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Highly Enantioselective Phenyl Transfer to Aryl Aldehydes Catalyzed by Easily Accessible Chiral Tertiary Aminonaphthol

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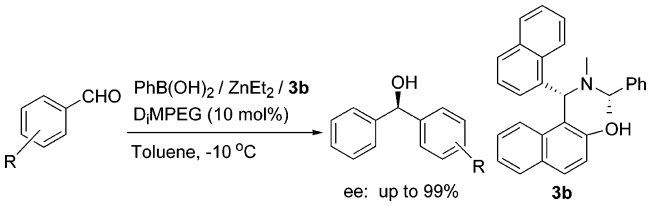

A new chiral tertiary aminonaphthol ligand **3b** served as a highly efficient ligand for the asymmetric catalytic phenyl transfer to aromatic aldehydes and a variety of chiral diarylmethanols was prepared in high ee values (ee up to 99%) and chemical yields. The straightforward syntheses of both **3b** and its enantiomer provide an excellent opportunity for large-scale applications.

Since chiral diarylmethanols are valuable intermediates in the manufacture of pharmacologically and biologically active compounds,[1] the development of effective catalyst systems for the synthesis of these compounds is of substantial interest not only to the academia but also to industrial scientists. Two conceptually different approaches have been used, namely (1) asymmetric reduction of the corresponding unsymmetrical diaryl ketones[2] and (2) enantioselective phenyl transfer to aromatic aldehydes.[3] The reduction method requires the presence of electronically and/or stereochemically differentiated aryls for optimum results, and the second method seems more suitable for chiral induction because of the large steric and electronic differences between an aryl group and a hydrogen atom on an aldehyde substrate.

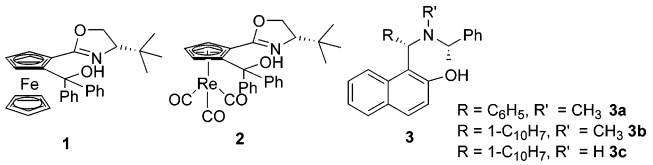

FIGURE 1. Planar-chiral ligands and optically active aminonaphthol.

However, two major factors have hindered the development of the practical catalytic asymmetric phenyl transfer reaction as compared to the well-established enantioselective alkylations[4] of aldehydes: the lack of appropriate and affordable chiral ligands and phenyl transfer reagent. While diphenylzinc has been used as a phenyl transfer reagent in the catalytic reaction, its considerable background reaction with aldehydes is a bane to achieving good results.[4] Modification was later made to moderate its undesired activity by the concomitant use of diethylzinc.[5a] Recently, Bolm and co-workers reported an excellent protocol wherein the aryl transfer reagent was generated by mixing arylboronic acids, substantially more stable and less expensive reagents than diphenylzinc, with diethylzinc.[6] Unfortunately, ligands which effectively catalyze the phenyl transfer reactions to aryl aldehydes with high ee values are relatively rare,[3] and the known catalysts largely comprise planar-chiral ligands[7] such as ferrocene **1**,[5,7b] cyrhetrene **2**[7c] (Figure 1), or other axially chiral ligands.[8,9] In most previously reported preparations for these chiral ligands, multistep syntheses are required, and/or the desired enantiomers are unavailable. Thus, the development of new easily prepared and effective chiral ligands is an important challenge for the practical applications of phenyl transfer reactions. In this paper, we wish to report our successful endeavor in this area by using new readily accessible chiral tertiary aminonaphthol **3b** as ligand.

A preliminary study was performed to test the catalytic property of the known ligand **3a** in the phenyl transfer

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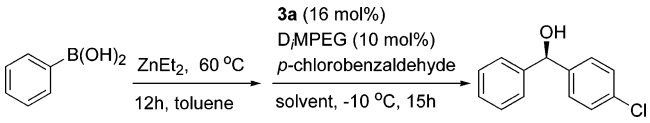
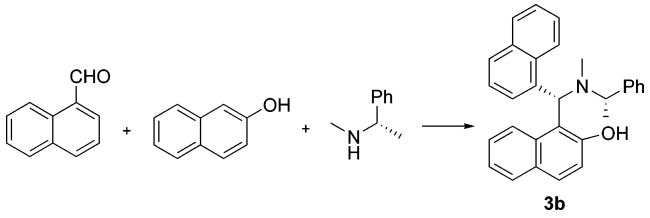
TABLE 1. Catalytic Asymmetric Phenyl Transfer to *p*-Chlorobenzaldehyde[a]



entry	solvent	T (°C)	yield (%)[c]	ee (%)[d]
1	THF[b]	0	92	82
2	Et_2O[b]	0	88	79
3	toluene	0	94	86
4	toluene	−10	91	89
5	hexane[b]	0	44	63

[a] 2.0 equiv of $PhB(OH)_2$ and 6.0 equiv of $ZnEt_2$ were used for preparation of the phenyl transfer reagent as described in the typical procedure. [b] The addition was conducted in a mixture of toluene and other solvent in the ratio of 1:2. [c] Isolated yield. [d] Determined by HPLC analysis.

