Highly Efficient Asymmetric Additions of Diethylzinc to Aldehydes Triply Activated by Chiral Phosphoramide-Zn(II) Complexes Derived From Cinchona Alkaloids

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ABSTRACT New chiral phosphoramide ligands derived from cinchona alkaloids were developed, which react with diethylzinc to form chiral phosphoramide-Zn(II) complexes containing two Lewis bases and one Lewis acid. These trifunctional complexes can serve as highly efficient chiral catalysts for triple activation of enantioselective addition reactions of diethylzinc with aldehydes to give desired alcohol products with excellent yields and enantiomeric excess (*ee*) values up to 99%. *Chirality 25:561–566, 2013.*

KEY WORDS: phosphoramide; cinchona alkaloids; diethylzinc; triple activation; enantioselective addition

INTRODUCTION

Enantioselective catalytic transformations which involve carbon–carbon bond formation are probably one of the most attractive reactions for organic synthesis.[1–3] Concerning this subject, the asymmetric additions of organometallic reagents to carbonyl groups have been extensively studied.[4–9] The design of catalysts for the asymmetric additions of organozinc reagents to aldehydes and ketones to give chiral alcohols has been the focus of intensive research and a large number of diverse catalysts have been developed.[10–19] Naturally occurring cinchona alkaloids and their derivatives have been widely used in a variety of asymmetric reactions with high catalytic efficiencies,[20–28] but they are less efficient[29–32] in the asymmetric organozinc addition reactions compared to other chiral ligands such as Walsh's HOCSAC[33–39] (a bis (hydroxycamphorsulfonamide) ligand derived from (*R*, *R*)-1,2-cyclohexyl diamine) and DAIB[40–45] (3-exo-dimethylaminoisoborneol). Herein, we report the development of a highly efficient trifunctional chiral phosphoramide-Zn(II) complex which can activate the asymmetric additions of diethylzinc with aldehydes to give desired alcohol products with excellent yields and enantiomeric excess (*ee*) values up to 99% by modifying the hydroxyl group at C-9 of quinidine to phosphoramide group. The corresponding alcohol products with opposite configurations can also be obtained with the use of the trifunctional chiral ligand derived from quinine.

MATERIALS AND METHODS

General Information

All reations were carried out in dried glassware with magnetic stirring under an N_2 atmosphere. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solutions using a Bruker Avance 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm, δ) relative to $CDCl_3$ (δ 7.26 for ^{1}H NMR), and $CDCl_3$ (δ 77.0 for ^{13}C NMR). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). All of the solvents were purified and dried prior to use according to standard methods.[46] Optical rotations were measured on a polarimeter and reported as follows: $[\alpha]_D^T$ (c g/100 mL, solvent). GC analysis was performed on a gas chromatograph with an FID detector on fused silica chiral capillary column (Chirasil Dex CB column, 25 m Length × 0.32 mm ID × 0.25 mm film thickness).

Experimental Procedure for the Preparation of L4-L7

Using quinidine (Qd) as a starting material, we synthesized **L4** as shown in Scheme 1. **L5**, **L6** and **L7** were synthesized using the same procedure started from cinchonine (Cn), quinine (Qn), and cinchonidine (Cd).

(*S*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl](6-methoxyquinolin-4-yl)methyl 4-methylbenzene-1-sulfonate (L1):[47]. To a 100-mL flask containing quinidine (1622.3 mg, 5.0 mmol), DMAP (31.0 mg, 0.25 mmol), and Et_3N (2.5 mL, 17.5 mmol), a solution of TsCl (1926.2 mg, 10.0 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise at 0 °C. After being refluxed overnight, the mixture was cooled down to room temperature and quenched with saturated aqueous $NaHCO_3$ solution. Extraction with CH_2Cl_2 gave combined organic layers that were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc /*n*-hexane/ Et_3N = 50/50/4), which afforded 2216.1 mg (95%) of **L1** as a white solid.

4-[(*R*)-azido[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]methyl]-6-metho-xyquinoline (L2):[47]. Sodium azide (260.1 mg, 4.0 mmol) was added to a solution of **L1** (955.3 mg, 2.0 mmol) in DMF (10 mL) in a 50-mL flask with a condenser. The mixture was refluxed at 90 °C for 5 h. After that, the mixture was cooled down to room temperature and quenched with water. Extraction with EtOAc gave combined organic layers that were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc /*n*-hexane/ Et_3N = 20/80/4), which afforded 575.4 mg (82%) of **L2** as a white solid.

