Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 921–924

New bidentate alkoxy-NHC ligands for enantioselective copper-catalysed conjugate addition

Hervé Clavier, Ludovic Coutable, Jean-Claude Guillemin and Marc Mauduit*

UMR CNRS 6052, Laboratoire de Synthèses et Activations de Biomolécules, Ecole Nationale Supérieure de Chimie de Rennes, Institut de Chimie de Rennes, 35700 Rennes, France

Received 9 December 2004; accepted 10 January 2005

Abstract—Chiral alkoxy-imidazolinium salts are easily available via a five-step procedure starting from β-aminoalcohols. This new family of alkoxy-*N*-heterocyclic carbene (NHC) precursors is shown to be highly active in the enantioselective copper-catalysed conjugate addition to cyclic enones. Complete conversion with low catalyst loading and good enantiomeric excesses up to 93% were obtained at room temperature.

1. Introduction

Since the first isolation and characterisation of stable *N*-heterocyclic carbenes (NHC) by Arduengo 13 years ago,[1] NHC's have become extremely popular ligands in organometallic reactions. Indeed, many complexes bearing NHC's have been used for several synthetic transformations including the C–C and C–N cross-coupling[2] and metathesis reactions.[3] Several applications of chiral NHC in asymmetric catalysis have been reported with moderate to high enantiomeric excess.[4]

In the area of copper-catalysed reaction, Alexakis and co-workers[5] have described the synthesis of chiral NHC precursors **1** derived from C_2 symmetric diamines and their use in the enantioselective copper-catalysed conjugate addition.[6] Recently, Okamoto and co-workers[7] have used the same ligands **1** in copper catalysed allylic alkylations and obtained moderate enantioselectivity. In the development of chelating alkoxy-NHC ligands,[8a] Arnold et al. have reported the isolation of the first chiral copper(II) alkoxy-NHC complex based on salt **3**[8b] and obtained moderate enantioselectivity in the copper conjugate addition of diethylzinc to cyclohexenone (up to 51% ee). At the same time, Hoveyda and co-workers[9] described a chiral bidentate alkoxy-NHC precursor **2** derived from axial symmetric aminohydroxybinaphthalene and obtained high enantioselectivities (up to 98% ee) in copper catalysed allylic alkylations.

Herein, we report the synthesis of a new class of chiral alkoxy-imidazolinium salts **4** (Fig. 1) derived from commercially available β-aminoalcohols. These salts have been evaluated as chiral bidentate NHC ligand precursors and lead to an efficient copper(II)-alkoxy-NHC catalyst for the enantioselective copper-catalysed conjugate addition to cyclic enones.

2. Results and discussion

A simple procedure for synthesising alkoxy-imidazolinium salts **4a–f** from enantiopure aminoalcohols is described in Scheme 1.[10] Ethyloxalylchloride **5** is condensed onto substituted aniline to give the corresponding oxanilinic diethylester **6**. Treatment with the desired aminoalcohol in refluxing dichloromethane provided oxalamide **7** in pure form. After $LiAlH_4$ reduction, the resulting diamine **8** was treated with anhydrous HCl followed by condensation with trimethylorthoformate to provide the desired imidazolinium chloride. The salt was easily purified by a simple anion exchange to give the corresponding potassium hexaflurophosphate alkoxy-imidazolinium salts **4a–d** in pure form with high overall yields (59% to 76%). Importantly, all salts are air stable and easy to handle and can be synthesised on a multigram scale without further purification.

* Corresponding author. Tel.: +33 2 23 23 81 12; fax: +33 2 23 23 81 08; e-mail: marc.mauduit@ensc-rennes.fr