SCHEME 1. Synthesis of 3b



reaction to *p*-chlorobenzaldehyde. Indeed, the reaction of the nucleophile, preformed from phenylboronic acid and diethylzinc in toluene according to the Bolm's protocol, with *p*-chlorobenzaldehyde in the presence of **3a** (16 mol % with respect to the aldehyde) and a polyether (DiMPEG) in various solvents and temperatures afforded (*R*)-*p*-chlorobenzhydrol in 63−89% ee and in good yields (Table 1). The optimum yield and ee were obtained when the reaction was performed at −10 °C in toluene during 15 h (entry 4).

With this encouraging result, attention was turned to designing a new optically active tertiary aminonaphthol ligand for this reaction. We surmised that the attachment of a bulkier group at the new chiral center should favor selection of a conformationally more restricted transition state, which should be beneficial for stereochemical induction.

Thus, we tried to adopt the one-step procedure for the preparation of **3a**[10] to synthesize ligand **3b**. The direct condensation of 1-naphthaldehyde, 2-naphthol, and (*S*)-(−)-*N*,α-dimethylbenzylamine in the absence of solvent gave a homogeneous phase (Scheme 1). After 3 days of stirring at 85 °C, the product **3b** was precipitated directly as a white solid (51% yield, diastereomeric ratio >98.5:1.5) by simply adding methanol to the reaction mixture at room temperature. Up to 50 g of **3b** can be prepared in one batch, which underscores the practicality of this method. Further, the product can be used directly in the phenyl transfer reactions without any further purification. The reaction is also "atom-economic" in that no solvent is required and water is the only byproduct. This simple and environmentally friendly operational procedure, coupled with the use of inexpensive reagents, renders the synthesis amenable to industrial application.

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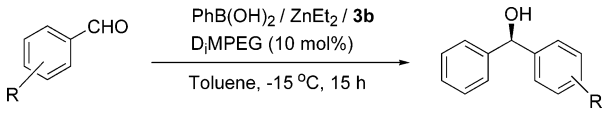
TABLE 2. Catalytic Asymmetric Phenyl Transfer to Various Aldehydes[a]



4a-4i 5a-5i

entry	aldehyde	R	(*S*,*S*)-**3b** (mol %)	yield (%)[b]	ee (%)[c]
1	**4a**	*p*-Cl	16	90	94
2	**4a**	*p*-Cl	8	89	92
3	**4b**	*o*-Cl	16	93	97
4	**4b**	*o*-Cl	8	91	97
5	**4c**	*o*-F	8	93	97
6	**4d**	*o*-Br	8	90	97
7	**4e**	*o*-OMe	8	93	96
8[d]	**4e**	*o*-OMe	8	87	97
9	**4f**	*o*-Me	8	94	98
10[e]	**4f**	*o*-Me	8	95	98
11[d]	**4f**	*o*-Me	8	90	99
12	**4g**	*m*-Me	16	87	95
13	**4h**	*p*-Br	16	90	94
14	**4i**	p-Me	16	93	94

[a] 2.0 equiv of $PhB(OH)_2$ and 6.0 equiv of $ZnEt_2$ were used for preparation of the phenyl transfer reagent as described in the typical procedure. [b] Isolated yield. [c] Determined by HPLC analysis. All products were of *R*-configuration, except for that in entry 10. [d] $ZnMe_2$ was used instead of $ZnEt_2$. [e] (*R*,*R*)-**3b** was used as catalyst to give the product with *S*-configuration.

The absolute configuration of **3b** was established by chemical correlation. Thus, *N*-methylation[11] of known compund **3c**[12] gave a product with NMR spectra and an optical rotation value ($[\alpha]^{20}_D$ +773 (*c* 1.2, $CHCl_3$)) identical or consistent with those of **3b** ($[\alpha]^{20}_D$ +770 (*c* 1.1, $CHCl_3$)).

Ligand **3b** induced a higher enantioselectivity than **3a** in the catalytic phenyl transfer reaction to *p*-chlorobenzaldehyde under the same conditions (Table 2, entry 1), which was in line with our anticipation. In Table 2 are given the results of asymmetric phenyl transfer to a variety of aryl aldehydes catalyzed by **3b** to provide the corresponding chiral diarylmethanols with high ee values and yields. Dimethylzinc in toluene could also be used to generate the phenyl transfer reagent with $PhB(OH)_2$, giving similar ee's values but with lower chemical yields under otherwise identical reaction conditions (entries 8 and 11). Even for ortho-substituted benzaldehydes, which are problematic with some other catalyst−ligand systems, a catalyst loading of 8 mol % was sufficient to achieve high ee (entry 4 vs 3). Interestingly, in contrast to the trends that have been observed previously with planar[7b,c] and axial[8] chiral ligands, ortho-substituted benzaldehydes gave higher ee values than other substrates under the catalysis with **3b**. Particularly noteworthy is that (*S*)-*o*-methyl benzhydrol **5f**, obtained in 99% ee, is the direct precursor of orphenadrine **6** (Figure 2), an anticholinergic and antihistaminic agent (entry 10). In all cases, no ethyl transfer is observed even in the presence of an excessive amount of diethylzinc, which is consistent with Bolm's results[6] and related theoretical

