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The novel chiral *N*,*N*,*O*-tridentate ligand (BinThro) containing an axially chiral binaphthyl moiety and phenanthroline unit was synthesized from BINOL. The enantioselective 1,2-addition of dialkylzinc to aldehydes was performed in the presence of BinThro, thus giving optically active secondary alcohol with high enantioselectivity (up to 95% ee).

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

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The novel N,N,O-tridentate phenanthroline ligand (BinThro) bearing an axially chiral binaphthyl backbone prepared from BINOL was 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 two cis-oriented 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 created an obstacle in the development of chiral ligands based on the 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, most of the chiral ligands have been prepared from the condensation of chiral natural carbonyl compounds such as pinanone and camphor.⁴ Therefore, these types of ligands 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 *BIN*OL-derived phenan*thro*line (*S*)-1 (abbreviated as BinThro)

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

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 the MOM protecting group under acidic conditions afforded the desired products (*S*)-1. In the 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

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(*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 a readily tunable axially chiral binaphthyl unit. Two divided roles are assumed as the phen backbone for the coordinative site and the binaphthyl backbone for the chiral environment.

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 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 have been rarely studied.⁸ Although a variety of chiral ligands for the enantioselective addition of organozinc reagents has been discovered so far, 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 the substituent effect of (*S*)-**1** identified that the introduction of an aromatic group at the 2-position of one naphthyl moiety without phen backbones (Ar group of (*S*)-**1**) led to the dramatic increase of not only the yield but also enantioselectivity. For example, the use of ligand (*S*)-**1c** bearing a 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

Table 1 S	creening of ligan	ds (S)- 1 ^a	
		-BinThro 1 (5 mol%) Et ₂ Zn (2 equiv)	OH
Ph		Et ₂ O, 0 °C, 12 h	
	2a		3a
Entry	1	$\operatorname{Yield}^{b}(\%)$	ee ^c (%)
1	1a	37	3 (R)
2	1b	17	2(R)
3	1c	85	84 (R)
4	1d	99	85 (R)
5	1e	98	87 (R)
6	1f	99	90 (R)
7	1g	44	86 (R)
8^d	1f	96	90 (R)

^{*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%.

 Table 2
 Scope of substrate^a

	1		
	(S)-BinThro 1f	(2 mol%)	
	0 Et₂Zn (2 e	quiv) OH	
	R H Et ₂ O, 0 °C, 12 h R		
	2	3	
Entry	R	$\operatorname{Yield}^{b}(\%)$	ee ^c (%)
1	<i>o</i> -Tolyl (2 b)	67 (3b)	90 (R)
2	m-Tolyl (2c)	87 (3c)	91 (R)
3	p-Tolyl (2d)	70 (3d)	88 (R)
4^d	p-MeO-C ₆ H ₄ (2e)	94 (3e)	88 (R)
5	$p-F_{3}C-C_{6}H_{4}(2f)$	84 (3f)	93 (R)
6	p-Ac-C ₆ H ₄ (2g)	75 (3g)	93 (R)
7	p-CN-C ₆ H ₄ (2h)	51 (3h)	91 (R)
8	1-Np (2i)	$45(85)^{e}(3i)$	95 (R)
9	2-Np (2j)	>99(3j)	88 (R)
10	PhCH=CH (2k)	52 (3k)	59 (R)

^{*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%.

catalytic activity (entry 2). Therefore, we conducted a further detailed study on the substituent effect of the phenyl group of (*S*)-**1c**. The attachment of the *p*-tolyl or 3,5-xylyl group improved the enantioselectivity slightly (entries 4 and 5). Finally, we determined (*S*)-**1f** with a 3,5-bistrifluoromethyl 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).

Next, we examined the scope of aromatic aldehydes 2 (Table 2). Regardless of the position of the 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 the electronic effect of the substrate, both p-anisaldehyde 2f and p-trifluoromethylbenzaldehyde 2g can be employed for this transformation (entries 4 and 5). The aldehyde (2h) bearing an electrophilic keto moiety was also tolerated without giving the side products *via* nucleophilic addition to ketone⁹ (entry 6). Similarly, the aldehyde (2h) with a 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 reagents 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).

To reveal more about the essential functionality within the 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 the phen structure to the monodentate quinoline scaffold¹² had a negative influence on the result (54% yield, -15% ee). In addition, the protection of the hydroxyl group with a methyl group resulted in the dramatic decrease of ee (34% yield, 5% ee). These experiments suggest a structural importance of the combination of the phen backbone and the phenoic



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



hydroxyl group within BinThro ligands which provide monoanionic *N*,*N*,*O*-tridentate coordination with a central Zn metal.¹³

With these observations in mind, the plausible mechanism of asymmetric induction is illustrated in Fig. 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 a Lewis acid and dialkylzinc is activated by the coordination of the 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 the bulky 3,5-bistrifluoromethylphenyl group and the aldehyde in TS-2. The subsequent nucleophilic addition occurs from the Re-face of carbonyl carbon to furnish (R)-3a. This plausible mechanism clearly matches the fact that (S)-1a having no substituent on the naphthyl group did not work as an effective ligand at all (Table 1, entry 1).

In summary, we developed a novel type of axially chiral, N,N,O-tridentate phen ligand, BinThro ligand (*S*)-1. Design of the BinThro ligand is based on the concept of innovation utilizing phen units which has superior coordination ability with a wide range of metal ions. The first attempt testing the

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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