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Original article

Synthesis of novel cyclohexanediol-derived chiral phosphite ligands and their application in the Cu-catalyzed conjugate addition of organozinc to cyclic enones

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ABSTRACT

A series of novel chiral diphosphite ligands have been synthesized from (1*R*,2*R*)-*trans*-1,2-cyclohexanediol, (1*S*,2*S*)-*trans*-1,2-cyclohexanediol, racemic *trans*-1,2-cyclohexanediol and chlorophosphoric acid diary ester, and were successfully employed in the Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to cyclohexenone with up to 99% *ee*. It was found that ligand 1,2-bis[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol **6a** derived from racemic diol skeleton can show similar catalytic performance compared with ligand (1*R*,2*R*)-bis[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol **6a**′ derived from enantiopure starting material. A significant dependence of stereoselectivity on the type of enone and the ring size of the cyclic enone was observed. Moreover, the configuration of the products was mainly determined by the configuration of the binaphthyl moieties of diphosphite ligands in the 1,4-addition of cyclic enones.

1. Introduction

The development of efficient methodologies to provide optically active products has aroused great interest between academia and industry due to the ever increasing demands for chiral chemicals. Among the various approaches employed for this purpose, asymmetric catalysis represents one of the most general and attractive strategies in terms of chirality economy and environment considerations [1,2]. The asymmetric conjugate addition (ACA) of carbon nucleophiles to α,β-unsaturated compounds is an important method for carbon–carbon bond formation in asymmetric catalysis [3–6]. To achieve maximum chiral multiplication, an impressive array of chiral ligands, such as phosphoramidite [7–14], phosphite ligands [15–21], P,N-ligands [22–26] and others [27–35], have been developed to control the stereochemistry of ACA. Among these ligands, phosphite ligands have shown significant promise because of their facile synthetic method, and efficiency for 1,4-addition. In spite of huge achievements in this area, however, further research is needed to understand how to obtain an efficient enantiocontrol [36,37]. In this context, the design of new ligands is still an important area of research, thus the careful selection of a suitable alcohol backbone has become a meaningful procedure for us.

1,2-Cyclohexanediol (CHD) is widely used in preparing polyester, epoxy resin thinner, *o*-dihydroxybenzene and so on. As an important organic intermediate, CHD has enjoyed great success over the years in the fields of medicine, pesticides, spices and organic synthesis [38–41]. For example, Spilling *et al.* [42] found that catalysts formed by mixing (1*S*,2*S*)-*trans*-1,2-cyclohexanediol **1** and $Ti(O^iPr)_4$ at a 1.1:1 ratio proved to be effective for the phosphonylation of cinnamaldehyde providing hydroxyphosphonate with good enantiomeric excesses (up to 70% *ee*) (Fig. 1.). Subsequently, RajanBabu *et al.* [43] undertook a study of the hydrocyanation of 1,3-dienes using bis-1,2-diphenylphosphinite **2** derived from racemic *trans*-1,2-cyclohexanediol, and over 95% yield was gained. Recently, the Mercè Rocamora group [44] used *N*,*N*'-dibenzylcyclohexane-1,2-diamine and CHD as starting materials, and prepared enantiopure bidentate bis(diamidophosphite) ligand **3**, which is employed in Rh-catalyzed asymmetric hydrogenation of methyl (Z)-α-acetamidocinnamate with up to 76% *ee*. Previous results found the CHD skeleton was successfully applied in asymmetric catalytic reactions, and extremely useful for

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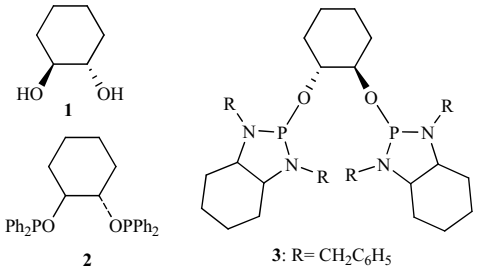
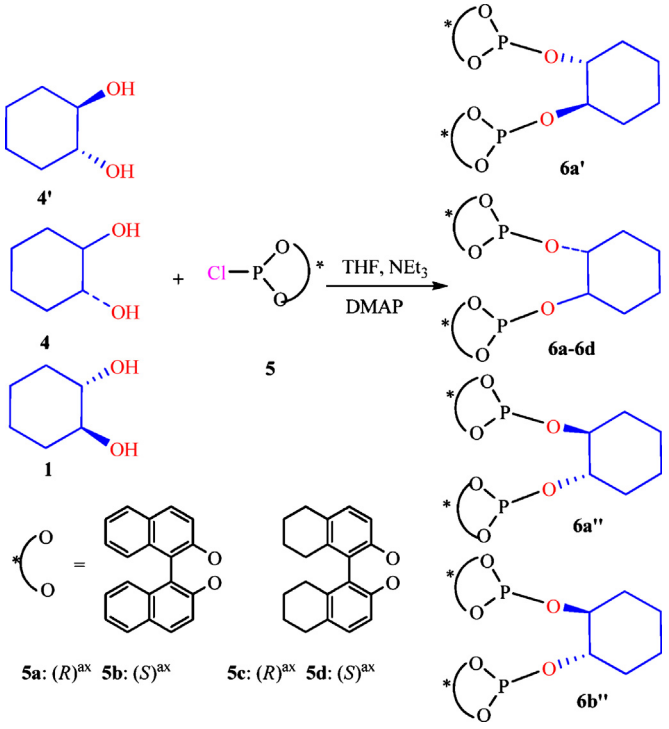


