed conjugate addition of diethylzinc to cyclohexenone. A comparison with related iminoalkyl imidazol-2-ylidenes is also presented.

The aim was to develop a short route for the synthesis of a small library of chiral ammoniumalkyl imidazolium salts that would serve as precursors to bidentate amidoalkyl imidazol-2-ylidenes.

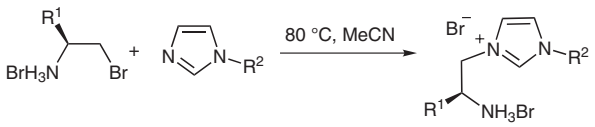
β-Amino alcohols **1** were converted into the aminoalkyl bromide hydrobromide salts **2** in high yields by stirring with thionyl bromide and DMF in cyclohexane for 16 hours, according to the method of Jung (Equation 1).[13] The amino group enhances the rate of bromination and the reaction proceeds with retention of configuration. The salts are conveniently isolated from the reaction by filtration. Aminoalkyl bromide hydrobromides were coupled to N-substituted imidazoles **3** to give ammoniumalkyl imidazolium salt derivatives **4** (Equation 2). The salts were most conveniently obtained by heating the reactants in acetonitrile under reflux for 16 hours. After the volatiles



1a R = *i*-Bu
1b R = Bn

2a 85%
2b 55%

Equation 1 Synthesis of chiral aminoalkyl bromide hydrobromide



2a,**b** **3**

4a R^1 = *i*-Bu, R^2 = Me 40%
4b R^1 = *i*-Bu, R^2 = Bn 37%
4c R^1 = *i*-Bu, R^2 = Ph 21%
4d R^1 = *i*-Bu, R^2 = Mes 20%
4e R^1 = Bn, R^2 = Bn 32%

Equation 2 Synthesis of chiral aminoalkyl imidazolium salts

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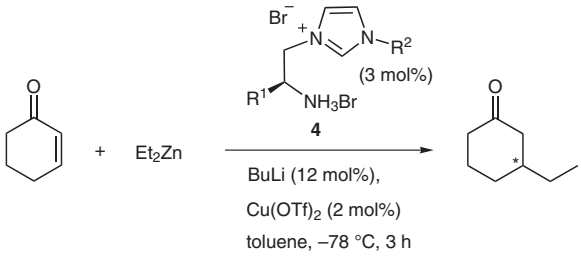
were removed under vacuum, the residues were recrystallised from acetonitrile and diethyl ether.

The potential of amidoalkyl imidazol-2-ylidenes, derived from ammoniumalkyl imidazolium salt precursors, as ligands for enantioselective copper-catalysed conjugate addition was investigated. The addition of diethylzinc to cyclohexenone was chosen as the test reaction. The copper(II) amidoalkyl imidazol-2-ylidene catalyst was generated by adding more than three equivalents of *n*-butyllithium in hexanes to a toluene solution of ammoniumalkyl imidazolium salt **4** and $Cu(OTf)_2$ at –78 °C. Two equivalents of base are required to deprotonate the ammonium group to give an amido group and a further equivalent is required to generate the carbene from the imidazolium salt. A 2:3 copper-to-ligand ratio was employed, as used by Mauduit et al.[10] for alkoxy imidazolidin-2-ylidenes. After stirring at –78 °C for 30 minutes, an internal standard (dodecane), diethylzinc, and then cyclohexenone were added. Under these conditions the reaction is complete after three hours. Results of some initial ligand screening are presented in Table 1. Reactions were carried out in duplicate. Enantioselectivities were determined by chiral GC using a Supelco Alpha-dex 220 column.

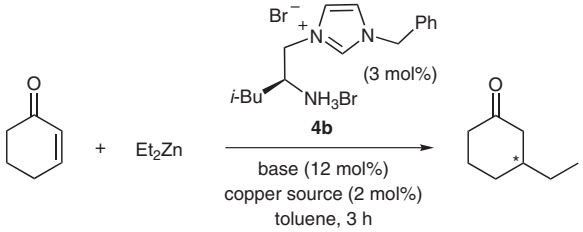
Table 1 Evaluation of Ligands **4a–e** for Enantioselective Copper-Catalysed Addition of Diethyl Zinc to Cyclohexenone



Ligand	R^1	R^2	Conv. (%)	ee (%)
4a	*i*-Bu	Me	48	12 (*S*)
4b	*i*-Bu	Bn	98	61(*S*)
4c	*i*-Bu	Ph	72	9 (*S*)
4d	*i*-Bu	Mes	77	7 (*S*)
4e	Bn	Bn	87	28 (*S*)

