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Synthesis of C_2-Symmetric Bisphosphines and Their Application in Enantioselective Transition Metal Catalysis

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Abstract: C_2-symmetric bisphosphine ligands (with a dioxolane backbone) have been synthesized by using corresponding chiral bromo-substituted hydrobenzoin derivatives in two steps with moderate yields. The last step for desired bisphosphines defined the electronic and steric properties of the chelating atoms by the treatment of aryl or alkyl substituted chlorophosphine compounds in the presence of a base. These synthesized ligands have been evaluated in different catalytic reactions. The first application has been the palladiumcatalyzed enantioselective allylic alkylation which is regarded as a remarkable reaction for forming enantioselective carbon-carbon bond (up to 63 % ee and 98 % chemical yield). The ruthenium-catalyzed enantioselective transfer hydrogenation reaction has been the second application for the evaluating of the catalysts (up to > 99 % conversion with no enantioselectivity).

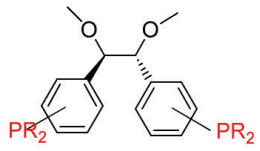
Keywords: synthesis, bisphosphine, catalysis, chirality, enantioselectivity.

INTRODUCTION

CARBON-CARBON and carbon-heteroatom bonds forming reactions such as allylic substitutions have become part of modern organic chemistry.[1–7] In this context, there is a remarkable attention in this type of synthesis and over the past few years, extensive researches have been carried out in order to develop efficient chiral ligands.[8–19] The first known palladium-catalyzed enantioselective allylic alkylation was introduced by Trost and Strege with moderate enantioselectivities in the presence of chiral 2,3-*O*-isoproylidene-2,3dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP).[20] Since the initial report, it took many years to develop efficient enantioselective catalysts due to the complex enantiocontrol in allylic substitutions. Later on, different type of nitrogen, phosphorus, P,X (P,N-, P,O- and P,S-) ligands were developed and were utilized in the enantioselective allylic alkylation with successfully.[21–27]

The asymmetric transfer hydrogenation (ATH) or reduction of ketones allows the production of a large number of useful chiral alcohols that are ubiquitous in nature and are in great demand for flavors and fragrances, for pharmaceuticals, and for agrochemicals.[28–35] Apart from some procedures, ATH includes some interesting advantages such as using environmentally friendly solvents, low catalyst loading, safe application and volatile byproducts. Consequently, it can be easily applied to industrial processes. Thanks to noteworthy advantages, ATH is a transformation which is upmost significance. Therefore, ATH of ketones has been performed using different transition metals (Ru, Rh, Fe, Ir, Ni, Co etc.) in combination with chiral ligands containing coordinating atoms (phosphorous, oxygen, nitrogen and sulfur) by many researchers.[36–45]

Recently, we have reported on a set of six chiral modular bisphosphine ligands with dimethoxy backbone for enantioselective catalytic reactions (Figure 1.).[46] They have showed some promising results in the palladium(0)-catalyzed enantioselective allylic alkylation reaction (70 % chemical yield and 43 % ee) and the ruthenium(II)-catalyzed transfer hydrogenation (up to > 99 % conversion). As part of our ongoing interest towards the development of



PR_2= 2-PPh_2, 2-PCy_2
3-PPh_2, 3-PCy_2
4-PPh_2, 4-PCy_2

Figure 1. Bisphosphine ligands with dimethoxy backbone.

enantioselective catalysts, we have developed a set of six chiral bisphosphine ligands containing a dioxolane ring as backbone. A careful combination of a metal with an appropriate ligand is a key requisite in order to obtain high enantioselective inductions. Taking these data into account, our synthesized bisphosphine ligands allow rapid diversification such as variation of the bulkiness of the R substituents at the backbone and modification of the electronic and steric properties of the chelating phosphorus atoms. These synthesized ligands were tested and compared in the palladium-catalyzed enantioselective allylic alkylation and the ruthenium-catalyzed transfer hydrogenation.

EXPERIMENTAL SECTION

Materials

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 **1**, (1*R*,2*R*)-1,2-bis(3′-bromophenyl)-ethane-1,2-diol **2**, (1*R*,2*R*)-1,2-bis(4′-bromophenyl)-ethane-1,2-diol **3**, (4*R*,5*R*)4,5-bis-(2 -bromophenyl)-2,2-dimethyl-1,3-dioxolane **4** and (4*R*,5*R*)-4,5-bis-(4 bromophenyl)-2,2-dimethyl-1,3-dioxolane **6** were synthesized according to previously described procedures.[47–50] 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 NMR), 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 Analyser (CHNS 0932). Melting points were measured with a Thermo Scientific 9200 melting point apparatus.

