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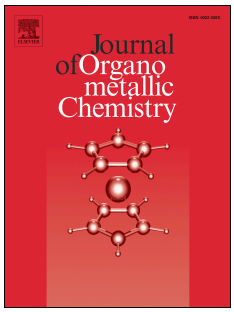

Modular bisphosphine ligands: Preparation and application in enantioselective catalytic reactions

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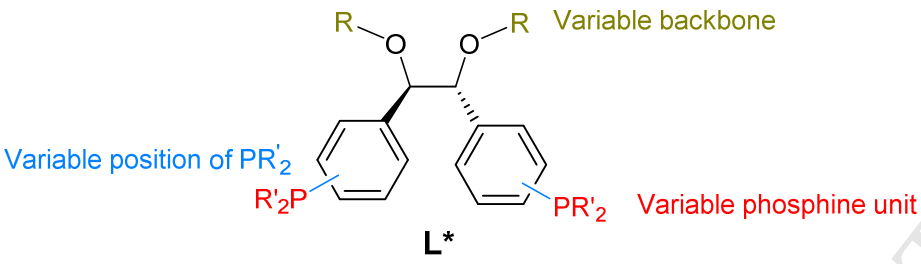

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Modular bisphosphine ligands: Preparation and application in enantioselective catalytic reactions

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Abstract

A set of six chiral modular C_2-symmetric bisphosphine ligands have been synthesized in a straightforward manner through a two-step reaction from the corresponding diols with moderate yields. The applicability of these chiral ligands was evaluated in ruthenium(II)-catalyzed transfer hydrogenation reactions (up to >99% conversion) and palladium(0)-catalyzed enantioselective allylic substitution reactions (up to 70% chemical yield and 43% ee).

Keywords: Bisphosphine; C_2-symmetric; Enantioselective; Allylic alkylation; Transfer hydrogenation

1. Introduction

In the past decades, chiral C_2-symmetric bidentate phosphorous ligands have received considerable attention in asymmetric transition metal catalysis due to their great success in a wide range of catalytic reactions [1-4]. Although, numerous chiral phosphine ligands have been

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significantly developed, it is still strongly required suitable electronic and steric needs of an appropriate ligand for the success of an enantioselective transition metal-catalyzed reaction. Given the complexity of most catalytic processes, the rational design of a chiral ligand is seldom straightforward. For this reason, we introduce a modular C_2-symmetric ligand structure, which allows rapid diversification, shown in Figure 1. Variation of the bulkiness of the R substituents at the backbone allows us to determine the optimal transfer of chirality from the backbone to the reaction center. The electronic and steric properties of the chelating atoms can also be tuned [5-7].

Herein we describe a series of chiral C_2-symmetric bisphosphine ligands by using corresponding chiral bromo-substituted hydrobenzoin derivatives which have been reported by our group [8,9] (Fig. 2). These synthesized ligands have been evaluated and compared in different types of catalytic reactions. The first one is palladium(0)-catalyzed enantioselective allylic alkylation which provides a very efficient route for enantioselective C-C and C-heteroatom bonds formation [10-16]. The second one is ruthenium(II)-catalyzed transfer hydrogenation reaction that leads secondary alcohols from the reduction of prochiral ketones which are key compounds for both academic and industrial areas [17-24].

2. Experimental

2.1. Materials and Equipment

All reagents were purchased and used without purification, unless otherwise noted. Compounds (1*R*,2*R*)-1,2-bis(2′-bromophenyl)-ethane-1,2-diol **10**, (1*R*,2*R*)-1,2-bis(3′-bromophenyl)-ethane-1,2-diol **11** and (1*R*,2*R*)-1,2-bis(4′-bromophenyl)-ethane-1,2-diol **12** were synthesized according to previously described procedures [8,9]. Analytical TLC was performed

using Macherey-Nagel SIL G-25 UV254 plates. Flash chromatography was carried out with Rocc silica gel (0.040–0.063 mm). ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer as indicated, with chemical shifts reported in ppm relative to TMS (for ^{1}H and ^{13}C), and relative to 85% aqueous phosphoric acid (for ^{31}P), using the residual solvent signal as a standard.^{13}C NMR spectra were recorded using the attached proton test. IR-spectra were recorded on a Perkin-Elmer Spectrum 65 FT-IR spectrometer. Analytical chiral HPLC separations were performed on a Shimadzu Prominence LC-20A with DAD detection. GC separations were performed on Shimadzu GC-2010 Plus. Optical rotations were measured with a Rudolph Autopol-I series polarimeter. Mass spectra were an Agilent LC-MS/MS 6460 Triple Quadrupole spectrometer. Elemental analyses were obtained with a LECO Elemental Analyzer (CHNS 0932). Melting points were measured with a Thermo Scientific 9200 melting point apparatus.

2.2. Synthesis

*2.2.1. (1R,2R)-1,2-bis(2′-bromophenyl)-1,2-dimethoxyethane (***10***)*[25]

