Structural Influence of Chiral Tertiary Aminonaphthol Ligands on the Asymmetric Phenyl Transfer to Aromatic Aldehydes

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ABSTRACT A series of chiral tertiary aminonaphthol ligands were prepared from 2-naphthol, (*S*)-1-phenylethylamine, and aldehydes with diverse substituted groups. The results of asymmetric phenyl transfer to aromatic aldehydes catalyzed by these chiral ligands indicated that enantioselectivities were greatly influenced by the electronic and steric effects of the ligands. *Chirality 23:222–227, 2011.*

KEY WORDS: aminonaphthol; asymmetric phenyl transfer; electronic and steric effects

INTRODUCTION

The asymmetric phenyl transfer to aromatic aldehydes or their derivatives has attracted much attention in recent years because the chiral diaryl alcohols or amines are key intermediates for biologically active compounds, e.g., (*R*)-neobenodine, (*R*)-orphenadrine, and (*S*)-cetirizine.[1–19] Since Fu and coworkers[20] reported the first enantioselective catalytic addition with diphenylzinc in 1997, many subsequent studies seeking higher enantioselectivity of the transformation were put in practice.[21–42] Among them, Bolm and Muñiz[21] made significant contribution by introducing planar-chiral ferrocene-based hydroxy oxazolines, 2-aminocyclohexanol derivatives,[28] and β-hydroxysulfoximines[30] as catalysts to this reaction. Pu and coworkers[32–34] used a series of binaphthol derivatives as the catalyst for reaction of aromatic aldehydes with diphenylzinc, gave the corresponding diaryl methanol in good yields and high ees. Simultaneously, chiral amino alcohols were also studied for the reaction by several groups and good to excellent eanatioselectivities were obtained, Ha and coworkers[35] prepared chiral amino alcohols from (*R*)-binaphthol, Wang and coworkers[36] developed cyclopropane-based chiral amino alcohols, Pericàs and coworkers[37] made a structural optimization of a family of amino alcohol ligands with a common 2-amino-2-aryl-1,1-diphenylethanol skeleton. On the other hand, some important arylzinc and other phenyl transfer reagents for the asymmetric reaction were also reported. Kim and Walsh[38] developed a versatile method for the asymmetric arylation of aldehydes beginning with aryl bromides. Cote and Charette[39] used the weak solubility of magnesium methoxide for development a method to access both functionalized dialkylzinc and diarylzinc reagents, Zhu and coworkers[40] reported the highly efficient and facile aryl transfer to aldehydes using $ArB(OH)_2$-Me_3Ga systems.

For the advancement of the practical application of this useful reaction, appropriate and affordable chiral ligands and phenyl transfer reagents remain to be a challenge for scientists in this field. In pursuit of more effective chiral ligands with the opportunity for large-scale application, Chan and coworkers[41] developed a new chiral tertiary aminonaphthol ligand for the asymmetric catalytic phenyl transfer to aromatic aldehydes. Herein, we expand the scope of the study and report a series of new chiral tertiary aminonaphthol ligands and their structural influence on the phenyl transfer reaction.

EXPERIMENTAL

General Methods

The NMR spectra were recorded with TMS as the internal standard on a Varian 400 spectrometer. Coupling constants were given in Hz. Enantiomeric excess was determined by HPLC on a Chiralcel OB-H column. Optical rotations were determined on a Perkin Elmer 341 polarimeter. MS spectra were recorded on a Shimadzu LCMS-IT-TOF. All the asymmetric phenyl transfer reactions were performed under an argon atmosphere.

Preparation of 1-[(1S)-Phenyl{methyl[(1′S)-1′-phenylethyl]-amino}methyl]-2-naphthol (3a)

A mixture of 2-naphthol (0.29 g, 2.0 mmol), benzaldehyde (0.26 g, 2.4 mmol), and (*S*)-(−)-1-phenylethylamine (0.26 g, 2.1 mmol) was stirred at 60°C under nitrogen atmosphere. After stirring at reflux for 8 h (monitored by TLC), EtOH (5 ml) was added to the reaction mixture at room temperature. The white crystals were collected, washed with EtOH (3 × 3 ml), and purified by crystallization from EtOAc/hexane to give the pure compound **1a**. Colorless crystals, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 6.9 Hz, 3H), 2.35 (brs, 1H), 3.92 (q, J = 6.9 Hz, 1H), 5.47 (s, 1H), 7.15–7.83 (m, 16H), 13.70 (brs, 1H).

