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Synthesis, characterization and first application of chiral C_2-symmetric bis(phosphinite)–Pd(II) complexes as catalysts in asymmetric intermolecular Heck reactions

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A series of new chiral C_2-symmetric bis(phosphinite) ligands and their palladium(II) complexes have been synthesized and for the first time used as catalysts in the palladium-catalysed asymmetric intermolecular Heck coupling reactions of 2,3-dihydrofuran with iodobenzene or aryl triflate. Under optimized conditions, products were obtained with high conversions and moderate to good enantioselectivities. The new C_2-symmetric bis(phosphinite) ligands and their palladium(II) complexes were characterized using multinuclear NMR and Fourier transform infrared spectroscopies and elemental analysis. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: palladium(II); C_2 symmetry; phosphinite; asymmetric Heck coupling

Introduction

Over the past few decades, transition-metal-catalysed reactions have undergone substantial development and found widespread applications in synthetic organic chemistry.[1] The noble metals of group VIII, which are also known as platinum group metals, ruthenium, osmium, rhodium, iridium, palladium and platinum, play prominent roles in homogeneous catalysis.[2] Among the platinum group metals, palladium has been successfully used as an efficient catalyst in the formation of C–C, C–O, C–N bonds, etc., in modern synthetic chemistry.[3]

The Mizoroki–Heck reaction, which was discovered in the 1970s by Mizoroki and Heck, involves the palladium-catalysed coupling of aryl or alkenyl halide or triflate to olefins. The reaction is often referred to as the 'Heck reaction'.[4] Chiral ligands bearing palladium(II) complexes have received wide attention due to their exclusive applications in asymmetric catalysis, especially in asymmetric intermolecular Heck coupling reactions.[5] Recently, research into the Heck reaction has focused on obtaining enantioselectivity.[6] Since the first reports in the late 1980s, various ligands have been developed for the asymmetric Heck reaction. Phosphorus-containing chiral ligands are of central importance for the asymmetric Heck reaction as well as for other asymmetric catalytic transformations. The first asymmetric variant of the Heck reaction was reported in 1989 by Shibasaki and co-workers and Overman and co-workers in which intramolecular cyclization of alkenyl iodide or triflate forms chiral cyclic compounds of around 45% enantiomeric excess.[7] The majority of the reported studies involve intramolecular reactions due the fact that the alkene regiochemistry and geometry in the product can be easily controlled.[8] In 1991, Hayashi and co-workers reported the first enantioselective intermolecular Heck reaction of 2,3-dihydrofuran and phenyl triflate, in which they used $Pd(OAc)_2$/2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)/i-Pr_2NEt and several other bidentate chiral phosphine ligands as catalysts and obtained high enantioselectivity (96%).[9] In this regard, chiral bidentate phosphorus-based ligands have been accepted to be excellent ligands for such processes.[10] The C_2 symmetry of BINAP limits the possible number of diastereomeric transition states formed, and the reactions performed using these ligands are therefore often highly selective.[11]

In following years, Pfaltz and co-workers[10a,b,12] and Hashimoto *et al.*[13] reported phosphorus-containing oxazolines as efficient ligands in the same type of asymmetric intermolecular Heck reaction. For the intermolecular Heck reaction, enantiomeric excess higher than 96% has been reached.[14] Lee and Hartwig reported rather low enantioselectivities using phosphoramidites as chiral ligands in asymmetric reactions.[15] Recently, phosphane oxazolines have been found to be efficient ligands for intermolecular asymmetric Heck reactions.[13] Peptide-derived phosphinite ligands showed good catalytic activity and very high enantiomeric excesses in intermolecular asymmetric Heck reactions. It is suggested that phosphinite dissociation occurs and the observed high stereocontrol is attributed to the inherent properties of the peptide backbone in the ligand structure.[16] Partly because of their straightforward synthesis from readily available chiral diols, C_2-symmetric bis(phosphinite) ligands also retain a privileged position in asymmetric transfer hydrogenation of ketones.[17–19]

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Herein we present the synthesis and characterization of new chiral C_2-symmetric bis(phosphinite) ligands and their palladium (II) complexes. To the best of our knowledge, these C_2-symmetric bis(phosphinite)–Pd(II) complexes were used as catalysts for the first time in the palladium-catalysed asymmetric intermolecular Heck coupling reactions of 2,3-dihydrofuran with iodobenzene or aryl triflate.