(1*R*,2*R*)-1,2-bis(2′-bromophenyl)-ethane-1,2-diol **7** (2.0 g, 5.3 mmol) in THF was added dropwise through a dropping funnel to a stirred solution of NaH (1.27 g, 26.5 mmol) in THF (40 mL) at 0 °C over a 0.5 h period. The resulting reaction mixture was stirred at 0 °C for an additional 10 min. At the end of this period, the mixture was allowed to warm to room temperature and CH_3I (2.62 g, 18.5 mmol) was added. After addition was complete, the reaction mixture was stirred for another 24 h at room temperature. The reaction was monitored by thin layer chromatography using hexane - ethyl acetate (8:2) as the solvent system. Next, EtOAc (100 ml) was added and the organic phase was separated, whereupon the aqueous phase was further

extracted with EtOAc (2 x 50 ml). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give the desired product as a white solid (2.14 g, 99%). mp: 66-68 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =-59,94 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 8.47 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; IR (KBr disc) ν_{max}/cm^{-1}: 3063, 2926, 2856, 2825, 1590, 1465, 1438, 1355, 1204, 1093, 1024, 747, 681. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.66 (dd *J* = 8.0 Hz, *J* = 1.7 Hz, 2H), 7.41 (dd *J* = 8.0 Hz, *J* = 1.0 Hz, 2H), 7.32 (dt *J* = 7.5 Hz, *J* = 1.0 Hz, 2H), 7.1 (dt *J* = 7.5 Hz, *J* = 1.7 Hz, 2H), 4.95 (s, 2H), 3.19 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 137.3, 132.4, 130.6, 129.3, 127.2, 124.1, 83.8, 77.3, 76.7, 57.4; MS (ES^+) MS calculated $[M+Na]^+$ for $C_{16}H_{16}Br_2O_2Na$: 422.1 found: 422.1.

*2.2.2. (1R,2R)-1,2-bis(3'-bromophenyl)-1,2-dimethoxyethane (**11**)*

Synthesis of **11** was performed by following the procedure for **10** by using (1*R*,2*R*)-1,2-bis(3′-bromophenyl)-ethane-1,2-diol **8** (2.0 g, 5.3 mmol), NaH (1.27 g, 26.5 mmol) and CH_3I (2.62 g, 18.5 mmol). Yield: 2.11 g, 99%; mp: 59-60 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =-119,87 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 7.51 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; Anal. calcd for $C_{16}H_{16}Br_2O_2$: C, 48.03; H, 4.03%. Found: C, 48.12; H, 4.17%. IR (KBr disc) ν_{max}/cm^{-1}: 3062, 2925, 1570, 1468, 1424, 1348, 1187, 1110, 997, 787, 747, 692; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.35 (d, *J* = 8.0 Hz, 2H), 7.21 (s, 2H), 7.07 (t, *J* = 7.5 Hz, 2H), 6.9 (d, *J* = 8.0 Hz, 2H), 4.25 (s, 2H), 3.27 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 140.4, 131.0, 130.7, 129.4, 126.5, 122.2, 86.5, 57.5; MS (ES^+) MS calculated $[M+Na]^+$ for $C_{16}H_{16}Br_2O_2Na$: 422.1 found: 422.1.

*2.2.3. (1R,2R)-1,2-bis(4'-bromophenyl)-1,2-dimethoxyethane (**12**)* [26]

Synthesis of **12** was performed by following the procedure for **10** by using (1*R*,2*R*)-1,2-bis(4′-bromophenyl)-ethane-1,2-diol **9** (2.0 g, 5.3 mmol), NaH (1.27 g, 26.5 mmol) and CH_3I (2.62 g, 18.5 mmol). Yield: 2.05 g, 99%; mp: 81-82 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =+59.92 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 9.94 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; IR (KBr disc) ν_{max}/cm^{-1}: 3060, 2926, 2858, 2825, 1591, 1485, 1459, 1403, 1188, 1102, 819; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.33 (d, *J* = 8.5 Hz, 4H), 6.87 (d, *J* = 8.5 Hz, 4H), 4.25 (s, 2H), 3.25 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 136.9, 131.1, 129.5, 121.8, 86.5, 57.3; MS (ES^+) MS calculated $[M+Na]^+$ for $C_{16}H_{16}Br_2O_2Na$: 422.1 found: 422.1.

*2.2.4. (1R,2R)-1,2-bis(2'-(diphenylphosphino)phenyl)-1,2-dimethoxyethane (**1**)*[25]

A mixture of (1*R*,2*R*)-1,2-bis(2-bromophenyl)-1,2-dimethoxyethane **10** (0.55 g, 1.25 mmol) and 15 ml of dry THF were placed under a nitrogen atmosphere in a standard Schlenk tube and cooled to -78 °C. To this solution was added BuLi (2.5 ml, 4.1 mmol) at -78 °C and stirred for 1h at that temperature. Ph_2PCl (0.59 ml, 2.9 mmol) was added dropwise to the resulting mixture. After addition was complete, the reaction mixture was stirred for another 1 h at room temperature. The reaction was monitored by thin layer chromatography using hexane - ethyl acetate (9:1) as the solvent system. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/AcOEt, 9:1) resulted in **1** as a pure white solid (0.4 g; 52%). mp: 162-164 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =-87.92 (*c*= 1 (g/100 ml)$CHCl_3$); retention time 9.79 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; IR (KBr disc) ν_{max}/cm^{-1}: 3055, 2922, 2822, 1584, 1473, 1434, 1186, 1092, 744, 697; ^{1}H NMR (400 MHz,

$CDCl_3$, ppm) δ: 7.75 (m, 4H, $H_{12,18}$), 7.14-7.26 (m, 16H, $H_{10,11,13,14,16,17,19,20}$), 7.02 (m, 2H, H_7), 6.81-6.87 (m, 6H, $H_{5,6,8}$), 5.76 (d, J = 6.5 Hz, 2H, H_2), 2.91 (s, 6H, H_1); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 143.8 (dd, J = 29.3 Hz, 2.9 Hz, C_3); 137.0 (dd, J = 13.2 Hz, 6.8 Hz, C_9), 137.4 (dd, J = 6.6 Hz, 4.4 Hz, C_{15}), 136.6 (dd, J = 15.4 Hz, 5.1 Hz, C_4), 129.2 (m, $C_{7,12,18}$); 128.1-128.5 (m, $C_{6,8,11,13,17,19}$); 127.7-127.8 (m, $C_{5,10,14,16,20}$), 83.1-83.4 (m, C_2), 56.8 (C_1); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: -19.2; MS (ES^+) MS calculated $[M+H]^+$ for $C_{40}H_{36}O_2P_2$: 611.3 found: 611.3.