Synthesis

(4*R*,5*R*)-4,5-BIS-(3 -BROMOPHENYL)-2,2-DIMETHYL-1,3-DIOXOLANE *(5)*

A mixture of (1*R*,2*R*)-1,2-bis(3′-bromophenyl)-ethane-1,2-diol **2** (2.5 g, 6.7 mmol), 2,2′dimethoxypropane (7.0 g, 67.2 mmol) and 3 drops of conc. HCl in a standart Schlenk tube was stirred at room temperature for 16 h. The reaction was monitored by thin layer chromatography using hexane - ethyl acetate (9 : 1) as the solvent system. At the end of this period, 10 ml of dichloromethane and 3 drops of triethyl amine were added and the reaction mixture was stirred for another 1 h at room temperature. The resulting mixture was passed through a short alumina column and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography over silica gel with dichloromethane resulting in 2.6 g (94 %) of pure **5** as a transparent oil. +91.93 (*c* = 1, $CHCl_3$); IR (KBr) 3064 (aromatic *v* CH), 2986 (aliphatic v CH), 2932 (aliphatic v CH), 2881 (aliphatic v CH), 1570 (aromatic v CC), 1473 (aliphatic v CH), 1427, 1374, 1236, 1064 (*v* C–O), 870, 784, 693; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 1.67 (6H, s), 4.65 (2H, s), 7.04 (2H, dt, *J* = 7.7 Hz *J* = 1.3 Hz), 7.19 (2H, d, *J* = 7.8 Hz), 7.44-7.48 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) *δ*: 27.1 (CH_3), 84.6 (CH), 110.0 (C), 122.8 (C), 125.5 (CH), 129.5 (CH), 130.0 (CH), 131.6 (CH), 138.7 (C); MS (ES^+): 397.9 ($[M\text{-}CH_3+H]^+$, $C_{16}H_{14}Br_2O_2$; calc. 397.3); Anal. calc. for $C_{17}H_{16}Br_2O_2$: C 49.55, H 3.91; found: C 49.17, H 3.88.

(4*R*,5*R*)-4,5-BIS(2 -(DIPHENYLPHOSPHINO)PHENYL)-2,2-DIMETHYL-1,3-DIOXOLANE (7)*[49]*

A mixture of (4*R*,5*R*)-4,5-bis-(2 -bromophenyl)-2,2-dimethyl-1,3-dioxolane **4** (0.5 g, 1.2 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 (2.4 ml, 3.9 mmol) at 78 °C and stirred for 1h at that temperature. Ph_2PCl (0.5 mL, 2.8 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 **7** as a pure white solid (0.5 g; 59 %). mp 71–72 °C. = –97,93 (*c*, 1.0, $CHCl_3$); IR (KBr) 3055,

2984, 2921, 1736, 1475, 1434, 1233, 1047, 742, 696; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.59 (s, 6H), 6.05 (d, J = 5.5 Hz, 2H), 6.75 (t, J = 7.7 Hz, 4H), 6.81 (ddd J = 7.8 Hz, J = 4.0 Hz, J = 1.2 Hz, 2H), 6.98–7.05 (m, 6H), 7.09–7.16 (m, 6H), 7.23–7.26 (m, 8H), 7.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 27.3 (CH_3), 81.9 (d, J = 28 Hz, CH), 109.1 (C), 128.0–128.5 (m, CH), 129.6 (CH), 133.1 (d, J = 20 Hz, CH), 133.4 (d, J = 19 Hz, CH), 134.4 (CH), 136.1 (d, J = 16 Hz, C), 136,6 (C), 137.9 (d, J = 11 Hz, C), 140.3 (d, J = 24.2 Hz, C); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: –18.27.

