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Application of tartarate derived bidentate bioxazolines in enantioselective addition of terminal alkynes to imines

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ABSTRACT

A series of highly efficient and inexpensive bioxazoline ligands were easily synthesized from tartaric acid and further explored for enantioselective addition of terminal alkynes to imines in combination with copper(II) salts. This is the first ever report showing application of bidentate bioxazoline ligands in the synthesis of propargylamines with good enantioselectivity.

Chiral propargylamines are one of the most important synthetic building blocks for the preparation of nitrogen heterocycles,[1] natural products,[2] and biologically active molecules.[3] Addition of metal acetylide to imine is the convenient and powerful method for the preparation of propargylamines and their derivatives.[4]

Enantioselective synthesis of propargylamines was achieved by Li and co-workers[5] using 1,3-bis(oxazolin-2-yl)pyridine ligands (pybox, **1**)[6] (Fig. 1) and copper salts led to the development of a three-component reaction of aldehyde, amine, and alkyne. Apart from pybox ligands, several catalysts were reported for the synthesis of chiral propargylamines.[7] Application of bidentate bis(oxazoline) ligands (**2**), which are privileged ligands to induce good enantioselectivity in propargylamine synthesis was not successful (<5% ee).[5,8] Similarly ligand **4** which is derived from tartaric acid and amenable to modification was completely overlooked by the research community because of its inability to promote mechanis-

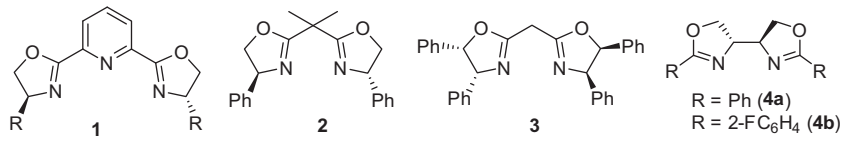
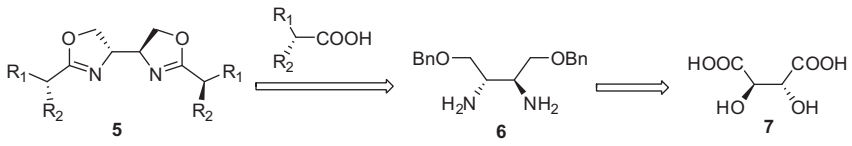


Figure 1. Structure of various bis(oxazoline) ligands.



Scheme 1. Retrosynthesis of bidentate bioxazoline.

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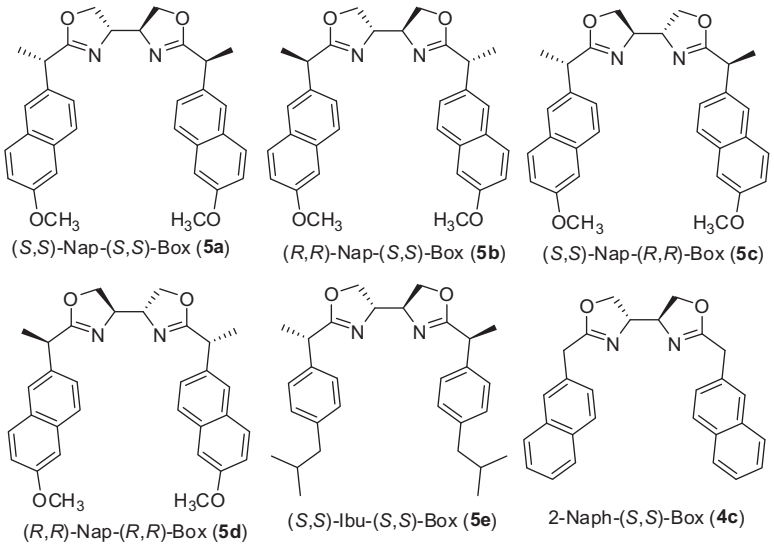


Figure 2. Structure of tartarate derived bioxazoline ligands.

tically different asymmetric transformations with good enantioselectivity.[9]

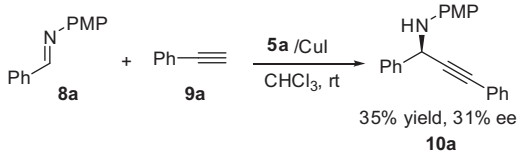
In our lab we re-designed tartaric acid derived bioxazoline ligand (**4**) by introducing another stereogenic center as shown in ligand **5** near the coordination sphere (Scheme 1). This modification mitigated the poor chirality transfer of ligand **4**, in asymmetric transformations.

