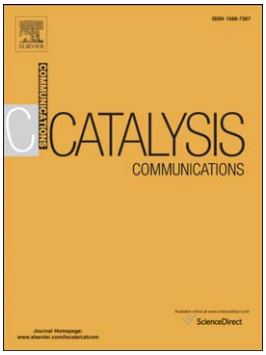

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Synthesis of chiral benzene-based tetraoxazolines and their application in asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes

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ABSTRACT

A series of new chiral benzene-based tetraoxazoline ligands were prepared in good yields through the reaction of 1,2,4,5-benzenetetracarboxylic acid and chiral β-amino alcohols by continuous removal of water, and the asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes was tested using the chiral catalysts, which were generated in situ by refluxing the above ligands and anhydrous zinc chloride in solvent. In most case, good yields (up to 99%) and excellent enantioselectivities (up to 98% ee) were obtained.

Keywords:

Tetraoxazoline

Asymmetric catalysis

Friedel-Crafts alkylation

Indole derivative

Nitroalkene

1. Introduction

Chiral oxazoline-based compounds are a class of privileged ligands and exist in a wide variety of forms containing mono-, bis- or multi-oxazolines. Andreasch firstly synthesized oxazoline-based compounds in 1884 [1], and until 1984, Brunner et al. introduced oxazoline-based ligands into asymmetric catalytic reactions [2]. Since then, a number of mono- and bis-oxazolines, derived from different linkages, backbones and amino alcohols, have already been applied to different types of asymmetric reactions [3, 4]. Trisoxazolines first emerged in 1993 [5]. Later, several types of trisoxazolines were developed and found widespread utility in asymmetric catalysis [6-9] and molecular recognition [10, 11]. However, in sharp contrast to the great success of mono-, bis- or tris-oxazolines, the development and application of tetraoxazolines are still lacking. Zhang and coworkers have reported the synthesis and applications of biphenyl-linked tetraoxazolines in asymmetric Wacker-type cyclization [12, 13]. Our group have also tried to apply several tetraoxazolines, derived from ethylenediaminetetraacetic acid or ethylene glycol-bis (2-aminoethylether)-N,N,N',N'-tetraac-etic acid, to the asymmetric hydrosilylation of aromatic ketones, however, they gave low enantioselectivities due to the flexible linkers of oxazoline rings [14]. Most recently, we have introduced benzene as a rigid linker unit and have synthesized tetraoxazoline **1a** (**Fig. 1**) [15].

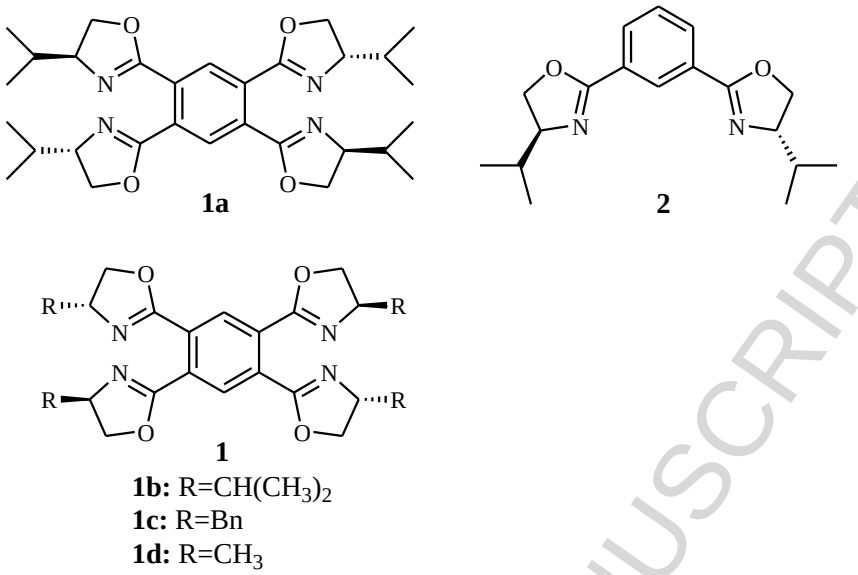


Fig. 1. Structures of chiral oxazolines.

