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Asymmetric Synthesis of Functionalized Diarylmethanols Catalyzed by a New γ-Amino Thiol

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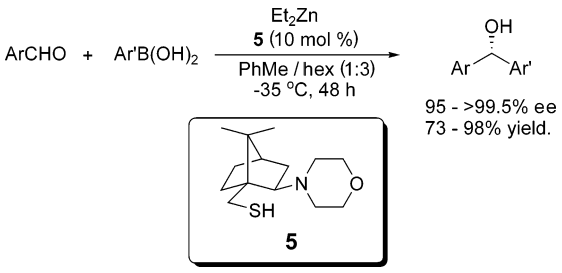

A mild asymmetric arylation of aromatic aldehydes catalyzed by γ-amino thiol **5** gave the corresponding diarylmethanols with 95 to >99.5% ee.

Chiral diarylmethanols play an important role in the synthesis of biologically active compounds,[1] such as orphenadrine (**1**), neobenodine (**2**),[1d] carbinoxamine (**3**)[1e] (Figure 1) and others[2] which possess a common core feature in novel drug design. In addition to their direct applications, chiral diarylmethanols could also serve as useful intermediates in the synthesis of drugs. For example, CDP-840 (**4**) (Figure 1)[3] and its analogues are PDE-IV inhibitors that are potent therapeutic agents for the treatment of asthma and chronic obstructive pulmonary disease.[4] Preparation of optically active trisubstituted diarylmethanes in this analogues can be achieved without any loss of optical purity by nucleophilic displacement[5] at the hydroxyl-bearing stereogenic center in optically active diarylmethanols.

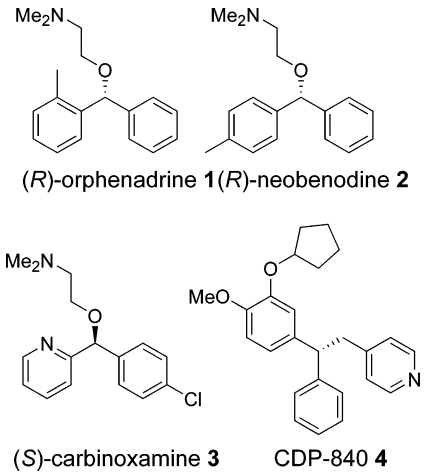

FIGURE 1. Biologically active diarylmathanol derivatives and CDP-840.

Among the methods available for the synthesis of chiral diarylmethanols,[6] the asymmetric addition of diphenylzinc[7−9]

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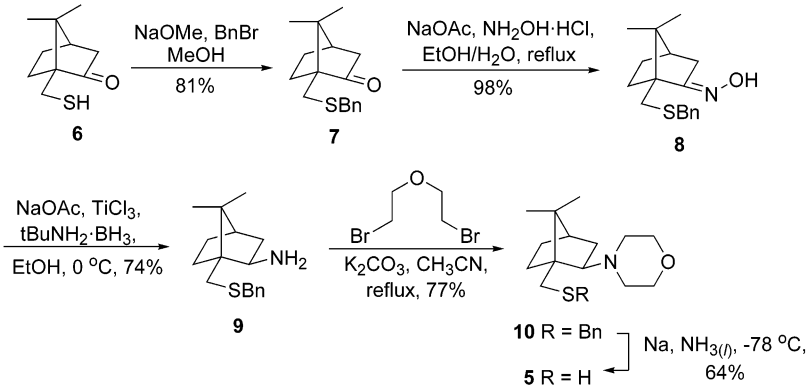
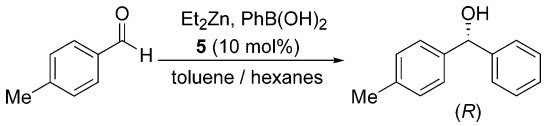
SCHEME 1. Synthesis of a New γ-Amino Thiol Ligand