(Diphenylphosphoryl)[(*R*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl] (6-methoxyquinolin-4-yl)methyl]amine (L4). To a 50-mL flask containing $LiAlH_4$ (200.2 mg, 5.0 mmol) in dry tetrahydrofuran (THF) (4 mL), a solution of **L2** (699.1 mg, 2.0 mmol) in 8 mL of THF

Additional Supporting Information may be found in the online version of this article.

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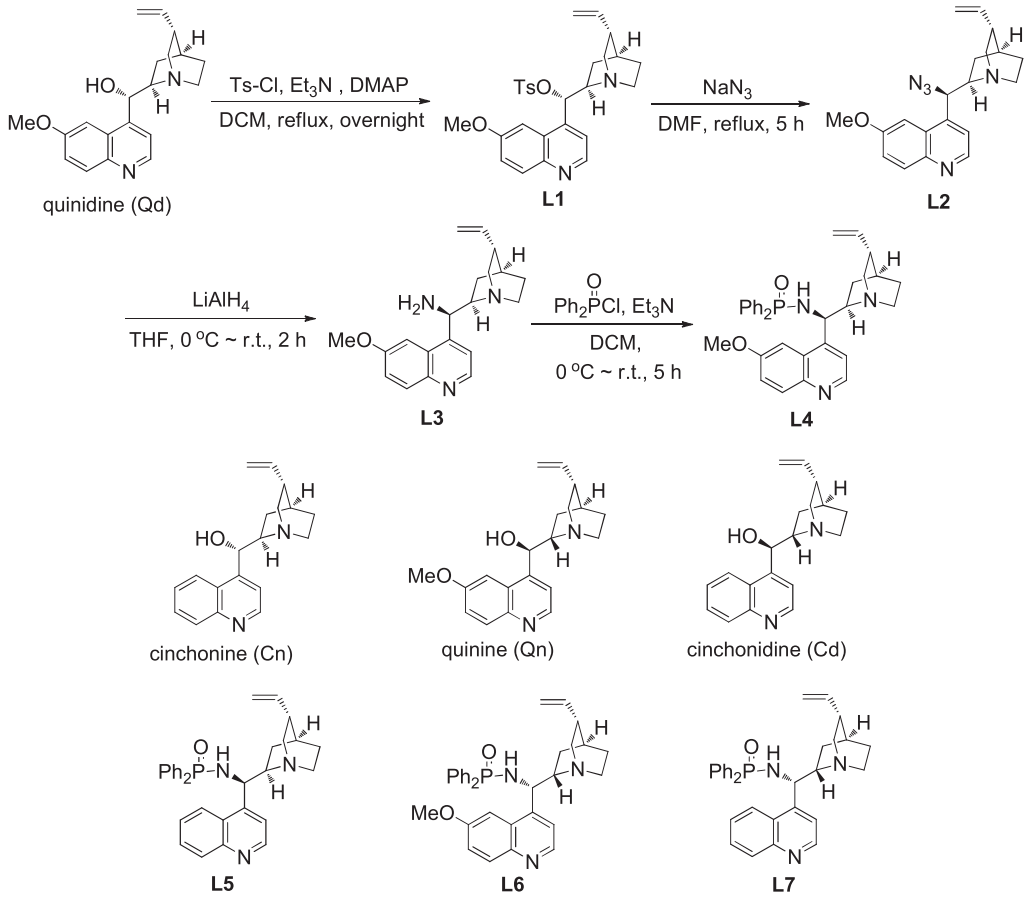


Scheme 1. Syntheses of **L4**-**L7**.