Fig. 1. The representative examples of the application of *trans*-1,2-cyclohexanediol in organic synthesis.

the synthesis of chiral ligands. Based on these findings and considering the importance of the electron density at the phosphorus atom and the configuration of the biaryl moieties in inducing high enantioselectivity, a series of new chiral aryl diphosphite ligands **6a** through **6d** using racemic *trans*-1,2-cyclohexanediol as the diol skeleton were designed and synthesized. At the same time, ligands **6a**′, **6a**″ and **6b**″ derived from enantiopure *trans*-1,2-cyclohexanediol were also prepared to compare to the asymmetric inducing ability of ligands **6a** through **6d**. The results indicated that ligand **6a** gave high activity (97% yield) and enantioselectivity (97% *ee*) in the Cu-catalyzed ACA of $ZnEt_2$ to 2-cyclohexenone. To our delight, similar results were obtained (98% yield, 99% *ee*) when ligand **6a**′ was used.



Scheme 1. The synthesis of diphosphite ligands derived from racemic *trans*-1,2-cyclohexanediol, (1*R*,2*R*)-*trans*-1,2-cyclohexanediol, and (1*S*,2*S*)-*trans*-1,2-cyclohexanediol.

2. Experimental

The NMR spectra were recorded on a Bruker 300 MHz, or Bruker 400 MHz spectrometer. The ^1H and ^{13}C NMR spectra were reported in parts per million (ppm) with TMS (δ = 0.00 ppm) as an internal standard. The ^{31}P NMR spectra were reported in ppm with 85% H_3PO_4 as an external reference. Proton chemical shifts (δ) and coupling constants (J) were reported in ppm and Hz, respectively. Spin multiplicities were given as s (singlet), d (doublet), t (triplet) and m (multiplet). High resolution mass spectra (HRMS) were recorded on a Bruker microTOF-QII mass spectrometer. All the melting points were determined on an X-4 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 MC polarimeter at 20 °C.

All non-aqueous reactions and manipulations were performed under an N_2 atmosphere with standard Schlenk techniques. Reactions were monitored by thin layer chromatography (TLC, silica gel GF254 plates). Column chromatography separations were conducted on silica gel (200–300 mesh). Reagents Et_3N, THF, Et_2O and toluene were distilled with Na and benzophenone as an indicator, and CH_2Cl_2 was dried over CaH_2 before use. The H_8-binaphthol was prepared according to a literature procedure [45]. All the other chemicals were obtained commercially and used without further purification.

2.1. Synthesis of diphosphites 6a–6d, 6a′, 6a″ and 6b″

As shown in Scheme 1, diphosphite ligands **6a** through **6d**, **6a**, **6a**″ and **6b**″ were easily synthesized in one step from racemic *trans*-1,2-cyclohexanediol **4**, (1*R*,2*R*)-*trans*-1,2-cyclohexanediol **4**′, (1*S*,2*S*)-*trans*-1,2-cyclohexanediol **1**, and chlorophosphoric acid diary ester **5**, which derived from 2,2'-dihydroxy-1,1'-binaphthol(-binaphthol), and 2,2'-dihydroxy-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthol (H_8-binaphthol). Ligand **6a** through **6d**, **6a**′, **6a**″ and **6b**″ were purified on a silica gel column under a nitrogen atmosphere with low to general yields. The ^{31}P NMR, ^1H NMR and ^{13}C NMR were consistent with the expectation for these ligands. The ratios of the two diastereoisomers for ligands **6a** through **6d** obtained by the integrated area of two singlets in the ^{31}P NMR of ligands were 1.18, 1.00, 1.43 and 1.12, respectively. It is worth mentioning that the ratio was changed slightly each time when the same ligand was synthesized.

