Pure Appl. Chem., Vol. 84, No. 7, pp. 1651–1657, 2012.
http://dx.doi.org/10.1351/PAC-CON-11-10-16

Chiral 2,6-bis(5',5'-diphenyloxazoline)pyridine as an efficient ligand for asymmetric catalysis*

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Abstract: A modified tridentate pyridine bisoxazoline (pybox) ligand, possessing *gem*-diphenyl substitution at C-5 of the oxazoline rings, has been proved to be a very efficient ligand for enantioselective allylic oxidation, one-pot three-component synthesis of propargylamines, and Friedel–Crafts alkylation of various aromatic compounds. We have shown that a 5',5'-diphenyl grouping in the oxazoline rings of chiral ligands is crucial for higher reaction rates as well as enhanced enantioselectivity.

Keywords: allylic oxidation; asymmetric catalysis; 2,6-bis(5',5'-diphenyloxazoline)pyridine; enantioselective reaction; Friedel–Crafts reaction; propargylamine; pyridine-bisoxazoline *gem*-diphenyl (pybox-diph).

INTRODUCTION

Chiral transition-metal complexes play a significant role in the synthesis of optically pure molecules [1]. Among various catalysts used, especially, bisoxazoline-metal complexes play a vital role in asymmetric catalysis because of their easy accessibility and modular nature [2]. Nishiyama first demonstrated the potential of the pyridine-bisoxazoline (pybox) **1** ligand for asymmetric catalysis [3], and it has since received much attention for this purpose [4]. For the past several years, our group has been involved in designing new catalysts for various enantioselective reactions. While working on enantioselective cyclopropanation and allylic oxidation of olefins catalyzed by chiral pybox-metal complexes, we modified the Nishiyama's pybox ligand **1** into ligand **2** having *gem*-diphenyl substitution at the C-5 position of oxazoline ring (henceforth abbreviated as pybox-diph) (Fig. 1) [5,6]. This ligand **2** has been successfully used in enantioselective allylic oxidation of olefin [6], allylation of aldehydes [7], propargylation of imines [8], and Friedel–Crafts alkylation of indoles [9] and pyrroles [10]. In this paper, we

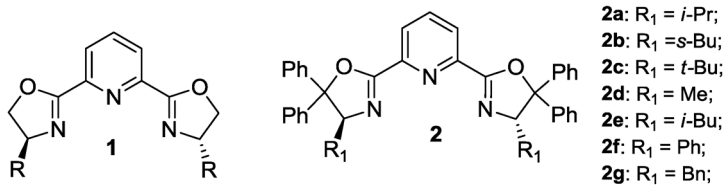

Fig. 1 Pyridine bisoxazoline ligand (pybox) and modified pyridine bis(oxazoline) ligands.

Pure Appl. Chem.* **84, 1543–1667 (2012). A collection of invited papers based on presentations at the 23rd International Conference on Heterocyclic Chemistry (ICHC-23), Glasgow, UK, 31 July–4 August 2011.

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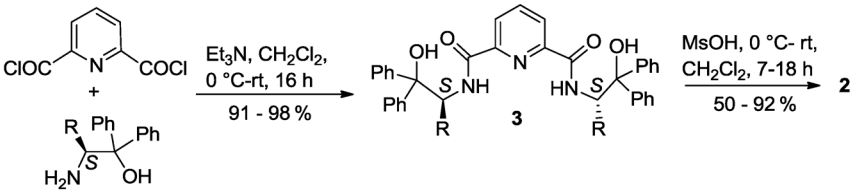
outline a full account of our studies in the area of enantioselective reactions catalyzed by pybox-diph-metal complexes.

SYNTHESIS OF PYBOX-DIPH LIGAND

The pybox-diph ligands can easily be synthesized in two steps, viz. by coupling of pyridine 2,6-dicarbonyl chloride and chiral β-amino alcohols followed by an intramolecular condensation promoted by methanesulfonic acid as shown in Scheme 1. The ligand was purified by column chromatography followed by recrystallization from ether (Scheme 1).



