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Enantioselective reactions catalyzed by chiral pyridine 2,6-bis(5',5'-diphenyloxazoline)-metal complexes*

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Abstract: A new class of tridentate pyridine-bis(oxazoline) ligand having *gem*-diphenyl groups at C5 of the oxazoline rings has been developed. Its metal complex exhibited high catalytic efficiency in asymmetric synthesis. We have shown that *gem*-diphenyl groups at C5 of the oxazoline rings are essential for getting high enantiomeric excess.

Keywords: allylic oxidation; asymmetric synthesis; enantiomeric excess; Friedel–Crafts alkylation; *gem*-diphenyl; propargylamine; pyridine-bis(oxazoline); tridentate pyridine-bis(oxazoline) ligand.

INTRODUCTION

The design, synthesis, and tuning of a suitable chiral ligand around a metal center are important tasks in asymmetric synthesis. Because of their easy accessibility, modular nature, and coordination with a wide range of metals, bis(oxazoline) compounds have become one of the most commonly used ligands for asymmetric synthesis [1]. Recently, much effort has been devoted to the modification of the bis(oxazoline) framework to create superior ligands by varying the amino alcohols or bridging substituents. In 1989, Nishiyama first reported the tridentate *N*,*N*,*N*-type pyridine-bis(oxazoline) **1** (abbreviated as pybox) ligand for asymmetric catalysis (Fig. 1) [2]. Since small changes in conformational, steric, and/or electronic properties of the chiral ligands can often lead to dramatic variation in the enantioselectivity, we have modified the pybox ligand **1** as pyridine 2,6-bis(5',5'-diphenyloxazoline) (henceforth, pybox-diph) **2** which has *gem*-diphenyl groups at C5 of the oxazoline rings (Fig. 1). We have successfully used the C_2-symmetric pybox-diph ligand in enantioselective cyclopropanation reactions, allylic oxidation of olefins, one-pot three-component synthesis of propargylamines, and Friedel–Crafts alkylation reactions. The ligand has also been used by Loh et al. in enantioselective allylation of carbonyls and by Zhao et al. in enantioselective synthesis of α-aminopropargylphosphonates. This manuscript provides an overview of the application of pybox-diph–metal complexes in catalytic enantioselective reactions.

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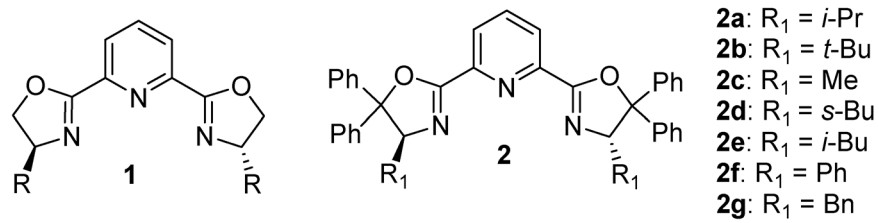
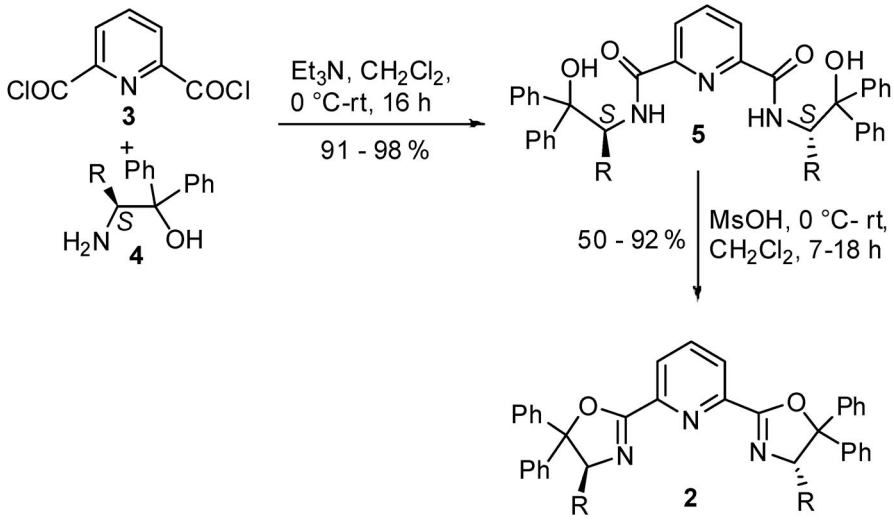


Fig. 1 Pybox and pybox-diph ligands.