was added dropwise at 0 °C. The solution was allowed to warm to room temperature. After being stirred for 2 h at room temperature, the mixture was quenched with saturated aqueous Na_2SO_4 solution, filtered under reduced pressure, and concentrated in vacuo to give a residue, which was dissolved in CH_2Cl_2/10% aqueous hydrochloric acid (15/15 mL). The aqueous layer was separated and washed with CH_2Cl_2 followed by the adjustment of its pH value to basic by adding aqueous ammonia. Extraction with CH_2Cl_2 gave combined organic layers that were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/CH_3OH = 9/1 followed by CH_2Cl_2/CH_3OH = 8/2), which afforded **L3** as a yellowish oil. To the solution of the obtained **L3** and Et_3N (850 μL, 6.0 mmol) in CH_2Cl_2 (8 mL), diphenylphosphinyl chloride (560 μL, 3.0 mmol) was added dropwise at 0 °C over 15 min. The resulting mixture was allowed to warm to room temperature. After being stirred at room temperature for 5 h, the solution was quenched with saturated aqueous $NaHCO_3$ solution. Extraction with CH_2Cl_2 gave combined organic layers that were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/n-hexane/Et_3N = 60/40/4), which afforded 568.3 mg (53%) of ***L4*** as a white solid. Melting point (mp) 55–56 °C; $[\alpha]_D^{22.6}$ 84.4 (c 1.00, CH_2Cl_2) ; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers): δ 0.82-0.93 (m, 1H), 1.15-1.29 (m, 3H), 1.51-1.62 (m, 2H), 2.23-2.41 (m, 1H), 2.91-3.12 (m, 3H), 3.18-3.30 (m, 1H), 3.88 (s, 2.2H), 4.00 (s, 0.8H), 4.53(t, 0.3H), 5.02-5.19 (m, 2H), 5.18-5.25(m, 0.7H), 5.40-5.51 (m, 1H), 5.73-5.99 (m, 1H), 6.71-6.78 (m, 0.7H), 6.79-6.85 (m, 1.3H), 6.93-7.02 (m, 1H), 7.03-7.08 (m, 1H), 7.18-7.23 (m, 1H), 7.30-7.45 (m, 5H), 7.64 (d, 0.6H), 7.76-7.91 (m, 3.1H), 7.99-8.02(m, 0.3H), 8.26(d, 0.3H), 8.63(d, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) : δ 24.7, 26.3, 27.3, 38.4, 46.0, 49.1, 55.3, 59.7, 61.2, 100.2, 103.9, 114.9, 120.5, 120.7, 121.8, 123.2, 126.9, 127.2, 128.2, 128.4, 130.6, 131.1, 131.5, 131.7, 131.9, 139.8, 140.1, 144.1, 145.7, 146.8, 147.2, 157.4. HRMS *m/z*: calcd. for $C_{32}H_{34}N_3O_2P$ (M + 1), 524.2447; found, 524.2461.

(Diphenylphosphoryl)[(*R*)-[(2*R*,4*S*,5*R*)-5-ethenyl-1-azabicyclo [2.2.2]octan-2-yl] (quinolin-4-yl) methyl]amine (L5). **L5** was synthesized from cinchonine following the same procedure described for **L4** on the same scale and was obtained as a white solid with the yield of 912.5 mg (37%). mp 69–70 °C; $[\alpha]_D^{22.9}$ 77.3 (c 1.00, CH_2Cl_2) ; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) : δ 0.82-0.92 (m, 1.3H), 1.09-1.17 (m, 0.7H), 1.18-1.27 (m, 1H), 1.48-1.54 (m, 1H), 1.56-1.66 (m, 1H), 2.12-2.34 (m, 1H), 2.90-3.12 (m, 4H), 3.32-3.45 (m, 1H), 4.55(t, 0.3H), 5.06-5.22 (m, 2.7H), 5.32-5.38 (m, 1H), 5.80-5.94 (m,1H), 6.66-6.72(m, 0.6H), 6.76-6.83 (m, 1.4H), 6.90-6.99 (m, 1H), 7.20-7.26 (m, 1H), 7.32-7.44 (m, 5H), 7.52-7.60 (m, 1H), 7.65 (d, 1H), 7.80-7.90 (m, 2.7H), 7.98(d, 0.3H), 8.40 (d, 0.3H), 8.74 (d, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) : δ 24.6, 26.4, 27.4, 38.8, 46.3, 49.1, 57.8, 62.2, 114.9, 120.4, 122.6, 123.0, 125.4, 126.2, 126.9, 127.1, 128.3, 128.7, 129.7, 130.5, 130.8, 131.3, 131.5, 131.9, 139.9, 144.2, 147.4, 147.8, 148.9, 149.2, 149.6. HRMS *m/z*: calcd. for $C_{31}H_{32}N_3OP$ (M + 1), 494.2353; found, 494.2356.

(Diphenylphosphoryl)[(*S*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2] octan-2-yl] (6-methoxyquinolin -4-yl)methyl]amine (L6):[48]. **L6** was synthesized from quinine following the same procedure described for **L4** on the same scale and was obtained as a white solid with the yield of 889.5 mg (34%). mp 77–78 °C; $[\alpha]_D^{21.5}$ -9.5 (c 1.00, CH_2Cl_2) ; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers[48]) : δ 0.71-0.83 (m, 1H), 1.25-1.42 (m, 2H), 1.56-1.65 (m, 2H), 2.23-2.38 (m, 1H), 2.66-2.85 (m, 2H), 2.94-2.97 (m, 0.3H), 3.18-3.31 (m, 1.7H), 3.49-3.62 (m, 1H), 3.92 (s, 1.9H), 4.00 (s, 1.1H), 4.83-4.99 (m, 2H), 4.48-4.56(t, 0.5H), 5.04-5.14 (m, 1H), 5.35(S, 0.5H), 5.55-5.73(m, 1H), 6.69-6.76 (m, 2H), 6.83-6.90 (m, 0.6H), 6.95-7.02 (M, 0.4H), 7.17-7.25 (m, 2H), 7.28-7.47 (m, 5H), 7.57 (d, 0.6H), 7.73-7.78

