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Enantioselective phenyl transfer to aldehydes using 1,1′-bi-2-naphthol-3,3′-dicarboxamide as chiral auxiliary

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Abstract—*N*,*N*,*N*′,*N*′-Tetra-*n*-butyl-BINOL-3,3′-dicarboxamide **5d** was found to promote phenyl transfer from ethylphenylzinc to both aromatic and aliphatic aldehydes with high enantioselectivity up to 96% ee in *tert*-butyl methyl ether.

Asymmetric synthesis of optically active arylcarbinols has attracted much attention due to their high usability as starting materials; for example, diarylcarbinols are useful precursors for the synthesis of pharmacologically active compounds such as (*R*)-neobenodine, (*R*)-orphenadrine and (*S*)-carbinoxamine.[1] Enantioselective aryl transfer to aldehydes is a straightforward method for the synthesis of chiral arylcarbinols. Ethyl transfer from diethylzinc to aldehydes shows high enantioselectivity in the presence of various chiral amino alcohols[2] and aryl transfer to aldehydes using diarylzinc also seems a promising approach to arylcarbinols. However, the aryl transfer has gained only limited success.[3] In 1997, Fu et al. for the first time reported phenyl transfer to aldehydes using diphenylzinc in the presence of azaferrocene **1**, albeit with moderate enantioselectivity of 57% ee (Fig. 1).[4] This sub-standard enantioselectivity has been attributed to an uncatalyzed phenyl transfer due to the relatively high reactivity of diphenylzinc. Subsequently to this, Pu et al. reported that 3,3′-diarylbinaphthol **2** was an excellent chiral auxiliary for phenyl transfer reaction; however, low substrate concentration (5 mM) and relatively high catalyst-loading (20 mol %) were required to suppress the undesired background reaction.[5a,b] Ha et al. recently reported that high enantioselectivity was achieved even under higher substrate concentration (50 mM) by using 2-dialkylaminomethyl-2′-hydroxy-1,1′-binaphthyl (10 mol %) as the chiral auxiliary, though good substrates are limited to aromatic aldehydes.[5c] On the other hand, Bolm et al. reported that the background reaction could be suppressed by using less reactive ethylphenylzinc that is readily available by mixing diphenylzinc and diethylzinc in a 1:2 ratio, as a phenyl transfer reagent[6] and excellent enantioselectivity was realized in the presence of ferrocene **3**[6a] or cyrhetrene **4**.[6b] In addition, Bolm et al. reported that mixing diethylzinc and phenylboronic acid[7a,c] or triphenylborane[6e,7b] was a practical method for the preparation of ethylphenylzinc, which enabled disuse of rather expensive diphenylzinc. Quite recently, 2-piperidino alcohol[8a] and aminonaphthol[8b] have been reported to be effective chiral auxiliaries for phenyl transfer to aldehydes, when ethylphenylzinc is used as a phenyl transfer reagent.

As described above, a BINOL derivative has been reported to be a useful chiral auxiliary for asymmetric ethyl and phenyl transfers, though low substrate concentration and relatively high catalyst loading (20 mol %) are required.[5a,b] We had also previously reported that *N*,*N*,*N*′,*N*′-tetraalkyl-1,1′-bi-2-naphthol-3,3′-dicarboxamides **5** serve as efficient chiral auxiliaries for enantioselective ethyl transfer to aldehydes.[9] Although the precise mechanism of this reaction is still unclear, we had proposed that ligand **5** makes a bi-zinc chelate intermediate, in which one zinc ion serves as a Lewis acid and the nucleophilicity of the other diethylzinc captured by