To an aminonaphthol **1a** (2.0 mmol) solution in THF (3 ml), 35% aqueous formaldehyde (0.17 ml, 2.2 mmol) was added, and the mixture was stirred for 15 h at room temperature. Solvent was removed, and the residue was dried under reduced pressure to afford the crude oil, which was purified by column chromatography on silica gel to give **2a** as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (d, J = 6.5 Hz, 3H), 4.13 (q, J = 6.5 Hz, 1H), 4.46 (dd, J = 10.6, 2.0 Hz, 1H), 4.68 (d, J = 10.6, 1H), 5.76 (s, 1H), 7.10–7.80 (m, 16H).

To a solution of naphthoxazine **2a** (2.0 mmol) in THF (3.5 ml), $NaBH_4$ (0.15 g, 4.0 mmol) was added at 0°C in one pot. The solution was vigorously stirred, and a solution of AcOH (2 ml) in THF (3 ml) was slowly added. After the addition, the mixture was warmed up to room temperature until complete consumption of the starting naphthoxazine (monitored by TLC) and then saturated Na_2CO_3 was added. When the emission of CO_2 ceased, the organic layer was extracted with CH_2Cl_2, dried

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(Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluted with petroleum ether/AcOEt mixture to afford white crystals of **3a**. M.p. 157–160°C, $[\alpha]_D^{20}$ = +270.5 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, *J* = 6.6 Hz, 3H), 2.14 (s, 3H), 4.25 (brq, *J* = 6.6 Hz, 1H), 5.37 (s, 1H), 7.10–8.00 (m, 16H), 14.00 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 33.2, 57.4, 68.6, 116.4, 120.2, 121.2, 122.6, 126.7, 127.9, 128.2, 128.4, 128.5, 128.8, 129.0, 129.1, 129.2, 129.3, 129.8, 132.3, 140.3, 156.1.

Similar procedures were used for the preparation of compounds **3b–3l**.

Preparation of 1-[(1S)-(2-Methylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3b)

Intermediate **1b:** colorless crystals, 83% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 8.4 Hz, 3H), 1.91 (brs, 3H), 3.86 (q, *J* = 8.4 Hz, 1H), 5.58 (s, 1H), 6.96–7.73 (m, 15H), 13.74 (brs, 1H).

Intermediate **2b:** white crystals, 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.8 Hz, 3H), 2.03 (s, 3H), 4.07 (q, *J* = 6.6 Hz, 1H), 5.00 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.07 (d, *J* = 10.8 Hz, 1H), 5.43 (s, 1H), 6.75–7.30 (m, 13H), 7.74–7.77 (m, 2H).

Ligand **3b:** white crystals, 86% yield, m.p. 152–153°C, $[\alpha]_D^{20}$ = +406.72 (*c* 0.922, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 7.2 Hz, 3H), 1.91 (s, 3H), 2.01 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 1H), 5.77 (s, 1H), 7.01–7.74 (m, 15H), 14.47 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 19.6, 29.9, 59.7, 61.2, 116.2, 120.3, 120.7, 122.3, 126.5, 127.0, 127.7, 128.2, 128.2, 129.0, 129.4, 129.5, 130.0, 130.5, 132.6, 136.1, 136.3, 137.4, 157.8. HRMS *m/z* calcd for $C_{27}H_{27}NO$ $(M+1)^+$ 382.2153, found: 382.2168.

Preparation of 1-[(1S)-(3-Methylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3c)

Intermediate **1c:** colorless crystals; 80% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, *J* = 9.2 Hz, 3H), 2.22 (brs, 3H), 3.87 (q, *J* = 9.2 Hz, 1H), 5.41 (s, 1H), 6.96–7.72 (m, 15H), 13.72 (brs, 1H).

Intermediate **2c:** white crystals, 93% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.4 Hz, 3H), 2.22 (s, 3H), 3.96 (q, *J* = 6.4Hz, 1H), 4.97 (d, *J* = 10.4 Hz, 1H), 5.12 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.16 (s, 1H), 6.79–7.40 (m, 13H), 7.73–7.77 (m, 2H).

Ligand **3c:** white crystals, 79% yield, m.p. 175.7–176.8°C, $[\alpha]_D^{20}$ = +259.5 (*c* 0.504, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 7.2 Hz, 3H), 2.10 (s, 3H), 2.26 (s, 3H), 4.21 (q, *J* = 7.0 Hz, 1H), 5.29 (s, 1H), 6.97–7.84 (m, 15H), 14.01 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 21.7, 31.9, 56.4, 67.3, 115.2, 118.9, 120.0, 121.3, 125.1, 125.4, 125.7, 126.4, 126.6, 127.2, 127.5, 127.7, 127.8, 127.9, 128.2, 128.5, 131.1, 137.4, 138.9, 154.9. HRMS *m/z* calcd for $C_{27}H_{27}NO$ $(M+1)^+$ 382.2153, found: 382.2171.