(m, 0.6H), 7.79-7.93 (m, 2.4H), 7.96-8.00(m, 0.4H), 8.23(d, 0.3H), 8.62 (d, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers[48]) : δ 25.4, 26.7, 27.4, 39.1, 40.4, 49.7, 55.5, 57.1, 61.6, 100.7, 103.4, 114.8, 120.4, 120.9, 121.4, 123.5, 126.9, 127.2, 128.3, 130.3, 130.8, 131.1, 131.3, 131.7, 131.9, 140.6, 144.0, 145.5, 146.7, 147.1, 157.4. HRMS *m/z*: calcd. for $C_{32}H_{34}N_3O_2P$ (M + 1), 524.2449; found, 524.2461.

(Diphenylphosphoryl)[(*S*)-[(2*S*,4*S*,5*R*)-5-ethenyl-1-azabicyclo[2.2.2] octan-2-yl] (quinolin -4-yl)methyl]amine (L7). **L7** was synthesized from cinchonidine following the same procedure described for **L4** on the same scale and was obtained as a white solid with the yield of 1085.1 mg (44%). mp 190–191 °C; $[\alpha]_D^{23.1}$ -4.4 (c 1.00, CH_2Cl_2) ; ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of rotamers) : δ 0.73-0.90 (m, 1H), 1.19-1.30 (m, 2H), 1.53-1.64 (m, 2H), 2.24 (s, 1H), 2.63-2.80 (m, 2H), 2.92-2.99 (m, 1H), 3.14-3.28 (m, 1H), 3.35-3.51 (M, 1H), 4.54(t, 0.4H), 4.78-4.98 (m, 2H), 5.19 (t, 1.2H), 5.30(s, 0.4H), 5.49-5.76 (m, 1H), 6.62-6.73 (m, 2H), 6.80-6.87 (m,1H), 6.95(t, 0.3H), 7.15-7.24 (m, 0.7H), 7.27-7.32 (m, 1H), 7.35-7.44 (m, 3H), 7.51-7.57 (m, 1H), 7.58-7.62 (m, 1H), 7.66(t, 0.4H), 7.78-7.92 (m, 2.6H), 8.00 (d, 1H), 8.37(d, 0.3H), 8.74 (d, 0.7H) ; ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) : δ 25.4, 27.4, 27.6, 39.5, 40.3, 55.7, 55.9, 62.2, 114.4, 120.3, 122.7, 123.2, 125.4, 126.2, 126.9, 127.4, 128.4, 128.7, 129.6, 130.4, 130.7, 131.4, 131.7, 131.9, 133.3, 141.2, 144.0, 147.7, 148.8, 149.1, 149.5. HRMS *m/z*: calcd. for $C_{31}H_{32}N_3OP$ (M + 1), 494.2352; found, 494.2356.

Experimental Procedure for Enantioselective Addition of Diethylzinc to Aldehyde

To a solution of **L4** (26.2 mg, 0.05 mmol) in toluene (0.5 mL), diethylzinc (0.5 mL of 1.5 M solution in toluene, 0.75 mmol) was slowly added at –30 °C under nitrogen atmosphere and stirred for 30 min. Then benzaldehyde (53.9 mg, 0.5 mmol) was added dropwise. The reaction temperature was allowed to warm to room temperature. After being stirred at room temperature for 6 h, the solution was quenched with saturated aqueous NH_4Cl solution. Extraction with EtOAc gave combined organic layers that were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane = 1/10), which afforded (*R*)-1-phenylpropan-1-ol.

(*R*)-1-phenylpropan-1-ol (B1, entry 1 in Table 3):[49]. Colorless oil (67.4 mg, 99% yield); 95% *ee* value was determined by Chiral GC Chirasil Dex CB [130 °C, t_R = 7.4 min (major, *R*), t_R = 7.8 min (minor, *S*)]. $[\alpha]_D^{20.9}$ +20.3 (c 1.00, $CHCl_3$) [Lit. 49 $[\alpha]_D^{26.0}$ +40.3 (c 1.21, $CHCl_3$) for 95% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, 3H), 1.70-1.88 (m, 2H), 1.92-1.98 (br, 1H), 4.60 (t, 1H), 7.26-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 31.9, 75.9, 126.1, 127.4, 128.3, 144.8.