The nature of the N-substituent (R^2) has a profound effect on the enantioselectivity of the reaction. The N-benzyl derivative gave a significantly higher ee than the smaller methyl derivative and the N-aryl derivatives. This differs from the results observed for alkoxy imidazolidin-2-ylidenes, where mesityl derivatives generally gave the highest ee. However, N-benzyl derivatives did give higher enantioselectivities than ligands bearing an N-phenyl substituent.[10b] Hoveyda[14] and Gade[15] have also observed dramatic effects on ee for copper-catalysed enantioselective allylic substitution and rhodium-catalysed asymmetric hydrosilylation by varying the N-substituents on heterobidentate NHC ligands. One of the attractive design features of our ligands is that the stereogenic centre is β to the NHC nitrogen and fairly close to the metal centre. The amidoalkyl imidazol-2-ylidene **4b** with the stereogenic centre β to the NHC nitrogen gave better results than the analogous alkoxy NHC, 61% compared with 53% and 17%.[11] However, Mauduit et al. obtained superior results with ligands containing the stereogenic centre α to the NHC nitrogen and hence further away from the metal centre, suggesting that a substituent next to the chelating group induces a sizeable steric hindrance to enantiocontrol of the addition. Changing the alkyl group at the stereogenic centre of the amino side chain of the ligand precursors **4**[17] has a substantial influence on enantioselectivity. Replacing the isobutyl group with a benzyl group results in the ee being reduced from 61% to 28%. This is consistent with a substituent next to the chelating amido group having an influence on the enantiocontrol of the reaction. In comparison, Mauduit noted that varying the alkyl substituent for ligands in which the stereogenic centre is further removed from the chelating group had only a minor effect on enantioselectivity.

Table 2 Evaluation of Ligands **4b** for Enantioselective Copper-Catalysed Addition of Diethyl Zinc to Cyclohexenone

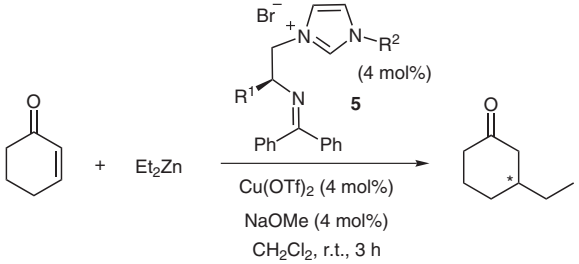


Copper source	Base	Temp (°C)	Conv. (%)	ee (%)
$Cu(OTf)_2$	BuLi	–78	98	61 (*S*)
$Cu(OTf)_2$	BuLi	20	94	48 (*S*)
$Cu(OTf)_2$	DBU	–78	93	31 (*S*)
$Cu(OAc)_2$	BuLi	–78	88	38 (*S*)

Results of some attempts to optimise enantioselectivity using **4b** are presented in Table 2. A lower enantioselectivity is observed at higher temperature (20 °C). This is different to the behaviour observed for alkoxy NHC,[10] where higher ee were obtained at 20 °C, but similar to that reported for other NHC systems.[7] Studies on copper-catalysed conjugate addition using NHC-based ligands have shown that enantioselectivity is very sensitive to temperature, solvent, substrate structure, copper source, and base. This is attributed to the formation of different types of copper and metal alkyl aggregates, leading to the possibility of a number of different mechanisms operating. An organic base, DBU, was tested as an alternative base to BuLi with ligand **4b**; it gave 93% conversion but a reduced ee of 31%. Use of copper acetate as an alternative copper source with **4b** also resulted in a lower ee (38%).

Chiral iminoalkyl imidazolium salts **5** have been previously synthesised and evaluated as ligand precursors for palladium-catalysed allylic substitution.[16] A number of these ligands were screened for copper-catalysed conjugate addition of diethylzinc to cyclohexenone, the results are presented in Table 3. For these ligands 4 mol% of catalyst with 4 mol% of sodium methoxide as a base and a reaction temperature of 20 °C were the most efficacious conditions. The ligands were shown to be active towards conjugate addition but only **5d** gave a significant ee. An ee of only 8% was obtained when BuLi was used as a base with **5d**. Again the difference in performance could be due to the formation of different types of copper and metal–alkyl aggregates.

Table 3 Evaluation of Ligands **5a–f** for Enantioselective Copper-Catalysed Addition of Diethylzinc to Cyclohexenone



Ligand	R^1	R^2	Conv. (%)	ee (%)
5a	*i*-Bu	Bn	88	3
5b	*i*-Bu	Ph	97	2
5c	Me	Bn	78	7
5d	Me	Ph	85	18
5e	Me	Mes	98	3
5f	Bn	Ph	92	2

The superior results observed for **4** suggest that the formation of a covalent metal–nitrogen bond, which is envisaged for **4**, is more conducive to stereoinduction than a dative metal–nitrogen bond that is expected for **5**. Similar observations have been made for alkoxy NHC, where protecting the hydroxyl group with a *tert*-butyldimethylsilyl group to prevent covalent bonding, resulted in reduced enantioselectivity.[10] Therefore, we speculate that a copper species with a chelating ligand (Figure 1), is a key intermediate in obtaining enantiocontrol.