(4*R*,5*R*)-4,5-BIS(3 -(DIPHENYLPHOSPHINO)PHENYL)-2,2-DIMETHYL-1,3-DIOXOLANE *(8)*

Synthesis of **8** was performed by following the procedure for **7** by using (4*R*,5*R*)-4,5-bis-(3 bromophenyl)-2,2-dimethyl-1,3-dioxolane **5** (0.5 g, 1.21 mmol), BuLi (2.4 mL, 3.9 mmol) and Ph_2PCl (0.5 ml, 2.8 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: 0.4 g; 46 %. mp 53–55 °C. +109.93 (c = 1, $CHCl_3$); IR (KBr) 3054 (aromatic ν CH), 2985 (aliphatic ν CH), 2931 (aliphatic ν CH), 2880 (aliphatic ν CH), 1957, 1736, 1586 (aromatic ν CC), 1477 (aliphatic ν CH), 1431 (ν P–C), 1374, 1233 (ν P–O), 1064, 823, 742, 697; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.49 (6H, s), 4.56 (2H, s), 7.10–7.12 (4H, m), 7.21–7.25 (10H, m), 7.31 (10H, m), 7.42–7.62 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 27.0 (CH_3), 85.5 (CH), 109.6 (C), 127.1 (CH), 128.7 (CH), 128.5 (d, J = 6.6 Hz, CH), , 131.7 (CH), 131.9 (CH), 133.5–133.8 (m, CH), 136.8 (d, J = 6.6 Hz, C), 136.9 (d, J = 4.4 Hz, C), 137.0 (d, J = 3.6 Hz, C), 137.7 (d, J = 11.7 Hz, C); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: -5.4; MS (ES$^+$): 623.2 ([M+H]$^+$, $C_{41}H_{36}O_2P_2$; calc. 623.3). Anal. calc. for $C_{41}H_{36}O_2P_2$: C 79.08, H 5.83; found: C 78.84, H 5.92.

(4*R*,5*R*)-4,5-BIS(4 -(DIPHENYLPHOSPHINO)PHENYL)-2,2-DIMETHYL-1,3-DIOXOLANE *(9)*

Synthesis of **9** was performed by following the procedure for **7** by using (4*R*,5*R*)-4,5-bis-(4 bromophenyl)-2,2-dimethyl-1,3-dioxolane **5** (0.5 g, 1.2 mmol), BuLi (2.4 ml, 3.9 mmol) and Ph_2PCl (0.5 ml, 2.8 mmol). The crude product was purified by silica gel chromatography. The elution was carried out with hexane-ethyl acetate (8:2). The product was obtained as a white solid. Yield: 0.5 g; 63 %. mp 75–77 °C. +175.86 (c = 1, $CHCl_3$); IR (KBr) 3054 (aromatic ν CH), 2983 (aliphatic ν CH), 2931 (aliphatic ν CH), 2885, 1432 (ν P–C), 1233 (ν P–O), 1062, 824, 744, 696; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.64 (6H, s), 4.75 (2H, s), 7.20–7.35 (24H, m), 7.49–7.65 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 27.1 (CH_3), 85.0 (CH), 109.6 (C), 126.9 (d, J = 6.6 Hz, CH), 128.6 (d, J = 6.6 Hz, CH), 128.9 (CH), 132.0-132.5 (m) (CH), 133.9–133.7 (dd, J = 19 Hz, J =4.4 Hz, CH), 137.2 (C), 137.3 (C), 137.4 (C); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: –5.9; MS (ES$^+$): 623.2 ([M+H]$^+$, $C_{41}H_{36}O_2P_2$; calc. 623.3); Anal. calc. for $C_{41}H_{36}O_2P_2$: C 79.08, H 5.83; found: C 78.82, H 6.15.

(4*R*,5*R*)-4,5-BIS(2 -(DICYCLOHEXYLPHOSPHINO)PHENYL)-2,2- DIMETHYL-1,3-DIOXOLANE *(10)*

Synthesis of **10** was performed by following the procedure for **7** by using (4*R*,5*R*)-4,5-bis-(2 bromophenyl)-2,2-dimethyl-1,3-dioxolane **4** (0.5 g, 1.2 mmol), BuLi (2.4 mL, 3.9 mmol) and Cy_2PCl (0.6 ml, 2.8 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: 0.5 g; 65 %. 7.99 (c = 1, $CHCl_3$); IR (KBr) 3053 (aromatic ν CH), 2982 (aliphatic ν CH), 2924 (aliphatic ν CH), 1446 (ν P–C), 1372, 1231 (ν P–O), 1168, 1048, 893, 697; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 0.93–1.73 (50H, m), 4.75 (2H, s), 7.21–7.31 (2H, m), 7.50 (2H, m), 7.74 (2H, m), 7.93 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ: 25.3–27.8 (m) (CH_3, CH_2), 29.7 (CH_2), 32.8 (CH), 85.5 (CH), 109.4 (C), 126.0 (C), 126.7 (CH), 127.4 (CH), 128.2 (CH), 128.4 (CH), 136.8 (C); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: –15.7; MS (ES$^+$): 647.4 ([M+H]$^+$, $C_{41}H_{60}O_2P_2$; calc. 647.5); Anal. calc. for $C_{41}H_{60}O_2P_2$: C 76.13, H 9.35; found: C 75.82, H 9.05.