(*R*)-1-(4-trifluoromethylphenyl)-1-propanol (B2, entry 2 in Table 3):[50]. Colorless oil (102.0 mg, >99% yield); 95% *ee* value was determined by Chiral GC Chirasil Dex CB [150 °C, t_R = 4.7 min (major, *R*), t_R = 5.1 min (minor, *S*)]. $[\alpha]_D^{32.0}$ +46.7 (c 1.80, $CHCl_3$) [Lit. 50 $[\alpha]_D^{25.0}$ +40.3 (c 1.30, $CHCl_3$) for 72% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.69-1.83 (m, 2H), 2.31 (br, 1H), 4.64 (t, *J* = 6.2 Hz, 1H), 7.39-7.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.8, 32.0, 75.2, 122.8, 125.2, 125.5, 126.2, 129.4, 129.7, 148.5.

(*R*)-1-(4-chlorophenyl)-1-propanol (B3, entry 3 in Table 3):[49]. Colorless oil (84.2 mg, 99% yield); 94% *ee* value was determined by Chiral GC Chirasil Dex CB [150 °C, t_R = 8.7 min (major, *R*), t_R = 9.4 min (minor, *S*)]. $[\alpha]_D^{32.4}$ +37.8 (c 1.50, $CHCl_3$) [Lit. 49 $[\alpha]_D^{26.0}$ +30.6 (c 2.08, $CHCl_3$) for 96% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.5 Hz, 3H), 1.62-1.82 (m, 2H), 2.32-2.39 (br, 1H), 4.53 (t, *J* = 6.8 Hz, 1H), 7.19-7.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.9, 31.8, 75.2, 127.3, 128.4, 133.0, 142.9.

(*R*)-1-(4-methoxyphenyl)-1-propanol (B4, entry 4 in Table 3):[49]. Colorless oil (70.6 mg, 85% yield); 88% *ee* value was determined by Chiral GC Chirasil Dex CB [150 °C, t_R = 8.7 min (major, *R*), t_R = 9.0 min (minor, *S*)]. $[\alpha]_D^{32.0}$ +34.5 (c 2.00, $CHCl_3$) [Lit. 49 $[\alpha]_D^{26.0}$ +38.9 (c 1.23, $CHCl_3$) for 96% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H), 1.62-1.90 (m, 2H), 2.27-2.69 (br, 1H), 3.80 (S, 3H), 4.50 (s, 1H), 6.83-7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 31.6, 55.1, 75.4, 113.6, 127.1, 136.8, 158.8.

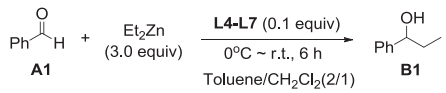
(*R*)-1-(2'-methoxyphenyl)-1-propanol (B5, entry 5 in Table 3):[49]. Colorless oil (81.4 mg, 98% yield); 96% *ee* value was determined by Chiral GC Chirasil Dex CB [150 °C, t_R = 6.6 min (minor, *S*), t_R = 7.4 min (major, *R*)]. $[\alpha]_D^{32.4}$ +22.8 (c 1.50, $CHCl_3$) [Lit. 49 $[\alpha]_D^{26.0}$ +23.7 (c 1.40, $CHCl_3$) for 95% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H), 1.79-1.89 (m, 2H), 2.82 (d, 1H), 3.86 (S, 3H), 4.79-4.86 (m, 1H), 6.87-7.36 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 30.1, 55.1, 71.9, 110.4, 120.5, 126.9, 128.0, 132.4, 156.4.

(*R*)-1-(2-methylphenyl)-1-propanol (B6, entry 6 in Table 3):[50]. Colorless oil (74.3 mg, 99% yield); 99% *ee* value was determined by Chiral GC Chirasil Dex CB [150 °C, t_R = 5.2 min (major, *R*), t_R = 5.5 min (minor, *S*)]. $[\alpha]_D^{32.0}$ +63.9 (c 1.30, $CHCl_3$) [Lit. 50 $[\alpha]_D^{26.0}$ +40.5 (c 0.45, $CHCl_3$) for 70% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.4 Hz, 3H), 1.73-1.83 (m, 2H), 2.19 (br, 1H), 2.37 (s, 3H), 4.87 (t, 1H), 7.13-7.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 19.0, 30.8, 71.9, 125.1, 126.1, 127.0, 130.2, 134.5, 142.7.

