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RESEARCH PAPER

New Chiral Monophosphite Ligands Containing BINOL and/or H$_8$-BINOL Bearing Adamantyl Substituents: Effect of Ligand Scaffold on the Enantioselective 1,4-Conjugate Addition of Diethylzinc to Cyclic Enones

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Abstract: A series of new bulky monophosphite ligands were synthesized from axially chiral BINOL/H$_8$-BINOL (BINOL: 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol) and highly sterically hindered adamantylcarbonyl chloride. The effectiveness of these ligands was evaluated by the Cu-catalyzed asymmetric 1,4-conjugate addition of diethylzinc to cyclic enones with enantioselectivities of up to 79% ee. The results showed that a ligand structure comprising a partially hydrogenated 2,2′-(1,1′-binaphthyl)phosphite scaffold and an adamantyl moiety was effective in improving the enantioselectivity.

Key words: enantioselective 1,4-conjugate addition; phosphite ligand; copper salt; cyclic enone; adamantyl; H$_8$-binaphtyl

Asymmetric syntheses have been successful in the preparation of chiral motifs for the manipulation of optically active compounds in pharmaceutical and medicinal science. In particular, the enantioselective conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds is an attractive method for the stereoselective construction of carbon-carbon bonds in organic synthesis [1–4]. These addition products have been shown to have many applications in the synthesis of natural and biologically active compounds such as (*R*)-Muscone [5–7], Clavularin B [8,9], and Pumiliotoxin C [10]. Cu-catalyzed enantioselective 1,4-conjugate addition using chiral trivalent phosphorous ligands has been investigated extensively since the pioneering report by Alexakis et al. in 1993 [11]. A plethora of chiral phosphorous ligands such as phosphoramidites [1,12–14], phosphite ligands [15–17], and chiral P, N ligands [18–21] have been synthesized and successfully applied in reactions to afford good to excellent enantioselectivities. Nevertheless, the dynamic behavior of the equilibria among several species of organocuprate compounds in solution is problematic. Therefore, if the more reactive cuprates give racemic products a loss of enantioselectivity is unavoidable [22,23]. The design and synthesis of new chiral ligands that can rapidly react with substrates and suppress the formation of unwanted competing products is desirable.

Recently, Reetz et al. [24] reported a helical C$_3$-symmetric monophosphite ligand with a sterically encumbered adamantyl group (Scheme 1), which gave respectable enantioselectivities (79%–98% ee) in Rh-catalyzed asymmetric hydrogenation. Inspired by this excellent work, we undertook phosphite ligand development and focused on the bulky adamantyl moiety (Scheme 2, R group).

In addition to the chiral element from the binaphthyl skeleton, the partially hydrogenated H$_8$-binapthyl (5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl) scaffold is also of interest.

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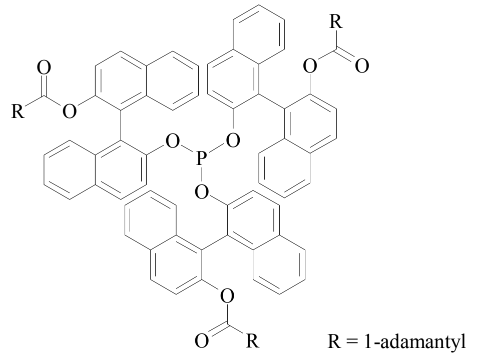
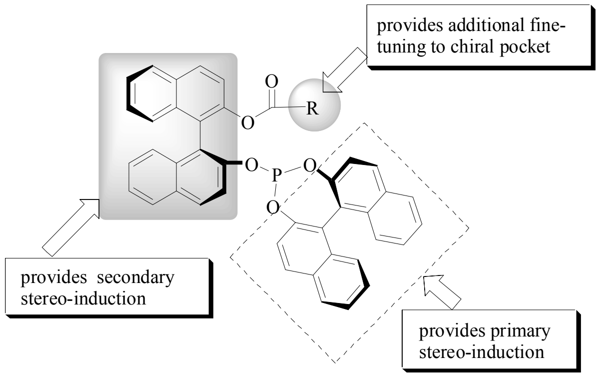


Scheme 1. Reetz's helical C_3-symmetric monophosphite ligand.



Scheme 2. Design of a modulated ligand bearing a bulky R group.