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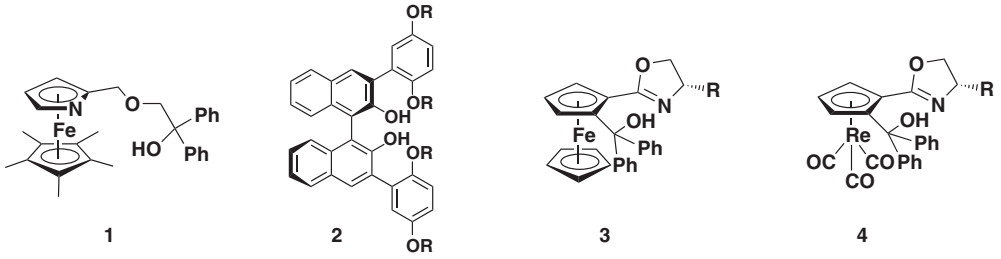
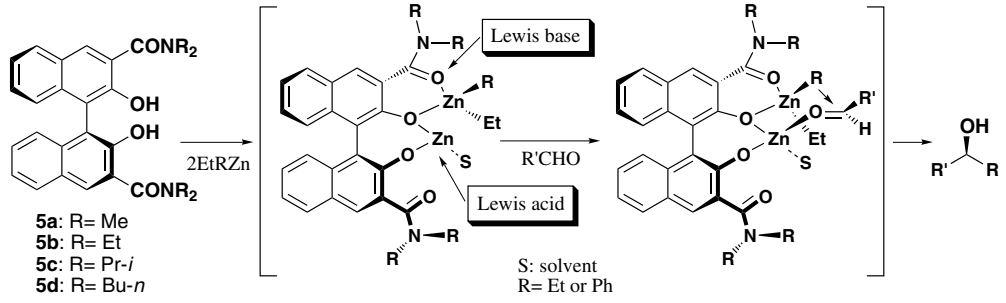


Figure 1.

5 is enhanced by the coordination of an amide carbonyl group, based on the X-ray analysis and the NMR study (Scheme 1, R = Et). Consequently, we expected that phenyl transfer from ethylphenylzinc ligated to **5** would be much faster than that from free phenyl transfer and the undesired uncatalyzed reaction should be suppressed. Thus, we examined enantioselective phenyl transfer using ethylphenylzinc[7a] in the presence of **5**.

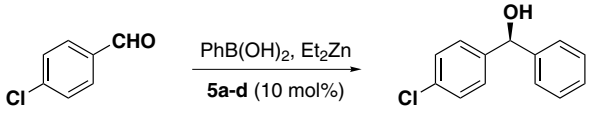
Different from ethyl transfer, however, the orientation of ethylphenylzinc (R = Ph) anchored to the chiral auxiliary must be regulated appropriately in the phenyl transfer (Scheme 1) and the solvent coordinated to the Lewis acidic zinc ion was considered to play an important role in the regulation of the intermediate. Taking into account this possibility, we set out a study on asymmetric phenyl transfer.

First, we examined the phenyl transfer to *p*-chlorobenzaldehyde as the test substrate using 10 mol % of chiral auxiliaries **5** in toluene (Table 1). A toluene solution of the ethylphenylzinc used was prepared according to Bolm's procedure[7a] (see experimental procedure). The rate and the enantioselectivity of the reactions depended



Scheme 1.

Table 1. Enantioselective phenyl transfer to *p*-chlorobenzaldehyde using **5a–d** as chiral auxiliaries[a]



Entry	Auxiliary	Solvent	Time (h)	Yield (%)	ee[b] (%)	Config.[c]
1	**5a**	Toluene	2.5	93	83	*S*
2	**5b**	Toluene	2.5	88	86	*S*
3	**5c**	Toluene	2.5	89	62	*S*
4	**5d**	Toluene	2.5	100	88	*S*
5[d]	**5d**	Toluene	18	72	84	*S*
6	**5d**	Toluene–CH_2Cl_2 (1:1)	4	86	83	*S*
7	**5d**	Toluene–AcOEt (1:1)	2	95	81	*S*
8	**5d**	Toluene–CH_3CN (1:1)	24	59	2	*S*
9	**5d**	Toluene–DMF (1:1)	—[e]	—	—	—
10	**5d**	Toluene–THF (1:1)	72	85	81	*S*
11	**5d**	Toluene–Et_2O (1:1)	4	89	93	*S*
12	**5d**	Toluene–TBME (1:1)	2.5	93	95	*S*

[a] All reactions were carried out with molar ratio of *p*-chlorobenzaldehyde/$PhB(OH)_2$/diethylzinc/**5** = 1:2.5:7.5:0.1. The substrate concentration is 36 mM.

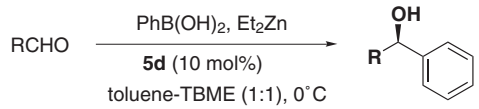
[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralcel OB-H; hexane/*i*-PrOH = 70:30).

[c] Determined by comparison of elution order of HPLC with the reported value (Refs. 6a and 8a).

[d] 10 mol % of DiMPEG was added.

[e] No reaction occurred.