(*R*)-1-(naphthalen-2-yl)-1-propanol (B7, entry 7 in Table 3):[50]. Colorless oil (90.3 mg, 97% yield); 95% *ee* value was determined by Chiral GC Chirasil Dex CB [170 °C, t_R = 13.2 min (major, *R*), t_R = 13.7 min (minor, *S*)]. $[\alpha]_D^{32.5}$ +58.2 (c 1.50, $CHCl_3$) [Lit. 50 $[\alpha]_D^{25.0}$ +28.6 (c 0.77, $CHCl_3$) for 81% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H), 1.78-1.97 (m, 2H), 2.61 (br, 1H), 4.71 (t, 1H), 7.43-7.55 (m, 3H), 7.73-7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 31.6, 75.9, 124.1, 124.6, 125.6, 126.0, 127.6, 127.8, 128.1, 132.8, 133.1, 141.8.

(*R*)-1-(1-naphthyl)-1-propanol (B8, entry 8 in Table 3):[49]. Colorless oil (89.3 mg, 96% yield); 96% *ee* value was determined by Chiral GC Chirasil Dex CB [170 °C, t_R = 13.0 min (minor, *S*), t_R = 13.9 min (major, *R*)]. $[\alpha]_D^{32.5}$ +58.2 (c 1.50, $CHCl_3$) [Lit. 49 $[\alpha]_D^{26.0}$ +60.3 (c 1.11, $CHCl_3$) for 97% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (t, 3H), 1.84-2.08 (m, 2H), 2.95 (br, 1H), 5.32 (t, 1H), 7.44-8.15 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.3, 30.9, 72.1, 122.8, 123.1, 125.3, 125.2, 125.7, 127.6, 128.7, 130.3, 133.6, 140.1.

TABLE 1. Asymmetric additions of Et_2Zn to PhCHO catalyzed by L4-L7[a]



Entry	Ligand	Yield[b]	*ee*[c]	Config.[d]
1	**L4**	97	94	*R*
2	**Qd**[e]	90	48	*S*
3	**L5**	77	77	*R*
4	**Cn**[e]	90	46	*S*
5	**L6**	94	90	*S*
6	**Qn**[e]	92	68	*R*
7	**L7**	72	72	*S*
8	**Cd**[e]	89	58	*R*

[a]All reactions were conducted with PhCHO (0.5 mmol) and Et_2Zn (1.5 M in toluene, 1.0 mL; 1.5 mmol) in the presence of 10 mol% of chiral ligand.
[b]Isolated yield based on PhCHO.
[c]Determined by chiral GC analysis.
[d]The configuration was determined by comparing the sign of specific rotation value with the literature value.
[e]Ref. 29.

(*R*)-1-(thiophen-2-yl)propan-1-ol (B9, entry 9 in Table 3):[51]. Colorless oil (68.9 mg, 97% yield); 96% *ee* value was determined by Chiral GC Chirasil Dex CB [130 °C, t_R = 8.0 min (major, *R*), t_R = 8.5 min (minor, *S*)]. $[\alpha]_D^{31.6}$ +14.3 (c 1.00, $CHCl_3$) [Lit. 51 $[\alpha]_D^{26.0}$ +25.9 (c 2.02, $CHCl_3$) for 95% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H), 1.76-1.96 (m, 2H), 3.16 (br, 1H), 4.78 (t, 1H), 6.90-7.27 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 31.9, 71.3, 123.5, 124.1, 126.3, 148.5.

(*R*)-1-cyclohexylpropan-1-ol (B10, entry 10 in Table 3):[49]. Colorless oil (57.6 mg, 81% yield); 97% *ee* value was determined by Chiral GC Chirasil Dex CB [105 °C, t_R = 17.4 min (minor, *S*), t_R = 17.7 min (major, *R*)]. $[\alpha]_D^{32.4}$ +18.1 (c 1.30, $CHCl_3$) [Lit. 49 $[\alpha]_D^{26.0}$ +5.4 (c 0.61, $CHCl_3$) for 93% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.4 Hz, 3H), 0.92-1.40 (m, 7H), 1.42-1.54 (m, 1H), 1.54-1.64 (m, 2H), 1.64-1.80 (m, 3H), 2.00 (br, 1H), 3.16-3.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 26.1, 26.2, 26.4, 26.6, 27.7, 29.1, 43.0, 77.3.