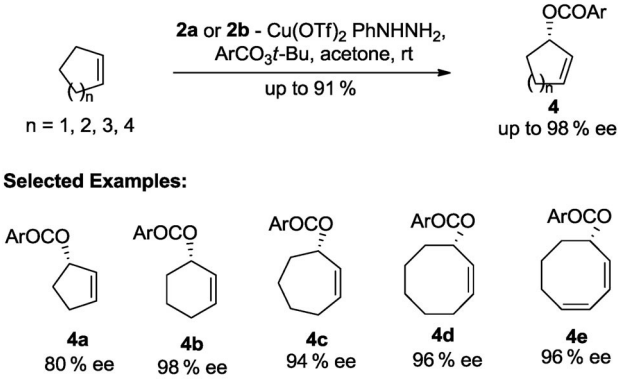
Scheme 1 Synthesis of pybox-diph ligands.

PYBOX-DIPH LIGAND IN ENANTIOSELECTIVE CATALYSIS

Enantioselective allylic oxidation of olefins

While using copper complex of pyridine 2,6-bis(4'-isopropyl-5',5'-diphenyloxazoline) **2a** ligand in enantioselective allylic oxidation of olefins [6a], we found that the Cu(I) species prepared by the in situ reduction of Cu(II) with phenylhydrazine in acetone, is more efficient than the commercially available Cu(I) salts such as $(CuOTf)_2 \cdot PhH$ [6b]. The reduction of Cu(II) to Cu(I) by phenylhydrazine and phenylhydrazone has been confirmed by electron paramagnetic resonance (EPR) study.

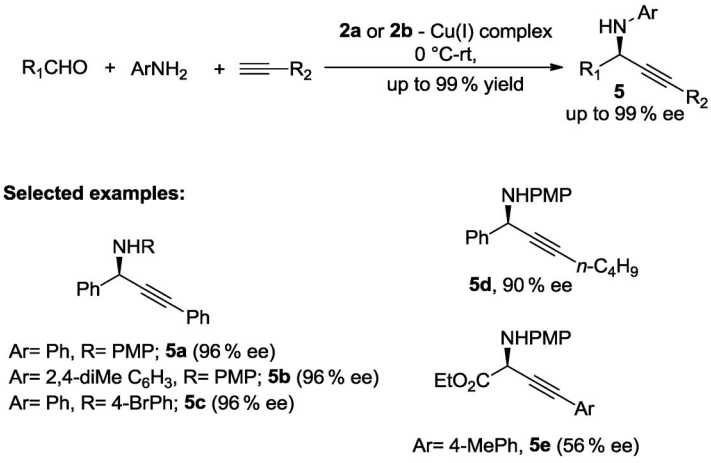
The pybox-diph ligand **2a** catalyzed the reaction with a faster reaction rate and provided better enantioselectivity than the pybox ligand **1**, showing the beneficial effect of *gem*-diphenyl groups at oxazoline rings. A catalyst loading of just 5 mol % led to the product with excellent enantioselectivities [6c]. Also, we have shown that the enantioselectivity of the product can be further improved by the use of different peresters. We have achieved a maximum of 98 % ee for cyclohexene, 96 % ee for cyclooctene and 1,3-cyclooctadiene, and 94 % ee for cycloheptene by choosing a unique combination of a chiral ligand and perester at room temperature (Scheme 2).



Scheme 2 Enantioselective allylic oxidation catalyzed by pybox-diph-Cu(II) complexes.

Enantioselective one-pot three-component synthesis of propargylamines

The potential of the ip-pybox-diph ligand was further explored by its use in the enantioselective one-pot three-component synthesis of propargylamines. 5–10 mol % Cu(I)-complex of ip-pybox-diph **2a** or sb-pybox-diph **2b** furnished various propargylamines from a variety of aldehydes, amines, and terminal alkynes with excellent yields (up to 99 %) and enantioselectivities (up to 99 % ee). It is noteworthy that aliphatic alkynes also afforded good yields and enantioselectivities [8a]. The reaction was then extended to synthesis of β,γ-alkynyl-α-amino esters by three-component coupling of glyoxylate, amine, and terminal alkynes. Using 10 mol % Cu(II)-complex of sb-pybox-diph **2b**, a maximum of 56 % ee was obtained (Scheme 3) [8b].