Preparation of 1-[(1S)-(4-Methylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3d)

Intermediate **1d:** colorless crystals, 50% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, *J* = 9.2 Hz, 3H), 2.31 (s, 3H), 2.35 (b, 1H), 3.95 (b, *J* = 9.2 Hz, 1H), 5.51 (s, 1H), 7.07–7.80 (m, 15H), 13.86 (b, 1H).

Intermediate **2d:** white crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.6 Hz, 3H), 2.32 (s, 3H), 4.02 (q, *J* = 6.6 Hz, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 5.19 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.21 (s, 1H), 6.90–7.50 (m, 13H), 7.80–7.90 (m, 2H).

Ligand **(3d):** white crystals, m.p. 155–160°C, $[\alpha]_D^{20}$ = +238.5 (*c* 1.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 7.0 Hz, 3H), 2.14 (s, 3H), 2.26 (s, 3H), 4.24 (q, *J* = 7.0 Hz, 1H), 5.34 (s, 1H), 7.00–8.00 (m, 15H), 14.10 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 21.2, 33.1, 57.2, 68.3, 116.6, 120.1, 121.2, 122.6, 123.0, 126.6, 127.8, 128.5, 128.6, 129.0, 129.2, 129.3, 129.6, 131.4, 132.3, 137.2, 137.8, 156.0.

Preparation of 1-[(1S)-(2-Furylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3e)

Intermediate **1e:** colorless crystals, 85% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.33 (brs, 1H), 3.93 (q, *J* = 6.8 Hz, 1H), 5.84 (s, 1H), 6.92–7.78 (m, 15H), 13.55 (brs, 1H).

Intermediate **2e:** white crystals, yield 92%. ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.8 Hz, 3H), 4.10 (q, *J* = 6.8 Hz, 1H), 5.012 (d, *J* = 11.2, 1H), 5.05 (dd, *J* = 11.2, 1.6 Hz, 1H), 5.56 (s, 1H), 6.75–7.33 (m, 13H), 7.72–7.76 (m, 2H).

Ligand **3e:** white crystals, 81% yield, m.p. 134.2–134.8°C, $[\alpha]_D^{20}$ = +255.9 (*c* 1.11, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.4 Hz, 3H), 2.21 (s, 3H), 4.27 (q, *J* = 6.4 Hz, 1H), 5.98 (s, 1H), 6.86–8.00 (m, 15H), 14.09 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 30.3, 54.8, 58.5, 113.9, 114.1, 114.3, 118.9, 118.9, 121.6, 123.9, 125.7, 125.8, 127.0, 127.1, 127.7, 127.8, 128.7, 128.8, 129.2, 131.1, 134.9, 154.5, 157.5, 160.0. HRMS *m/z* calcd for $C_{26}H_{24}FNO$ $(M+1)^+$ 386.1920, found: 386.1926.

Preparation of 1-[(1S)-(3-Furylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3f)

Intermediate **1f:** colorless crystals, 82% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.0 Hz, 3H), 2.28 (brs, 1H), 3.89 (q, *J* = 6.0 Hz, 1H), 5.47 (s, 1H), 6.90–7.78 (m, 15H), 13.55 (brs, 1H).

Intermediate **2f:** white crystals, 90% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.4 Hz, 3H), 3.96 (q, *J* = 6.4 Hz, 1H), 4.90 (d, *J* = 10.4, 1H), 5.13 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.16 (s, 1H), 6.78–7.35 (m, 13H), 7.73–7.74 (m, 2H).

Ligand **3f:** white crystals, 78% yield, m.p. 162.6–163.8°C, $[\alpha]_D^{20}$ = +246.0 (*c* 1.0.08, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, *J* = 7.0 Hz, 3H), 2.03 (s, 3H), 4.14 (q, *J* = 7.0 Hz, 1H), 5.23 (s, 1H), 6.77–7.72 (m, 15H), 13.72 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 31.8, 56.5, 66.7, 113.8, 114.0, 114.6, 114.8, 119.0, 119.7, 121.5, 123.6, 125.6, 126.8, 127.3, 127.8, 128.0, 128.8, 129.2, 130.9, 141.5, 141.6, 154.9, 160.6, 163.1. HRMS *m/z* calcd for $C_{26}H_{24}FNO$ $(M+1)^+$ 386.1920, found: 386.1923.