SYNTHESIS OF PYBOX-DIPH LIGAND

The pybox-diph ligands can be easily synthesized from pyridine 2,6-dicarbonyl chloride **3** in two steps: bisamide **5** formation with chiral β-amino alcohols **4** followed by cyclization of bisamide to bis-oxazoline **2** by methanesulfonic acid. The ligand was purified by column chromatography followed by recrystallization from ether (Scheme 1).

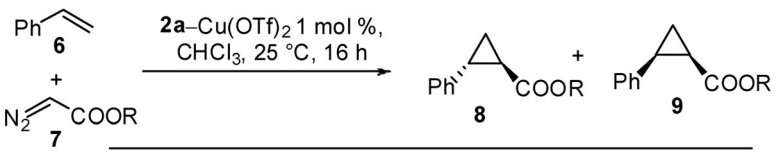


Scheme 1 Synthesis of pybox-diph ligands.

ENANTIOSELECTIVE CYCLOPROPANATION REACTIONS

The pybox-diph ligands were first introduced for the enantioselective cyclopropanation reaction (Table 1). The Cu(II) complex of pybox-diph ligand catalyzed the enantioselective cyclopropanation reaction of styrene **6** with diazoacetate **7** at 1 mol % catalyst loading. Although the enantioselectivities were not good (Table 1), a new pybox-type ligand could be introduced. It is shown with the help of UV–vis and electron paramagnetic resonance (EPR) spectroscopy that the reaction was catalyzed by Cu(I) which is formed, in situ, at room temperature by the reduction of Cu(II) complex with the diazoester used in the reaction [3a]. Thus, the activation of Cu(II) catalysts by external means is not needed for this kind of reaction. The reaction was extended to other olefins as well, but enantioselectivity remained poor [3b].

Table 1 Enantioselective cyclopropanation catalyzed by pybox-diph-Cu(II) complex.



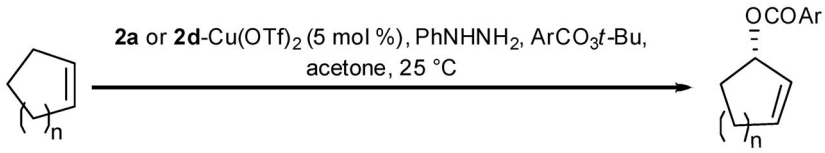
		enantioselectivity		
R	trans : cis	trans (% ee)	cis (% *ee*)	yield (%) trans+cis
ethyl	66 : 34	28	8	93
t-butyl	70 : 30	35	6	80

ENANTIOSELECTIVE ALLYLIC OXIDATION OF OLEFINS

After application of the pybox-diph ligand in enantioselective cyclopropanation, we turned our attention to the enantioselective allylic oxidation of olefins [4a]. It was observed that the rate of reaction depended upon how the catalyst was prepared. Cu(I) species prepared by the reduction of Cu(II) with phenylhydrazine in acetone is more efficient than use of Cu(I) salt directly [4b]. The reaction rate was very fast as compared to previous reported methods requiring several days for completion and sometimes close to a month [4b]. Five mol % catalyst loading gave the product in a maximum of 98 % ee in the case of a cyclic substrate. A catalyst loading of as low as 1 mol % gave similar chemical and optical yields, but longer reaction times discouraged us to do the reaction at 1 mol % catalyst loading. We have studied the effect of phenylhydrazine and the phenylhydrazone of acetone on the rate of reaction in different solvents. From experimental and EPR studies, we have shown that the rate of the reaction is not specific to the presence of phenylhydrazine or phenylhydrazone, but both were equally responsible, provided acetone was used as a solvent [4c]. We found that *gem*-diphenyl groups on the oxazoline rings are essential for getting high enantioselectivity. The stereochemical outcome has been explained on the basis of the presumed transition state. The favored transition state **TS1** was stabilized by the π–π stacking between the C5 aromatic ring of the oxazoline ring and the ester aromatic ring (Fig. 2). The fact that the presence of a *gem*-diphenyl group at C5 of the oxazoline ring is crucial for high enantioselectivity supports the π–π stacking.

