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Communication

Synthesis of new C_1-symmetric bis(oxazoline) ligands with a chelating sidearm for stereoselective Mukaiyama aldol condensations

Simonetta Orlandi [a], Maurizio Benaglia [a,*], Gianmaria Dell'Anna [a], Giuseppe Celentano [b]

[a] *Centro di Eccellenza CISI, Dipartimento di Chimica Organica e Industriale, via Golgi 19, I-20133 Milano, Italy*
[b] *Istituto di Chimica Organica, Facolta' di Farmacia, Universita' degli Studi di Milano, via Golgi 19, I-20133 Milano, Italy*

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Abstract

Novel C_1-symmetric bis(oxazoline) ligands with a secondary binding sidearm were prepared in enantiomerically pure form in good yields, in only four steps starting from commercially available reagents. These new chiral ligands were tested in the enantioselective Mukaiyama aldol condensation between the trimethylsilyl keteneacetal of methyl isobutyrate and a non-chelating substrate such as benzaldehyde to afford the product in up to 55% ee.

Keywords: Chiral bis-oxazolines; Copper complexes; Enantioselective catalysis; Mukaiyama aldol condensation; Chelation

1. Introduction

The versatility of chiral bis(oxazolines) to act as ligands in a variety of catalytic enantioselective transformations is well recognised [1]. For example, copper (II) complexes of C_2-symmetric ligand type **1** were shown to be efficient catalysts for several stereoselective C–C bonds formation reactions [2] (see Scheme 1).

However, with these chiral catalytic systems very high enantioselectivities are obtained only by employing substrates which can participate in catalyst chelation. The strict requirement of using a bidentate substrate that contributes in determining a well-defined geometry of the catalyst/substrate complex represents an obvious limitation to the methodology's generality.

The idea to introduce an extra chelating element into the chiral ligand has been recently explored and has led to the development of tris(oxazoline) [3] ligand types **2** (see Scheme 1). The reasons beyond the preparation of this class of molecules were basically to build a deeper chiral concave pocket around the metal center and to synthesize a more stable catalytic system. Alternatively tridentate bis(oxazolinyl)-type ligands have been designed by introducing a donor atom into the link connecting two chiral oxazoline rings [4]. Among the different structures it is worth mentioning Kanemasa's ligand **3** [5], Zhang's bis(oxazolinyl-methyl)amine **4** [6] and specially the "pybox" ligands **5** first developed by Nishiyama [7] (Scheme 1).

However it must be noted that also these tridentate catalytic systems usually promote high enantioselective C–C bond formation reactions with bidentate chelating structures.

2. Results and discussion

In order to overcome this substrate limitation we decided to explore a different approach. The idea was to synthesize a Evan's bis(oxazoline) type **1** ligand but with a chelating sidearm, to afford a structure of type **6**; the new ligand should bind the copper (II) ion following the coordination behaviour of the C_2-symmetric analogs whose complexes geometry has been well studied [8] (see Scheme 2). The active catalytic species has now only one coordination site

* Corresponding author. Tel.: +39 0 25031 4171; fax: +39 0 25031 4159.
E-mail address: maurizio.benaglia@unimi.it (M. Benaglia).

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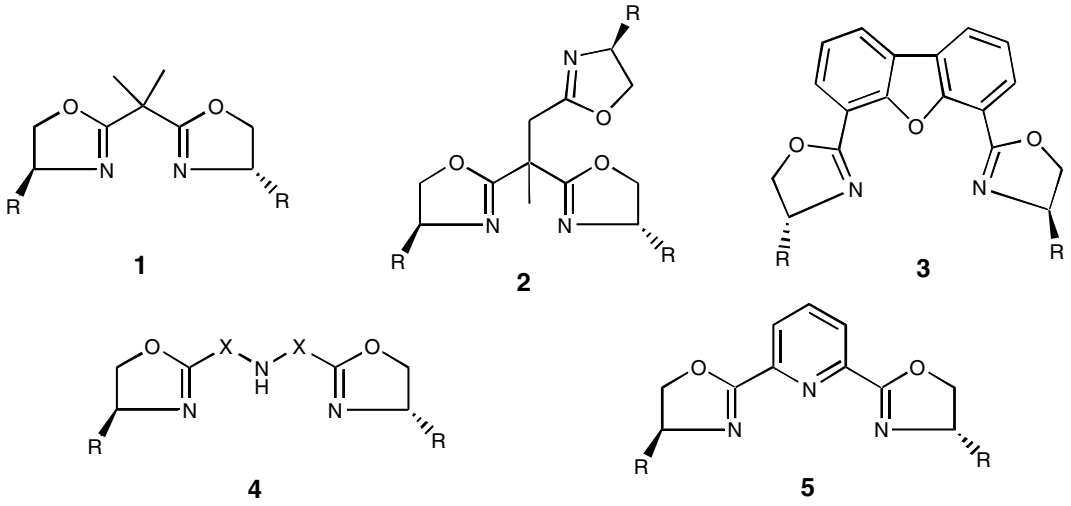