*2.2.5. (1R,2R)-1,2-bis(3′-(diphenylphosphino)phenyl)-1,2-dimethoxyethane (**2**)*

Synthesis of **2** was performed by following the procedure for **1** by using (1*R*,2*R*)-1,2-bis(3′-bromophenyl)-1,2-dimethoxyethane **11** (0.55 g, 1.25 mmol), BuLi (2.5 ml, 4.1 mmol) and Ph_2PCl (0.59 ml, 2.9 mmol). The crude product was purified by silica gel chromatography. The elution was carried out with hexane-ethyl acetate (9:1). The product was obtained as a white solid. Yield: 0.3 g, 37%; mp: 48-50 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =49.95 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 13.95 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; Anal. calcd for $C_{40}H_{36}O_2P_2$: C, 78.67; H, 5.64%. Found: C, 78.97; H, 5.88%. IR (KBr disc) ν_{max}/cm^{-1}: 3053, 2982, 2929, 2821, 1584, 1475, 1433, 1186, 1097, 744, 697; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.44-7.54 (m, 4H, $H_{12,18}$), 7.29-7.33 (m, 16H, $H_{10,11,13,14,16,17,19,20}$), 6.92-7.11 (m, 8H, $H_{4,6,7,8}$), 4.20 (s, 2H, H_2), 3.18 (s, 6H, H_1); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 138.3 (d, J = 7.3 Hz, C_3), 136.8 (m, $C_{5,9,15}$), 133.5-133.8 (m, $C_{8,12,18}$), 132.9-133.3 (m, $C_{4,6,10,14,16,20}$) 127.7-128.8 (m, $C_{7,11,13,17,19}$), 87.4 (C_2), 57.1 (C_1); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: -5.44; MS (ES^+) MS calculated $[M+H]^+$ for $C_{40}H_{36}O_2P_2$: 611.3 found: 611.3.

*2.2.6. (1R,2R)-1,2-bis(4′-(diphenylphosphino)phenyl)-1,2-dimethoxyethane (**3**)*

Synthesis of **3** was performed by following the procedure for **1** by using (1*R*,2*R*)-1,2-bis(4′-bromophenyl)-1,2-dimethoxyethane **12** (0.55 g, 1.25 mmol), BuLi (2.5 ml, 4.1 mmol) and Ph_2PCl (0.59 ml, 2.9 mmol). The crude product was purified by silica gel chromatography. The elution was carried out with hexane-ethyl acetate (9:1). The product was obtained as a white solid. Yield: 0.25 g, 32%; mp: 44-46 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =59.94 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 10.35 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; Anal. calcd for $C_{40}H_{36}O_2P_2$: C, 78.67; H, 5.64%. Found: C, 78.43; H, 5.59%. IR (KBr disc) ν_{max}/cm^{-1}: 3055, 2982, 2929, 2823, 1479, 1434, 1188, 1098, 1021, 743, 696; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.40-7.58 (m, 4H, $H_{12,18}$), 7.28-7.31(m, 8H, $H_{11,13,17,19}$), 7.10-7.24 (m, 12H, $H_{5,7,10,14,16,20}$), 6.94 (dd, *J* = 8.5 Hz, 4H, $H_{4,8}$), 4.30 (s, 2H, H_2), 3.29 (s, 6H, H_1); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 138.94 (C_3), 136.6-137.0 (m, $C_{6,9,15}$), 133.0-133.8 (m, $C_{12,18}$), 131.5-132.0 (m, $C_{5,7,10,14,16,20}$), 128.7-127.4 (m, $C_{11,13,17,19}$), 127.9-128.0 (m, $C_{4,8}$), 87.5 (C_2), 57.3 (C_1); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: -6.44; MS (ES^+) MS calculated $[M+H]^+$ for $C_{40}H_{36}O_2P_2$: 611.3 found: 611.3.

*2.2.7. (1R,2R)-1,2-bis(2'-(dicyclohexylphosphino)phenyl)-1,2-dimethoxyethane (**4**)*

Synthesis of **4** was performed by following the procedure for **1** by using (1*R*,2*R*)-1,2-bis(2′-bromophenyl)-1,2-dimethoxyethane **10** (0.55 g, 1.25 mmol), BuLi (2.5 ml, 4.1 mmol) and PCy_2Cl (0.65 ml, 2.9 mmol). The crude product was purified by silica gel chromatography. The elution was carried out with hexane-ethyl acetate (9:1). The product was obtained as a white solid. Yield: 0.41 g, 51%; mp: 120-122 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =-23.97 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 7.26 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; Anal. calcd for $C_{40}H_{60}O_2P_2$: C, 75.68; H, 9.53%. Found: C, 75.54; H, 9.79%. IR (KBr

disc) ν_{max}/cm^{-1}: 3052, 2923, 2850, 1446, 1092, 746; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.70 (d, *J* = 7.3 Hz, 2H, H_5), 7.34 (m, 4H, $H_{6,8}$), 7.20 (t, *J* = 7.3 Hz, 2H, H_7), 5.74 (s, 2H, H_2), 3.15 (s, 6H, H_1), 1.92-0.98 (m, 44H, $H_{10\text{-}14,16\text{-}20}$); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 145.7 (d, *J* = 9.5 Hz, C_3), 132.4 (m, C_8), 130.8 (d, *J* = 8.1 Hz, C_5), 129.5 (C_6), 128.5 (d, *J* = 41 Hz, C_4), 126.8 (d, *J* = 7.3 Hz, C_7), 86.4 (C_2), 56.0 (C_1), 35.7 (d, *J* = 33 Hz, C_9), 34.7 (d, *J* = 33 Hz, C_{15}), 26.9-27.8 (m, $C_{10,11,13,14,16,17,19,20}$), 25.9-26.0 (m, $C_{12,18}$); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: -18.74; MS (ES^+) MS calculated $[M+H]^+$ for $C_{40}H_{60}O_2P_2$: 635.4 found: 635.5.