To find out the role of π–π stacking in the transition state, a variety of *tert*-butyl peresters having different substituents on the aryl ring have been used. Surprisingly, electron-donating groups such as methoxy and alkyl group on the phenyl ring of the perester gave similar results as that of phenyl (Table 2, entries 5, 7, and 8), while pentafluoro substitution on the phenyl ring of the perester, which is known to show strong π–π interaction with phenyl, has a detrimental effect on enantioselectivity as well as reaction rate (Table 2, entry 9). These anomalies can be rationalized using the fact that electron-withdrawing groups at the phenyl ring of the perester will show better π–π stacking. This additional attractive interaction stabilizes the disfavored transition state **TS2**, overweighing the steric repulsion caused by the alkyl group on the chiral carbon, resulting in lowering of the enantioselectivity (Fig. 2) [4d].

Table 2 Enantioselective allylic oxidation catalyzed by pybox-diph-Cu(II) complex.



entry	Olefin	Ar	time		% yield		% *ee*	
			2a	**2d**	**2a**	**2d**	**2a**	**2d**
1		phenyl	3 h	20 h	76	75	70	65
2		*p*-nitrophenyl	13 h	6 h	47	42	62	58
3		*p*-methoxyphenyl	3 h	3 h	55	57	77	72
4		*o*-methoxyphenyl	4 h	4 h	71	74	80	80
5		phenyl	1 h	8 h	67	57	91	91
6		*p*-nitrophenyl	10 h	15 h	65	49	86	87
7		*p*-methoxyphenyl	2 h	5 h	60	61	93	92
8		*o*-methoxyphenyl	5 h	2 h	50	71	91	98
9		pentafluorophenyl	32 h	56 h	56	68	40	52
10		*p*-methoxyphenyl	96 h	18 h	45	45	91	94
11		*o*-methoxyphenyl	13 h	16 h	42	39	91	87
12		*p*-methoxyphenyl	21 h	19 h	31	42	96	90
13		*o*-methoxyphenyl	33 h	48 h	38	43	91	92
14		*p*-methoxyphenyl	29 h	15 h	49	50	95	96
15		*o*-methoxyphenyl	10 h	16 h	62	52	86	82

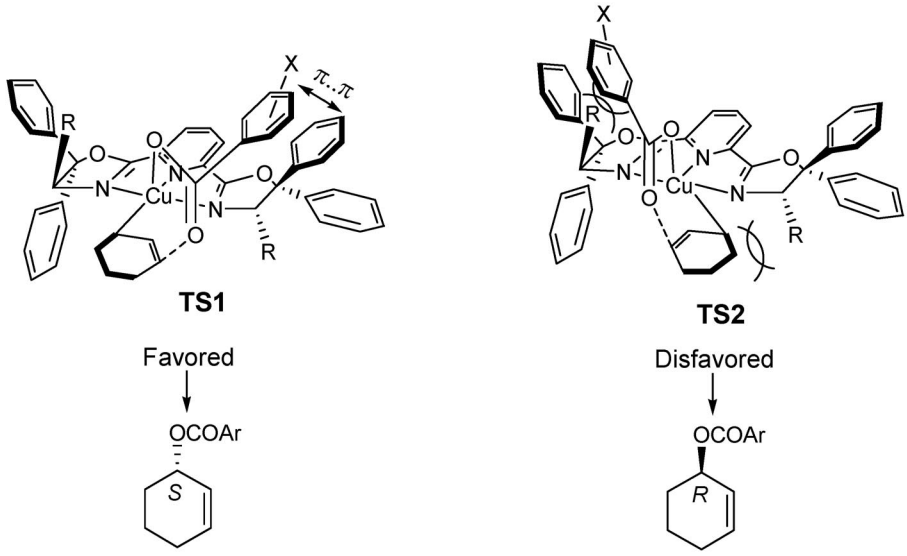
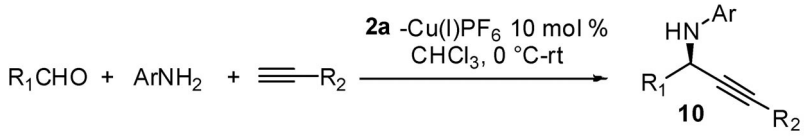


Fig. 2 Proposed transition-state model for enantioselective allylic oxidation.