Experimental

Materials and methods

All reactions were carried out under inert atmosphere of argon in flame-dried glassware using conventional Schlenk techniques. Solvents were dried using established procedures and distilled under argon just prior to use. Analytical-grade and deuterated solvents were purchased from Merck. The starting materials were purchased from Sigma Aldrich or Merck and used as received. (2*R*)-2-[benzyl({[6-({benzyl[(2*R*)-1-hydroxy-3-phenylpropan-2-yl]amino}methyl) pyridine-2-yl]methyl})amino]-3-phenylpropan-1-ol (**1**), (2*R*)-2-[benzyl({[3-({benzyl[(2*R*)-1-hydroxy-3-phenylpropan-2-yl]amino}methyl) phenyl]methyl})amino]-3-phenylpropan-1-ol (**2**), (2*R*)-1-[benzyl({[6-({benzyl[(2*R*)-2-hydroxypropyl]amino}methyl)pyridin-2-yl]methyl}) amino]propan-2-ol (**3**), (2*R*)-1-[benzyl({[3-({benzyl[(2*R*)-2-hydroxypropyl]amino}methyl)phenyl] methyl})amino]propan-2-ol (**4**)[17] and $Pd(cod)Cl_2$[20] (cod = 1,5-cyclooctadiene) were prepared according to literature procedures.

^{1}H NMR (at 400.1 MHz), ^{13}C NMR (at 100.6 MHz) and ^{31}P-{^{1}H} NMR (at 162.0 MHz) spectra were recorded using a Bruker AV 400 spectrometer, with tetramethylsilane as an internal reference for ^{1}H NMR and ^{13}C NMR or 85% H_3PO_4 as an external reference for ^{31}P-{^{1}H} NMR. Attenuated total reflectance Fourier transform infrared (FT-IR) spectra were recorded with a PerkinElmer Spectrum 100. Specific rotations were obtained with a PerkinElmer 341 model polarimeter. Elemental analysis was carried out on with a Costech ECS 4010 instrument. Melting points were recorded with a Gallenkamp model apparatus with open capillaries.

GC analyses were performed using a Shimadzu GC 2010 Plus instrument equipped with a Chiraldex G-TA (Supelco) capillary column (30 m × 0.25 mm inner diameter × 0.12 μm film thickness). The GC parameters for asymmetric intermolecular Mizoroki–Heck reactions of 2,3-dihydrofuran were as follows: initial temperature, 70°C; initial time, 5 min; solvent delay; temperature ramp, 0.5°C min^{-1}; 90°C; initial time, 0 min; temperature ramp, 5°C min^{-1}; final temperature, 120°C; initial time, 5 min; final time, 56 min; injector port temperature, 200°C; detector temperature, 200°C; injection volume, 1.0 μl.

General procedure for preparation of chiral C_2-symmetric aminoalcohols[17]

Corresponding chiral aminoalcohol (30 mmol), 2,6-bis(bromomethyl)pyridine or 1,3-bis(bromomethyl)benzene (15 mmol), sodium carbonate (46 mmol) and KI (50 mg) in EtOH (50 ml) were stirred at 100°C for 12 h under argon. Then the mixture was cooled and $CHCl_3$ (100 ml) was added to the mixture and refluxed for 2 h. The solution was filtered, EtOH was removed *in vacuo* and $CHCl_3$ (50 ml) was added to the residue. The solution was washed with water and brine (50 ml) twice. The aqueous solution was extracted with $CHCl_3$ (2 × 50 ml). The combined $CHCl_3$ phases were dried over anhydrous Na_2SO_4.

Synthesis of ***1***

The crude product was purified by column chromatography over silica gel using *n*-hexane–ethyl acetate (2:1) to afford **1** (7.0 g, 80%) as a colourless solid. M.p. 126.5–128C; $[\alpha]_D^{20} = -37.0°$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{39}H_{43}O_2N_3$ (%): C, 79.97; H, 7.40; N, 7.17. Found (%): C, 79.83; H, 7.32; N, 7.04. ^{1}H NMR (CD_3CN, δ, ppm): 7.51 (t, 1H, J = 8.0 Hz, C_5H_3N), 7.17–7.30 (m, 20H, C_6H_5), 7.07 (d, 2H, J = 8.0 Hz C_5H_3N), 4.75 (broad, 2H, –CH_2OH), 4.03–4.07 (m, 2H, –CH_2N (b)), 3.76–3.80 (m, 6H, –;CH_2Ph + –;CH_2N (a)), 3.60–3.75 (m, 2H, –CH_2OH (b)), 3.34–3.36 (m, 2H –CH_2OH (a)), 2.98–3.11 (m, 4H, –CHCH_2 (b) + –CHCH_2), 2.57–2.60 (m, 2H, –CHCH_2 (a)). ^{13}C NMR (CD_3CN, δ, ppm): 159.77 (i-C_5H_3N), 140.44, 139.94 (i-C_6H_5), 137.05 (C_5H_3N), 129.18, 128.88, 128.33, 125.87, 128.03, 126.76 (C_6H_5), 121.39 (C_5H_3N), 63.50 (–CHCH_2), 60.83 (–CH_2OH), 54.78 (–CH_2N), 54.14 (–CH_2Ph), 32.65 (–CHCH_2). FT-IR (KBr pellet, cm^{-1}): ν(OH), 3402; ν(CH), 3024, 2922, 2864; ν(C=C), 1587, 1496, 1452.