This improvement make its bivalent copper ion catalyst exhibit efficient catalytic activities and high enantioselectivities in the same reaction. The ligand **1a** has more tunable chiral spaces than bisoxazoline **2** due to its four cavities, and it may selectively coordinate with metal cations and increase the stability of active intermediates, so that the chiral catalyst might be air- and water-tolerant. As an extension of my project, I design the benzene-based tetraoxazolines **1b-d**, as illustrated in Figure 1. Herein, I would like to report my recent results on their synthesis and application in asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes.

2. Experimental

2.1 Materials and methods

1,2,4,5-Benzenetetracarboxylic acid, anhydrous zinc chloride, D-valinol, D-phenylalaninol and (*R*)-2-amino-1-propanol were purchased from Alfa Aesar Co. 1,2,4,5-Tetra[(4'*S*)-isopropyloxazolin-2'-yl]benzene (**1a**) and 1,3-bis[(4'*S*)-isopropyloxazolin-2'-yl]benzene (**2**) were prepared according to the literatures' approaches [15, 16]. Other reagents were of all analytical grade. Melting points were measured on an X-6 precision melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500, Bruker DRX-400, Bruker DRX-300 or DRX-100 NMR spectrometers, using TMS as an internal standard ; chemical shift, multiplicity (s = single, d = doublet, t = triplet, m = multiplet) are given in parts per million and are referenced to residual solvent peaks. Mass spectra were measured on a LCQ DECA XP LC/MS system. Optical rotation values were recorded on a Polartronic HNQW 5 polarimeter. The enantiomeric excesses were carried out using chiral HPLC with a Daicel Chiracel OD-H column on Waters with a 996 UV-detector.

2.2 General procedure for the synthesis of tetraoxazolines **1b-d**

1,2,4,5-benzenetetracarboxylic acid (0.63 g, 2.5 mmol), chiral β-amino alcohol (D-valinol, D-phenylalaninol or (*R*)-2-amino-1-propanol) (10.0 mmol) and DMF (20 mL) were added to a three-neck flask equipped with a water segregator, a reflux condenser and a magnetic stirring bar. The mixture was refluxed with continuous removal of water for 10 h. After cooling to room temperature, DMF was removed under reduced pressure and the residue was

purified by silica gel column chromatography with trichloromethane as eluant to obtain the pure **1b-d**.

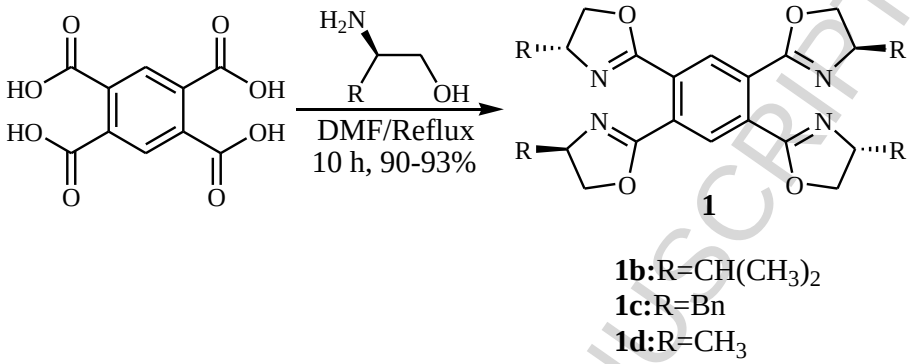
2.3 General procedure for asymmetric Friedel-Crafts reactions

The ligand **1** (0.01 mmol) and anhydrous zinc chloride (0.02 mmol) were added to a three-neck flask under the protect of a nitrogen atmosphere, followed by addition of solvent (5.0 mL). The mixture was refluxed for 0.5 h and cooled to room temperature, then nitroalkene **4** (0.5 mmol) was added. The mixture was stirred for 10 min at the same temperature and then cooled to -10 ℃. Indole derivative **3** (0.5 mmol) was added at -10 ℃. After completion of the addition, the mixture was stirred at the same temperature until indole derivative **3** had disappeared. The reaction solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography with petroleum ether-ethyl acetate 4:1 to 2:1 (V/V) as eluant to obtain the desired product **5**. The configuration of the product was determined by optical rotation and the enantiomeric excess was determined by HPLC analysis using a Daicel Chiracel OD-H column.

