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# Design and synthesis of new bidentate alkoxy-NHC ligands for enantioselective copper-catalyzed conjugate addition

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## Abstract

A new family of chiral alkoxy-*N*-heterocyclic carbene (NHC) ligands has been designed for the enantioselective copper-catalyzed conjugate addition of dialkylzincs to enones. These new bidentate NHC ligands were synthesized in high overall yields using a five-step procedure starting from commercially available β-aminoalcohols. Influence of the temperature, base, solvent and copper source were studied in order to optimize the stereoselectivity of the addition. High reactivity and excellent enantioselectivity were obtained at ambient temperature with a range of cyclic enones and dialkylzinc. Addition to acyclic enones has also been studied.

*Keywords:* Chiral *N*-heterocyclic carbene; Alkoxy-imidazolinium salts; Asymmetric catalysis

## 1. Introduction

During the last decade, the chemistry of carbene has gained importance in the catalysis area through the use of carbene species as spectator ligands for transition-metal centers. The spectacular advance in this area is due to the remarkable efforts and strategies developed by chemists to build stable and isolable carbene species [1]. *N*-Heterocyclic carbenes (NHC) are the most well known example of this phenomenon [2]. Indeed, since the first isolation and characterization of stable NHC **1** by Arduengo et al. [3] in 1991 (see Fig. 1), many complexes containing NHC have been synthesized and used in important organometallic transformations including many C–C and C–N cross-coupling [4] and the popular metathesis reactions [5]. These new NHC complexes showing an exceptional catalytic activity associate to a better thermal stability than complexes containing phosphine units, allow many synthetic transformations requiring harsher conditions. Use of NHCs in enantioselective catalysis is a natural extension in this field and many complexes containing chiral NHC unit have been synthesized and used in stereoselective catalysis with moderate to high enantiomeric excess [6] (see Fig. 2).

In the copper-catalyzed area, Arduengo has developed a few NHC–copper complexes in 1993 but the catalytic properties of these complexes were not investigated [7]. It was not until 1999 that Woodward et al. could demonstrated that a copper complex containing an Arduengo-type carbene **1** accelerates considerably the copper-catalyzed addition of diethylzinc to cyclohexenone [8]. In light of these results, Alexakis and Mangeney [9] have reported the use of chiral NHCs in the copper-catalyzed conjugate addition [10] in 2001. Designed a $C_2$-symmetry strategy, the chiral NHC precursors **2** (Fig. 2) gave low to good enantioselectivities in the alkylation of diethylzinc to cyclic enones (up to

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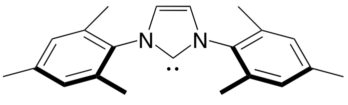
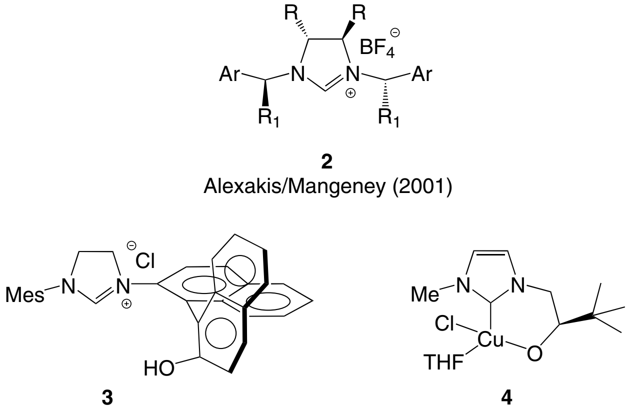


**1**

Fig. 1.