Preparation of 1-[(1S)-(4-Furylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3g)

Intermediate **1g:** colorless crystals, 83% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.21 (brs, 1H), 3.87 (q, *J* = 6.8 Hz, 1H), 5.43 (s, 1H), 6.88–7.75 (m, 15H), 13.63 (brs, 1H).

Intermediate **2g:** white crystals, 94% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 6.4 Hz, 3H), 3.96 (q, *J* = 6.4 Hz, 1H), 5.13 (dd, *J* = 11.2, 1.6 Hz, 1H), 5.15 (d, *J* = 11.2 Hz, 1H), 6.76–7.38 (m, 13H), 7.73–7.77 (m, 2H).

Ligand **3g:** white crystals, 80% yield, m.p. 167.1–168.3°C, $[\alpha]_D^{20}$ = +254.3 (*c* 0.97, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 7.2 Hz, 3H), 2.08 (s, 3H), 4.33 (q, *J* = 7.2 Hz, 1H), 5.31 (s, 1H), 6.91–7.90 (m, 15H), 13.91 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 32.9, 57.7, 67.5, 115.7, 116.1, 120.0, 120.7, 122.5, 126.6, 127.8, 128.3, 128.8, 129.1, 129.7, 129.9, 130.6, 131.9, 135.9, 135.9, 155.8, 161.0, 163.5. HRMS *m/z* calcd for $C_{26}H_{24}FNO$ $(M+1)^+$ 386.1920, found: 386.1924.

Preparation of 1-[(1S)-(3,5-Dimethylphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3h)

Intermediate **1h:** colorless crystals, 94% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (d, *J* = 6.8 Hz, 3H), 2.17 (s, 6H), 3.85 (q, *J* = 6.8 Hz, 1H), 5.36 (s, 1H), 6.78–7.71 (m, 14H), 13.77 (brs, 1H).

Intermediate **2h:** white crystals, 95% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.6 Hz, 3H), 2.17 (s, 6H), 3.95 (q, *J* = 6.8 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 1H), 5.12 (s, 1H), 5.14 (dd, *J* = 10.4, 2.0 Hz, 1H), 6.62–7.40 (m, 13H), 7.73–7.76 (m, 2H).

Ligand **3h:** white crystals, 87% yield, m.p. 185.7–198.3°C, $[\alpha]_D^{20}$ = +232.6 (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, *J* = 6.8 Hz, 3H), 2.10 (s, 3H), 2.21 (s, 6H), 4.21 (q, *J* = 6.8 Hz, 1H), 5.23 (s, 1H), 6.78–7.85 (m, 14H), 14.02 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 21.7, 57.4, 59.2, 74.4, 112.4, 118.5, 122.8, 123.1, 126.5, 127.0, 127.5, 128.0, 128.5, 128.6, 128.9, 129.0, 129.1, 133.0, 137.5, 143.3, 145.5, 152.8. HRMS *m/z* calcd for $C_{28}H_{29}NO$ $(M+1)^+$ 396.2327, found: 396.2315.

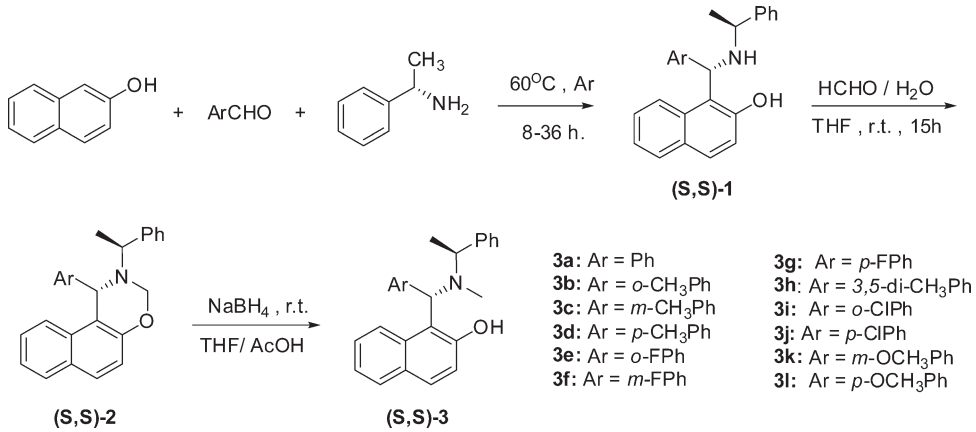


Fig. 1. The preparation of chiral aminonaphthol ligands.

Preparation of 1-[(1S)-(2-Chlorophenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3i)

Intermediate **1i:** colorless crystals, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, J = 6.8 Hz, 3H), 2.18 (brs, 1H), 3.98 (q, J = 6.8 Hz, 1H), 5.93 (s, 1H), 7.05–7.78 (m, 15H), 13.63 (brs, 1H).