3. Results and discussion

Previously, we reported a facile and efficient synthesis of the tetraoxazoline **1a** [15]. Here the tetraoxazolines **1b-d** could be prepared conveniently in good yields from

1,2,4,5-benzenetetracarboxylic acid and the corresponding β-amino alcohols using a similar strategy for the preparation of tetraoxazoline **1a** (**Scheme 1**) [15].



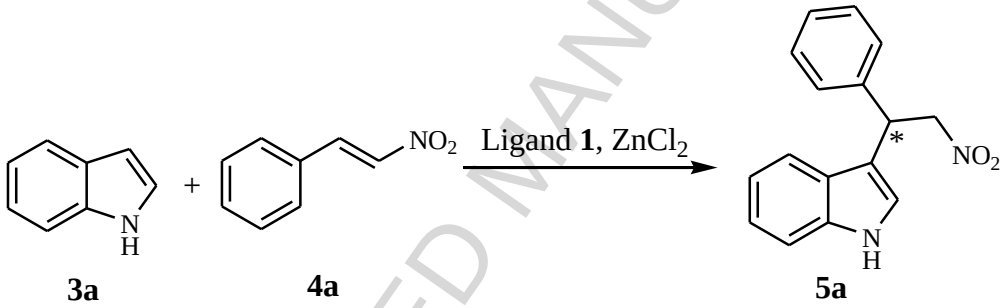
Scheme 1. Synthesis of chiral tetraoxazolines.

The development of efficient Friedel-Crafts alkylations of arenes and heteroarenes using only catalytic amounts of a Lewis acid has gained much attention over the last decade [17-21]. Indole derivatives as heteroarenes represent a class of biologically active compounds [22-24], and they often have chiral carbon chains attached to indole rings. The asymmetric Friedel-Crafts alkylation to indoles is a versatile method for preparing such chiral indole derivatives. Up to now, a number of Friedel-Crafts alkylations by either metal catalysts or organocatalysts have been reported [25-30]. In particular, the metal catalysts with chiral oxazoline-based ligands have been demonstrated to possess a high feasibility for preparing chiral indole derivatives through asymmetric Friedel-Crafts alkylation reactions [31-35]. However, to date, most of these reactions were routinely conducted by the metal catalysts with mono- or bisoxazoline ligands. Herein, I investigated the asymmetric Friedel-Crafts

alkylation of indole derivatives with nitroalkenes using the zinc catalysts with tetraoxazolines **1a-d**.

Table 1

Optimizations for enantioselective Friedel-Crafts alkylation of indole with β-nitrostyrene.[a]



3a **4a** **5a**

Entry	Ligand	Loading (mol%) [b]	Solvent	Time (h)	Temp (℃)	Yield (%) [c]	*ee* (%) [d]	Abs. config [e]
1	**1a**	2.0	toluene	14	-10	89	83	*S*
2	**1b**	2.0	toluene	14	-10	88	82	*R*
3	**1c**	2.0	toluene	14	-10	98	95	*R*
4	**1d**	2.0	toluene	14	-10	87	85	*R*
5	**2**	2.0	toluene	14	-10	76	64	*S*
6	**1c**	2.0	toluene	8	10	98	87	*R*
7	**1c**	2.0	toluene	10	-5	98	92	*R*

8	**1c**	2.0	toluene	22	-20	91	96	*R*
9	**1c**	2.0	CH_2Cl_2	14	-10	90	80	*S*
10	**1c**	2.0	$CHCl_3$	14	-10	89	77	*R*
11	**1c**	2.0	THF	14	-10	82	74	*R*
12	**1c**	2.0	benzene	14	-10	92	90	*R*
13	**1c**	1.0	toluene	14	-10	74	83	*R*
14	**1c**	1.5	toluene	14	-10	90	88	*R*
15	**1c**	2.5	toluene	14	-10	99	96	*R*

[a] The catalyst was prepared in situ by refluxing ligand **1** and anhydrous zinc chloride in 5 mL of solvent.