ENANTIOSELECTIVE ONE-POT THREE-COMPONENT SYNTHESIS OF PROPARGYLAMINES

The potential of the ip-pybox-diph ligand was further explored by its use in enantioselective synthesis of propargylamines **10** (Table 3). The catalytic system works well in one-pot fashion with aldehydes, amines, and terminal alkynes, and there is no need of preformed imine. Five to ten mol % Cu(I)-complex of ip-pybox-diph **2a** ligand turned out to be the best, and a maximum of 99 % enantioselectivity was obtained with excellent yields. Most of the substrates employed viz. aldehydes, anilines, and terminal alkynes gave high enantioselectivity.

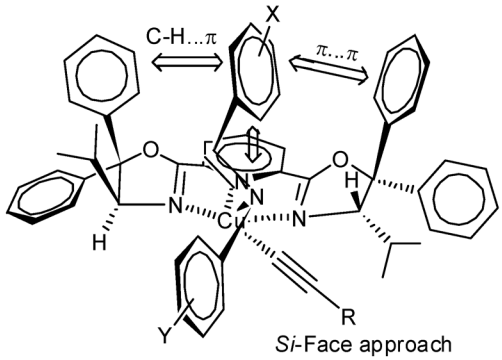
Table 3 Enantioselective one-pot synthesis of propargylamine.



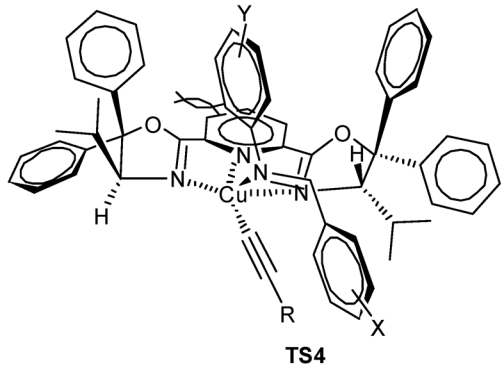
entry	R_1	Ar	R_2	time	yield (%)	*ee* (%)
1	Ph	Ph	Ph	12 h	98	96[a]
2	Ph	4-BrC_6H_4	Ph	24 h	98	96[a]
3	Ph	PMP	Ph	16 h	98	90
4	4-ClC_6H_4	PMP	Ph	28 h	91	90
5	2-ClC_6H_4	PMP	Ph	16 h	94	97
6	2,4-$Me_2C_6H_3$	PMP	Ph	18 h	97	99
7	Ph	PMP	4-$MeOC_6H_4$	20 h	96	93
8	Ph	PMP	4-BrC_6H_4	20 h	93	90
9	Ph	PMP	*n*-Bu	28 h	67	87

[a]5 mol % catalyst was used.

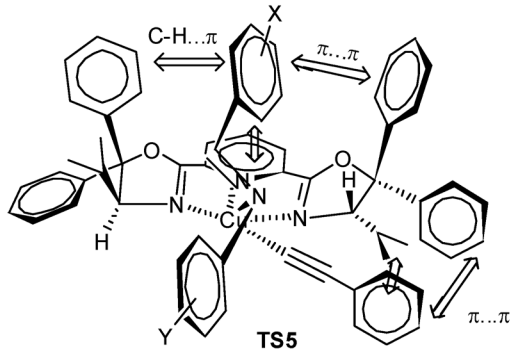
The sense of asymmetric induction was explained by invoking transition-state assembly stabilized by three π–π interactions, two C–H···π and one π–π interaction as shown in **TS3** (Fig. 3). Because of these three stabilizing interactions, the transition state becomes highly organized. The copper acetylide attacks the imine from the *si*-face to provide propargylamine. The *re*-face attack is disfavored because of the steric repulsion of the alkyl group on the chiral carbon of the oxazoline ring. Aromatic alkynes gave better results than aliphatic alkynes, which can be explained by considering one more C–H···π interaction between the aromatic ring of the terminal alkynes with C–H of *i*-Pr group and a π···π interaction between aromatic ring of the terminal alkynes with the phenyl ring of *gem*-disubstituted pybox in transition state **TS5** [5a]. The reaction was extended to ethyl glyoxylate to get non-racemic α-amino ester **11**. Using 10 mol % Cu(II)-complex of sb-pybox-diph **2d**, a maximum of 56 % ee was obtained (Table 4) [5b].