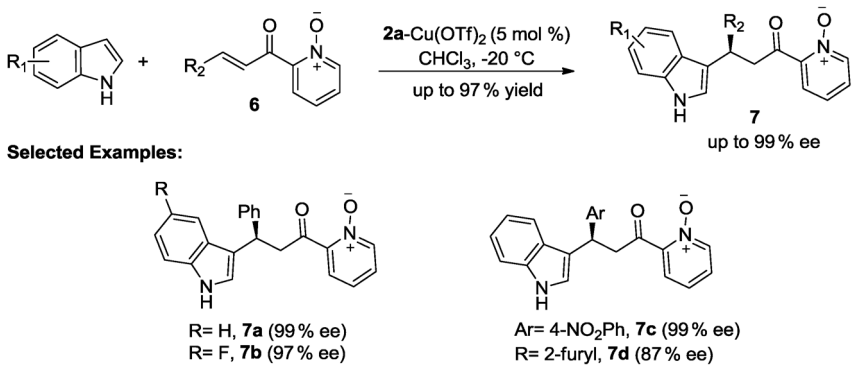


Scheme 3 Enantioselective one-pot three-component synthesis of propargylamines.

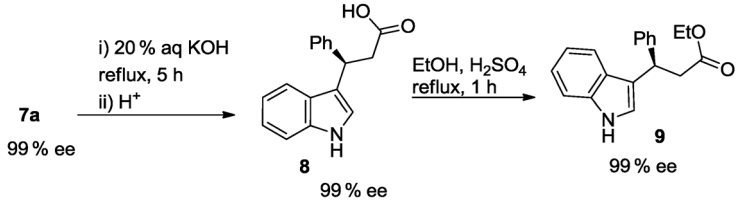
Enantioselective Friedel–Crafts alkylation reaction

Recently, we investigated pybox-diph-metal complexes-catalyzed enantioselective Friedel–Crafts alkylation reactions. Initially, the enantioselective Friedel–Crafts alkylation of indole was explored. A variety of indoles underwent pybox-diph **2a**-Cu(II) catalyzed enantioselective Friedel–Crafts alkylation with 2-enoylpyridine *N*-oxides.

The reaction was catalyzed by 5 mol % complex and furnished the corresponding products with excellent yields and enantioselectivities (up to 99 % ee) (Scheme 4). The potential of our catalytic system was demonstrated by cleavage of the pyridine *N*-oxide ring to give synthetically useful acid **8** without any loss in enantioselectivity. The acid **8** was converted to the corresponding ester to determine the absolute stereochemistry (Scheme 5) [9].

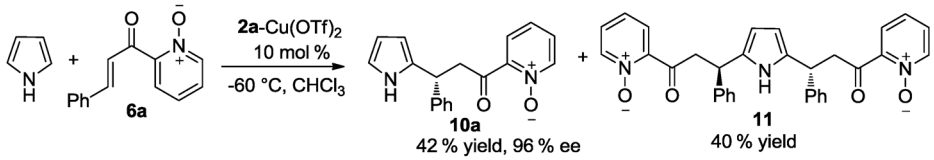


Scheme 4: Enantioselective Friedel–Crafts alkylation of indoles with 2-enoylpyridine *N*-oxides.