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.01.015

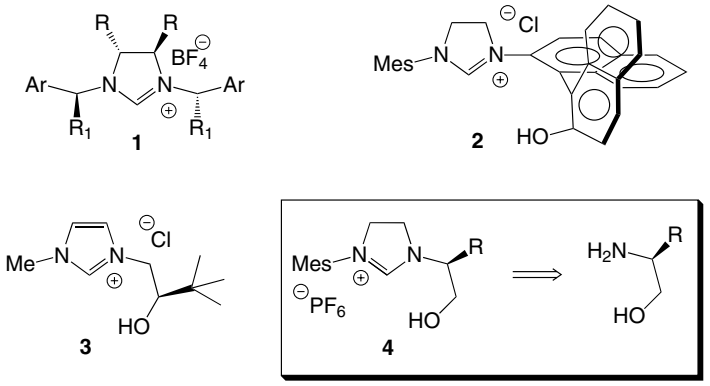
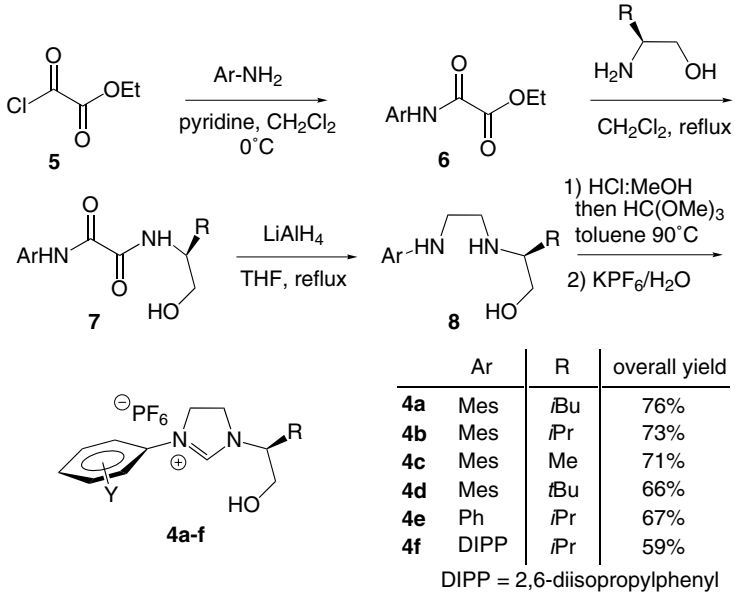


Figure 1.



	Ar	R	overall yield
4a	Mes	*t*Bu	76%
4b	Mes	*i*Pr	73%
4c	Mes	Me	71%
4d	Mes	*t*Bu	66%
4e	Ph	*i*Pr	67%
4f	DIPP	*i*Pr	59%

DIPP = 2,6-diisopropylphenyl

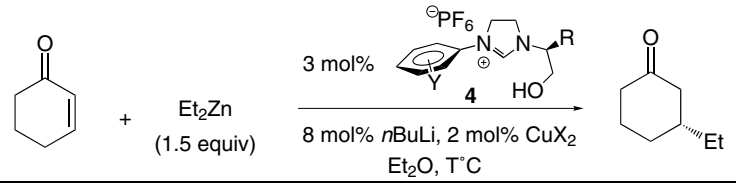
Scheme 1. Synthesis of alkoxy-imidazolinium salts.

We then evaluated their potential in the enantioselective copper-conjugate addition of diethylzinc to cyclohexenone (Table 1). When formed in situ the desired copper(II)-alkoxy-NHC catalyst, and 2 equiv of *n*-butyllithium were used to produce the carbene ligand and generate the alkoxylate. Under these conditions, using 3 mol% of imidazolinium salt **4a** as ligand and 2 mol% of copper(II) triflate ($Cu(OTf)_2$) as precatalyst, complete conversion was obtained in diethyl ether after 4 h at −50 °C with 75% ee (entry 1). Replacement of the precatalyst by a more soluble copper complex, such as copper(II) ethylacetoacetate [$Cu(eaa)_2$] accelerates the reaction allowing the addition to be carried out at a lower temperature (−78 °C) with complete conversion in 4 h (entry 2). Curiously, in this case, the enantioselectivity decreased to 70% ee. We then decided to perform the reaction at a higher temperature. Whereas at −25 °C, the enantioselectivity increased to 78% ee (entry 3), 86% ee was observed at room temperature with a complete conversion after only 30 min (entry 4). Similar enantioselectivity was obtained when the reaction was performed at 40 °C (entry 5). Hoveyda and co-workers[11] and Krauss and Leighton[12] have recently observed a similar unusual relationship between temperature and enantioselectivity in the copper-catalysed enantioselective conjugate addition using chiral phosphine ligands.