showed the advantages of wide substituent tolerance, mild reaction conditions, and the use of low-toxic zinc metal. Although high enantioselectivities have been achieved, the nonsubstituted phenyl group as a transferring nucleophile limited the application. More recently, an elegant method where arylzinc reagent was prepared by transmetalation between arylboronic acids and diethylzinc was reported by Bolm's group[10] and later by others including other arylation compounds as aryltransfer reagents.[11] This modified methodology broadened the scope of such an addition reaction and enabled synthetic chemists to elaborate functionalized arylzinc reagents as nucleophiles in salt-free conditions. Nevertheless, unlike some of the previous reports in the asymmetric addition of diphenylzinc, an additive such as DiMPEG[12] was usually used to ensure high selectivities in Bolm's and Chan's examples. Therefore, the search for a catalytic system that catalyzes the asymmetric arylation of aromatic aldehydes and will not require an additive remains attractive.

We are interested in employing camphor-derived ligands in asymmetric catalysis.[13] Here, we report our findings in the asymmetric arylation reaction of aromatic aldehydes catalyzed by (−)-2-*exo*-morpholinoisobornane-10-thiol **5**. Amino thiol **5** was prepared from keto thiol **6**[14] in five steps, as outlined in Scheme 1. Direct formation of **10** from **7** by reductive amination with morpholine was unsuccessful. As a result, **10** was prepared by the condensation of **7** with hydroxyamine, followed by reduction with $TiCl_3$ and $^tBuNH_2{\cdot}BH_3$ with >95% diastereoselectivity[15] and N,N-dialkylation with 2-bromoethyl ether in a reasonable yield. Amino thiol **5** was obtained from the reduction of **10** with sodium in liquid ammonia at −78 °C in 64% yield.

TABLE 1. Asymmetric Phenylation of 4-Tolualdehyde Catalyzed by 5[a]



entry	temp (°C)	time (h)	T/H[b]	yield (%)[c]	ee (%)[d]
1	18	5	0/1	81	90
2	18	5	1/3	90	92
3	18	5	5/3	80	90
4	0	12	1/3	83	95
5	−20	24	1/3	83	96
6	−35	48	1/3	84	97
7[e]	0	24	1/3	67	95

[a] Conditions: 2 equiv of $PhB(OH)_2$ and 6 equiv of Et_2Zn was used with respect to ArCHO. [b] The ratio of solvents: T, toluene; H, hexanes. [c] Isolated yield. [d] Determined by chiral HPLC; see the Supporting Information. [e] 10 mol % of DiMPEG was added.

The asymmetric phenylation reaction catalyzed by **5** was first tested in the case of 4-tolualdehyde. The phenylzinc reagent was prepared in situ by heating a mixture of diethylzinc and phenylboronic acid in hexanes to 60 °C for 12 h. When the phenylzinc reagent was mixed sequencially with 10 mol % of **5** and 4-tolualdehyde in hexanes at 18 °C and stirred for 5 h, the corresponding diarylmethanol was obtained in 90% ee (Table 1, entry 1), and **5** was recovered in >95% yield. It was found that a slightly better selectivity could be achieved simply by using a mixed solvent containing toluene and hexanes in a 1:3 ratio (entry 2). There was no improvement of the enantioselectivity on increasing the content of toluene in the mixed solvent (Table 1, entry 3). With this encouraging result, the temperature effect of the catalytic phenylation reaction was studied. When the reaction was conducted at 0 °C, improvement of the enantioselectivity was observed (entry 4). There was some improvement of the enantioselectivity if the reaction was conducted at a lower reaction temperature (entries 5 and 6). These results were compatible with those observed in the literature,[10,11a] where 10 mol % of DiMPEG was required as an additive. It is interesting to note that the asymmetric phenylation reaction catalyzed by **5** took a longer reaction time and gave a lower yield with a similar ee in the presence of 10 mol % of DiMPEG (entries 4 and 7). Similar observations were reported recently by Ito[11b] and Zhao.[11d] The synthesis of a direct precursor for (*R*)-neobenodine (**2**) (Figure 1), an antihistamine drug, was achieved by the addition of phenylzinc reagent with 4-tolualdehyde in a simple operation with high ee.