*2.2.8. (1R,2R)-1,2-bis(3′-(dicyclohexylphosphino)phenyl)-1,2-dimethoxyethane (**5**)*

Synthesis of **5** was performed by following the procedure for **1** by using (1*R*,2*R*)-1,2-bis(3′-bromophenyl)-1,2-dimethoxyethane **11** (0.55 g, 1.25 mmol), BuLi (2.5 ml, 4.1 mmol) and PCy_2Cl (0.65 ml, 2.9 mmol). The crude product was purified by silica gel chromatography. The elution was carried out with hexane-ethyl acetate (9:1). The product was obtained as oil. Yield: 0.27 g, 34%; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =9.39 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 6.97 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; Anal. calcd for $C_{40}H_{60}O_2P_2$: C, 75.68; H, 9.53%. Found: C, 75.33; H, 9.29%. IR (KBr disc) ν_{max}/cm^{-1}: 3049, 2925, 2853, 2447, 1416, 1171, 1108, 999, 704; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.59-7.56 (m, 2H, H_7), 7.54 (d, *J* = 9.8 Hz, 2H, H_4), 7.30 (m, 2H, H_6), 7.18 (d, *J* = 7.8 Hz, 2H, H_8), 4.44 (s, 2H, H_2), 3.24 (s, 6H, H_1), 2.01-1.14 (m, 44H, $H_{10\text{-}14,16\text{-}20}$); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 138.3-138.2 (d, *J* = 10.1 Hz, C_3), 134.5-134.8 (m, C_7), 131.3-131.4 (m, $C_{4,6}$), 130.4-130.6 (m, C_8), 128.5-128.6 (d, *J* = 9.5 Hz, C_5), 86.7 (C_2), 57.3 (C_1), 35.5 (d, *J* = 22 Hz, C_9), 34.8 (d, *J* = 22 Hz, C_{15}), 25.5-26.7 (m, $C_{10,11,13,14,16,17,19,20}$), 24.6 (m, $C_{12,18}$); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: 2.75 MS (ES^+) MS calculated $[M+H]^+$ for $C_{40}H_{60}O_2P_2$: 635.4 found: 635.5.

*2.2.9. (1R,2R)-1,2-bis(4′-(dicyclohexylphosphino)phenyl)-1,2-dimethoxyethane (**6**)*

Synthesis of **6** was performed by following the procedure for **1** by using (1*R*,2*R*)-1,2-bis(4′-bromophenyl)-1,2-dimethoxyethane **12** (0.55 g, 1.25 mmol), BuLi (2.5 ml, 4.1 mmol) and PCy_2Cl (0.65 ml, 2.9 mmol). The crude product was purified by silica gel chromatography. The elution was carried out with hexane-ethyl acetate (9:1). The product was obtained as a white solid. Yield: 0.56 g, 71%; mp: 48-50 °C. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ =27.97 (*c*= 1 (g/100 ml), $CHCl_3$); retention time 6.79 min, Chiral ART Amylose-C, 90:10 *n*-hexane-^{i}PrOH, flow rate of 0.5 ml/min, 254 nm, t = 40 °C; Anal. calcd for $C_{40}H_{60}O_2P_2$: C, 75.68; H, 9.53%. Found: C, 75.86; H, 9.94%. IR (KBr disc) ν_{max}/cm^{-1}: 3050, 2925, 2851, 1448, 1173, 1105, 821; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.44-7.40 (m, 4H, $H_{5,7}$), 6.81-7.17(m, 4H, $H_{4,8}$), 4.38 (s, 2H, H_2), 3.34 (s, 6H, H_1), 1.14-2.00 (m, 44H, $H_{10\text{-}14,16\text{-}20}$); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 141.4-141.5 (d, *J* = 2.9 Hz, C_3), 130.9 (d, *J* = 8.1 Hz, $C_{4,8}$), 129.5 (d, *J* = 81 Hz, C_6), 127.4-127.7 (m, $C_{5,7}$), 86.9 (C_2), 57.7 (C_1), 35.4 (d, *J* = 37 Hz, C_9), 34.7 (d, *J* = 37 Hz, C_{15}), 25.4-26.5 (m, $C_{10,11,13,14,16,17,19,20}$), 24.6-24.7 (m, $C_{12,18}$); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: 1.92 MS (ES^+) MS calculated $[M+H]^+$ for $C_{40}H_{60}O_2P_2$: 635.4 found: 635.5.

*2.2.10. Ruthenium(II) complex of (1R,2R)-1,2-bis(4′-(diphenylphosphino)phenyl)-1,2-dimethoxyethane (*Ru(II)-**3**)*

Ru(II)-**3** complex was prepared by the reaction of (*1R,2R*)-1,2-bis(4′-(diphenylphosphino)phenyl)-1,2-dimethoxyethane **3** (0.2 g, 0.3 mmol) with $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-}Cl)Cl]_2$ (0.2 g, 0.3 mmol) in 15 ml of toluene at room temperature for 2 hours. The solvent was evaporated to dryness under reduced pressure and addition of 10 ml of diethtyl ether gave Ru(II)-**3** as an orange solid. The product was collected by filtration and dried in vacuum. Yield: 0.19 g