Intermediate **2i:** white crystals, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J = 6.8 Hz, 3H), 4.45 (q, J = 6.8 Hz, 1H), 4.80 (dd, J = 10.8, 2.0 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 5.76 (s, 1H), 6.85–7.44 (m, 13H), 7.72–7.76 (m, 2H).

Ligand **3i:** white crystals, 83% yield, m.p. 135–136.3°C, $[\alpha]_D^{20}$ = +407.8 (*c* 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62 (d, J = 6.8 Hz, 3H), 2.07 (s, 3H), 4.27 (q, J = 6.8Hz, 1H), 6.07 (s, 1H), 7.06–8.20 (m, 15H), 14.10 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.0, 30.5, 59.9, 61.6, 115.8, 120.2, 121.2, 122.6, 126.9, 127.8, 128.2, 128.3, 128.6, 128.8, 128.9, 129.2, 129.5, 129.8, 131.5, 132.6, 134.4, 137.2, 142.3, 155.7, 157.6. HRMS *m/z* calcd for $C_{26}H_{24}ClNO$ $(M+1)^+$ 402.1625, found: 402.1593.

Preparation of 1-[(1S)-(4-Chlorophenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3j)

Intermediate **1j:** colorless crystals, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, J = 6.8 Hz, 3H), 2.13 (brs, 1H), 3.95 (q, J = 6.8 Hz, 1H), 5.47 (s, 1H), 7.08–7.73 (m, 15H), 13.58 (brs, 1H).

Intermediate **2j:** white crystals, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J = 6.4Hz, 3H), 3.95 (q, J = 6.4 Hz, 1H), 4.85 (d, J = 10.8 Hz, 1H), 5.11 (dd, J = 10.8, 1.8 Hz, 1H), 5.14 (s, 1H), 6.94–7.35 (m, 13H), 7.71–7.74 (m, 2H).

Ligand **3j**: white crystals, 82% yield, m.p. 198–199.4°C, $[\alpha]_D^{20}$ = +219.9 (*c* 1.06, CHCl3). 1H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J = 7.0 Hz, 3H), 2.09 (s, 3H), 4.21 (q, J = 7.0 Hz, 1H), 5.29 (s, 1H), 7.16–7.74 (m, 15H), 13.87 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 32.9, 57.1, 67.5, 115.8, 120.0, 120.7, 122.6, 124.4, 126.6, 127.8, 128.3, 128.8, 129.0, 129.1, 129.8, 130.3, 131.9, 133.7, 137.0, 138.7, 155.8. HRMS *m/z* calcd for $C_{26}H_{24}ClNO$ $(M+1)^+$ 402.1625, found: 402.1595.

Preparation of 1-[(1S)-(3-Methoxyphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3k)

Intermediate **1k:** colorless crystals, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, 3H), 2.28 (brs, J = 6.8 Hz, 1H), 3.65 (d, 3H), 3.87 (q, J = 6.8 Hz, 1H), 5.41 (d, 1H), 6.69–7.72 (m, 15H), 13.68 (brs, 1H).

Intermediate **2k:** white crystals, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, J = 6.8 Hz, 3H), 3.69 (s, 3H), 3.96 (q, J = 6.8 Hz, 1H), 4.96 (d, J = 11.2 Hz, 1H), 5.13 (dd, J = 11.2, 1.6 Hz, 1H), 5.16 (s, 1H), 6.56–7.41 (m, 13H), 7.72–7.76 (m, 2H).

Ligand **3k:** white crystals, 81% yield, m.p. 147.3–148.6°C, $[\alpha]_D^{20}$ = +239.8 (*c* 0.226, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (d, J = 5.6 Hz, 3H), 2.11 (s, 3H), 3.709 (s, 3H), 4.22 (q, J = 5.6 Hz, 1H), 5.30 (s, 1H), 6.69–7.85 (m, 15H), 13.95 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 32.9, 55.1, 57.2, 68.4, 112.9, 114.9, 116.1, 119.9, 121.0, 121.3, 122.4, 126.4, 127.7, 128.3, 128.7, 128.8, 129.0, 129.6, 129.8, 130.3, 132.1, 141.6, 155.9, 159.8. HRMS *m/z* calcd for $C_{27}H_{27}NO_2$ $(M+1)^+$ 398.2120, found: 398.2103.