2.1.1. 1,2-bis[(R)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol 6a

To a 100 mL Schlenk flask equipped with a condenser were added 2.0 g of (*R*)-binaphthol, 20 mL of toluene, and 12 mL of PCl_3. Under a nitrogen atmosphere the mixture was refluxed for 20 h. After removal of the excessive PCl_3 and toluene, the residue was dissolved in 20 mL of toluene, and then was transferred to another Schlenk flask, and toluene was removed in vacuo to obtain compound (*R*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphite (**5a**) as a white powder, which was used directly in the following step without further purification. To a stirred solution of compound **4** (87.5 mg, 0.75 mmol), compound **5a** (529.3 mg, 1.51 mmol), and 4-dimethylaminopyridine (DMAP) (18.4 mg, 0.15 mmol) in THF (10 mL) at −15 °C, Et_3N (0.32 mL) was slowly added using a syringe over 1 min, and the solution was stirred at −15 °C for 0.5 h. The mixture was then stirred at r.t. for 1 h. THF was distilled off in vacuo, and then toluene (20 mL) was added. The solid was removed by filtration through a pad of silica gel, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (R_f = 0.53, *n*-hexane:THF = 3:1, v:v), and furnished ligand **6a** as a white foamy solid (169.3 mg, 30.34% yield). $[\alpha]_D^{20}$ −253(*c* 0.19, CH_2Cl_2); Mp 153–154 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 8.16 (dd, 2*H*, *J* = 8.8, 6.4 Hz, Ar), 8.10–7.98 (m, 6*H*, Ar), 7.58 (d, 1*H*, *J* = 8.8 Hz, Ar), 7.56–7.45 (m, 7*H*, Ar), 7.34 (dd, 4*H*, *J* = 12.4, 7.4 Hz, Ar), 7.27 (d, 1*H*, *J* = 8.8 Hz, Ar), 7.21 (dd, 3*H*, *J* = 8.4, 2.8 Hz, Ar), 4.35–4.13 (m, 2*H*, CH), 2.24–2.09 (m, 1*H*, CH_2), 1.91 (d, 1*H*, *J* = 12.8 Hz, CH_2), 1.63 (s, 1*H*, CH_2), 1.57–1.41 (m, 3*H*, CH_2), 1.27 (m, 2*H*, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 148.10, 148.06, 147.94, 147.91, 147.34, 147.31, 132.45, 132.16, 131.57, 131.28, 131.22, 131.08, 130.46, 130.36, 129.06, 128.93, 127.12, 127.11,

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126.98, 126.39, 126.34, 125.71, 125.51, 124.07, 123.96, 123.86, 123.81, 122.45, 122.35, 122.32, 122.11, 122.02, 121.95, 77.59, 77.38, 77.12, 76.95, 32.76, 31.96, 23.30, 22.62. ^{31}P NMR (162 MHz, DMSO-d_6): δ 150.75, 149.31. HRMS (ESI$^+$): calcd. for $C_{46}H_{34}NaO_6P_2$ [M + Na]$^+$ 767.1723; found: 767.1738.

2.1.2. (1R,2R)-Bis[(R)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol ***6a′***

Treatment of compound **4′** (77.6 mg, 0.67 mmol), **5a** (507.5 mg, 1.45 mmol), and DMAP (17.7 mg, 0.15 mmol) as described for the synthesis of ligand **6a** afforded ligand **6a′**, which was purified by flash chromatography (R_f = 0.48, *n*-hexane:THF = 3:1) to produce a white solid (223.2 mg, 44.77% yield). $[\alpha]_D^{20}$ -449 (*c* 0.15, CH_2Cl_2); Mp 132–133 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, 2*H*, *J* = 8.8 Hz, Ar), 8.06 (d, 4*H*, *J* = 8.2 Hz, Ar), 7.99 (d, 2*H*, *J* = 8.8 Hz, Ar), 7.47–7.57 (m, 6*H*, Ar), 7.44 (d, 2*H*, *J* = 8.8 Hz, Ar), 7.35 (dd, 4*H*, *J* = 15.6, 8.0 Hz, Ar), 7.25–7.29 (m, 2*H*, Ar), 7.22 (s, 2*H*, Ar), 4.17 (m, 2*H*, CH), 2.14 (t, 2*H*, *J* = 12.0 Hz, CH_2), 1.62 (s, 2*H*, CH_2), 1.47 (d, 2*H*, *J* = 10.0 Hz, CH_2), 1.17–1.27 (m, 2*H*, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 147.94, 147.34, 132.46, 132.17, 131.58, 131.28, 131.09, 130.36, 129.08, 128.93, 127.13, 126.98, 126.39, 126.34, 125.72, 125.68, 124.02, 123.97, 122.45, 121.95, 77.56, 77.39, 32.75, 23.30. ^{31}P NMR (162 MHz, DMSO-d_6): δ 150.74. HRMS (ESI$^+$): calcd. for $C_{46}H_{34}NaO_6P_2$ [M + Na]$^+$ 767.1723; found: 767.1725.