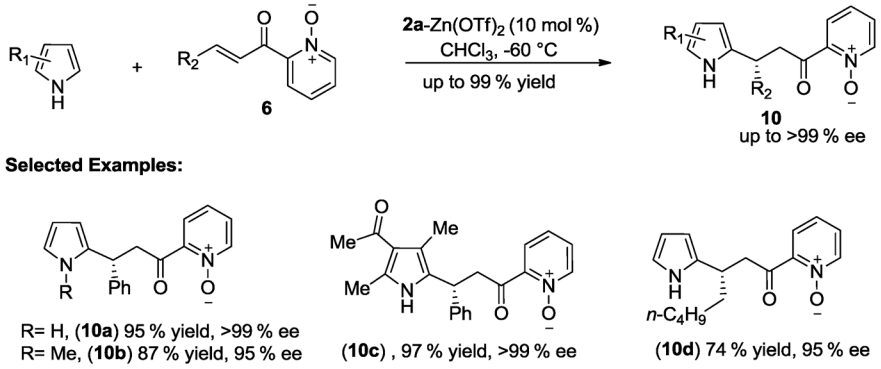


Scheme 5 Cleavage of pyridine *N*-oxide ring.

Further, the catalytic system was extended to analogous pyrrole alkylation. The reaction of pyrrole with 2-enoylpyridine *N*-oxide catalyzed by pybox-diph **2a**-Cu(II) complex was very fast, and the dialkylated product **11** was also isolated along with the desired monoalkylated product (Scheme 6). To suppress the formation of dialkylated product, we carried out the reaction with less acidic Lewis acid $Zn(OTf)_2$. As expected, the pyrrole alkylation catalyzed by pybox-diph **2a**-Zn(II) complex was slower, and monoalkylated product **10a** was isolated with good yields and enantioselectivities up to >99 % ee. The method showed substantial substrate scope as it worked well with pyrrole, *N*-substituted pyrrole, and *C*-substituted pyrrole. Moreover, good enantioselectivities were obtained with β-alkyl-substituted 2-enoylpyridine *N*-oxides (Scheme 7) (e.g., **10d**).

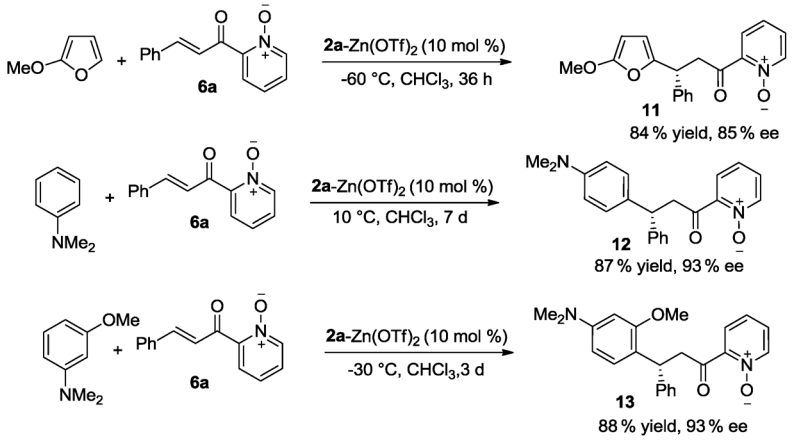


Scheme 6 Enantioselective Friedel–Crafts alkylation of pyrrole with 2-enoylpyridine *N*-oxides catalyzed by **2a**-Cu(II) complex.



Scheme 7 Enantioselective Friedel–Crafts alkylation of pyrroles with 2-enoylpyridine *N*-oxides catalyzed by **2a**-Zn(II) complex.

We have also evaluated the ip-pybox-diph **2a**-Zn(II) complex in enantioselective Friedel–Crafts alkylation reactions of other aromatic nucleophiles (Scheme 8). 2-Methoxyfuran gave the corresponding Friedel–Crafts product **11** in 85 % ee. Next, the catalyst system was extended to anilines. The Friedel–Crafts reaction of *N*,*N*-dimethylaniline and 3-methoxy-*N*,*N*-dimethylaniline with benzylidene-2-acetylpyridine *N*-oxide catalyzed by 10 mol % of **2a**-Zn(OTf)$_2$ was slow and gave the corresponding product with good yields and enantioselectivities (up to 93 % ee) (Fig. 2) [10].



Scheme 8 Substrate scope of enantioselective Friedel–Crafts alkylation catalyzed by **2a**-Zn(II) complex.