Favored Transition State Assembly



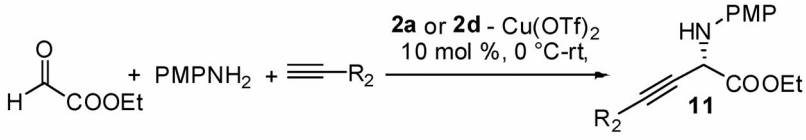
Disfavored Transition State



Si-Face approach

Fig. 3 Proposed transition-state model of one-pot synthesis of propargylamines.

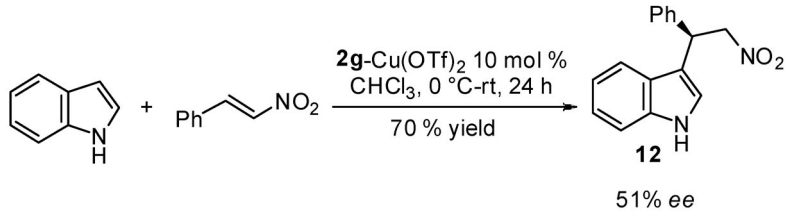
Table 4 Enantioselective one-pot synthesis of α-aminoester.



entry	R_2	time		% yield		% *ee*	
		2a	**2d**	**2a**	**2d**	**2a**	**2d**
1	Ph	12 h	12 h	90	92	39	43
2	$PhCH_2CH_2$	48 h	20 h	69	79	39	46
3	*n*-Bu	48 h	48 h	80	83	41	48
4	4-$^n C_5H_{11}C_6H_4$	10 h	10 h	91	97	50	52
5	4-BrC_6H_4	12 h	12 h	90	88	20	21
6	4-$MeOC_6H_4$	16 h	16 h	92	91	38	38
7	4-MeC_6H_4	12 h	12 h	94	88	48	56

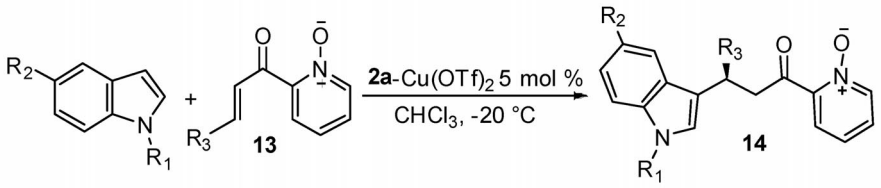
ENANTIOSELECTIVE FRIEDEL–CRAFTS REACTIONS

Recently, we have shown the application of pybox-diph ligand in enantioselective Friedel–Crafts alkylation of indoles. First, we tried the enantioselective Friedel–Crafts alkylation of indole with nitrostyrene. Using bn-pybox-diph (**2g**)-Cu(II) complex, we could get the product **12** with 51 % enantioselectivity (Scheme 2) [6]. Later, the use of pybox-diph-metal complex was extended to indole alkylation with 2-enoylpyridine *N*-oxides **13** [7]. The ip-pybox-diph-Cu(II) complex was very efficient and gave the alkylated indoles **14** in excellent yields and enantioselectivities (up to 99 % ee) (Table 5). We found that the 2-enoylpyridine *N*-oxides are better substrates than the corresponding 2-enoylpyridines for the **2a**-Cu(II)-catalyzed enantioselective Friedel–Crafts alkylation reaction [8].



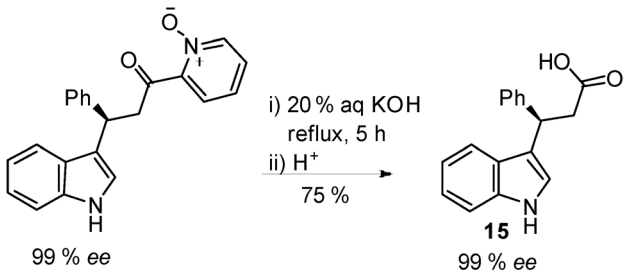
Scheme 2 Enantioselective Friedel–Crafts reaction of indole with nitrostyrene.