2.1.3. (1S,2S)-Bis[(R)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol ***6a′′***

Treatment of compound **4′** (77.6 mg, 0.67 mmol), **5a** (507.5 mg, 1.45 mmol), and DMAP (17.7 mg, 0.15 mmol) as described for the synthesis of ligand **6a** afforded ligand **6a′′**, which was purified by flash chromatography (R_f = 0.48, *n*-hexane:THF = 3:1) to produce a white solid (184.0 mg, 36.90% yield). $[\alpha]_D^{20}$ −246 (*c* 0.11, CH_2Cl_2); Mp 112–113 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (d, 2*H*, *J* = 8.8 Hz, Ar), 8.09 (t, 2*H*, *J* = 6.8 Hz, Ar), 8.03 (t, 4*H*, *J* = 8.2 Hz, Ar), 7.61 (d, 2*H*, *J* = 8.8 Hz, Ar), 7.51 (q, 6*H*, *J* = 6.2 Hz, Ar), 7.35 (t, 4*H*, *J* = 8.0 Hz, Ar), 7.30–7.23 (m, 4*H*, Ar), 4.31 (m, 2*H*, CH), 1.92 (d, 2*H*, *J* = 11.8 Hz, CH_2), 1.79–1.74 (m, 1*H*, CH_2), 1.60–1.39 (m, 5*H*, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 148.12, 147.32, 132.46, 132.17, 131.58, 131.24, 131.10, 130.48, 129.08, 128.96, 127.12, 127.00, 126.42, 126.36, 125.54, 123.88, 123.83, 122.33, 122.13, 122.04, 77.17, 77.01, 31.99, 22.65. ^{31}P NMR (162 MHz, DMSO-d_6): δ 149.44. HRMS (ESI$^+$): calcd. for $C_{46}H_{34}NaO_6P_2$ [M + Na]$^+$ 767.1723; found: 767.1738.

2.1.4. 1,2-Bis[(S)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol ***6b***

(*S*)-1,1′-Binaphthyl-2,2′-diyl-chlorophosphite **5b** was synthesized by the same procedure as **5a**, and was used directly without further purification. Treatment of compound **4** (62.3 mg, 0.54 mmol), **5b** (412.7 mg, 1.18 mmol), and DMAP (14.4 mg, 0.12 mmol) as described for the synthesis of ligand **6a** afforded ligand **6b**, which was purified by flash chromatography (R_f = 0.51, *n*-hexane:THF = 3:1) to produce a white solid (160.1 mg, 39.83% yield). $[\alpha]_D^{20}$ 180 (*c* 0.18, CH_2Cl_2); Mp 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (dd, 2*H*, *J* = 8.8, 6.4 Hz, Ar), 8.05 (dt, 6*H*, *J* = 22.0, 7.6 Hz, Ar), 7.59 (d, 1*H*, *J* = 8.8 Hz, Ar), 7.57–7.42 (m, 7*H*, Ar), 7.36 (m, 4*H*, Ar), 7.30–7.21 (m, 4*H*, Ar), 4.24 (m, 2*H*, CH), 2.15 (t, 1*H*, *J* = 12.6 Hz, CH_2), 1.91 (d, 1*H*, *J* = 11.6 Hz, CH_2), 1.63 (s, 1*H*, CH_2), 1.49 (d, 3*H*, *J* = 21.6 Hz, CH_2), 1.25 (d, 2*H*, *J* = 12.0 Hz, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 148.11, 148.06, 147.93, 147.92, 147.34, 147.31, 132.45, 132.16, 131.57, 131.27, 131.22, 131.08, 130.46, 130.36, 129.06, 128.93, 127.12, 127.10, 126.97, 126.40, 126.34, 125.68, 124.02, 123.97, 123.87, 123.82, 122.45, 122.34, 122.32, 122.11, 122.02, 121.95, 77.56, 77.39, 77.15, 76.98, 32.77, 31.98, 23.30, 22.63. ^{31}P NMR (162 MHz, DMSO-d_6): δ 150.77, 149.32. HRMS (ESI$^+$): calcd. for $C_{46}H_{34}NaO_6P_2$ [M + Na]$^+$ 767.1723; found: 767.1732.

2.1.5. (1S,2S)-Bis[(S)-1,1′-binaphthyl-2,2′-diyl]phosphitecyclohexanediol ***6b′′***

Treatment of compound **1** (62.3 mg, 0.54 mmol), **5b** (412.7 mg, 1.18 mmol), and DMAP (14.4 mg, 0.12 mmol) as described for the synthesis of ligand **6a** afforded ligand **6b′′**, which was purified by flash chromatography (R_f = 0.50, *n*-hexane:THF = 3:1) to produce a white solid (175.1 mg, 39.13% yield). $[\alpha]_D^{20}$ 98 (*c* 0.14, CH_2Cl_2); Mp 135–136 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, 2*H*, *J* = 8.8 Hz, Ar), 8.10–8.03 (m, 4*H*, Ar), 8.00 (d, 2*H*, *J* = 8.8 Hz, Ar), 7.57–7.47 (m, 6*H*, Ar), 7.44 (d, 2*H*, *J* = 8.8 Hz, Ar), 7.36 (dd, 4*H*, *J* = 15.6, 7.6 Hz, Ar), 7.26 (d, 2*H*, *J* = 8.4 Hz, Ar), 7.23–7.17 (m, 2*H*, Ar), 4.18 (m, 2*H*, CH), 2.23–2.11 (m, 2*H*, CH_2), 1.63 (s, 2*H*, CH_2), 1.48 (d, 2*H*, *J* = 10.0 Hz, CH_2), 1.23 (d, 2*H*, *J* = 7.2 Hz, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 147.94, 147.33, 132.45, 132.17, 131.57, 131.29, 131.09, 130.37, 129.08, 128.93, 127.14, 127.00, 126.38, 126.34, 125.73, 125.52, 124.00, 123.96, 122.45, 122.34, 77.57, 77.39, 32.76, 23.30. ^{31}P NMR (162 MHz, DMSO-d_6): δ 150.72. HRMS (ESI$^+$): calcd. for $C_{46}H_{34}NaO_6P_2$ [M + Na]$^+$ 767.1723; found: 767.1733.