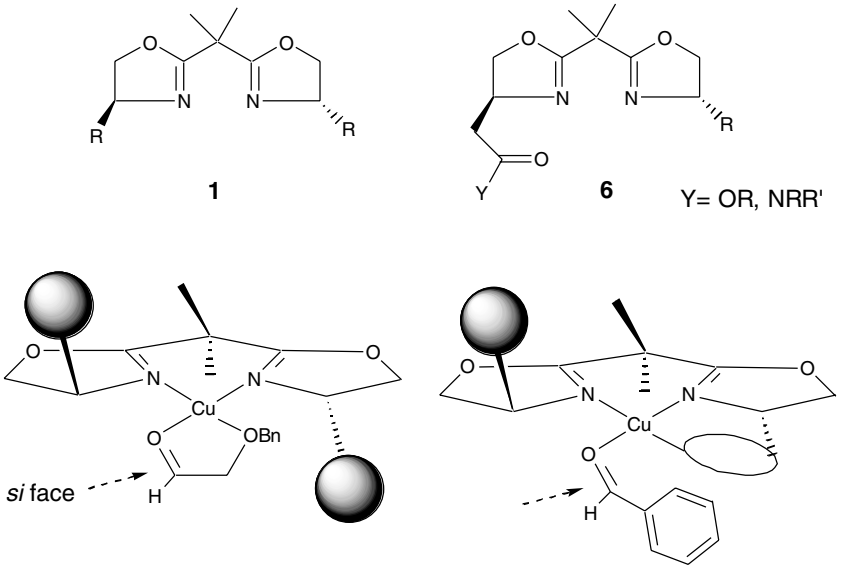
Scheme 1. Oxazoline-type ligands in asymmetric catalysis.

for the substrate that should be attacked by the reagent under the stereocontrol exerted by the substituents at the stereocentres of the oxazoline moieties [9].

Here, we wish to report the synthesis of new C_1-symmetric bis(oxazoline) ligands with a secondary binding element to be employed in promoting reactions that do not require the use of bidentate substrates. Preliminary studies on the use of these novel chiral ligands in the Mukaiyama aldol condensation of trimethylsilyl keteneacetal of methyl isobutyrate with benzaldehyde will be also described.

The synthesis of the new ligands follows the classical route that involves the reaction of a dimethyl malonic acid derivative with amino-alcohols to give a bis-amide intermediate that is converted into bis-oxazoline (see Scheme 3). In our synthesis the first step is the EDC- promoted condensation of dimethyl malonic acid monomethylester **7** with (*S*)-phenyl glycinol or (*S*)-*t*-leucinol to afford the amide **8** or **9**, in 81% and 85% yield, respectively. In order to build the oxazoline ring bringing the chelating sidearm we decided to employ the amino alcohol **10**, easily prepared in only three steps from the commercially available 4-benzyl-(*S*)-aspartic acid [10]. After hydrolysis of esters **8** and **9**, the corresponding carboxylic acid amides were condensed to the amino-alcohol **10** to give the corresponding dissimetric bis amides **12** and **11** basically in quantitative yields, as pure compounds without the need of chromatographic purification [11].

Several methodologies were attempted for the closure of bis-amides to the corresponding bis(oxazolines) **13** and **14** [12]. Finally, best results were obtained by reacting **11** and **12** with methansulfonyl chloride and triethylamine to convert them in the corresponding mesylate derivatives which were treated in situ with triethylamine and a catalytic amount of DMAP to afford bis(oxazolines) **13** and



Scheme 2. Novel bis(oxazoline) with a chelating sidearm.