The application of newly developed bioxazoline ligands **5** (Fig. 2) in asymmetric catalysis was successfully demonstrated in copper catalyzed enantioselective Henry reaction and good enantioselectivities with a broad range of substrates were achieved.[10] We applied the same ligand to achieve asymmetric allylic alkylation (AAA) with >95% ee.[11] Since the amino acid derived bidentate bis(oxazolines) **2** and **3** are inefficient in catalyzing enantioselective synthesis of propargylamines, we decided to explore the efficiency of tartaric acid derived bidentate bioxazoline **5** for the same synthesis. Only unnatural and highly expensive amino acid (*tert*-leucine, phenylglycine) derived pybox ligands **1** are responsible for very good enantioselectivity to synthesize propargylamines, whereas our catalytic system was prepared using inexpensive and naturally available tartaric acid. This makes tartarate derived bidentate bioxazoline **5** as an alternative in terms of price and availability to achieve enantioselective synthesis of chiral propargylamines.

An initial exploration of enantioselective propargylamine synthesis was carried out using ligand **5a** which was identified as a suitable ligand for the asymmetric Henry reaction. The reaction of phenylacetylene (**9a**) and imine **8a** was performed in chloroform ($CHCl_3$) at 25 °C using 5 mol % CuI and 10 mol % of **5a**. The desired product **10a** was obtained with 35% yield and 31% enantiomeric excess after 72 h (Scheme 2).

This superiority of ligand **5a** over bis(oxazoline) ligands **2** & **3** encouraged us to optimize the reaction conditions further to increase enantioselectivity of the product.

In an attempt to enhance the efficiency of the reaction, we carried out the reaction in one pot manner using benzaldehyde (**11a**),



Scheme 2. Copper catalyzed enantioselective addition of alkyne to imine.

4-methoxyaniline (**12a**), and phenylacetylene (**9a**) under similar reaction conditions. Propargylamine **10a** with 22% enantioselectivity in low yield (30%) was obtained (Scheme 3). Apart from low yield, very low enantioselectivity was also observed when compared with the addition of alkyne to imine **8a** (Scheme 2). Use of cyclic amines such as piperidine and pyrrolidine instead of anilines led to the formation of 1,3-diynes (Scheme 3).[12] These two demerits forced us to optimize reaction conditions by using the preformed imine **8a**.

Other Cu(I) and Cu(II) pre-catalysts such as Cu(OTf), CuCl, CuBr, $Cu(PF_6)(CH_3CN)_4$, $Cu(OTf)_2$, $Cu(ClO_4)_2{\cdot}6H_2O$, and $Cu(OAc)_2{\cdot}H_2O$ were investigated in this reaction in order to choose a suitable metal partner (Table 1). Except $Cu(OAc)_2{\cdot}H_2O$, every other copper salts catalyzed the formation of propargylamine **10a** in moderate to good yields. Among them $Cu(ClO_4)_2{\cdot}6H_2O$ fared better in inducing enantioselectivity (43%) at ambient temperature (Table 1 entry 8). Further attempts to enhance enantioselectivity by reducing the temperature to 0 °C were not fruitful. Even after 2 days, no formation of propargylamine **10a** was observed (Table 1, entry 9).

5 mol % of $Cu(ClO_4)_2{\cdot}6H_2O$ with 10 mol % of **5a** at ambient temperature furnished the target product **10a** with better enantioselectivity (81% yield, 52% ee) (Table 1, entry 10). After identification of $Cu(ClO_4)_2{\cdot}6H_2O$ as a suitable metal partner and 25 °C as an optimal reaction temperature we went ahead to choose the appropriate reaction medium (Table 2).

Under the same reaction conditions optimized previously, a profound solvent effect on the yield and the enantioselectivity was observed. No product was isolated when the reaction was carried out in acetonitrile, acetone, and dimethoxyethane (DME) (Table 2, entries 4, 6, and 9). Reaction in dichloroethane, diethyl ether, and tetrahydrofuran (THF) contrived only a trace amount of propargylamine **10a** in TLC visualization and hence no attempts were made to isolate the product (Table 2, entries 3, 8, and 10). Up to 70% yield was obtained with toluene, *tert*-butyl methyl ether (TBME), and dimethylformamide (DMF) as a reaction medium but very poor enantioselectivity was observed (up to 17%) in these cases (Table 2, entries 5, 7, and 11). Excellent conversion (up to 87%) was observed only in chlorinated solvents such as dichloromethane and chloroform. Enantioselectivity observed in chloroform was better (52%) (Table 2, entry 1) than of enantioselectivity in dichloromethane (29%) (Table 2, entry 2). Thus chloroform was identified as the most suitable reaction medium for the enantioselective synthesis of propargylamines using ligand **5a**.