2.1.6. 1,2-Bis[(R)-1,1′-H$_8$-binaphthyl-2,2′-diyl]phosphitecyclohexanediol ***6c***

(*R*)-1,1′-H$_8$-Binaphthyl-2,2′-diyl-chlorophosphite **5c** was synthesized by the same procedure as **5a**, and was used directly without further purification. Treatment of compound **4** (77.9 mg, 0.67 mmol), **5c** (530.0 mg, 1.48 mmol), and DMAP (18.0 mg, 0.15 mmol) as described for the synthesis of ligand **6a** afforded ligand **6c**, which was purified by flash chromatography (R_f = 0.54, *n*-hexane:toluene = 2:1) to produce a white solid (124.0 mg, 24.34% yield). $[\alpha]_D^{20}$ −153 (*c* 0.11, CH_2Cl_2); Mp 91–92 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (d, 2*H*, *J* = 8.8 Hz, Ar), 7.04 (dd, 3*H*, *J* = 15.2, 8.0 Hz, Ar), 6.98 (d, 1*H*, *J* = 8.0 Hz, Ar), 6.86 (dd, 2*H*, *J* = 16.0, 8.2 Hz, Ar), 4.09 (m, 2*H*, CH), 2.90–2.54 (m, 12*H*, CH_2), 2.23–2.02 (m, 6*H*, CH_2), 1.86–1.59 (m, 14H, CH_2), 1.58–1.32 (m, 8*H*, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 146.32, 146.17, 145.83, 145.80, 138.37, 138.26, 137.35, 137.29, 134.99, 134.90, 133.89, 133.81, 129.84, 129.82, 129.40, 129.39, 127.75, 127.61, 127.60, 119.37, 119.23, 119.06, 118.99, 77.18, 77.15, 76.97, 76.95, 32.76, 28.83, 27.70, 27.67, 27.58, 23.39, 22.49, 22.40, 22.38, 22.32, 22.27. ^{31}P NMR (162 MHz, DMSO-d_6): δ 145.11, 142.80. HRMS (ESI$^+$): calcd. for $C_{46}H_{50}NaO_6P_2$ [M + Na]$^+$ 783.2975; found: 767.3010.

2.1.7. 1,2-Bis[(S)-1,1′-H$_8$-binaphthyl-2,2′-diyl]phosphitecyclohexanediol ***6d***

(*S*)-1,1′-H$_8$-Binaphthyl-2,2′-diyl-chlorophosphite **5d** was synthesized by the same procedure as **5a**, and used directly without further purification. Treatment of compound **4** (64.9 mg, 0.56 mmol), **5d** (500.0 mg, 1.40 mmol), and DMAP (17.1 mg, 0.14 mmol) as described for the synthesis of ligand **6a** afforded ligand **6d**, which was purified by flash chromatography (R_f = 0.45, *n*-hexane:toluene = 2:1) to produce a white solid (132.7 mg, 31.16% yield). $[\alpha]_D^{20}$ 170 (*c* 0.10, CH_2Cl_2); Mp 105–106 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.13 (d, 2*H*, *J* = 8.2 Hz, Ar), 7.04 (dd, 3*H*, *J* = 15.4, 8.2 Hz, Ar), 6.98 (d, 1*H*, *J* = 8.4 Hz, Ar), 6.86 (dd, 2*H*, *J* = 16.0, 8.0 Hz, Ar), 4.10 (m, 2*H*, CH), 2.79 (m, 8*H*, CH_2), 2.68–2.54 (m, 4*H*, CH_2), 2.26–1.97 (m, 6*H*, CH_2), 1.84–1.60 (m, 14H, CH_2), 1.58–1.36 (m, 8*H*, CH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 146.32, 146.17, 145.82, 145.80, 138.37, 138.26, 137.34, 137.28, 134.99, 134.90, 133.89, 133.81, 129.84, 129.82, 129.40, 129.39, 127.75, 127.60, 119.37, 119.23, 119.05, 118.99, 77.18, 77.13, 76.97, 76.94, 32.77, 30.17, 28.83, 27.70, 27.67, 27.58, 23.39, 22.49, 22.40, 22.38, 22.33, 22.27. ^{31}P NMR (162 MHz, DMSO-d_6): δ 145.14, 142.85. HRMS (ESI$^+$): calcd. for $C_{46}H_{50}NaO_6P_2$ [M + Na]$^+$ 783.2975; found: 767.3002.