[b] Loading: catalyst/indole (molar ratio).

[c] Conditons: indole (0.5 mmol), β-nitrostyrene (0.5 mmol) and solvent (5.0 mL). The reactions were carried out under the protect of a nitrogen atmosphere.

[d] Enantiomeric excesses were determined by HPLC using a Daicel Chiracel OD-H column.

[e] All absolute configurations were determined by optical rotation measurements.

With the desired tetraoxazolines **1a-d** in hand, I first examined their catalytic reactivities in the asymmetric Friedel-Crafts alkylation of indole **3a** with β-nitrostyrene **4a**. The results are presented in **Table 1**. Compared with the bisoxazoline **2**/$ZnCl_2$ complex, the catalytic activity

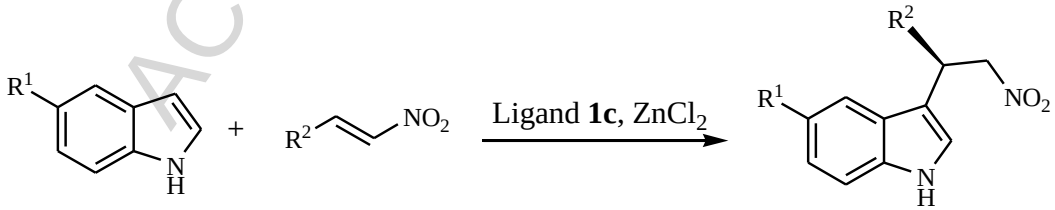
and enantioselectivity of the ligand **1a**/$ZnCl_2$ complex were greatly increased (**Table 1**, entry 1 *vs.* entry 5). For the ligands **1a-d**, their reactivities and enantioselectivities are sensitive to the substituents on oxazoline ring. **1c** with benzyl group on the 4-position of oxazoline ring obtained good yield and enantioselectivity (**Table 1**, entry 3), while the yields and enantioselectivities decreased dramatically with the bulkier isopropyl group and relatively smaller methyl group (**Table 1**, entries 1, 2 and 4). Next, for ligand **1c**, I investigated the effect of temperature on the catalytic reaction. Longer reaction times were necessary and the enantioselectivity increased when the reaction temperature was decreased (**Table 1**, entries 3 and 6-8). When the reaction was operated at -10 ℃, the enantioselectivity can be improved to 95% ee (**Table 1**, entry 3). As for solvent effects, the reaction gave a preference for toluene as solvent (**Table 1**, entry 3 *vs.* entries 9-12). The use of aprotic solvents such as dichloromethane, chloroform and tetrahydrofuran gave **5a** in good yield with low enantioselectivity (**Table 1**, entries 9-11). Catalyst concentrations have a significant effect on both the yield and enantioselectivity. Increasing the catalyst loading not only obtained good yield but also increased the enantioselectivity (**Table 1**, entries 3 and 13-15). Enhancing the catalyst loading to 2.5 mol% to give 99% yield and 96% ee, but it showed no significant improvement. The optimized loading of the catalyst employed at 2.0 mol%, relative to indole.

After the reaction conditions were optimized, this asymmetric catalytic reaction was further explored using more indole derivatives and nitroalkenes (**Table 2**). A few indole derivatives **3a-d** bearing different substitutes were first examined in the reaction. An electron-donating substitute such as methyl or methoxy in the 5-position of the indole ring caused a slight increase in enantioselectivity (**Table 2**, entries 2-3 *vs.* entry 1), while lower

yield and enantiomeric excess were obtained for electron-deficient 5-chloroindole (**Table 2**, entry 4). Then the generality of this reaction was further evaluated by a variety of structurally different nitroalkenes. The *ortho*-substitution on the phenyl in nitrostyrenes, either electron-donating or electron-withdrawing groups decreased the enantiomeric excesses of products, perhaps due to the steric effect of *ortho*-substitutes (**Table 2**, entries 5 and 6). Good yields and high enantioselectivities could be achieved for the nitrostyrenes with both electron-donating and electron-withdrawing groups on the *meta* or *para* positions of the phenyl ring and the aliphatic-substituted nitroalkenes (**Table 2**, entries 7-10 and 12). The nitroalkene containing furan gave 89% yield and 83% ee (**Table 2**, entry 11).