(4*R*,5*R*)-4,5-BIS(3 -(DICYCLOHEXYLPHOSPHINO)PHENYL)-2,2- DIMETHYL-1,3-DIOXOLANE *(11)*

Synthesis of **11** was performed by following the procedure for **7** by using (4*R*,5*R*)-4,5-bis-(3 bromophenyl)-2,2-dimethyl-1,3-dioxolane **5** (0.5 g, 1.2 mmol), BuLi (2.4 mL, 3.9 mmol) and Cy_2PCl (0.6 mL, 2.8 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: 0.7 g; 84 %. +37.97 (c = 1, $CHCl_3$); IR (KBr) 3053 (aromatic ν CH), 2928 (aliphatic ν CH), 2852 (aliphatic ν CH), 1448 (ν P–C), 1373, 1229 (ν P–O), 1170, 1061, 1110, 702; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ: 1.13–2.04 (50H, m), 4.76 (2H, s), 7.30 (2H, d, J = 6.8Hz), 7.40 (2H, dt, J = 7.8Hz, J = 1.8 Hz), 7.56 (2H, d, J = 9.5Hz) 7.30 (2H, d, J = 6.8Hz), 7.30 (2H, d, J = 8.2Hz); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) δ:25.9 (CH_2), 26.2 (dd J = 10.2 Hz, J = 2.9 Hz, CH_2) 26.2 (d J = 4.4 Hz, CH_2), 26.7 (d J = 11.7 Hz, CH_2), 27.1 (CH_3), 31.3 (dd, J = 33Hz, J = 4.5 Hz, CH_2) 85.4 (CH), 110.2 (C), 126.4 (d, J = 46 Hz, C), 128.6 (d, J = 9.5 Hz, CH), 129.3 (d, J = 2.2 Hz, CH), 131.6 (d, J = 7.3 Hz, CH), 133.6 (d, J = 7.3 Hz, CH), 136.9 (d, J = 8.8 Hz, C); ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) δ: 3.1; MS (ES$^+$): 647.4 ([M+H]$^+$, $C_{41}H_{60}O_2P_2$: calc. 647.5); Anal. calc. for $C_{41}H_{60}O_2P_2$: C 76.13, H 9.35; found: C 76.64, H 9.61.

(4*R*,5*R*)-4,5-BIS(4 -(DICYCLOHEXYLPHOSPHINO)PHENYL)-2,2- DIMETHYL-1,3-DIOXOLANE *(12)*

Synthesis of **12** was performed by following the procedure for **7** by using (4*R*,5*R*)-4,5-bis-(4 bromophenyl)-2,2-

dimethyl-1,3-dioxolane **6** (0.5 g, 1.2 mmol), BuLi (2.4 mL, 3.9 mmol) and Cy_2PCl (0.6 mL, 2.8 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: 0.4 g; 48 %. +97.92 (*c* = 1, $CHCl_3$); IR (KBr) 3053 (aromatic *v* CH), 2924 (aliphatic *v* CH), 2852 (aliphatic *v* CH), 1446 (*v* P–C), 1373, 1232 (*v* P–O), 1062, 892, 822, 738, 699; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) *δ*: 0.93–1.84 (50H, m), 4.78 (2H, s), 7.14 (4H, d, *J* = 8 Hz), 7.42 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$, ppm) *δ*: 25.9 (CH_2), 26.3 (dd *J* = 8.0 Hz, *J* = 2.2 Hz, CH_2) 26.5–26.8 (m, CH_2), 27.1 (CH_3), 31.0-31.5 (m, CH_2) 84.7 (CH), 110.1 (C), 126.3, 125.8 (d, *J* = 48 Hz, C), 133.6 (d, *J* = 9.5 Hz, CH), 133.7 (d, *J* = 7.3 Hz, CH), 139.8 (d, *J* = 2.2 Hz, C) ^{31}P-NMR: (162 MHz, $CDCl_3$, ppm) *δ*: 2.4; MS (ES^+): 647.4 ($[M+H]^+$, $C_{41}H_{60}O_2P_2$: calc. 647.5); Anal. calc. for $C_{41}H_{60}O_2P_2$: C 76.13, H 9.35; found: C 48.41, H 9.33.