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2.2. Representative procedure for the 1,4-addition of Et_2Zn to 2-cyclohexenone **7a**

A solution of CuTc (0.005 mmol, 1.0 mg) and ligand **6a** (0.005 mmol, 3.7 mg) in Et_2O (4 mL) was stirred for 1 h at r.t. under nitrogen. After the solution was cooled to 0 °C, 2-cyclohexenone **7a** (0.25 mmol, 0.025 mL) was added and the solution was stirred for 10 min at 0 °C. Then Et_2Zn (1.2 mmol, 1.2 mL of 1.0 mol/L solution in hexane) was added dropwise using a syringe within 2 min. After 4 h, the reaction was quenched by H_2O (2 mL) and 2 mol/L HCl (2 mL), and extracted with ethyl acetate (5 mL × 3). The combined organic layer was washed with saturated $NaHCO_3$ solution, brine, and then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to obtain the crude product. The conversion and the yield were determined by GC equipped with a SE-30 column (30 m × 0.32 mm ID) using dodecane as an internal standard. The enantiomeric excess was determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm ID), or a CP-Chirasil-Dex CB column (25 m × 0.25 mm ID). The absolute configuration was determined by comparison with authentic samples.

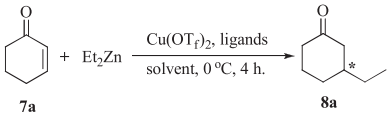
3. Results and discussion

The asymmetric induction ability of the chiral phosphite ligands was thoroughly explored in the Cu-catalyzed ACA of diethylzinc to cyclic enones. Owing to lower sensitivity to air and moisture, $Cu(OTf)_2$ was chosen as the Cu source for the preparation of the optically active catalysts. And 2-cyclohexenone was used as a substrate because this reaction has been performed with a wide range of ligands with several donor groups enabling the direct comparison of the efficiency of various ligand systems. The catalytic system was generated *in situ* by adding the corresponding ligand to a suspension of catalyst precursor. Results for the application of ligands **6a** through **6d** are shown in Table 1 (entries 1–4). The use of ligand **6a** gave 3-ethylcyclohexanone (**8a**) in 29% yield and 42% *ee* (*R*) (Table 1, entry 1). And ligand **6b**, which bears (*S*)-binaphthyl moieties in comparison with ligand **6a**, gave 12% yield and 17% *ee* (*S*) (Table 1, entry 2). A 35% yield and 20% *ee* (*R*) was gained when using **6c** as the ligand (Table 1, entry 3). In contrast, the use of ligand **6d**, in which the configuration of the H_8-binaphthyl moiety was opposite to that of **6c**, gave 17% yield and 15% *ee* (*S*) (Table 1, entry 4). It was found that the catalyst prepared *in situ* from $Cu(OTf)_2$ and ligand **6a** was more effective than that from either ligands **6b**, **6c**, or **6d** (Table 1, entries 2, 3, and 4 *vs.* entry 1). It is interesting to note that the sense of enantioselectivity was mainly determined by the configuration of the binaphthyl or H_8-binaphthyl moiety of ligands **6a** through **6d** from Table 1.

A screening of the solvents revealed that the reaction proceeded with significantly higher enantioselectivity in coordinating solvents (Et_2O and THF, Table 1, entries 5 and 6) than non-coordinating solvents (toluene and CH_2Cl_2, Table 1, entries 1 and 7). This result was consistent with the observations of Alexakis *et al.* [46] and Chan *et al.* [47] that the asymmetric conjugate addition of diethylzinc to enones gave higher ee values using coordinating solvents when compared to other reaction media. Although THF leads to slightly higher *ee* values, Et_2O was chosen as an appropriate solvent among the solvents examined because of the higher yield.

It is well known that the copper precursor plays a crucial role in the high catalytic activity and enantioselectivity of these reactions [48,49]. So the influence of the copper precursor as well as the copper/ligand ratio on the catalytic performance was examined (Table 2, entries 1–6). In comparison to $Cu(OTf)_2$, $(CuOTf)_2{\cdot}C_6H_6$ as a catalytic precursor could dramatically enhance the enantioselectivity in the presence of ligand **6a**, but much lower yield was realized (Table 2, entry 1). Interestingly, a better yield (97%) and enantioselectivity (97% *ee*) were obtained when $(CuOTf)_2{\cdot}C_6H_6$ was replaced by CuTc in the presence of ligand **6a** (Table 2, entry 4), which suggested that the matched combination of CuTc and ligand **6a** under the reaction conditions gave an excellent enantioselectivity and chemical yield of the product **8a**. An enhancement in

Table 1
The Cu-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexenone.[a]