RESULTS AND DISCUSSION

Table 1 shows the enantioselectivities of **L4**-**L7** for the asymmetric additions of diethylzinc to benzaldehyde. As reported,[29] naturally occurring cinchona alkaloids (Qd, Cn, Qn, and Cd) could only give 46–68% *ee* values for the asymmetric addition reactions (entries 2, 4, 6, and 8). By modifying the hydroxyl groups at C-9 of these four cinchona alkaloids accordingly, the corresponding **L4**-**L7** ligands provided **B1** with improved enantioselectivities with opposite configurations (entries 1, 3, 5, and 7). Among them, **L4** containing the OMe group on the aromatic ring gave us 97% yield and 94% *ee* value of the desired alcohol product with *R* configuration (entry 1). On the other hand, **L5** without the OMe group only provided (*R*)-**B1** with moderate yield and *ee* value, 77% and 77%, respectively (entry 3). These results indicate that the OMe group of **L4** should participate with the phosphoramide and triamine groups in the active center serving as a Lewis base to promote the asymmetric addition reaction with improved catalytic efficiency. Under the same reaction conditions, (*S*)-**B1** was afforded in 94% yield and 90% *ee* with **L6** and only 72% yield and 72% *ee* with **L7** (entries 5 and 7). These results demonstrate that the importance of the OMe group on the aromatic ring of these chiral phosphoramide ligands derived from cinchona alkaloids in catalysis for both enantioselectivity and yield of addition products.

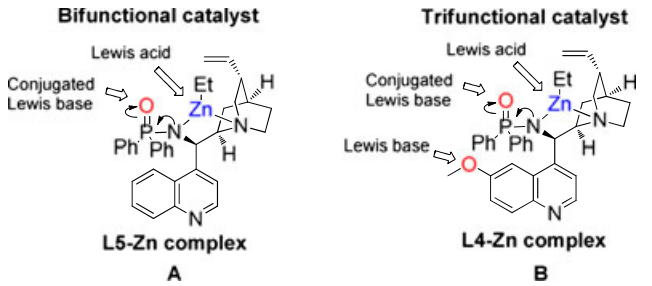
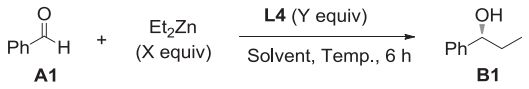


Fig. 1. Chiral catalysts in asymmetric additions of diethylzinc to aldehydes.

On the basis of Ishihara's conjugate Lewis acid- Lewis base double activated transition state mode for chiral phosphoramide derived from (*S*)-alanine,[16] the role of **L5** is proposed as follows: chiral ligand **L5** reacts with diethylzinc to form chiral **L5**-Zn complex (**Fig. 1A**) which serves as a bifunctional catalyst containing *N*,*N*-chelated Zn metal center as a Lewis acid to activate benzaldehyde and P=O moiety coming from phosphoramide group as a conjugate Lewis base to activate Et_2Zn through conjugation among Zn-N-P=O bonds. Since our investigation has demonstrated that the existence of the OMe group on the aromatic ring of **L4** is important for both enantioselectivity and yield of addition products of **L4** catalyzed asymmetric addition reactions, we further propose the role of **L4** as follows: with the OMe group

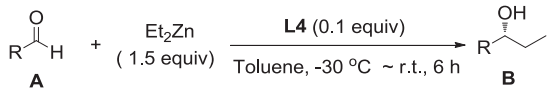
TABLE 2. Optimization of reaction conditions for the asymmetric addition of Et_2Zn to PhCHO catalyzed by L4[a]



Entry	Solvent	Temp.	Et_2Zn (X equiv)	**L4** (Y equiv)	Yield[b] (%)	*ee*[c] (%)	Config.[d]
1	*n*-hexane	0 °C ~ r.t.	3.0	0.1	98	93	*R*
2	THF	0 °C ~ r.t.	3.0	0.1	84	80	*R*
3	Toluene	0 °C ~ r.t.	3.0	0.1	99	94	*R*
4	Toluene	-30 °C	3.0	0.1	94	95	*R*
5	Toluene	0 °C	3.0	0.1	99	94	*R*
6	Toluene	r.t.	3.0	0.1	99	91	*R*
7	Toluene	-30 °C ~ r.t.	3.0	0.1	>99	95	*R*
8	Toluene	-30 °C ~ r.t.	2.5	0.1	99	95	*R*
9	Toluene	-30 °C ~ r.t.	2.0	0.1	99	95	*R*
10	Toluene	-30 °C ~ r.t.	1.5	0.1	99	95	*R*
11	Toluene	-30 °C ~ r.t.	1.5	0.2	99	95	*R*
12	Toluene	-30 °C ~ r.t.	1.5	0.08	95	93	*R*
13	Toluene	-30 °C ~ r.t.	1.5	0.05	90	92	*R*
14	Toluene	-30 °C ~ r.t.	1.5	0.02	25	77	*R*

[a]All reactions were conducted with PhCHO (0.5 mmol) and Et_2Zn (1.5 M in toluene) in the presence of **L4** for 6 h.
[b]Isolated yield based on PhCHO.
[c]Determined by chiral GC analysis.
[d]The configuration was determined by comparing the sign of specific rotation value with the literature value.