**2**

Alexakis/Mangeney (2001)

**3**

Hoveyda (2002/2004)

**4**

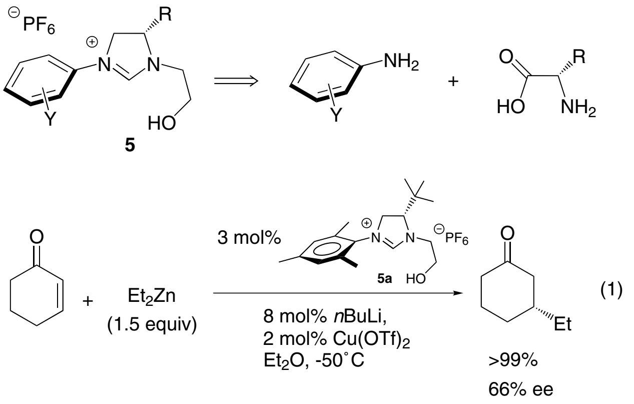
Arnold (2004)

Fig. 2.

93% ee). Recently, Okamoto et al. [11] have used the same ligands **2** in copper-catalyzed allylic alkylations, but moderate enantioselectivities were obtained (up to 70% ee).

In 2002, Hoveyda et al. [12] described a very efficient chiral bidentate NHC precursor **3** based on an axial symmetric aminohydroxybinaphtalene, which was first used to form a chiral Ru-complex for asymmetric olefin metathesis (up to 96% ee). Hoveyda has recently studied its use in copper-catalyzed allylic alkylations and obtained high enantioselectivities (up to 98% ee) showing the power of this new class of chelating NHCs. At the same time, Arnold et al. [13] isolated the first chiral chelating alkoxy-NHC–copper (II) complex **4** and use it in the copper conjugate addition of diethylzinc on cyclohexenone. However, moderate enantioselectivity was obtained (up to 51% ee).

Recently, we have reported the first synthesis of chiral alkoxy-imidazolinium salts **5** [14] (Scheme 1) derived from amino acid in a six-step procedure. These salts have been first used as chiral derivatizing agents for ee determination of chiral carboxylate. Based on the work of Woodward and Alexakis and Mangeney, we decided to evaluate their potential as new chelating alkoxy-NHC ligands in the enantioselective copper-conjugate addition of diethylzinc to cyclohexenone (Eq. (1)). The desired copper (II)-alkoxy-NHC catalyst is formed in situ by adding two equivalents of *n*-butyllithium to the alkoxy-imidazolinium salt **5** in the presence of the copper salt $Cu(OTf)_2$ at −50 °C in diethylether. Under these conditions, the conjugate addition of diethylzinc to 2-cyclohexenone is finished within 4 h. However, low to moderate enantioselectivities were obtained, reaching 66% ee with imidazolinium salt **5a** derived from *tert*-leucine [15].

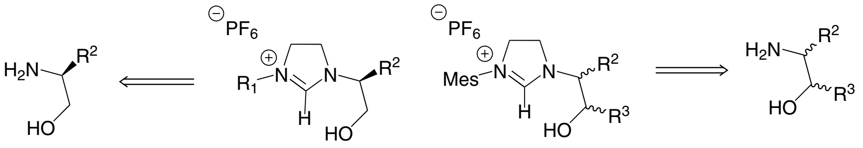


**5**

Scheme 1. Use of chiral alkoxy-imidazolinium salts **5** in enantioselective 1,4-addition.

The high reactivity but modest enantioselectivity obtained with these salts **5** led us to place the chiral center on the alkoxy side chain near the imidazolinium ring. As reported in a preliminary study [16], the alkoxy-imidazolinium salts **6** (Fig. 3) lead to efficient copper (II)-alkoxy-NHC catalysts for the enantioselective copper-catalyzed conjugate addition to 2-cyclohexenone.

Herein, we report an extension of this new class of chiral chelating alkoxy-imidazolinium salts through the synthesis of several other salts **6** and **7** (Fig. 3) easily accessible from commercially available β-aminoalcohols and various substituted anilines or alkylamines. A complete study of these new ligands in the enantioselective conjugate addition to various cyclic enones and also other Michael acceptors involving acyclic enones and nitroalkenes was performed. Influence of the aryl and alkyl groups of the ligand in the stereoselective induction and the reaction conditions (effect of the temperature, the base, the solvent and the copper source) were fully studied for optimization of the enantioselective addition.



**6** **7**

Fig. 3.