Table 2. Enantioselective phenyl transfer to aldehydes using **5d** as a chiral auxiliary[a]



Entry	R in RCHO	Time (h)	Yield (%)	ee[b] (%)	Config.[c]
1	2-Naphthyl (**6a**)	2.5	100	96	*S*
2	4-Biphenylyl (**6b**)	1	86	94	*S*
3	4-Methoxyphenyl (**6c**)	4.5	98	86	*S*
4	2-Methylphenyl (**6d**)	2	87	88	*S*
5	*i*-Propyl (**6e**)	2.5	63	91	*R*
6	*n*-Hexyl (**6f**)	1	81	91	*R*

[a] All reactions were carried out with molar ratio of aldehyde/$PhB(OH)_2$/diethylzinc/**5** = 1:2.5:7.5:0.1.
[b] Determined by HPLC analysis using chiral stationary phase column according to the literature (Refs. 6a and 8a).
[c] Determined by comparison of elution order of HPLC with the reported value (Refs. 6a and 8a).

on the *N*-alkyl group of **5**. Of the auxiliaries **5a**–**d** examined, those (**5b** and **5d**) bearing a primary alkyl group served well and the best enantioselectivity of 88% ee was obtained when **5d** was used (entry 4). The reaction with **5c** that bears a bulky *N*-isopropyl group showed reduced enantioselectivity (entry 3). We examined the additive effect of a polar solvent on enantioselectivity of the reaction by using **5d** as the chiral auxiliary, based on the above hypothesis (vide supra). Bolm et al. reported that the enantioselectivity was improved by the addition of a catalytic amount of DiMPEG,[7a,c] but the addition of DiPMEG to the present reaction medium somewhat deteriorated enantioselectivity and chemical yield (entry 5). Addition of acetonitrile or *N*,*N*-dimethylformamide (DMF) as co-solvent had adverse effect (entries 8 and 9) and the effect of that of dichloromethane, ethyl acetate, or tetrahydrofuran (THF) also was somewhat negative (entries 6, 7 and 10). However, addition of ethyl ether or *tert*-butyl methyl ether (TBME) exerted a positive effect and the enantioselectivity was enhanced to 95% ee, especially when TBME was used as the co-solvent (entries 11 and 12).[10]

Under the optimized conditions, we next examined the reactions of several other aldehydes (Table 2). Reactions of aromatic aldehydes showed high enantioselectivity without using low substrate concentration and with relatively less catalyst loading (10 mol %), though the presence of an electron-donating or *ortho*-substituted group somewhat reduced enantioselectivity (entries 3 and 4). In the previous studies,[5c,6b,8a] the phenyl transfer to linear aliphatic aldehydes generally showed diminished enantioselectivity, except for only a few examples.[5a,b,7b] To our delight, the reactions of aliphatic aldehydes, with or without a substituent, under the present conditions proceeded with high enantioselectivity of 91% ee (entries 5 and 6). It is noteworthy that the *si*-face of aldehyde was preferentially attacked by the phenyl group and this sense of asymmetric induction is comparable to that observed in the ethyl transfer to aldehydes, as described in Scheme 1.

In conclusion, we have demonstrated that *N*,*N*,*N*′*N*′-tetra-*n*-butyl-BINOL-3,3′-dicarboxamide **5d** is an efficient chiral auxiliary for phenyl transfer to both aromatic and aliphatic aldehydes. The present results indicated that a 1,1′-bi-2-naphthol derivative bearing an ancillary nucleophilic subunit can be a promising chiral auxiliary for asymmetric aryl transfer reaction. Further studies on the construction of a new chiral auxiliary and clarification of the reaction mechanism are underway in our laboratory.

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10. Typical experimental procedure is exemplified by enantioselective phenyl transfer to *p*-chlorobenzaldehyde: To a stirring suspension of phenylboronic acid (60.9 mg, 0.5 mmol) in toluene (2.0 ml) was added diethylzinc (1.5 ml, 1.02 mol dm^{-3} in hexane) at room temperature and then raised to 60 °C. After being stirred for 12 h at the temperature, the mixture was cooled to room temperature and added to a solution of **5d** (11.9 mg, 0.02 mmol) in *tert*-butyl methyl ether (2.0 ml) at 0 °C. The mixture was stirred for another 15 min and, subsequently, *p*-chlorobenzaldehyde (28.1 mg, 0.2 mmol) was added. After being stirred for 2.5 h at the same temperature, the mixture was quenched with water, allowed to warm to room temperature, and extracted with dichloromethane. The organic extract was dried over anhydrous $MgSO_4$, and concentrated. Silica gel chromatography of the residue (hexane–ethyl acetate = 19:1–9:1) gave the desired product (40.7 mg, 93%) as an oil. Enantiomeric excess of the product was determined to be 95% by HPLC using chiral stationary phase column (Refs. 6a and 8a).