TABLE 3. Enantioselectivities using L4 as the catalyst with various aldehydes[a]



Entry	R =	Product	Yield[b] (%)	*ee*[c] (%)	Config.[d]
1	Ph	**B1**	99	95	*R*
2	4-CF_3-Ph	**B2**	>99	95	*R*
3	4-Cl-Ph	**B3**	99	94	*R*
4	4-CH_3O-Ph	**B4**	85	88	*R*
5	2-CH_3O-Ph	**B5**	98	96	*R*
6	2-CH_3-Ph	**B6**	99	99	*R*
7	2-Nap	**B7**	97	95	*R*
8	1-Nap	**B8**	96	96	*R*
9	2-Thienyl	**B9**	97	96	*R*
10	Cyclohexyl	**B10**	81	97	*R*

[a]All reactions were conducted with RCHO (0.5 mmol) , Et_2Zn (1.5 M in toluene, 500 uL; 0.75 mmol) in toluene in the presence of 10 mol% of **L4** from –30 °C to r.t. for 6 h.
[b]Isolated yield based on RCHO.
[c]Determined by chiral GC analysis.
[d]The configuration was determined by comparing the sign of specific rotation value with the literature value.

(**L4**), the chiral **L4**-Zn complex (**Fig. 1B**) serves as a trifunctional catalyst which uses the OMe group as the second Lewis base to assist the P=O moiety to increase the nucleophilicity of Et_2Zn for higher reactivity and make the conformation of the transition state more rigid for better enantioselectivity in the meantime.

Using **L4** as the catalyst, we further optimized the reaction conditions. All results are listed in Table 2. Compared with THF, nonpolar solvents were suitable solvents for this kind of reaction and the best one was toluene, with 99% yield and 94% *ee* value (entries 1–3). Temperature also showed an effect on the reaction (entries 4–6). Decreasing the temperature increased the enantioselectivity, but reduced the yield at the same time. The best result was obtained by adding diethylzinc at –30 °C and then stirring the reaction from –30 °C to room temperature. With the above optimized conditions, reducing the amount of Et_2Zn from 3.0 equiv to 1.5 equiv still provided the desired addition alcohol product with excellent yield and enantioselectivity (entries 7–10). Compared with 0.1 equiv of **L4** used, doubling the loading amount of **L4** from 0.1 equiv to 0.2 equiv did not improve the reaction (entry 11), but reducing the loading amount of **L4** to 0.05 equiv could still give us 90% yield and 92% enantioselectivity (entry 13). Further reducing the loading amount of **L4** to 0.02 equiv resulted in dramatic decreases of both yield and enantioselectivity (entry 14). Thus, the finally optimized reaction conditions for the asymmetric addition reactions of Et_2Zn to PhCHO were 1.5 equiv of Et_2Zn in toluene using 0.1 equiv of **L4** as catalyst with the reaction temperature from –30 °C to room temperature.

With the optimized reaction conditions in hand, we investigated the substrate scope of the asymmetric ethylation with various aldehydes shown in Table 3. Different electronic effects varied the enantioselectivities and yields of aromatic alcohol products. The trifunctional chiral **L4** worked very well for nonsubstituted and the electron-withdrawing group substituted PhCHO (entries 1–3). However, for 4-OMe substituted PhCHO, **L4** gave only 85% yield and 88% *ee* value of alcohol product (entry 4). Interestingly, for 2-OMe substituted PhCHO, the corresponding alcohol product was obtained with 98% yield and 96% *ee* value, respectively (entry 5). Steric hindrance also showed a positive effect on enantioselectivity. Compared with nonsubstituted PhCHO, methyl group substituted at C-2 of benzaldehyde improved the enantioselectivity from 95% to 99% *ee* (entry 6). With an aliphatic aldehyde as the substrate, this ligand also gave an excellent *ee* value, but lower yield of the addition product (entry 10).

CONCLUSIONS

In summary, we have developed trifunctional chiral phosphoramide-Zn(II) complexes to catalyze highly efficient asymmetric addition reactions of a variety of aldehydes with diethylzinc by modifying the hydroxyl groups at C-9 of quinidine and quinine to phosphoramide groups to give the desired addition products with opposite configurations. The OMe group on aromatic ring of the chiral phosphoramide ligand derived from quinidine or quinine serves as the second Lewis base to assist the corresponding phosphoramide group to activate Et_2Zn for a faster ethyl transfer to the carbonyl group of aldehyde, while the participation of OMe in active center also makes the conformation of the transition state more rigid for better enantioselectivity.

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