Preparation of 1-[(1S)-(4-Methoxyphenyl){methyl[(1′S)-1′-phenylethyl]amino}methyl]-2-naphthol (3l)

Intermediate **1l:** colorless crystals, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (d, J = 7.2 Hz, 3H), 2.25 (q, J = 7.2 Hz, 1H), 3.67 (s, 3H), 3.86 (d, J = 7.2 Hz, 1H), 5.40 (s, 1H), 6.72–7.72 (m, 15H), 13.75 (brs, 1H).

Intermediate **2l:** white crystals, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, J = 6.8 Hz, 3H), 3.72 (s, 3H), 3.96 (q, J = 6.8 Hz, 1H), 4.95 (d, J = 10.0 Hz, 1H), 5.12 (dd, J = 10.0, 2.0 Hz, 1H), 5.14 (s, 1H), 6.71–7.38 (m, 13H), 7.72–7.76 (m, 2H).

Ligand **3l:** white crystals, 83% yield, m.p.178.3–182.5°C, $[\alpha]_D^{20}$ = +215.3 (*c* 1.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, J = 6.0 Hz, 3H), 2.09 (s, 3H), 3.69 (s, 3H), 4.20 (q, J = 6.0 Hz, 1H), 5.29 (s, 1H), 6.77–7.82 (m, 15H), 14.04 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 32.9, 55.0, 57.5, 67.6, 114.1, 116.5, 120.0, 121.0, 122.4, 126.4, 126.6, 127.6, 128.3, 128.8, 129.0, 129.1, 129.9, 130.1, 132.0, 132.1, 155.7, 159.1. HRMS *m/z* calcd for $C_{27}H_{27}NO_2$ $(M+1)^+$ 398.2120, found: 398.2100.

Typical Procedure for the Phenyl Transfer Reaction

A solution of phenyl boronic acid (122 mg, 1.0 mmol) and diethylzinc (3.0 mmol, 1M in hexane) in toluene was added to a dry flask under an argon atmosphere at 0°C, then with constant stirring at 60°C for 12 h to prepare a transfer reagent. After cooling to −10°C, ligand (16 mmol %) and DiMPEG (10 mol %) were added. The resulting mixture was stirred for 0.5 h at −10°C, then *p*-chlorobenzaldehyde (70 mg, 0.5 mmol) in toluene was subsequently added dropwise via a syringe. After being stirred for 15 h at −10°C, the reaction was quenched with 1M HCl, extracted with ethyl acetate, and concentrated in vacuo. The extracts were applied directly onto a silica gel column (1:20 ethylacetate/petroleumether as eluent) to give the desired diarylmethanol. The enantiomeric excess was determined by chiral HPLC, using a Chiralcel OB-H column with 10% isopropanol in hexane as eluent.

RESULTS AND DISCUSSION

The aminonaphthol ligands were first used in the asymmetric addition of dialkylzincs to aldehydes by Palmieri et al.[42,43] They found that a catalytic amount of enantiopure aminophenol or aminonaphthol considerably accelerated the addition of dialkylzincs to aldehydes, affording the corresponding alcohols in good enantioselectivity. Wang and coworkers[44] reported the effective enantioselective ethylation of aryl aldehydes at room temperature by a chiral aminonaphthol, which was obtained by condensation of 2-naphthol,