Table 2

Asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes.



3a-d **4a-i** **5a-l**

Entry	Product	R^1	R^2	Yield (%) [a]	*ee* (%) [b]
1	**5a**	H	Ph	98	95
2	**5b**	Me	Ph	96	97

3	**5c**	MeO	Ph	95	98
4	**5d**	Cl	Ph	89	82
5	**5e**	H	2-$MeOC_6H_4$	98	78
6	**5f**	H	2-ClC_6H_4	85	75
7	**5g**	H	3-BrC_6H_4	87	96
8	**5h**	H	3-$NO_2C_6H_4$	95	94
9	**5i**	H	4-$MeOC_6H_4$	91	90
10	**5j**	H	4-ClC_6H_4	94	95
11	**5k**	H	2-furyl	89	83
12	**5l**	H	$CH_3(CH_2)_3$	91	92

[a] Conditions: catalyst/indole derivative = 2.0 mol%, indole derivative (0.5 mmol), nitroalkene (0.5 mmol), toluene (5.0 mL), -10 ℃, 14 h.

[b] Enantiomeric excesses were determined by HPLC using a Daicel Chiracel OD-H column. All absolute configurations were determined as *R* by optical rotation measurements.

In the asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes catalyzed by the complexes of tetraoxazolines **1a-d** with anhydrous zinc chloride, their catalytic mechanisms are still not clear at this stage. As shown in **Table 1**, the absolute configurations of the resulting products were in good agreement with those of the

corresponding chiral β-amino alcohols. This result indicates that the enantioselectivities may be determined by the chirality of oxazoline rings derived from the chiral amino alcohols.

In conclusion, the novel chiral benzene-based tetraoxazolines **1b-d** have been synthesized in high yields from 1,2,4,5-benzenetetracarboxylic acid and chiral β-amino alcohols. In most cases, the catalytic system with the tetraoxazoline **1c** and anhydrous zinc chloride gave good yields (up to 99%) and high enantioselectivities (up to 98% *ee*) in the asymmetric Friedel-Crafts alkylation of indole derivatives with nitroalkenes. Further applications in other asymmetric catalytic reactions catalyzed by the new benzene-based tetraoxazolines are in progress in my laboratory.

Acknowledgments

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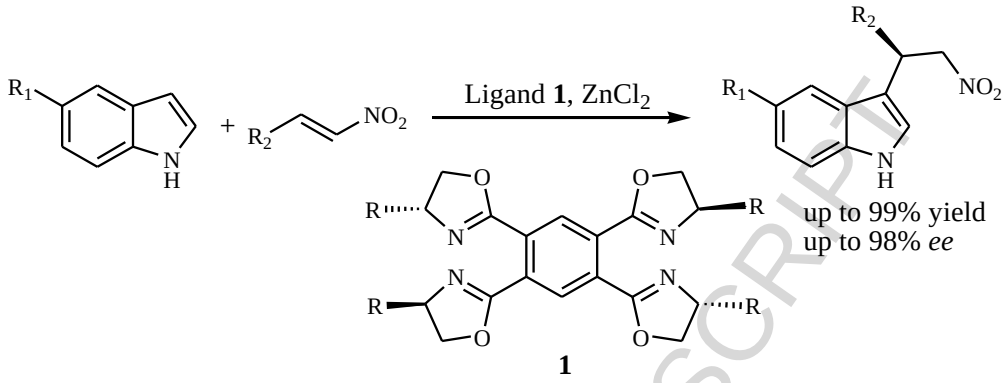
Graphical abstract



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Highlights

- A series of new chiral benzene-based tetraoxazoline ligands were prepared.
- The catalytic system is composed of the synthesized tetraoxazoline and $ZnCl_2$.
- The catalytic system was tested in asymmetric Friedel-Crafts alkylations.
- The catalytic system presented excellent activities and enantioselectivities.