Synthesis of ***2***

The crude product was purified by column chromatography over silica gel using *n*-hexane–ethyl acetate (2.5:1) to afford **2** (6.0 g, 68%) as a colourless solid M.p. 121–123°C; $[\alpha]_D^{20} = -40.0°$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{40}H_{44}O_2N_2$ (%): C, 82.15; H, 7.60; N, 4.79. Found (%): C, 82.00; H, 7.42; N, 4.54. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.15–7.33 (m, 24H, C_6H_5), 3.95–3.99 (m, 4H, –NCH_2), 3.54–3.59 (m, 2H, –CH_2OH (a) + 4H, –NCH_2Ph), 3.40–3.42 (m, 2H, –CH_2OH (b)), 3.14–3.17 (m, 2H, –CHCH_2Ph (b) + 2H, –NCH), 2.97 (broad, 2H, –OH), 2.48–2.54 (m, 2H, –CHCH_2Ph (a)). ^{13}C NMR ($CDCl_3$, δ, ppm): 139.14, 139.27, 139.59 (i-C_6H_5), 126.27, 127.34, 127.96, 128.60, 128.75, 129.01, 129.06, 129.50 (C_6H_5), 61.29 (–NCH), 60.58 (–CH_2OH), 53.60 (–NCH_2), 53.28 (–NCH_2Ph), 31.96 (–CHCH_2Ph). FT-IR (KBr pellet, cm^{-1}): ν(OH), 3419; ν(CH), 3061, 3027, 2834; ν(C=C), 1493, 1480, 1451.

Synthesis of ***3***

The crude product was obtained as a yellow oil without further purification (5.5 g, 85%). $[\alpha]_D^{20} = -82.7°$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{27}H_{35}O_2N_3$ (%): C, 74.79; H, 8.15; N, 9.69. Found (%): C, 74.20; H, 8.03; N, 9.32. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.56–7.05 (m, 13H, aromatic protons), 3.99–3.87 (m, 2H, –CHCH_3 + 4H, –NCH_2), 3.71–3.61 (m, 4H, –CH_2Ph), 2.64–2.51 (m, 4H, –CHCH_2), 1.11 (d, 6H, J = 6.2 Hz, –CHCH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 136.91 (i-C_6H_5), 121.40, 127.13, 128.30, 129.00 (aromatic carbons), 63.89 (–CHCH$_3$), 62.77 (–CHCH_2), 59.37, 59.61 (–CH_2Ph + –CH_2Py), 20.03 (–CHCH_3). FT-IR (KBr pellet, cm^{-1}): ν(OH), 3367; ν(CH), 3062, 3027, 2967, 2928; ν(N=C), (1603); ν(C=C), 1592, 1576, 1453.

Synthesis of ***4***

The crude product was obtained as a yellow oil without further purification (5.3 g, 82%). $[\alpha]_D^{20} = -106.5°$ (c 1, CH_2Cl_2). Anal. Calcd for $C_{28}H_{36}O_2N_2$ (%): C, 77.74; H, 8.40; N, 6.48. Found (%): C, 77.40; H, 8.18; N, 6.19. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.21–7.37 (m, 14H, C_6H_5), 3.83–3.89 (m, 2H, CHCH$_3$ + 4H, –CH_2Ph), 3.41–3.47 (m, 4H, –CH_2Ph), 3.22 (broad, 2H, OH), 2.44 (d, 4H, J = 6.6 Hz, –CHCH_2), 1.07 (d, 6H, J = 6.1 Hz, –CHCH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 138.60, 138.87 (i-C_6H_5), 127.28, 128.01, 128.46, 128.54, 129.03, 129.70 (C_6H_5), 63.26 (–CHCH$_3$), 61.55 (–CHCH_2), 58.50, 58.71 (–CH_2Ph, CH_2Ph), 19.96 (–CHCH_3). FT-IR (KBr pellet, cm^{-1}): ν(OH), 3434; ν(CH), 3028, 2968, 2930; ν(C=C), 1495, 1451, 1408.