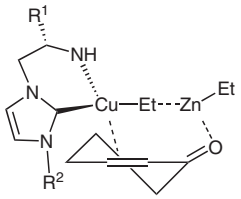


Figure 1 Possible copper intermediate with chelating ligand

In conclusion, the synthesis of new class of chiral amidoalkyl imidazol-2-ylidenes, via a simple two-step procedure from commercially available amino alcohols, has been achieved. Preliminary results indicate that the alkyl group at the stereogenic centre and the N-alkyl/aryl substituent have an effect on enantioselectivity. Comparisons between imino- and amino-based ligands suggest that covalent bonding of the nitrogen group is critical for significant enantioselectivity. Further optimisation of the reaction conditions should realise an improvement on the enantioselectivities reported so far. Testing on additional organic substrates is also planned. The synthesis of additional ligands, informed by the results obtained and facilitated by our conveniently simple route is ongoing. Further variation of R^2 and the use of chiral dihydroimidazoles to introduce additional stereogenic centres are expected to generate more selective ligands.

Acknowledgment

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(17) **Experimental and Spectroscopic Data for Ligand Precursors 4a–e**

Compound **4a**: 1-methylimidazole (5 mmol, 0.4 g) and (*S*)-1-bromo-2-amino-4-methylpentane hydrobromide (5 mmol, 1.3 g) were dissolved in anhyd MeCN (50 mL) and heated to reflux for 20 h under a nitrogen atmosphere. On cooling, a white solid precipitated and was filtered and dried under vacuum; yield 40% (0.68 g). ^{1}H NMR (400 MHz, D_2O): δ = 0.91 (3 H, d, ^3J = 6.6 Hz), 0.95 (3 H, d, ^3J = 6.6 Hz), 1.50–1.64 (2 H, m), 1.70–1.80 (1 H, m), 3.85 (1 H, m), 3.91 (3 H, s), 4.48 (1 H, dd, ^2J = 15 Hz, ^3J = 7.6 Hz), 4.57 (1 H, dd, ^2J = 15 Hz, ^3J = 5 Hz), 7.56 (2 H, m), 8.90 (1 H, s). ^{13}C NMR (100 MHz, D_2O): δ = 21.2, 21.9, 23.6, 36.3, 38.8, 49.5, 50.8, 122.9, 124.8, 137.2. Mp 242–244 °C. HRMS: *m/z* calcd for [M – 2 Br – H]$^+$ 182.1652; found: 182.1651. Anal. Calcd (%): C, 35.01; H, 6.17; N, 12.25. Found: C, 34.68; H, 6.13; N, 12.13.

Compound **4b**: 1-benzylimidazole (8 mmol, 1.26 g) and (*S*)-1-bromo-2-amino-4-methylpentane hydrobromide (5 mmol, 1.3 g) were dissolved in anhyd MeCN (50 mL) and heated to reflux for 20 h under a nitrogen atmosphere. On cooling, a white solid precipitated and was filtered and dried under vacuum; yield 37% (0.79 g). ^{1}H NMR (400 MHz, D_2O): δ = 0.86 (3 H, d, ^3J = 6.5 Hz), 0.90 (3 H, d, ^3J = 6.5 Hz), 1.40–1.69 (3 H, m), 3.79–3.88 (1 H, m), 4.45 (1 H, dd, ^2J = 15 Hz, ^3J = 7.2 Hz), 4.52 (1 H, dd, ^2J = 15 Hz, ^3J = 5.5 Hz), 5.41 (2 H, s), 7.45 (5 H, m), 7.59 (2 H, m), 8.97 (1 H, s). ^{13}C NMR (100 MHz, D_2O): δ = 21.1, 21.8, 23.8, 38.9, 49.2, 50.9, 53.5, 123.3, 123.6, 129 (2 C), 129.6 (2 C), 129.7, 133.2, 136.7; mp 238.5–240 °C. HRMS: *m/z* calcd for [M – 2 Br – H]$^+$: 258.1968; found: 258.1965.

