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COMMUNICATION

Design of novel chiral *N,N,O*-tridentate phenanthroline ligands and its application to enantioselective addition of organozinc reagents to aldehydes

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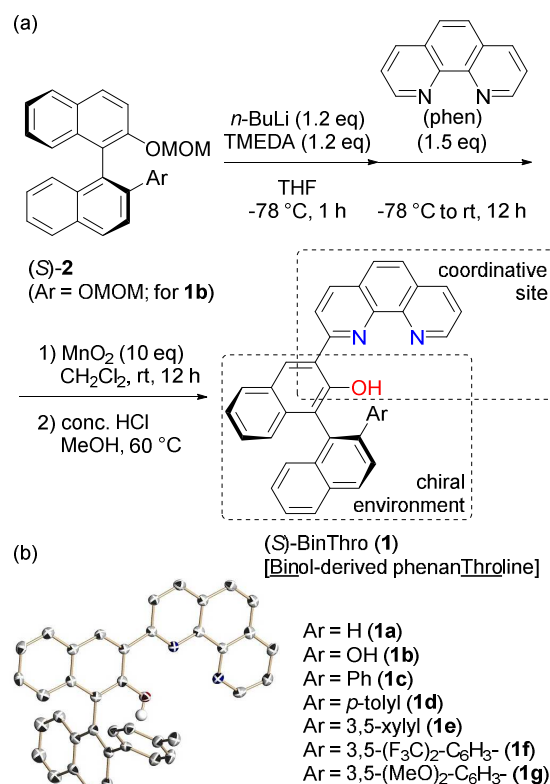
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The novel *N,N,O*-tridentate phenanthroline ligands (BinThro) bearing axially chiral binaphthyl backbone prepared from BINOL were found to be an effective chiral catalyst for enantioselective addition of diethylzinc to aromatic aldehydes with high enantioselectivity (up to 95% ee).

Since the first synthesis of 1,10-phenanthroline (phen) by Blau and Gerdiessen, this classical *N,N*-bidentate ligand has played an important role in both organic and inorganic chemistry.¹ Also in the field of synthetic organic chemistry, the powerful catalytic utility of phen-based ligands has been demonstrated in conjunction with the noteworthy coordinative ability toward various ions including not only transition metals but also typical elements.² This strong affinity with a wide range of metal ions is due to the rigid and planar structure containing *cis*-oriented two nitrogen atoms, thus enabling the formation of entropically-favored strong complexes compared to structurally similar 2,2'-bipyridine ligands.¹ However, these features of phen derivatives put obstacle in the development of chiral ligands based on phen scaffold with no sp³ carbons to which a chiral carbon center is readily introduced in routine ways.³ Although several studies on chiral phen derivatives have been performed and their abilities were investigated in several asymmetric reactions, almost of them are prepared from the condensation of chiral natural carbonyl compounds such as pinanone and camphor.⁴ Therefore, these types of ligand relying on the use of natural chiral resources are immature from the view point of difficulty in the precise molecular design of ligand structures.⁵

To overcome this drawback, we designed the novel ligand of chiral BINOL-derived phenanthroline (*S*)-**1** (abbreviated as BinThro) prepared as shown in Scheme 1 (a). Starting from the reported compounds (*S*)-**2**,⁶ the treatment of *ortho*-lithiated **2** with phen (1.5 eq.), the oxidation with excess MnO₂ followed by the removal of MOM protecting group in acidic condition afforded the desired products (*S*)-**1**. In preparation step of the starting material (*S*)-**2**, various aromatic substituents (Ar group in (*S*)-**1**) can be readily introduced for the rigorous molecular modification of the ligand structure. The structure of (*S*)-**1d** was unambiguously confirmed by X-ray crystallographic analysis (Scheme 1 (b)).⁷ The clear difference from the previously reported chiral phen ligands is the *N,N,O*-tridentate property and the introduction of readily tunable axially

chiral binaphthyl unit. Two divided roles are assumed as the phen backbone for coordinative site and the binaphthyl backbone for chiral environment.



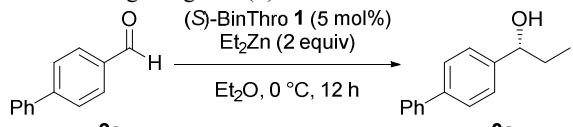
Scheme 1. (a) Preparation scheme of (*S*)-BinThro ligand (**1**). (b) ORTEP diagram of (*S*)-**1d** (50% probability). Hydrogen atoms except OH group are omitted for clarify.