Table 5 Enantioselective Friedel–Crafts reaction of indoles with various 2-enoylpyridine-*N*-oxides.



entry	R_1	R_2	R_3	time	yield (%)	*ee* (%)
1	H	H	Ph	15 min	97	99
2	H	F	Ph	1 h	97	97
3	H	OCH_3	Ph	15 min	98	95
4	CH_3	H	Ph	30 min	97	86
5	H	H	4-$CH_3OC_6H_4$	3 h	97	94
6	H	H	4-$NO_2C_6H_4$	15 min	95	99
7	H	H	3-$NO_2C_6H_4$	15 min	97	98
8	H	H	2-$NO_2C_6H_4$	15 min	96	97
9	H	H	1-naphthyl	2 h	83	89
10	H	H	2-furyl	3 h	97	87

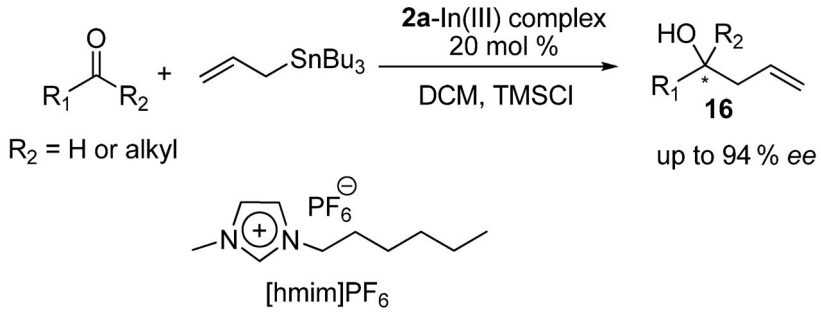
The pyridine *N*-oxide ring of alkylated indole was cleaved to give synthetically useful yields of the acid **15** [9] without any loss in enantioselectivity (Scheme 3).



Scheme 3 Cleavage of pyridine-*N*-oxide ring.

ENANTIOSELECTIVE ALLYLATION OF CARBONYL COMPOUNDS

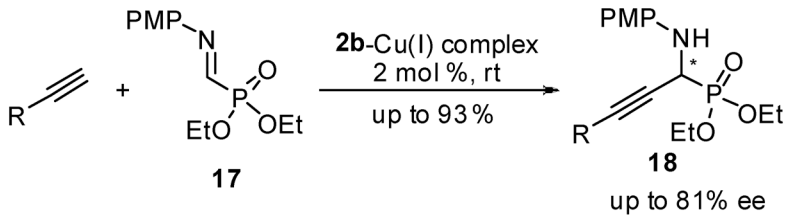
T.-P. Loh and co-workers have used ip-pybox-diph-In(III) complex in allylation of aldehydes and ketones [10a,c]. With 20 mol % catalyst, allyltributylstannane reacted with aldehydes and ketones in the presence of 1.2 equiv TMSCl (Scheme 4) to give homoallylic alcohols in excellent enantioselectivity (up to 95 % ee). They have extended this methodology in ionic liquids ([hmim]PF_6) and shown the recyclability of the catalytic system. The catalyst has been recycled four times with comparable enantioselectivity and yield [10b,d]. Later, W.-Y. Chen and X.-S. Li used a variety of pybox-diph ligands in enantioselective allylation of aldehyde and ketone to show the effect of substituent at chiral carbon C4 of the oxazoline ligand [10e].



Scheme 4 Enantioselective allylation of carbonyl compounds.

ENANTIOSELECTIVE SYNTHESIS OF α-AMINOPROPARGYLPHOSPHONATES

Zhao and co-workers have used tb-pybox-diph (**2b**)-Cu(I) triflate complex for the first enantioselective synthesis of α-aminopropargylphosphonates **18** by terminal alkyne addition to α-iminophosphonates **17** (Scheme 5). A low catalyst loading of 2 mol % gave the product in high yields and good enantioselectivity (60–81 % ee). The reaction works well with aliphatic as well as aromatic terminal alkynes [11].



Scheme 5 Enantioselective synthesis of α-aminopropargylphosphonates.

CONCLUSIONS

We have introduced new types of tridentate *N*,*N*,*N*-type pyridine bis(oxazoline) ligands. These ligands have increased the ligand diversity for asymmetric synthesis. Metal complexes of these ligands gave impressive results in enantioselective allylic oxidation, one-pot three-component synthesis of propargylamine, Friedel–Crafts alkylation reaction, and allylation of carbonyl compounds. Efforts to extend the utility of these ligands in other enantioselective reactions are in progress in our laboratory.

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