(47%); mp: 214-215 °C. $[\alpha]_D^{20}$ = 39.95 (c = 0.5 (g/100 ml), $CHCl_3$); Anal. calcd for $C_{60}H_{64}Cl_4O_2P_2Ru_2$: C, 58.92; H, 5.27%. Found: C, 58.76; H, 5.14%. IR (KBr disc) ν_{max}/cm^{-1}: 3053, 2982, 2929, 2821, 1637, 1435, 1094, 748, 698; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 7.72-7.62 (m, 12H), 7.34-7.29 (m, 12), 6.96 (dd, *J* = 8.3 Hz, *J* = 1.5 Hz, 4H), 5.19 (t, *J* = 5.7 Hz, 4H), 4.94 (d, *J* = 6.0 Hz, 2H), 4.91 (d, *J* = 6.0 Hz, 2H), 4.30 (s, 2H), 3.26 (s, 6H), 2.84 (m, 2H), 1,78 (s, 6H), 1,10 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 140.1, 134.4-134.3 (m), 133.72-133.63 (d, *J* = 9.3 Hz), 133.5, 133.3-133.2 (d, *J* =7.3 Hz), 130.2, 127.9-128.04 (m), 127.41-127.31 (d, *J* = 10.3 Hz), 111.1, 95.9, 89.3, 88.8, 87.48-87.42 (d, *J* = 5.1 Hz), 87.13-87.08 (d, *J* = 5.9 Hz), 86.6, 57.5, 30.3, 22.1, 21.8, 17.8; ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: 24.52; Maldi-Tof calculated $[M]^+$ for $C_{60}H_{64}Cl_4O_2P_2Ru_2$: 1226.1 found: 1226.4.

2.2.10. General procedure for the asymmetric transfer hydrogenation of aromatic ketones

A mixture of [Ru(*p*-cymene)Cl_2]$_2$ (0.004 mmol) and corresponding chiral bisphosphine ligand (**1**-**6**) (0.004 mmol) in ^{i}PrOH (7 ml) were placed under a nitrogen atmosphere in a standard Schlenk tube. The reaction mixture was heated and stirred under nitrogen at 82 °C for 2 h. After cooling to room temperature, the aromatic ketone (1 mmol) was added to this mixture and the solution was then heated to 82 °C. To initiate the reaction, the solution of ^{t}BuOK (0.05 mmol) in ^{i}PrOH was added to the stirring reaction mixture. To monitor the conversions of ketones to corresponding secondary alcohols, a small volume of reaction mixture was taken from Schlenk tube via micro syringe and diluted with ^{i}PrOH, and then passed from microfilter. The conversion and enantiomeric excess were monitored by GC using Agilent HP-Chiral 20B column.

2.2.11. General procedure for Pd(0)-catalyzed enantioselective allylic alkylation

Corresponding bisphosphine ligand (**1-6**) (0.05 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol) were dissolved in degassed CH_2Cl_2 under argon atmosphere using Schlenk techniques. The reaction mixture was stirred for 1h at 50 °C and cooled to room temperature. Then (*E*)-1,3-diphenylallyl acetate (**13**) (1 mmol) in CH_2Cl_2 was added and stirred at room temperature for 30 min. Finally, a solution of BSA (3 mmol), AcOLi or AcOK (0.1 mmol) and dimethylmalonate (3 mmol) was added to the mixture. The reaction mixture was stirred for 16 h at room temperature. Next, diethylether was added, washed with saturated NH_4Cl, dried on $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (Hexane/AcOEt, 90/10) to afford the target compound. All adducts were fully characterized by comparison of their spectral data with those reported in the literature. The absolute configurations were assigned via correlation of their optical rotation with literature values [27]. The enantiomeric excess was determined by chiral HPLC analysis: Chiral OD-H column (250 x 4.6 mm, particle size 10 µm), solvent: n-hexane/ ^{i}PrOH (50/50), flow rate 0.5 ml /min, t = 40 °C, retention times: 10.9 min for (*R*)-(-)-**14** and 12.9 min for (*S*)-(+)-**14**.

3. Result and Discussion

A two-step synthetic route towards chiral C_2-symmetric bisphosphine ligands started with the corresponding enantiomerically pure bromo-substituted diols **7-9** which were earlier described by our group [8,9]. Chiral bromo-substituted diols are the key structures in our synthesis of bisphosphine ligands **1-6** (Scheme 1). Bisphosphine ligand **1** has been synthesized by Brunner [25]. However, moderate chemical yields or needing more purification procedures reported in the literature prompted us to devise a different route involving more chemical yields and less purification procedures. Thus, bisphosphine ligand **1** was synthesized in two steps in good overall yields. The first step was methylated of compound **7** via CH_3I in the presence of a base yielded

99% [26]. The second step gave bisphosphine ligand **1** (60%) by reacting the compound **10** with the desired chlorodiphenylphosphine in the presence of a base. Novel bisphosphine ligands **2** and **3** were synthesized from the corresponding diols **11** and **12** according to this procedure, respectively. Dicyclohexylphosphine substituted ligands **4-6** were synthesized from the corresponding diols (**10-12)** by the treatment of chlorodicyclohexylphosphine in the presence of a base. It should be noted that diphenylphosphine substituted ligands **1-3** are stable in air at room temperature for a few days, while dicyclohexylphosphine substituted ligands **4-6** are stable for a couple of hours.

The reaction of [Ru(*p*-cymene)Cl_2]$_2$ with one equivalent of bisphosphine **3** in toluene at room temperature gave the orange compound Ru(II)-**3** (Scheme 2). The reaction between ruthenium (II) precursor and bisphosphine ligand **3** is not affected by the molar ratio of [Ru(*p*-cymene)Cl_2]$_2$ as well as the steric and electronic properties of the donor atoms. The initial color changed from orange to orange-red, attributed to the dimer cleavage most probably by the bisphosphine ligand [28]. Ru(II)-**3** was isolated as indicated by singlet in the ^{31}P NMR spectrum at 24.52 ppm.