Chiral phosphorus donor ligands based on the H_8-binaphtyl moiety have received considerable attention recently [25–29]. The improved stereo-communication in H_8-BINOL compared to BINOL in asymmetric reactions has been explicitly highlighted [30–33]. Herein, we report the synthesis of a new series of bulky monophosphite ligands **L1**–**L9** based on the (*S*)-BINOL and the (*S*)-H_8-BINOL skeleton. The effectiveness of these ligands was examined in the copper-catalyzed enantioselective 1,4-conjugate addition of diethylzinc to cyclic enones.

1 Experimental

1.1 General

All experiments were carried out under nitrogen using standard Schlenk techniques. Reactions were monitored by thin layer chromatography (TLC). Column chromatography was carried out using silica gel. Toluene, ether, and tetrahydrofuran (THF) were distilled from sodium. Dichloromethane was distilled over calcium hydride. The other commercially available reagents were used as received without further purification. NMR (nuclear magnetic resonance) spectroscopy was recorded on a Bruker 400 MHz spectrometer. ^{1}H NMR and ^{13}C NMR spectra are reported in parts per million and TMS (δ = 0.00) was used as an internal standard. ^{31}P NMR spectra are reported in parts per million and 85% H_3PO_4 was used as an external reference. Proton chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. Spin multiplicities are reported as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). All the melting points were determined on an X-4 melting point apparatus and were uncorrected.

1.2 Synthesis of chiral monophosphite ligands

1.2.1 General protocol for the preparation of carboxylic acid esters of BINOL

A flame-dried flask was charged with BINOL (2.5 mmol), 4-dimethylaminopyridine (DMAP, 25 mg), 10 ml of THF, and Et_3N (3.25 mmol), and cooled to –10 °C. Acyl chloride or acetic anhydride (2.5 mmol) was added to the above-mentioned solution dropwise. Once the addition was complete the reaction mixture was left at room temperature until the near complete disappearance of the starting material. After 24 h, the reaction was quenched with distilled water (2.5 ml) and the mixture was extracted with ethyl acetate (5 ml × 3). The combined organic phases were washed successively with a saturated aqueous solution of $NaHCO_3$, brine, and then dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc/ hexanes) to provide the title compound (*S*)-**2a**, (*S*)-**2b**, or (*S*)-**2c** as a solid with > 95% yield (Scheme 3).

(*S*)-**2a**: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (s, 1H), 7.14−7.15 (m, 1H),7.16−7.45 (m, 8H), 7.54−7.56 (m, 2H), 7.65−7.67 (m, 2H), 7.78−7.80 (m, 2H), 8.00 (d, *J* = 8.4, 1H), 8.12 (d, *J* = 8.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.9, 118.2, 121.9, 123.2, 123.4, 124.6, 125.8, 126.3, 126.7, 127.5, 128.0, 128.3, 128.4, 128.7, 129.0, 130.0, 130.4, 130.8, 132.3, 133.5, 133.6, 133.7, 148.3, 151.8, 165.9.

(*S*) **2b**: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (s, 3H), 5.20 (s, 1H), 7.03 (d, 1H, *J* = 8.4 Hz), 7.23−7.49 (m, 7H), 7.85 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 9.2 Hz), 7.96 (m, 1H), 8.06 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 114.0, 118.2, 121.8, 123.1, 123.5, 124.5, 125.7, 126.3, 126.7, 127.5, 128.0, 128.3, 129.0, 130.4, 130.8, 132.2, 133.4, 133.5, 148.0, 151.7, 170.4.

(*S*)-**2c**: White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39−1.45 (m, 9H), 1.54−1.57 (d, *J* = 12.4, 3H), 1.77 (s, 3H), 5.14 (s, 1H), 7.05 (d, *J* = 8.4, 1H), 7.25−7.38 (m, 6H), 7.50 (m, 1H), 7.82 (d, *J* = 8.0, 1H), 7.88 (d, *J* = 9.2, 1H), 8.00 (d, *J* = 8.4, 1H), 8.06 (d, *J* = 8.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.6, 36.2, 38.0, 40.7, 114.3, 118.3, 121.9, 123.0, 123.5, 124.6, 125.6, 126.1, 126.6, 127.4, 127.9, 128.3, 129.0, 130.2, 130.7, 132.2, 133.5, 133.6, 148.4, 151.8, 177.0.

1.2.2 Synthesis of chiral monophosphite ligands

In a typical procedure for ligand synthesis, to a stirred solution of compound **2** (1.0 mmol) in THF (10 ml) was added Et_3N