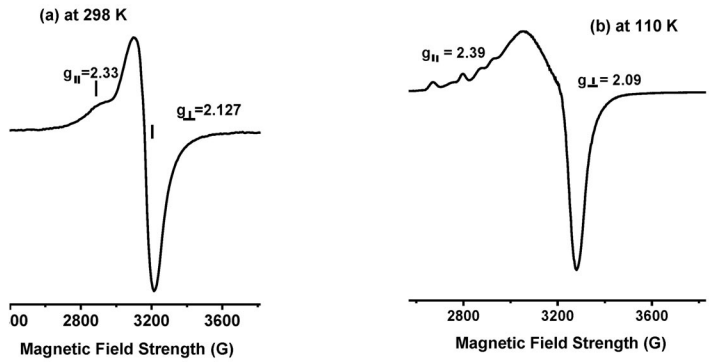


Fig. 2 EPR spectra of [Cu(**2a**)(**6a**)](OTf)$_2$ complex in dichloromethane/toluene (a) at 298 °K (b) at 110 °K.

The stereochemical outcome has been explained by proposed transition-state models as shown in Fig. 3. Three donor sites of the ligand and two donor sites of substrate will lead to a five-coordinated Cu(II) complex. The five-coordinated complex may possess two geometries, i.e., trigonal bipyramidal and square pyramidal. EPR spectra of complex [Cu(**2a**)(**6a**)](OTf)$_2$ support the formation of square pyramidal geometry [11].

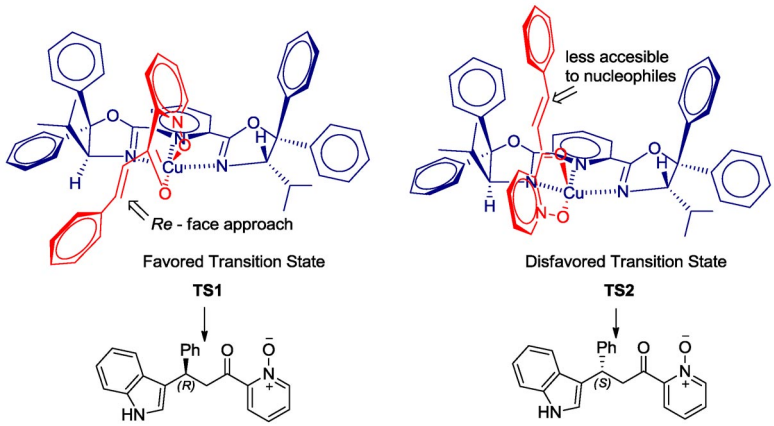


Fig. 3 Proposed transition state (TS) for enantioselective Friedel–Crafts reaction.

Two transition states (TSs) having a square pyramidal geometry are possibly **TS1** and **TS2**. Between two TSs, **TS1** will be more reactive owing to *trans*-influence of pyridine. Furthermore, in **TS2** the reacting center of 2-enoylpyridine *N*-oxide **6a** is less accessible than in **TS1** to a nucleophile owing to steric hindrance of the phenyl rings at C-5 of the oxazoline ring. In **TS1**, the indole attacks the 2-enoylpyridine *N*-oxide from the *Re* face leading to the observed enantiomer. *Si* face attack is hindered by the presence of an isopropyl group at C4 of the oxazoline ring. A sixth weak axial coordination of the triflate ion that leads to an elongated tetragonal TS cannot be completely excluded.

CONCLUSIONS

We have introduced modified tridentate *N*,*N*,*N*-pyridine bis(oxazoline) ligands for asymmetric catalysis. Metal complexes of these ligands give impressive results in enantioselective allylic oxidation, one-

pot three-component synthesis of propargylamines and Friedel–Crafts alkylation reactions. Further efforts to extend the utility of these ligands in other enantioselective reactions are in progress in our laboratory.

ACKNOWLEDGMENTS

V.K.S. thanks the Department of Science and Technology, Government of India for a research grant through the J. C. Bose Fellowship.

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