Transfer hydrogenation reaction was chosen as the first catalytic test reaction in order to determine the efficiency of the bisphosphine ligands **1-6**. This type of reaction is one of the mild methodologies for reduction of ketones using 2-propanol as a hydrogen source [29-33]. Initial tests were carried out in order to determine efficient reaction parameters such as amount of base, type of base and substrate/catalyst ratio using acetophenone as a substrate in refluxing ^{i}PrOH (Table 1). According to the method, chiral bisphosphine ligand and [Ru(*p*-cymene)Cl_2]$_2$ were dissolved in ^{i}PrOH and heated to reflux for 2h. Ketone and base were added to the reaction mixture after cooling to room temperature. Adding all reagents, reaction was heated to reflux for 24h. To find efficient reaction conditions, we investigated catalytic activities of all bisphosphine ligands in the presence of NaOH (0.05 mmol) with a low substrate/catalyst (1000/1) ratio. We determined some conversions but any enantioinduction (Table 1, entries 1-6). Bisphosphine

ligand **3** gave a slightly higher conversion among the all ligands (Table1, entry 3). Next, we increased the concentration of NaOH in same conditions under the catalysis bisphosphine ligand **3** (Table 1, entries 7-11). It showed that increasing the concentration of the base resulted in high conversions (up to 98%). Despite the high conversions, we focused our attention on mild condition in related with using low concentration of the base with slightly higher substrate/catalyst ratio. When we performed the reaction with 500/1 (substrate/catalyst) ratio in the presence of 0.05 mmol of NaOH, moderate conversion was detected (Table 1, entry 12). However, an increase in the concentration of NaOH to 0.4 was resulted in acceptable conversion (Table1, entry 13). 100/1 (substrate/catalyst) ratio with 0.05 mmol and 0.1 mmol of NaOH gave excellent conversions (Table 1, entries 14-16, up to 99%). Changing substrate/catalyst ratio as 250/1 using with 0.05 mmol of NaOH gave 98% conversion. In a low concentration of NaOH, all results showed that the best reactivity was observed using with 250/1 (substrate/catalyst) ratio. After finding the ratio of substrate-catalyst as 250/1, next study was planned to compare the base activity in conversion of aromatic ketones to corresponding secondary alcohols. Various bases such as NaOH, KOH and ^{t}BuOK have been explored under the same reaction conditions. All three bases gave the same conversion as 98% (Table 1, entries 17-19). Extended study was applied in order to determine the best base (Table 2). Therefore, conversions were compared for each base every hour till 24h. Conversion obtained with ^{t}BuOK gave the highest result in 2h (91%). We examined control experiments for the reactivity data. Performing the control experiments showed that the base, the pre-catalyst and the ligand were required for the catalysis (Table 1, entries 20-22).

With the appropriate condition in hand (250/1 substrate/catalyst ratio and 0.05 mmol ^{t}BuOK), a series of ketones were investigated in transfer hydrogenation reaction (Table 3). In general excellent conversions ranging between 93% and 99% were observed in the reduction of

acetophenone derivatives (Table 3, entries 2-10) exception of *p*-chloro substituted acetophenone (Table 3, entry 1, 71%)

Bisphosphine ligands **1**-**6** were further tested in the palladium-catalyzed enantioselective allylic substitution of 1,3-diphenyl-2-propenyl acetate **13** with dimethylmalonate (DMM), which is regarded as a standard test substrate for evaluating the catalysts (Table 4). The nucleophile was generated from DMM (3 equiv) in the presence of N-O-bis(trimethylsilyl)acetamide (BSA) (3 equiv) and 0.1 mol % BSA activator. With bisphosphine ligand **1**, we obtained poor results with both chemical yield and enantioselectivity (Table 4, entry 1). When we used AcOK as a BSA activator, a slightly higher enantioselectivity was obtained (Table 4, entry 2). When we performed the reaction with ligands **2** and **3**, we observed low catalytic activities (Table 4, entries 3-6). While bisphosphine ligand **4** catalyzed the reaction with moderate enantioselectivity (43%) and good activity (70%) in the presence of AcOLi, poor results were detected with AcOK (Table 4, entries 7 and 8). We determined almost racemic results under the catalysis of bisphosphine ligands **5** and **6** (Table 4, entries 9-12).

4. Conclusion

In conclusion, we have synthesized a set of six C_2-symmetric bisphosphine ligands as five of them are novel and one of them is known. As proof of their potential in enantioselective transition metal catalysis, these ligands were evaluated in ruthenium(II)-catalyzed transfer hydrogenation reactions and palladium(0)-catalyzed enantioselective allylic substitution reactions. The best catalytic results were obtained in the presence of diphenylphosphine substituted ligand **3** in the reduction of acetophenone derivatives (up to >99% conversion). Remarkably, with bisphosphine ligand **4**, good activities were observed in the palladium(0)-catalyzed enantioselective allylic alkylation reaction (70% chemical yield and 43% ee). Current

studies are focused upon expanding the scope of these novel ligands backbone by variation of its steric and electronic properties. These results will be reported in due course.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://

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Figure captions:

Fig. 1. General structure of modular C_2-symmetric bisphosphine ligands **L***.

Fig. 2. Retrosynthetic analysis of C_2-symmetric bisphosphine ligands **1-6**.

Scheme 1. Synthesis of C_2-symmetric bisphosphine ligands **1-6**.

Scheme 2. Reaction of $[Ru(p\text{-cymene})Cl_2]_2$ with bisphosphine ligand **3**.

Table 1. Reaction optimization for transfer hydrogenation of acetophenone.