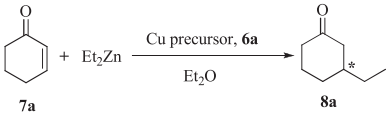


7a 8a

Entry	L.	Solvent	Con.[b] (%)	Yield (%)[b]	% *ee* (Conf.) [c]
1	**6a**	Toluene	66	29	42 (*R*)
2	**6b**	Toluene	45	12	17 (*S*)
3	**6c**	Toluene	69	35	20 (*R*)
4	**6d**	Toluene	60	17	15 (*S*)
5	**6a**	THF	59	19	54 (*R*)
6	**6a**	Et_2O	99	69	52 (*R*)
7	**6a**	CH_2Cl_2	91	61	37 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (0.005 mmol), ligand (0.005 mmol), Et_2Zn (1.0 mol/L in hexane, 0.6 mmol), **7a** (0.25 mmol), solvent (4 mL), 0 °C, 4 h.
[b] The data on conversion and yield were determined by GC using dodecane as internal standard with a SE-30 column (30 m × 0.32 mm I.D.).
[c] The enantiomeric excess of compound **8a** was determined by GC equipped with a Chiraldex A-TA column (50 m × 0.25 mm I.D.). The absolute configuration of **8a** was determined by comparison with authentic sample.

Table 2
The Cu-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexenone.[a]



7a 8a

Entry	Cu precursor	L/Cu	Temp (°C)	Time (h)	Con. (%)[b]	Yield (%)[b]	% *ee* (Conf.)[b]
1	$(CuOTf)_2{\cdot}C_6H_6$	1	0	4	50	19	98 (*R*)
2	$Cu(OAc)_2{\cdot}H_2O$	1	0	4	80	53	12 (*R*)
3	$Cu(acac)_2$	1	0	4	99	98	70 (*R*)
4	CuTc	1	0	4	99	97	97 (*R*)
5	CuTc	0.5	0	4	99	97	94 (*R*)
6	CuTc	2	0	4	71	43	97 (*R*)
7	CuTc	1	20	4	99	99	91 (*R*)
8	CuTc	1	−10	12	99	94	92 (*R*)
9	CuTc	1	−20	12	99	91	90 (*R*)
10	CuTc	1	−40	12	99	90	62 (*R*)
11[c]	CuTc	1	0	4	99	98	99 (*R*)
12[d]	CuTc	1	0	4	72	18	30 (*R*)
13[e]	CuTc	1	0	4	94	83	95 (*R*)
14[f]	CuTc	1	0	4	99	94	98 (*R*)
15[g]	CuTc	1	0	4	99	91	94 (*R*)
16[h]	CuTc	1	0	4	82	69	51 (*S*)
17[c]	CuTc	1	0	2	99	94	99 (*R*)

[a] Reaction conditions: Cu precursor (0.005 mmol), ligand **6a** (0.0025–0.01 mmol), Et_2Zn (1.0 mol/L in hexane, 0.6 mmol), **7a** (0.25 mmol), Et_2O (4 mL), −40–20 °C, 4–12 h.
[b] The data on conversion, yield, the enantiomeric excess, and the absolute configuration of the product were determined by the same condition as noted in Table 1.
[c] Using ligand **6a′**.
[d] Using ligand **6a″**.
[e] Ligands **6a′**/**6a″** = 1:2.
[f] Ligands **6a′**/**6a″** = 1:1.
[g] Ligands **6a′**/**6a″** = 2:1.
[h] Using ligand **6b″**.

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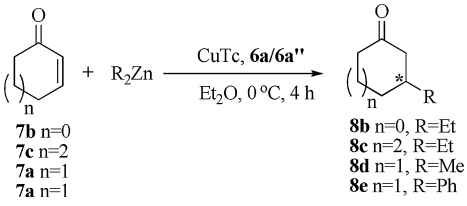
enantioselectivity was obtained when the molar ratio of ligand to CuTc ranged from 0.5/1 to 1/1 (Table 2, entries 4 and 5). Further increase of the ratio of ligand **6a**/CuTc resulted in no obvious change of the enantioselectivity, but the yield of the reactions significantly decreased (Table 2, entries 4 and 6) in agreement with our previous discovery [15]. Furthermore, the effect of reaction temperature on the enantioselectivity was investigated and when the temperature was decreased from 20 to 0 °C, the *ee* of (*R*)-enantiomers improved from 91% to 97% (Table 2, entries 4 and 7). With a further decrease of the temperature from 0 to −20 °C, a lower yield and enantioselectivity were gained (Table 2, entries 7–9). When the temperature was decreased to −40 °C, the enantioselectivity was significantly lowered to 62% (Table 2, entry 10). From these results, we can conclude that this novel catalytic system have shown excellent catalytic activity over a wide temperature range (Table 2, entries 7–9).