Replacement of the mesityl unit by phenyl (imidazolinium **4e**) or the 2,6-(*i*-Pr)-C_6H_3 group (imidazolinium **4f**) produced a dramatic effect on the enantioselectivity (54% and 29%, respectively, entries 9 and 10). Finally, the influence of the alkyl group bearing the imidazolinium alkoxy-side chain was examined. Except for the methyl group (imidazolinium **4c**, 79% ee, entry 7), we observed only 1–2% difference in the enantioselectivity between the more hindered *tert*-butyl group (**4d**, 87% ee, entry 8) and the other alkyl groups (**4a**, **b** entries 4 and 6). With the aim of developing efficient and inexpensive ligands, this result becomes important because valine and leucine α-aminoacid are less expensive than *tert*-leucine.

The hydroxymethylene side chain in the NHC ligand is probably crucial for the enantiocontrol of the conjugate

Table 1. Optimisation of reaction conditions and ligand

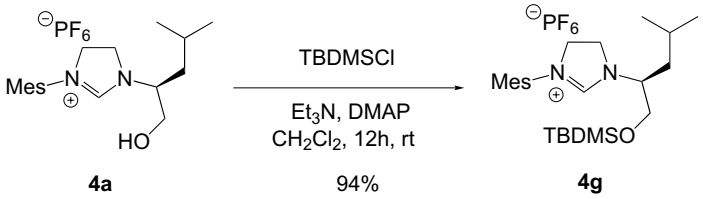


Entry	Ligand	CuX_2	Temp (°C)	Time	Yield[a]	Ee (%)[b]
1	**4a**	$Cu(OTf)_2$	−50 °C	4 h	>99	75 (*R*)
2	**4a**	$Cu(eaa)_2$	−78 °C	4 h	>99	70 (*R*)
3	**4a**	$Cu(OTf)_2$	−25 °C	4 h	>99	78 (*R*)
4	**4a**	$Cu(OTf)_2$	RT	30 min	>99	86 (*R*)
5	**4a**	$Cu(OTf)_2$	40 °C	30 min	>99	84 (*R*)
6	**4b**	$Cu(OTf)_2$	RT	30 min	>99	85 (*R*)
7	**4c**	$Cu(OTf)_2$	RT	30 min	>99	79 (*R*)
8	**4d**	$Cu(OTf)_2$	RT	30 min	>99	87 (*R*)
9	**4e**	$Cu(OTf)_2$	RT	30 min	>99	54 (*R*)
10	**4f**	$Cu(OTf)_2$	RT	30 min	>99	29 (*R*)

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis (Lipodex E).

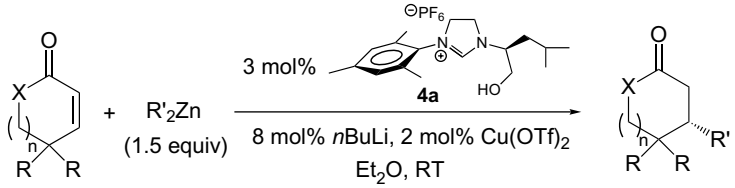
addition. To prove this, we protected the hydroxyl function by a *tert*-butyldimethylsilyl group. The protected imidazolinium **4g** was isolated in excellent yield from imidazolinium **4a** under standard conditions (Scheme 2). Its use in conjugate addition of diethylzinc to cyclohexenone at room temperature involved an important loss of enantioselectivity to 24% ee. The requirement of the hydroxyl function for high enantioselectivity strongly suggests that these alkoxy-NHC ligands have served as a LX bidentate ligand.

Having established the optimal conditions for the use of these salts in the conjugate addition, we then evaluated the activity of the ligand **4a** with other dialkylzinc and cyclic enones (Table 2). In the case of a more hindered enone, such as 4,4-dimethylcyclohexenone, complete conversion was obtained after 12 h at room temperature with 93% ee (entry 2). 2-Cyclohexenone may be alkylated with diisopropylzinc in complete conversion after 1 h with 79% ee (entry 3). Addition of Et_2Zn on 2-cycloheptenone (entry 4) was achieved in 1 h at room temperature with 90% ee. Lastly, we tried to alkylate the α,β-unsaturated lactone with Et_2Zn (entry 5) and obtained total conversion after 1 h. However, only moderate enantioselectivity was observed (72% ee).