GENERAL PROCEDURE FOR THE TRANSFER HYDROGENATION OF AROMATIC KETONES

A mixture of $[Ru(p\text{-cymene})Cl_2]_2$ (0.004 mmol) and corresponding chiral bisphosphine ligand (**7**–**12**) (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.

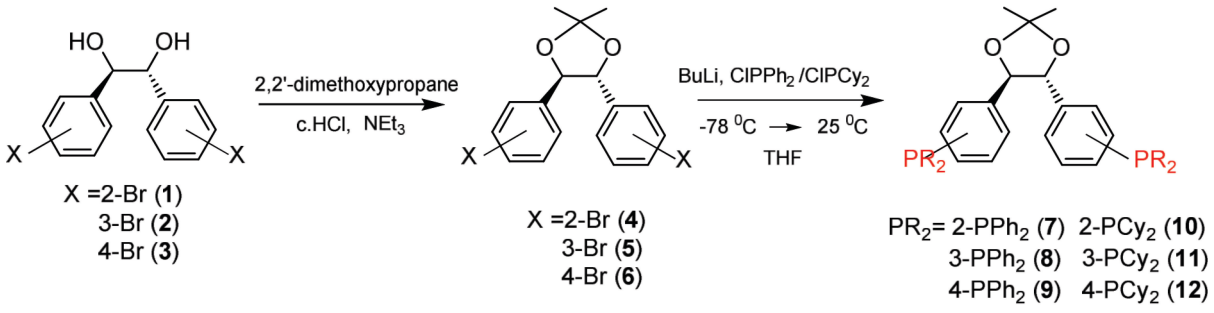
GENERAL PROCEDURE FOR PD-CATALYZED ENANTIOSELECTIVE ALLYLIC ALKYLATION

Corresponding bisphosphine ligand (**7**–**12**) (0.05 mmol) and $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol) were dissolved in degassed CH_2Cl_2 or THF 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) 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 or acetylacetone (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.[51–54] The enantiomeric excess was determined by chiral HPLC analysis.

RESULTS AND DISCUSSION

The synthetic routes towards the enantiomerically pure C_2-symmetric bisphosphine ligands with a dioxolane backbone started with the corresponding bromo-substituted diols **1**-**3** which were previously described by our group (Scheme 1).[47,48] Chiral bromo-substituted diols are the key structures in our synthesis of bisphosphine ligands **7**–**12**.

Bisphosphine ligand **7** has been synthesized by Brunner.[49] By using this literature procedure, the reaction of chiral bromo-substituted diol **1** with 2,2-dimethoxypropane afforded (4*R*,5*R*)-4,5-bis-(3 -bromophenyl)-2,2-dimethyl-1,3-dioxolane **4** with high chemical yield (90 %). The last step for desired bisphosphine **7** was the reaction of the compound **4** with chlorodiphenylphosphine in the presence of a base. Thus, bisphosphine ligand **7** was synthesized in two steps in good overall yields. Novel bisphosphine ligands **8** and **9** were synthesized from the corresponding compounds according to the same method as the synthesis of ligand **7**. Novel bisphosphine ligands **10**–**12** were synthesized from the corresponding compounds **4**–**6** by the treatment of chlorodicyclohexylphosphine in the presence of a base. Although bisphosphine ligands



Scheme 1. Synthesis of C_2-symmetric bisphosphine ligands **7–12.**

10–**12** are not stable enough in air at room temperature, it should be noted that bisphosphine ligands **7**–**9** are stable for a few days.

The palladium-catalyzed enantioselective allylic alkylation was chosen as the first catalytic test reaction in order to determine the efficiency of the synthesized bisphosphine ligands. Although the mechanism as well as the active species equilibria are known, the performance of the catalytic system depends on the fine tuning of factors such as type of substrate, nucleophile nature, reaction medium, catalytic precursor and type of ligand used. The chiral model formed by Pd-ligand fragment is believed to be related to the P-Pd-P bite angle.[23,55–57] According to all literature data, we tested all bisphosphine ligands **7**–**12** in the allylic alkylation of *rac*- 1,3-diphenyl-3-acetoxyprop-1-ene **13** with different nucleophiles (3 equiv) such as dimethylmalonate (DMM) and acetylacetone (Acac) in the presence of *N*-*O*bis(trimethylsilyl) acetamide (BSA) (3 equiv) and 0.1 mol % BSA activator (AcOLi or AcOK) in different solvents (dichlorometane or tetrahydrofurane) (Table 1).