Compound **4c**: 1-phenylimidazole (5 mmol, 0.72 g, 0.63 mL) and (*S*)-1-bromo-2-amino-4-methylpentane hydrobromide (5 mmol, 1.3 g) were dissolved in anhyd MeCN (50 mL) and heated to reflux for 20 h under a nitrogen atmosphere. The solvent was removed under vacuum and the residue dissolved in MeCN (3 mL), and then layered with Et_2O to precipitate a white solid. The solid was recrystallised from hot EtOH; yield 21% (0.42 g). ^{1}H NMR (400 MHz, D_2O): δ = 0.94 (3 H, d, ^3J = 6.4 Hz), 0.97 [3 H, d, $CH(CH_3)_2$, ^3J = 6.4 Hz], 1.57–1.70 (2 H, m), 1.72–1.82 (1 H, m), 3.93–3.99 (1 H, m), 4.59 (1 H, dd, ^2J = 15.0 Hz, ^3J = 7.9 Hz), 4.71 (1 H, dd, ^2J = 15.0 Hz, ^3J = 4.8 Hz), 7.63 (5 H, m), 7.79 (1 H, s), 7.99 (1 H, s), 9.45 (1 H, s). ^{13}C NMR (100 MHz, D_2O): δ = 21.1, 21.8, 23.8, 38.9, 49.5, 51.2, 122.5 (2 C), 123, 123.5, 130.5 (2 C), 130.6, 137.2. Mp 260–264 °C. HRMS: *m/z* calcd for [M – 2 Br – H]$^+$ ($C_{15}H_{22}N_3$): 244.1808; found: 244.1808. Anal. Calcd (%): C, 44.47; H, 5.72; N, 10.37. Found: C, 44.25; H, 5.70; N, 10.22.

Compound **4d**: 1-mesitylimidazole (5 mmol, 0.93 g) and (*S*)-1-bromo-2-amino-4-methylpentane hydrobromide (5 mmol, 1.3 g) were dissolved in anhyd MeCN (50 mL) and heated to reflux for 20 h under a nitrogen atmosphere. The solvent was removed under vacuum and the residue dissolved in MeCN (3 mL), which was layered with Et_2O to precipitate a white solid. The solid was recrystallised from hot EtOH, yield 20% (0.36 g). ^{1}H NMR (400 MHz, D_2O): δ = 0.88 (3 H, d, ^3J = 6.6 Hz), 0.93 (3 H, d, ^3J = 6.4 Hz), 1.47 (1 H, m), 1.61–1.73 (2 H, m), 2.02 (3 H, s), 2.03 (3 H, s), 2.31 (3 H, s), 3.92–3.97 (1 H, m), 4.62 (1 H, dd, ^2J = 14.7 Hz, ^3J = 6.4 Hz), 4.70 (1 H, dd, ^2J = 14.7 Hz, ^3J = 6.0 Hz), 7.13 (2 H, s), 7.68 (1 H, m) 7.87 (1 H, m), 9.18 (1 H, s). ^{13}C NMR (100 MHz, D_2O): δ = 16.6 (2 C), 20.3, 21.0, 21.9, 23.8, 39.1, 48.9, 51.5, 123.7, 125.3, 129.5 (2 C), 130.7, 134.8 (2 C), 137.7, 141.8. Mp 264–264.5 °C. HRMS: *m/z* calcd for [M – 2 Br – H]$^+$: 286.2283; found: 286.2277. Anal. Calcd (%): C, 48.34; H, 6.54; N, 9.39. Found: C, 47.70; H, 6.51; N, 9.15.

Compound **4e**: 1-benzylimidazole (8 mmol, 1.26 g) and (*S*)-1-bromo-2-amino-3-phenylpropane hydrobromide (5 mmol, 1.48 g) were dissolved in MeCN (30 mL) and heated to reflux for 20 h. The mixture was then allowed to cool to r.t. and the product precipitated as a white solid. This was isolated by filtration and dried under vacuum; yield 32% (0.74 g). ^{1}H NMR (400 MHz, D_2O): δ = 3.03 (1 H, dd, ^2J = 14.2 Hz, ^3J = 8 Hz), 3.12 (1 H, dd, ^2J = 14.2 Hz, ^3J = 6.6 Hz), 4.10–4.40 (1 H, m), 4.40–4.55 (2 H, m), 5.26 (2 H, s), 7.20–7.50 (12 H, m), 8.72 (1 H, s). ^{13}C NMR (100 MHz, D_2O): δ = 36.9, 50.7, 51.7, 53.4, 123.0, 123.3, 128.0, 129.2 (2 C), 129.3 (2 C), 129.4 (2 C), 129.6 (2 C), 129.7, 132.9, 134.1, 136.4. Mp 246–248 °C. HRMS: *m/z* calcd for [M – 2 Br – H]$^+$ 292.1808; found: 292.1808.