In the evaluation of new chiral BinThro ligands **1**, we considered that very limited metals such as Rh, Pd, and Cu have been applied to chiral phen ligand-catalyzed enantioselective reactions³ in the sharp contrast to the non-asymmetric reactions where a variety of metal

catalysts are used.² We expected BinThro ligands **1** would form the corresponding complexes with a wide range of metals and show the unexplored utility in asymmetric catalysis. Among the various metal candidates, we initially investigated the catalytic activity in 1,2-addition of organozinc reagents to carbonyl compounds which is one of the most important C-C bond formation reactions providing optically active alcohols. Zinc complexes with phen are also vastly reported in inorganic chemistry, however, the organic reactions catalyzed by these complexes has been rarely studied.⁸ Although a variety of chiral ligands for the enantioselective addition of organozinc reagents has been discovered so far, an employment of phen derivatives has been rarely examined, even achiral ones.^{9,10}

Thus, we began to investigate the catalytic activity of a series of BinThro ligands (*S*)-**1** in a model reaction of diethylzinc and *p*-phenylbenzaldehyde **2a** in Et₂O at 0 °C (Table 1). The reaction in the presence of the simplest BinThro ligand (*S*)-**1a** (5 mol%) provided the corresponding secondary alcohol **3a** in moderate yield, however almost no asymmetric induction was observed (entry 1). The study on substituent effect of (*S*)-**1** identified that the introduction of an aromatic group at 2-position of one naphthyl moiety without phen backbone (Ar group of (*S*)-**1**) lead to the dramatic increase of not only yield but also enantioselectivity. For example, the use of ligand (*S*)-**1c** bearing phenyl group at the position resulted in the formation of (*R*)-**3a** in 85% yield and with 84% ee (entry 3). On the other hand, ligand (*S*)-**1b** bearing another hydroxyl group showed poor catalytic activity (entry 2). Therefore, we conducted further detailed study on the substituent effect of phenyl group of (*S*)-**1c**. The attachment of *p*-tolyl or 3,5-xyllyl group improved enantioselectivity slightly (entries 4 and 5). Finally, we determined (*S*)-**1f** with 3,5-bis(trifluoromethyl)phenyl group as the most effective ligand giving the desired product quantitatively with 90% ee (entry 6). Furthermore, the efficiency was unchanged when the catalyst loading was reduced to 2 mol% (entry 8).

Table 1. Screening of ligands (*S*)-**1**^a



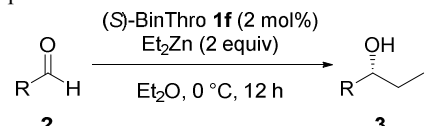
entry	1	% yield ^b	% ee ^c
1	1a	37	3 (<i>R</i>)
2	1b	17	2 (<i>R</i>)
3	1c	85	84 (<i>R</i>)
4	1d	99	85 (<i>R</i>)
5	1e	98	87 (<i>R</i>)
6	1f	99	90 (<i>R</i>)
7	1g	44	86 (<i>R</i>)
8 ^d	1f	96	90 (<i>R</i>)

^a Performed with *p*-phenylbenzaldehyde (0.2 mmol), diethylzinc (0.4 mmol), and **1** (0.01 mmol) in Et₂O (1 mL) at 0 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d Catalyst loading, 2 mol%

Next, we examined the scope of aromatic aldehydes **2** (Table 2). Regardless of the position of substituent on the aromatic ring, the reaction of *o*-, *m*- or *p*-tolualdehydes **2b-d** uniformly furnished the corresponding chiral secondary alcohols **3b-d** with high enantioselectivity (entries 1-3). Concerning of the electronic effect of substrate, both *p*-anisaldehyde **2f** and *p*-trifluoromethylbenzaldehyde **2g** can be employed for this transformation (entries 4 and 5). The aldehyde (**2h**) bearing electrophilic keto moiety was also tolerated without giving the side products via nucleophilic addition to ketone⁹ (entry 6). Similarly, the aldehyde (**2h**) with nitrile group was tolerated (entry 7). For the ring

size of aromatic aldehydes, both 1- and 2-naphthaldehyde **2i** and **2j** can be applied and the highest ee (95% ee) was obtained in the reaction of **2i** (entries 8 and 9). Although 1,4-addition of organozinc reagent to α,β -unsaturated carbonyl compounds has been well investigated (entry 10),¹¹ the reaction of α,β -unsaturated carbonyl compounds such as cinnamaldehyde **2k** gave 1,2-adduct **3k** regioselectively, albeit with lower enantioselectivity (entry 10).