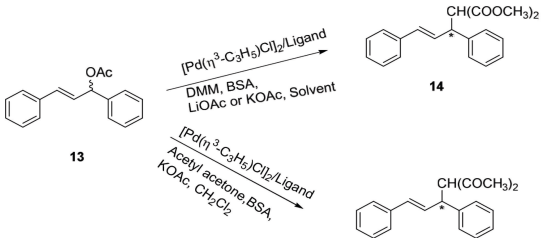
Despite the poor enantioselectivity, bisphosphine **7** catalyzed the reaction with quantitative yield in the presence of DMM with AcOLi in dichloromethane (Table 1, entry 1). When we used AcOK as a BSA activator, a slightly lower conversion was observed but no enantioinduction was obtained (Table 1, entry 2). Changing the solvent as tetrahydrofurane decreased the conversion in the presence of both BSA activator (AcOLi or AcOK) (Table 1, entries 3 and 4). However, obtaining moderate enantioselectivity with AcOK was noteworthy. The use of acetylacetone as a nucleophile and AcOK as a BSA-activator afforded the corresponding adduct with excellent yield but poor enantioselectivity (Table 1, entry 5). Bisphosphine **8** showed good reactivity but disappointed enantioselectivities in dichloromethane with both AcOLi and AcOK (Table 1, entries 6 and 7). Poor results were obtained in tetrahydrofurane (Table 1, entries 8 and 9). Changing the nucleophile as acetylacetone also gave unsatisfactory outcomes (Table 1, entry 5). With bisphosphine ligand **9**, we obtained moderate to good chemical yields but racemic mixtures in all conditions (Table 1, entries 11–14). Similarly, the use of acetylacetone resulted in high activity and almost racemic mixture (Table 1, entry 15). Among the phenyl-substituted bisphosphine ligands, ligand **7** gave the maximum enantioinduction with 53 %. When it came to cyclohexylsubstituted biphosphines, ligand **10** showed satisfactory results in dichloromethane using with both AcOLi and AcOK respectively (43 % ee, 62 % yield and 53 % ee, 98 % yield, Table 1, entries 16 and 17). When the reaction was performed at 0 °C, we observed sharp decrease conversion and a slighltly lower enantioselectivity (60 % ee, 40 % yield, Table 1, entry 18). In sharp contrast, poor results were observed when we changed the solvent as tetrahydrofurane (Table 1, entries 19 and 20). Changing the nucleophile as acetylacetone resulted in moderate enantioselectivity but poor activity (Table 1, entry 21). Performing the reaction with bisphosphine ligand **11**, we observed in all cases poor enantioselectivity and poor to excellent conversion (Table 1, entries 22–26). We determined poor results under the catalysis of bisphosphine ligand **12** except chemical yields of the reaction treating with AcOK (Table 1, entries 27–31).

Ortho-substituted phosphines catalyzed the alkylation reaction with highest enantioselectivity and conversion among the all ligands. However, *ortho*-substituted dicyclohexylphosphine ligand **10** showed higher enantioinduction and conversion than *ortho*substituted diphenylphosphine ligand **7** in same reaction conditions. Although *meta*substituted phosphines **8** and **11** gave some catalytic activity, *para*-substituted ones **9** and **12** showed almost racemic.

Bisphosphine ligands **7**–**12** were further tested in the ruthenium-catalyzed transfer hydrogenation of ketones. This type of reaction is one of the mild methodologies for obtaining secondary alcohols which are important building blocks in the synthesis of many biologically and optically active compounds.[58–60] 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 2).