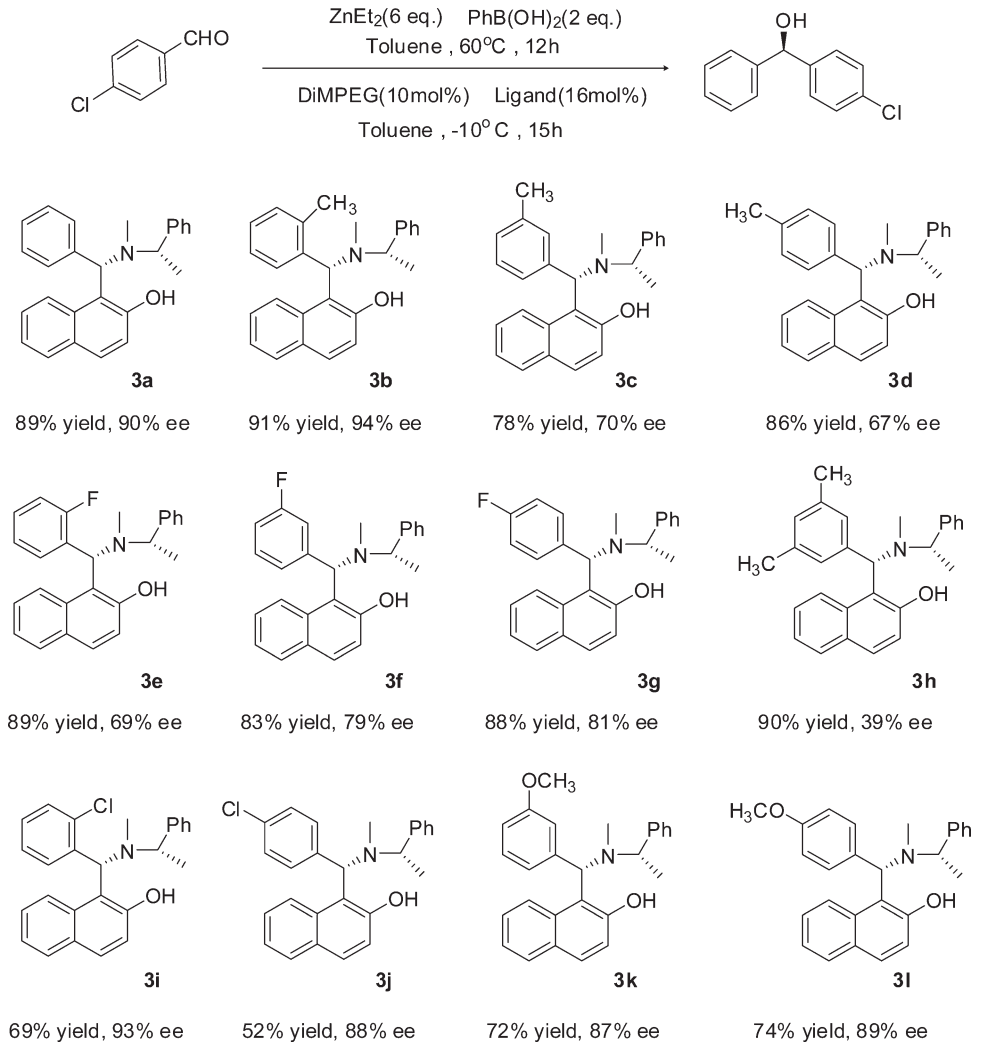
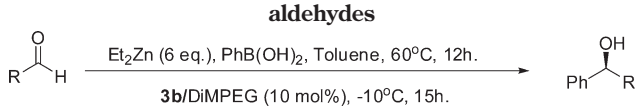


Fig. 2. The asymmetric phenyl transfer reaction using various chiral aminonaphthol ligands.

benzaldehyde, and (*S*)-methylbenzylamine followed by *N*-methylation. Expanding on our study of the asymmetric phenyl transfer to aromatic aldehydes catalyzed with tertiary aminonaphthol,[41] we synthesized a number of aminonaphthol ligands from *2*-naphthol, (*S*)-1-phenylethylamine and a variety of aldehydes to investigate the structural influence of the aminonaphthol ligands on the enantioselectivity of the phenyl transfer reaction. Initially, the reaction of *2*-naphthol with (*S*)-1-phenylethylamine and aromatic aldehydes gave 1-aminoalkylation compound **1** in high yields and diastereomeric ratio under mild conditions,[42,43] The reaction of compound **1** with formaldehyde in THF gave intermediates **2**, which were reduced with sodium boronhydride to afford the target products in moderate to good yields (Fig. 1).

To study the relationship between enantioselectivities and ligand structures for the asymmetric phenyl transfer reactions, we chose **3a** as a model ligand and used the optimal conditions previously established (i.e., carrying out the reaction at −10°C in toluene in the presence of 16 mol % of ligand, 6.0 equiv. of Et_2Zn, 2.0 equiv. of $PhB(OH)_2$ and 10 mol % of DiMPEG for 15 h[41]). In the presence of **3a** and a polyether (DiMPEG), the reaction of *p*-chlorobenzaldehyde with phenyl transfer reagent (prepared by mixing $PhB(OH)_2$ and 6.0 equiv. of $ZnEt_2$ afforded the (4-chlorophenyl)(phenyl)metha-

TABLE 1. The asymmetric phenyl transfer to other aromatic aldehydes



Entry	R	Yield (%)[a,b]	ee (%)[c,d]
1	*o*-Me-phenyl	63	95
2	*m*-Me-phenyl	67	93
3	*p*-Me-phenyl	52	80
4	*o*-Cl-phenyl	46	94
5	*o*-F-phenyl	45	95
6	*p*-F-phenyl	43	92
7	*p*-MeO-phenyl	55	70
8	1-Naphthyl	65	97
9	2-Furyl	76	87
10	*t*-Bu	58	73
11	n-Bu	34	62