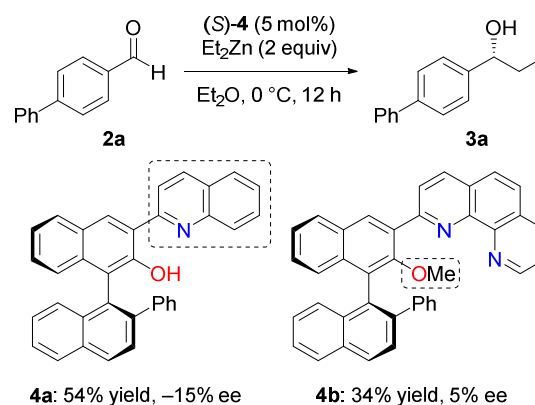
Table 2. Scope of substrate^a



entry	R	% yield ^b	% ee ^c
1	<i>o</i> -tolyl (2b)	67 (3b)	90 (<i>R</i>)
2	<i>m</i> -tolyl (2c)	87 (3c)	91 (<i>R</i>)
3	<i>p</i> -tolyl (2d)	70 (3d)	88 (<i>R</i>)
4 ^d	<i>p</i> -MeO-C ₆ H ₄ (2e)	94 (3e)	88 (<i>R</i>)
5	<i>p</i> -F ₃ C-C ₆ H ₄ (2f)	84 (3f)	93 (<i>R</i>)
6	<i>p</i> -Ac-C ₆ H ₄ (2g)	75 (3g)	93 (<i>R</i>)
7	<i>p</i> -CN-C ₆ H ₄ (2h)	51 (3h)	91 (<i>R</i>)
8	1-Np (2i)	45 (85) ^e (3i)	95 (<i>R</i>)
9	2-Np (2j)	>99 (3j)	88 (<i>R</i>)
10	PhCH=CH (2k)	52 (3k)	59 (<i>R</i>)

^a Performed with aldehyde (0.2 mmol), diethylzinc (0.4 mmol), and **1** (0.004 mmol) in Et₂O (1 mL) at 0 °C. ^b Isolated yield. ^c Determined by chiral HPLC analysis. ^d Performed at r.t. ^e Catalyst loading, 4 mol%

To reveal more about the essential functionality within BinThro ligand for this enantioselective organozinc addition, we prepared several analogous bidentate ligands (*S*)-**4** of BinThro ligand and conducted the asymmetric reactions (Scheme 2). The replacement of phen structure to monodentate quinoline scaffold¹² had a negative influence on the result (54% yield, -15% ee). In addition, the protection of hydroxyl group with methyl group resulted in the dramatic decrease of ee (34% yield, 5% ee). These experiments suggest a structural importance of the combination of phen backbone and phenoic hydroxyl group within BinThro ligands which provide monoanionic *N,N,O*-tridentate coordination with a central Zn metal.¹³



Scheme 2. Reaction with analogous bidentate ligands (*S*)-**4**.

With these observations in mind, the plausible mechanism of asymmetric induction was illustrated in Figure 1. For common chiral ligands applied to enantioselective carbonyl addition of organozinc reagents, it is proposed that dimeric zinc complexes are active

species in which zinc alkoxide works as Lewis acid and dialkylzinc is activated by the coordination of Lewis basic oxygen atom.^{9,10a,b} Since BinThro ligands display C_1 symmetry, the orientation of carbonyl coordination should be distinguished as in **TS-1** and in **TS-2**. We assume that the more favored transition state should be **TS-1** because of the steric repulsion between bulky 3,5-bis(trifluoromethyl)phenyl group and aldehyde in **TS-2**. The subsequent nucleophilic addition occurs from *Re*-face of carbonyl carbon to furnish (*R*)-**3a**. This plausible mechanism clearly matches the fact that (*S*)-**1a** having no substituent on naphthyl group did not work as an effective ligand at all (Table 1, entry 1).

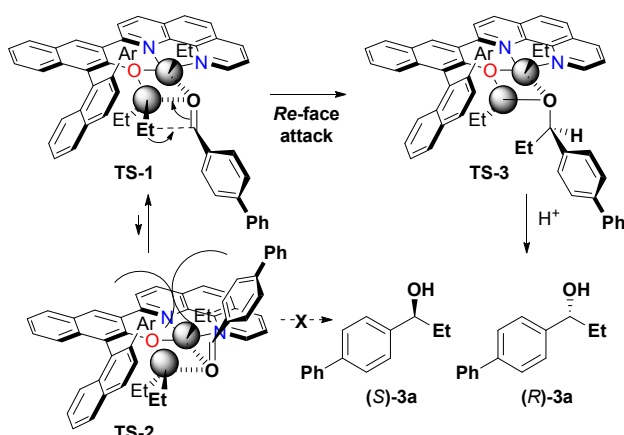


Figure 1. Plausible transition state.

In summary, we developed the novel class of axially chiral, *N,N,O*-tridentate phen ligand, BinThro ligand (*S*)-**1**. Design of BinThro ligand is based on the concept of innovation utilizing phen units which has superior coordination ability with wide range of metal ions. The first attempt testing ability of the BinThro ligand was successfully demonstrated in enantioselective addition of diethylzinc to aldehydes. Further studies applying these ligands with other metal catalyst are underway in our laboratory, and soon we will report in the following communications.

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† Electronic Supplementary Information (ESI) available: X-ray crystallographic data for (*S*)-**1d** in CIF format (CCDC 992290). General experimental procedures and spectroscopic characterization of new compounds. See DOI: 10.1039/c000000x/

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