According to the method, chiral bisphosphine ligand and [Ru(*p*-cymene)Cl_2]$_2$ were dissolved in ^{i}PrOH and heated to reflux for 2 h. Ketone and base were added to the reaction mixture after cooling to room temperature. Adding all reagents, reaction was heated to reflux for 24 h. To find efficient reaction conditions, we investigated catalytic activities of all bisphosphine ligands in the presence of NaOH (0.05 mmol) with a substrate / catalyst (250 / 1) ratio. We determined excellent conversions (Table 2, entries 1–6). Unfortunately, no enantioinduction was noted, which might be attributed to the chiral centers are remoteness to the monohapto P-coordinated ruthenium complexes.[46,61] Bisphosphine ligand **8** gave a slightly higher conversion among the all ligands (Table 2, entry 2). Next, we examined the role of the base under the catalysis of bisphosphine ligand **8**. Therefore, KOH and ^{t}BuOK were applied respectively (> 99 % and 94 %, Table 2, entries 7 and 8). KOH was chosen as a base for the catalytic reaction. After determining the appropriate base, it comes to find the best concentration of the base. Thus, we studied different amounts of KOH concentration. Decreasing the concentration of the base gave low conversion (Table 2, entry 9). In contrast, high conversions were obtained using with high concentration of KOH (Table 2, entries 10 and 11). The best conversion was obtained in the presence of

Table 1. *Pd*-catalyzed enantioselective allylic alkylation of **13** with dimethylmalonate and acetylacetone in the presence of using bisphosphine ligands **7**–**12**.



Entry	Ligand	BSA Activator	Nucleophile	Solvent	Yield / %[a]	ee / %[b,c]
1	**7**	LiOAc	DMM	Dichloromethane	99	15 (*S*)
2	**7**	KOAc	DMM	Dichloromethane	93	rac
3	**7**	LiOAc	DMM	Tetrahydrofurane	42	8 (*R*)
4	**7**	KOAc	DMM	Tetrahydrofurane	46	53 (*R*)
5	**7**	KOAc	Acac	Dichloromethane	99	5 (*S*)
6	**8**	LiOAc	DMM	Dichloromethane	68	22 (*R*)
7	**8**	KOAc	DMM	Dichloromethane	95	30 (*R*)
8	**8**	LiOAc	DMM	Tetrahydrofurane	5	16 (*R*)
9	**8**	KOAc	DMM	Tetrahydrofurane	2	30 (*R*)
10	**8**	KOAc	Acac	Dichloromethane	28	21 (*R*)
11	**9**	LiOAc	DMM	Dichloromethane	97	*rac*
12	**9**	KOAc	DMM	Dichloromethane	83	6 (*S*)
13	**9**	LiOAc	DMM	Tetrahydrofurane	62	*rac*
14	**9**	KOAc	DMM	Tetrahydrofurane	43	4 (*S*)
15	**9**	KOAc	Acac	Dichloromethane	99	4 (*S*)
16	**10**	LiOAc	DMM	Dichloromethane	62	43 (*R*)
17	**10**	KOAc	DMM	Dichloromethane	98	63 (*R*)
18[d]	**10**	KOAc	DMM	Dichloromethane	40	60 (*R*)
19	**10**	LiOAc	DMM	Tetrahydrofurane	2	29 (*R*)
20	**10**	KOAc	DMM	Tetrahydrofurane	10	13 (*R*)
21	**10**	KOAc	Acac	Dichloromethane	7	44 (*R*)
22	**11**	LiOAc	DMM	Dichloromethane	7	*rac*
23	**11**	KOAc	DMM	Dichloromethane	82	8 (*R*)
24	**11**	LiOAc	DMM	Tetrahydrofurane	4	18 (*S*)
25	**11**	KOAc	DMM	Tetrahydrofurane	98	6 (*R*)
26	**11**	KOAc	Acac	Dichloromethane	17	16 (*S*)
27	**12**	LiOAc	DMM	Dichloromethane	5	7 (*S*)
28	**12**	KOAc	DMM	Dichloromethane	95	20 (*S*)
29	**12**	LiOAc	DMM	Tetrahydrofurane	8	*rac*
30	**12**	KOAc	DMM	Tetrahydrofurane	93	*rac*
31	**12**	KOAc	Acac	Dichloromethane	25	8 (*S*)

[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.
[d] Reaction was performed at 0°C.