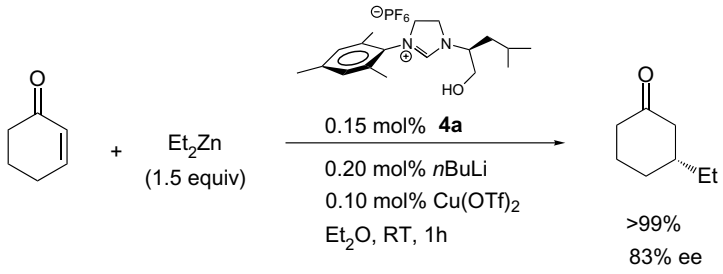
Scheme 2.

Table 2. Enantioselective copper-catalysed conjugate addition of dialkylzinc to cyclic enones



Entry	*n*	R	R′	X	Time	Yield[a]	Ee (%)[b]
1	1	H	Et	CH_2	30 min	>99	85 (*R*)
2	1	Me	Et	CH_2	12 h	>99	93 (*R*)
3	1	H	*i*-Pr	CH_2	1 h	>99	79 (*R*)
4	2	H	Et	CH_2	30 min	>99	90 (*R*)
5	1	H	Et	O	1 h	>99	72 (*R*)

[a] Determined by GC analysis.
[b] Determined by chiral GC analysis (Lipodex E).



Scheme 3. Optimisation of catalytic process.

To optimise the catalytic process, the catalyst loading was decreased from 2% to 0.10 mol% in the conjugate addition to 2-cyclohexenone. Total conversion was observed after 1 h without significant loss of enantioselectivity (Scheme 3).

3. Conclusion

In conclusion, this work shows the design of a new family of chiral alkoxy-NHC ligands easily synthesised in a five-step procedure. High reactivity and good enantioselectivity were obtained at room temperature in the copper-conjugate addition with low loading of catalyst (up to 0.10 mol%). A study of their use in conjugate additions with acyclic substrates is currently under progress. Replacement of the alkoxy group by other chelating groups (such as S-Ar or PPh_2) for cross-coupling and hydrogenation reactions will be also studied and reported in due course.

Acknowledgements

This work was supported by the CNRS and the Ministère de la Recherche et de la Technologie (Grant to H.C.). We thank Professor A. Alexakis for helpful discussion.

References

1. Arduengo, A. J., III; Harlow, R. L.; Kline, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 361.
2. For recent reviews, see: (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290; (b) Hillier, A. C.; Nolan, S. P. *Platinium Metals Rev.* **2002**, *46*, 50.
3. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
4. For recent reviews, see: (a) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619; (b) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951; For recent examples, see: (c) Gade, L. H.; Cesar, V.; Bellemin-Laponnaz, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014; (d) Ma, Y.; Song, C.; Ma, C.; Chai, Q.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871; (e) Bappert, E.; Helmchen, G. *Synlett* **2004**, 1789.
5. (a) Guillen, F.; Winn, C. L.; Alexakis, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2083; (b) Pytkowics, J.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2001**, *12*, 2087; (c) Alexakis, A.; Winn, C. L.; Guillen, F.; Pytkowics, J.; Roland, S.; Mangeney, P. *Adv. Synth. Catal.* **2003**, *345*, 345.
6. For a review on enantioselective Cu-catalysed conjugate addition, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221; For the first use of NHC ligand in Cu-catalysed conjugate addition, see: (b) Fraser, P. K.; Woodward, S. *Tetrahedron Lett.* **2001**, *42*, 2747.
7. Tominiga, S.; Oi, Y.; Kato, T.; An, D. K.; Okamoto, S. *Tetrahedron Lett.* **2004**, *45*, 5585.
8. (a) Arnold, P. L.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2001**, 2340; (b) Arnold, P. L.; Rodden, M.; Davis, K. M.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun.* **2004**, 1612.
9. Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 11130.
10. During the preparation of this paper, a similar synthesis using aminophenol was reported: Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004**, *23*, 3105.
11. (a) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779; (b) Hoveyda, A. H.; Hird, A. W.; Kacprzynski, M. *Chem. Commun.* **2004**, 1779.
12. Krauss, I. J.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3201.