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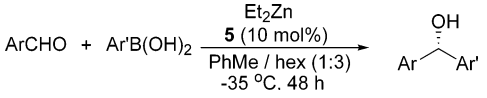
TABLE 2. Asymmetric Arylation with Aromatic Aldehydes Catalyzed by 5[a]



entry	Ar	Ar′	yield (%)[b]	ee (%)[c,d]
1	4-Tol	Ph	84	97
2	3-Tol	Ph	90	97
3	2-Tol	Ph	95	>99.5
4	4-Cl-Ph	Ph	96	96
5	3-Cl-Ph	Ph	96	95
6	2-Cl-Ph	Ph	90	98
7	4-MeO-Ph	Ph	73	97
8	4-CF_3-Ph	Ph	83	97
9	4-CO_2Me-Ph	Ph	84	96
10	2-Naph	Ph	73[e]	95
11	Ph	4-Tol	86	97
12	Ph	4-Cl-Ph	98	96

[a] Conditions: 2 equiv of $PhB(OH)_2$ and 6 equiv of Et_2Zn was used with respect to ArCHO. [b] Isolated yield. [c] Determined by chiral HPLC; see the Supporting Information. [d] In entries 1−10, the *R* form of the products was obtained, and in entries 11 and 12, the *S* form of the products was obtained. [e] 27% of the ethylation product was isolated.

To test the scope and limitations of **5** in the asymmetric catalytic arylation, we turned our attention to studying phenylation reactions with various aromatic aldehydes. When substituted aromatic aldehydes underwent phenylation under similar reaction conditions, 95 to >99.5% ee's and good to excellent chemical yields of the corresponding diarylmethanols were obtained (Table 2), except in the case of 2-naphthaldehyde, where the ethylation product was obtained in 27% yield (entry 10). An excellent enantioselectivity was observed in the case of 2-tolualdehyde, in which the product was obtained in >99.5% ee and 96% yield. The synthesis of a direct precursor for (*S*)-orphenadrine **1** (Figure 1) can be achieved by the reaction of 2-tolualdehyde in quite high efficiency. Other aryl transferring reagents also reacted very well, as demonstrated in entries 11 and 12. In general, γ-amino thiol **5** catalyzed arylation gave high chemical yields and enantioselectivities without the presence of an additional additive.[16]

In conclusion, an efficient and catalytic asymmetric synthesis of diarylmethanols by the γ-amino thiol **5** was demonstrated. This method provides a direct and convenient way to synthesize functionalized diarylmethanols with high enantioselectivities from the combination of readily available arylboronic acids and aldehydes. This is the first example of γ-amino thiol catalyzed asymmetric addition of arylzinc to aldehydes.

Experimental Section

Typical Experimental Procedure: Asymmetric Arylation of 4-Tolualdehyde Catalyzed by 5. A flask containing toluene (2 mL), phenylboronic acid (122 mg, 1 mmol), and diethylzinc (3.0 mmol, 1.0 M solution in hexanes) was heated at 60 °C for 12 h. After the flask was cooled to room temperature, the mixture was added into another flask containing **5** (12.8 mg, 0.05 mmol) and was stirred for 10 min. It was cooled to −35 °C, and a solution of 4-tolualdehyde (60 mg, 0.5 mmol) in hexanes (3 mL) was added with stirring. After 48 h at −35 °C, the reaction mixture was quenched with saturated aqueous ammonium chloride and then extracted with CH_2Cl_2 (3 × 70 mL). The organic extracts were combined, dried, and concentrated in vacuo to give the crude product. The crude product was purified on silica gel (EtOAc: hexanes = 1:6) to afford phenyl-*p*-tolylmethanol (83 mg, 84%; mp 58.5−59.5 °C) as colorless crystals.

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Note Added after ASAP Publication. There were errors in the version of Scheme 1 published ASAP December 6, 2005; the corrected version was published ASAP December 7, 2005.

Supporting Information Available: Text giving experimental procedures, ligand synthesis details, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In the case of aliphatic aldehydes, cyclohexanecarboxaldehyde was examined. The corresponding alcohol, cyclohexylphenylmethanol, was obtained in 78% yield and 98% ee.