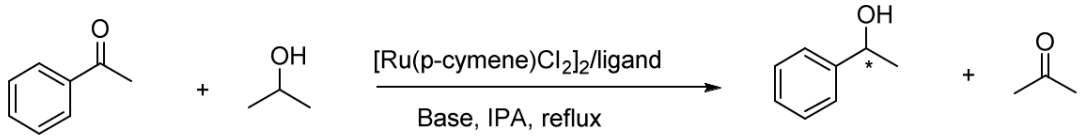
0.05 mmol of KOH which was quite good concentration for the catalytic reaction. Extended study was applied in order to determine the best substrate/catalyst ratio. When we performed the reaction with 1000 / 1 and 500 / 1 (substrate / catalyst) ratio in same condition, unsatisfactory results were obtained respectively (Table 2, entries 12 and 13). Increasing the substrate / catalyst ratio as 125 / 1 and 100 / 1 resulted with higher conversions (Table 2, entries 14 and 15). Performing the control experiments showed that the base, the precatalyst and the ligand were required for the catalysis (Table 2, entries 16–18). Among the all experiments we studied, the appropriate condition was designated as 250 / 1 substrate / catalyst ratio and 0.05 mmol KOH. According to determined parameters, a series of ketones were explored in ATH reaction (Table 3).

In general excellent conversions ranging between 94 % and > 99 % were observed in the reduction of acetophenone derivatives (Table 3, entries 2–10) except *p*-methoxy-substituted acetophenone (Table 3, entry 1, 78 %).

CONCLUSION

In summary, we have synthesized five novel and one known C_2-symmetric bisphosphine ligands with a dioxolane backbone. All bisphosphine ligands **7**–**12** were synthesized with good yields in a straightforward manner. Their effectiveness was illustrated in palladiumcatalyzed enantioselective allylic alkylation and ruthenium-catalyzed transfer hydrogenation. The best catalytic results were obtained with *ortho*-substituted bisphosphine ligands **7** and **10** in the enantioselective allylic alkylation of *rac*- 1,3-diphenyl-3-acetoxyprop-1-ene in the presence of DMM as nucleophile with KOAc. Chiral centers are connexion to the metal center and, therefore they directly influence the stereochemical outcome of the enantioselective reaction. When it came to the steric properties of the chelating atoms, making the ligand electron-rich led to higher enantioselectivity and conversion, as shown in the case of cyclohexyl-substituted bisphosphine **10** (63 % ee, 98 %

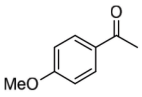
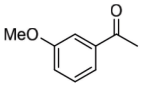
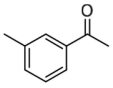
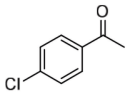
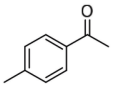
Table 2. Reaction optimization for transfer hydrogenation of acetophenone.



Entry	S/C	Ligand	Base	Base / mmol	Time / h	ee / %[b,c]
1	250/1	7	NaOH	0.05	24	96
2	250/1	8	NaOH	0.05	24	98
3	250/1	9	NaOH	0.05	24	97
4	250/1	10	NaOH	0.05	24	32
5	250/1	11	NaOH	0.05	24	95
6	250/1	12	NaOH	0.05	24	94
7	250/1	8	KOH	0.05	24	>99
8	250/1	8	*t*-BuOK	0.05	24	94
9	250/1	8	KOH	0.025	24	68
10	250/1	8	KOH	0.1	24	97
11	250/1	8	KOH	0.5	24	98
12	1000/1	8	KOH	0.05	24	7
13	500/1	8	KOH	0.05	24	13
14	125/1	8	KOH	0.05	24	99
15	100/1	8	KOH	0.05	24	97
16	250/1	8	–	–	24	5
17	250/1	–	KOH	0.05	24	50
18[c]	250/1	8	KOH	0.05	24	10

[a] Determined by GC (HP-Chiral-20B).
[b] PA (7mL), 82°C.

Table 3. *Ru*-catalyzed asymmetric transfer hydrogenation of ketones with C_2-symmetric bisphosphine ligand **8**.

Entry	Substrate	S/C	Time [h]	Conversion [%][a,b]	Entry	Substrate	S/C	Time [h]	Conversion [%][a,b]
1		250/1	24	78	**5**		250/1	24	>99
2		250/1	24	97	**6**		250/1	24	94
3		250/1	24	98	**7**		250/1	24	94
4		250/1	24	96	**8**		250/1	24	>99

[a] Determined by GC (HP-Chiral-20B).
[b] İPA (7ml), 82°C.

chemical yield) than phenylsubstituted bisphosphine **7** (53 % ee, 46 % chemical yield). Remarkably, by using all bisphosphine ligands excellent conversion but no enantioinduction were determined. Phenylsubstituted bisphosphine ligand **8** showed excellent conversion (up to > 99 %) in the reduction of acetophenone derivatives.

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