The ^{31}P spectrum of the ligand **6a** in DMSO-d_6 exhibits two singlets with parameters δ_p 150.75 and 149.31 at a 1.18:1 ratio. In order to verify the authentic catalytic species as racemic diols in the ligands, ligands **6a′** and **6a″** derived from enantiopure diols **4′** and **1** were prepared and applied in the same reaction, up to 99% *ee* (*R*) and 30% *ee* (*R*), respectively, were obtained. No significant changes in catalytic performance were observed by changing the ratio of ligands **6a′**/**6a″** (mol/mol) from 1/2 to 2/1 (Table 2, entries 13–15). From this we can conclude that **6a′**/CuTc is the actual catalytic species, however, noting the effect of ligand **6a″** was restrained when mixed ligands were used in the reaction. For ligand **6a′**, the result was similar to that of catalyst **6a**/CuTc. In other words, this reaction should proceed effectively by using **6a**, which is derived from cheaper racemic starting materials, instead of **6a′** as the ligand (Table 2, entries 11 and 12 *vs.* entry 4). Moreover, we can also conclude that the matching combination of (1*R*,2*R*)-*trans*-1,2-cyclohexanediol and (*R*)-binaphthyl moieties of ligand **6a′** was fundamental to obtaining higher enantioselectivity. Encouraged by this conclusion, we synthesized ligand **6b″** to verify the hypothesis whether there is a matching combination between (1*S*,2*S*)-*trans*-1,2-cyclohexanediol and (*S*)-binaphthyl moieties of ligand **6b″**, unfortunately, only 51% *ee* (*S*) was received (Table 2, entry 16). Although a standard reaction time of 4 h was chosen, the addition reaction was nearly complete within 2 h (Table 2, entry 17).

With the optimal reaction conditions in hand, the 1,4-addition of $ZnEt_2$ to 2-cyclopentenone **7b** and 2-cycloheptenone **7c** in the presence of ligand **6a**/CuTc was examined. It can be found that (*S*)-3-ethylcyclopentanone **8b** was obtained in 62% *ee*, while (*R*)-3-ethylcycloheptanone **8c** was obtained in 51% *ee* (Table 3, entries 1 and 2). It is interesting to note that the opposite configuration of the product was found when using 2-cyclopentenone instead of 2-cyclohexenone as the substrate. These results indicated a significant dependence of the enantioselectivity on the ring size of the cyclic enones. The Cu-catalyzed asymmetric 1,4-additions of other organozinc reagents, such as $ZnMe_2$ and $ZnPh_2$, to 2-cyclohexenone were also assessed. Unfortunately, when Me_2Zn or Ph_2Zn was utilized in the reaction, the enantioselectivity decreased to 25% (*R*) and 64% (*R*), respectively (Table 3, entries 3 and 4). Similarly, we obtained moderate enantioselectivity for **8e** using **6a′**/CuTc as the catalyst (Table 3, entry 5).

Table 3
The Cu-catalyzed enantioselective conjugate addition of dialkylzinc to cyclic enones.[a]



7b n=0
7c n=2
7a n=1
7a n=1

8b n=0, R=Et
8c n=2, R=Et
8d n=1, R=Me
8e n=1, R=Ph

Entry	Sub.	Product	Time (h)	Con.[b] (%)	Yield (%)[b]	% *ee* (Conf.)[b]
1	**7b**	**8b**	4	39	27	62 (*S*)
2[c]	**7c**	**8c**	4	58	49	51 (*R*)
3[c,d]	**7a**	**8d**	24	14	10	25 (*R*)
4[e]	**7a**	**8e**	24	70	30	64 (*R*)
5[f]	**7a**	**8e**	24	53	21	58 (*R*)

[a] Reaction conditions: CuTc (0.005 mmol), ligand **6a** (0.005 mmol), Et_2Zn (1.0 mol/L in hexane, 0.6 mmol), enone (0.25 mmol), Et_2O (4 mL), 0 °C, 4–24 h.
[b] The data on conversion, yield, the enantiomeric excess, and the absolute configuration of the product were determined by the same condition as noted in Table 1.
[c] The enantiomeric excess was determined by GC equipped with a CP-ChirasilDex CB (25 m × 0.25 mm I.D.).
[d] Me_2Zn (1.2 M in toluene, 1.2 mmol), 24 h.
[e] CuTc (0.005 mmol), **6a** (0.0015 mmol), Ph_2Zn (1.2 mol/L in toluene, 0.6 mmol), 24 h, isolated yield, the *ee* of **8e** was determined by HPLC (Daicel Chiralcel AD-H, hexane/*i*-PrOH = 99/1, 0.5 mL/min at 20 °C, detected at 209 nm.
[f] Using ligand **6a′**.

4. Conclusion

We have developed a new class of chiral diphosphite ligands derived from racemic and enantiopure diol materials. These ligands were successfully utilized in the copper-catalyzed asymmetric conjugate addition of dialkylzincs to cyclic enones with up to 99% *ee*. For substrate 2-cyclohexenone, similar catalytic performance was obtained when using ligand **6a** instead of ligand **6a′**. It was proven that the configuration of products was predominately determined by the configuration of the biaryl moieties of diphosphite ligands. Research concerning the use of these ligands in other transition metal-catalyzed asymmetric reactions is currently underway.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.10.009.

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