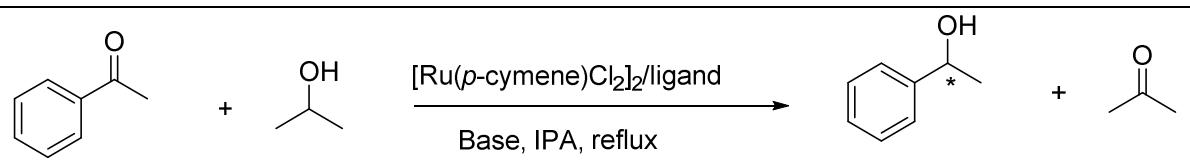
Table 2. Screening of the conversion against base and time.

Table 3. Ru-catalyzed asymmetric transfer hydrogenation of ketones with C_2-symmetric bisphosphine ligand **3**.

Table 4. Pd-catalyzed enantioselective allylic alkylation of **13** with dimethylmalonate in the presence of using bisphosphine ligands **1-6**.

A set of six chiral modular C_2-symmetric bisphosphine ligands have been synthesized in a straightforward manner through a two-step reaction from the corresponding diols with moderate yields. The applicability of these chiral ligands was evaluated in Ru-catalyzed enantioselective transfer hydrogenation reactions and Pd-catalyzed enantioselective allylic substitution reactions.

Table 1.



Entry	Acetophenone	S/C	Ligand	Base	Base mmol	Time (h)	Conversion (%)[a,b,c]
1	1 mmol	1000/1	**1**	NaOH	0.05	24	20
2	1 mmol	1000/1	**2**	NaOH	0.05	24	20
3	1 mmol	1000/1	**3**	NaOH	0.05	24	23
4	1 mmol	1000/1	**4**	NaOH	0.05	24	20
5	1 mmol	1000/1	**5**	NaOH	0.05	24	20
6	1 mmol	1000/1	**6**	NaOH	0.05	24	21
7	1 mmol	1000/1	**3**	NaOH	0.1	24	32
8	1 mmol	1000/1	**3**	NaOH	0.2	24	64
9	1 mmol	1000/1	**3**	NaOH	0.4	24	98
10	1 mmol	1000/1	**3**	NaOH	0.8	24	97
11	1 mmol	1000/1	**3**	NaOH	1	24	94
12	1 mmol	500/1	**3**	NaOH	0.05	24	50
13	1 mmol	500/1	**3**	NaOH	0.4	24	82
14	1 mmol	100/1	**3**	NaOH	0.05	24	92
15	1 mmol	100/1	**3**	NaOH	0.1	24	99
16	1 mmol	100/1	**3**	NaOH	0.2	24	95
17	1 mmol	250/1	**3**	NaOH	0.05	24	98
18	1 mmol	250/1	**3**	KOH	0.05	24	98
19	1 mmol	250/1	**3**	^{t}BuOK	0.05	24	98
20	1 mmol	250/1	**3**	-	-	24	5
21	1 mmol	250/1	**-**	^{t}BuOK	0.05	24	50
22[d]	1 mmol	250/1	**3**	^{t}BuOK	0.05	24	8

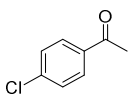
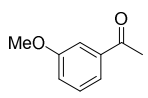
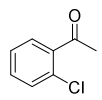
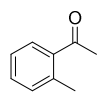
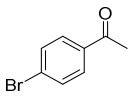
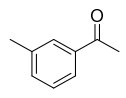
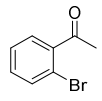
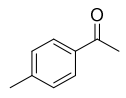
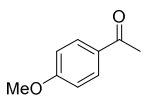
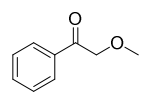
[a]: Determined by GC (HP-Chiral-20B); [b:] İPA (7ml), 82°C; [c:] No significant *ee* was observed; [d:] In absence of [Ru(*p*-cymene)Cl_2]$_2$.

Table 2.

Base	Ligand	S/C	% Conv. (0.5h)	% Conv. (1h)	% Conv. (2h)	% Conv. (4h)	% Conv. (6h)	% Conv. (8h)	% Conv. (24h)[a,b, c]
NaOH	**3**	250/1	3	5	45	61	79	91	98
KOH	**3**	250/1	18	47	81	93	97	97	98
^{t}BuOK	**3**	250/1	37	62	91	93	95	97	98

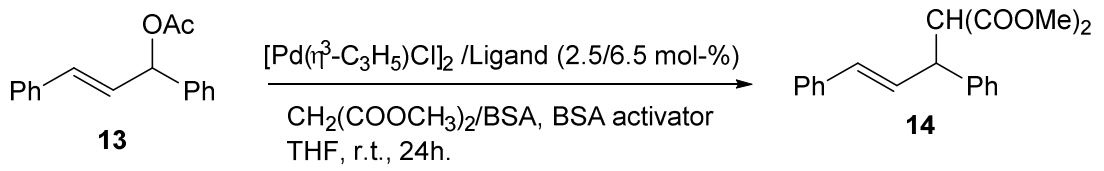
[a]: Determined by GC (HP-Chiral-20B); [b:] İPA (7ml), 82°C; [c:] No significant *ee* was observed

Table 3.

Entry	Substrate	S/C	Time (h)	Conversion (%)[a,b]	Entry	Substrate	S/C	Time (h)	Conversion (%)[a, b, c]
1		250/1	24	71	**6**		250/1	24	96
2		250/1	24	98	**7**		250/1	24	>99
3		250/1	24	97	**8**		250/1	24	98
4		250/1	24	98	**9**		250/1	24	96
5		250/1	24	93	**10**		250/1	24	>99

[a]: Determined by GC (HP-Chiral-20B); [b:] İPA (7ml), 82°C; [c:] No significant *ee* was observed

Table 4.