[a]All reactions were performed on a 0.5 mmol scale using 16 mol % of **3b**, 6 equiv. of Et_2Zn, 2.0 equiv. of $PhB(OH)_2$, 10 mol % of DiMPEG in toluene (first at 60°C for 12 h, then at −15°C for 15 h).
[b]Isolated yield.
[c]Determined by HPLC analysis.
[d]The absolute configuration was determined by comparison of the HPLC elution order with the literature data.[1]

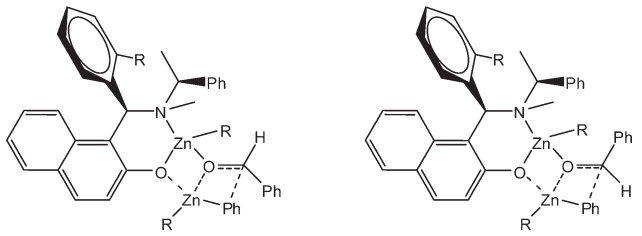


Fig. 3. The proposal transition states of asymmetric phenyl transfer to aldehydes.

nol in 89% yield with 90% ee (Fig. 2). Ligand **3b**, which was derived from 2-naphthol, *o*-methylbenzaldehyde, and (*S*)-1-phenylethylamine, gave better enantioselectivity (91% yield with 94% ee). On the other hand, ligands **3c** and **3d**, derived from *m*-methylbenzaldehyde and *p*-methylbenzaldehyde, afforded lower enantioselectivities (78% yield with 70% ee for **3c** and 86% yield with 67% ee for **3d**, respectively) under the same reaction conditions. These results implied that either the steric effect of the ligands played an important role for the reaction, or rather the ortho- electron-donating substituents on the aldehyde moiety of the ligands promoted high enantioselectivities. In contrast, strong electron-drawing groups were unfavorable to the ees. Chiral ligands **3e**, **3f**, and **3g**, with a fluoro atom on ortho-, meta-, and para-position of the aldehyde part of the ligand, gave 69%, 79%, and 81% ee, respectively. It was also observed that ligand **3h**, which was derived from 3,5-dimethylbenzaldehyde, gave only 39% ee under the same conditions. The ortho effect was also supported by the results of ligands **3i** and **3j**. With *o*-Cl on the aldehyde moiety of the ligand, **3i** gave 69% yield with 93% ee, while **3j**, which possessed *p*-Cl on the aldehyde moiety, afforded 88% ee. The enantioselectivities of ligands with meta- or para-substituents were quite similar. Chiral ligands **3k** and **3l**, with a methoxy group on the meta- or para-position, afforded 87% and 89% ee, respectively. Similar enantioselectivities were also found for ligands **3c** vs **3d** (70% and 67% ee) and **3f** vs **3g** (79% and 81% ee).

The asymmetric phenyl transfer to other aldehydes catalyzed by ligand **3b** was investigated in Table 1. The results indicated that enantioselectivity was also influenced by the steric effect of the substrates. *o*-Methylbenzaldehyde and *m*-methylbenzaldehyde gave 95% and 93% ee, respectively, but *p*-methylbenzaldehyde provided only 83% ee under the same reaction conditions (Table 1, entry 1–3). When *p*-methoxybenzaldehyde was used as the substrate, only 70% ee was obtained. On the other hand, a small substituted group on the ortho- or para-position of the aldehydes seemed to have little effect on the enantioselectivity (Table 1, entry 5 and 6), which was consistent with our expectation. On the other hand, aliphatic aldehydes were also tested with **3b** as the chiral ligand. Unlike aromatic aldehydes which provided good results, aliphatic aldehydes only gave moderated chemical yields and ees at the same reaction conditions (Table 1, entry 10 and 11).

In contrast to the enantioselective addition of dialkyl compounds to aldehydes of which the mechanism has been considerably studied, relatively less is known about the reaction of phenylation of aldehydes. According to reported mechanism[45–49] of the Ph_2Zn addition to aldehydes in the presence of a mixed Ph_2Zn/Et_2Zn species and amino alcohols, the proposed transition state of the reaction with aminonaphthol as the ligand is shown in Figure 3. The substituted groups on meta- and para-position of the aldehyde moiety of the ligands seemed to decrease the energy difference between the *R*-transition state and the *S*-transition state, which resulted in lower enantioselectivities. On the other hand, the ortho-groups led to an increase in energy difference between two transition states.

CONCLUSION

In conclusion, we have synthesized a series of new aminonaphthol ligands from 2-naphthol, (*S*)-1-phenylethylamine, and various aromatic aldehydes. Results of asymmetric phenyl transfer reactions with these chiral aminonaphthol ligands showed that the enantioselectivities were greatly influenced by the structures of the aminonaphthol ligands with a marked ortho-effect of the ligands.

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