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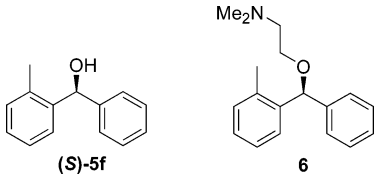

FIGURE 2. Compound (*S*)-**5f** and orphenadrine **6**.

TABLE 3. Preparation of (*S*)-5f on a 20-g Scale via Asymmetric Phenyl Transfer Reaction Catalyzed by (*R*,*R*)-3b[a]

entry	catalytic loading (mol %)	substrate concn (mol/L)	time (h)	yield (%)	ee (%)
1	5	0.2	30	93	97
2	3	0.2	48	93	96
3	1	0.5	48	89	96
4	1	0.8	36	92	95

[a] The reactions were performed in toluene according to the typical procedure.

study.[5b] As for the mechanism of this reaction, it appears that the phenylzinc species was produced in situ by boron-to-zinc exchange[6] and the reactive catalyst was formed from the aminonaphthol ligand and zinc species.

In light of the commercial importance of compound **5f**, we examined two additional reaction parameters, catalyst loading and substrate concentration, which are key determinants of the amount of product that can be produced with a finite catalyst amount and reactor volume. The experiments were performed on a 20-g scale (Table 3). It was noted that the resulting enantioselectivity was almost unaffected by the substrate concentration. The reaction can be performed at up to 4-fold higher concentrations than that employed under standard conditions, and still works at the relatively low catalyst loading of 1 mol % without severe erosion in ee and yield.

Another advantage of **3b** is that its enantiomer could be easily synthesized from the equally inexpensive (*R*)-(−)-*N*-α-dimethylbenzylamine. Hence, both enantiomers of the diarylmethanols are accessible (Table 2, entry 9 vs 10).

In conclusion, chiral tertiary aminonaphthol **3b** is a highly efficient ligand for the asymmetric catalytic phenyl transfer to aromatic aldehydes with the $PhB(OH)_2/ZnEt_2$ or $PhB(OH)_2/ZnMe_2$ systems. An array of chiral diarylmethanols were prepared in high ee values and chemical yields. The simple synthetic methodology used for the preparation of both **3b** and its enantiomer provide an excellent opportunity for large-scale applications.

Experimental Section

Preparation of 3b. 1-Naphthaldehyde (2.70 mL, 20 mmol), (*S*)-(−)-*N*,α-dimethylbenzylamine (2.60 g, 19 mmol), and 2-naphthol (2.43 g, 16 mmol) were charged into a 25-mL round-bottom flask with a magnetic stirring bar. The mixture was heated to 85 °C and stirred for 72 h. After the system was cooled to room temperature, methanol (5 mL) was added and the precipitated product was collected and washed with methanol (5 mL). White crystals of tertiary aminonaphthol **3b** (3.41 g, 51%) were obtained. $[\alpha]^{20}_D$ +770 (*c* 1.1, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz) δ 14.01 (br s, 1H), 7.77−7.02 (m, 18H), 6.45 (s, 1H), 4.40 (br s, 1H), 1.95 (s, 3H), 1.65 (br s, 3H). ^{13}H NMR ($CDCl_3$, 125 MHz) δ 19.0, 30.5, 60.1, 60.7, 116.2, 120.4, 121.3, 122.6, 125.5, 126.2, 126.6, 126.9, 127.6, 128.6, 128.68, 128.7, 128.9, 129.0, 129.1, 129.4, 129.7, 129.9, 132.9, 132.94, 133.9, 134.9, 136.6, 158.2. MS (EI) *m*/*z* (rel intensity) 418 ($M^+ + 1$), 283, 141, 136. HRMS (EI) calcd for $C_{30}H_{28}NO$ ($M^+ + 1$) 418.2171, found 418.2135.

Typical Procedure for the Phenyl Transfer Reaction. A solution of the phenylboronic acid (2.0 equiv) and diethylzinc (6.0 equiv) in toluene was stirred at 60 °C for 12 h then cooled to 0 °C, and ligand and D*i*MPEG (10 mol %) were then added. The mixture was cooled to −10 °C, then the aldehyde (1.0 equiv) was subsequently added. After being stirred for 15 h at −10 °C, the reaction was quenched with 1 N HCl, the mixture was extracted with EtOAc and dried over Na_2SO_4, and solvent was removed in vacuo. The purification of the residue by flash chromatography gave the diarylmethanol.

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Supporting Information Available: HPLC analysis and ^1H NMR spectral data for **5a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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