Entry	Ligand	BSA Activator	Yield [a]) %	ee [b])[c]) %
1	**1**	AcOLi	25	15 (*R*)
2	**1**	AcOK	30	33 (*R*)
3	**2**	AcOLi	16	13 (*R*)
4	**2**	AcOK	18	16 (*R*)
5	**3**	AcOLi	40	25 (*S*)
6	**3**	AcOK	15	rac
7	**4**	AcOLi	70	43 (*R*)
8	**4**	AcOK	34	12 (*R*)
9	**5**	AcOLi	12	11 (*S*)
10	**5**	AcOK	35	5 (*S*)
11	**6**	AcOLi	20	21 (*S*)
12	**6**	AcOK	15	rac

[a]) Yield of isolated product. [b]) Determined by HPLC analysis with a chiral stationary phase (*Chiralcel OD-H*). [c]) The absolute configuration was assigned by the sign of the optical rotation.

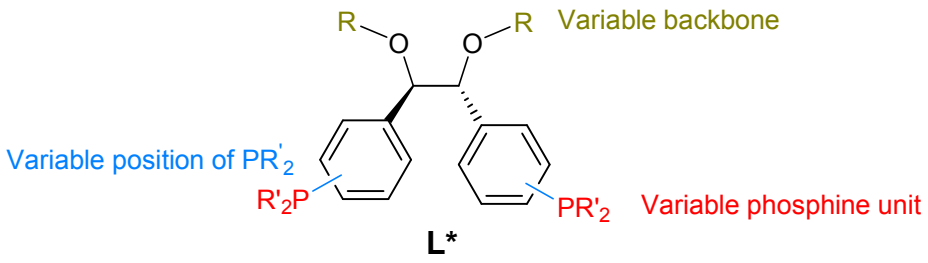


Fig. 1.

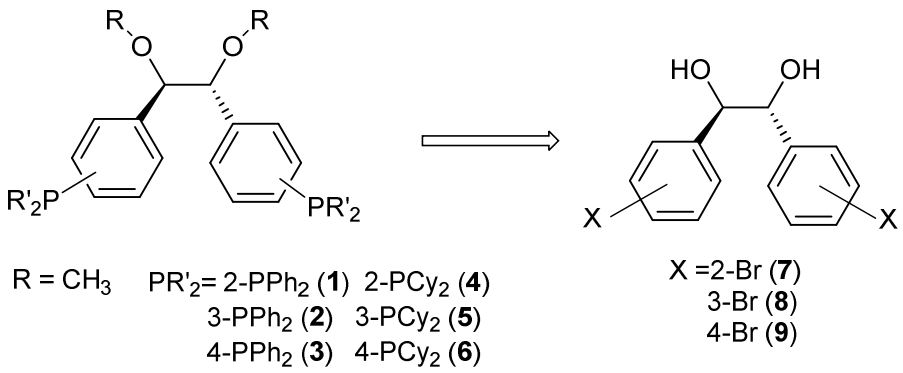
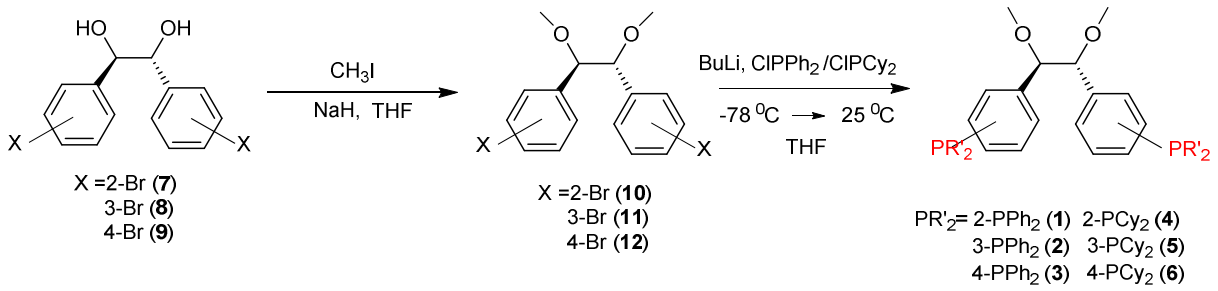
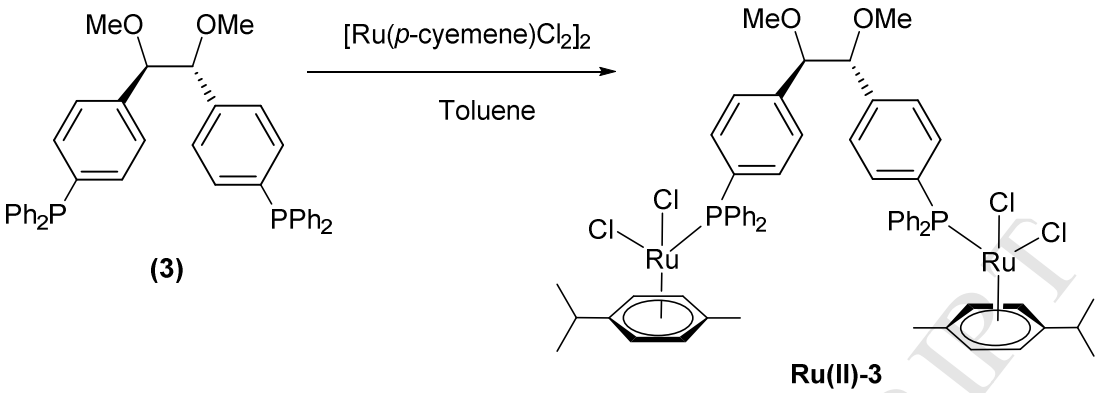


Fig. 2.



Scheme 1.



Scheme 2.

► A set of six chiral modular C_2-symmetric bisphosphine ligands have been synthesized

► C_2-symmetric modular ligand structure can be altered easily by using different alkyl or aryl groups.

► Catalytic activity of the ligands was investigated in enantioselective catalytic reactions.