General procedure for synthesis of chiral C_2-symmetric Bis (diphenylphosphinite) ligands (5–8)

To a solution of aminoalcohol **1–4** (1.5 mol) in dry toluene (20 ml) was added triethylamine (3.0 mmol) and the mixture was stirred for 10 min under argon atmosphere. To this solution was added dropwise monochlorodiphenylphosphine, Ph_2PCl (3.0 mmol). The mixture was then stirred at room temperature for 1 h and the triethylammonium chloride ($Et_3N.HCl$) was removed by filtration under argon.

*Synthesis of (2R)-2-[benzyl({[6-{[benzyl[(2R)-1-[(diphenylphosphanyl)oxy]-3-phenylpropan-2-yl]amino}methyl)pyridin-2-yl]methyl})amino]-3-phenylpropyl-diphenylphosphinite] (**5**)*

White viscous oily product **5** (0.13 g, 91%). Anal. Calcd for $C_{63}H_{61}N_3O_2P_2$ (%): C, 79.31; H, 6.46; N, 4.40. Found (%): C, 79.04; H, 6.3; N, 4.21. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.05–7.56 (m, 43H, aromatic protons), 3.97–4.08 (m, 4H, –NCH_2Py + 4H, CH_2OP), 3.79–3.85 (m, 4H, –NCH_2Ph), 3.25 (broad, 2H, –NC*H*), 2.99–3.07 (m, 2H, –CHCH_2Ph (b)), 2.85–2.90 (m, 2H, –CHCH_2Ph (a)). ^{13}C NMR ($CDCl_3$, δ, ppm): 137.29, 139.72, 141.80, 159.53 (i-carbons), 126.92, 127.41, 128.10, 128.22, 128.30, 128.81, 129.11, 129.19, 129.39, 130.20, 130.41, 130.51, 130.54, 130.73 (aromatic carbons), 69.33 (d, J = 18.1 Hz, –CH_2OP), 61.27 (d, J = 9.1 Hz, –NCH), 56.15 (–NCH_2Py), 55.11 (–NCH_2Ph), 34.11 (–CHCH_2Ph). ^{31}P-{^{1}H} NMR ($CDCl_3$, δ, ppm): 114.14 (s, O–*P*$(Ph)_2$) (see supporting information, Fig. S1). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3057, 3027, 2925; ν(C=N), 1642; ν(C=C), 1570, 1564, 1451; ν(O–P), 1021.

*Synthesis of (2R)-2-[benzyl({[3-({benzyl[(2R)-1-[(diphenylphosphanyl)oxy]-3-phenylpropan-2-yl] amino}methyl)phenyl]methyl})amino]-3-phenylpropyl diphenylphosphinite (**6**)*

White viscous oily product **6** (0.13 g, 91%). Anal. Calcd for $C_{64}H_{62}N_2O_2P_2$ (%): C, 83.00; H, 6.77; N, 3.02. Found (%): C, 82.85; H, 6.53; N, 2.91. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.02–7.55 (m, 44H, aromatic protons), 3.99 (broad, 4H, –CH_2OP), 3.73–3.78 (m, 4H, –NCH_2Ph + 4H, –NCH_2), 3.24 (broad, 2H, –C*H*CH$_2$Ph), 3.11–3.14 (m, 2H, –CHCH_2Ph (a)), 2.86–2.92 (m, 2H, –CHCH_2Ph (b)). ^{13}C NMR ($CDCl_3$, δ, ppm): 139.92, 140.01, 140.23, 141.52, 142.10 (i-carbons), 125.88, 126.68, 127.12, 128.12, 128.18, 128.38, 128.43, 128.63, 129.05, 129.28, 129.42, 129.47, 130.26, 130.48, 130.62, 130.84 (aromatic carbons), 60.29 (d, J = 17.1 Hz, –CH_2OP), 60.13 (d, J = 10.7 Hz, –CHCH$_2$Ph), 54.31, 54.53 (–NCH_2Ph + NCH_2), 34.58 (–CHCH_2Ph). ^{31}P-{^{1}H} NMR ($CDCl_3$, δ, ppm): 114.58 (s, O–*P*$(Ph)_2$) (see supporting information, Fig. S1). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3060, 3026, 2962; ν(C=C), 1434, 1453, 1437; ν(O–P), 1015.

*Synthesis of (2R)-1-[benzyl({[6-({benzyl[(2R)-2-[(diphenylphosphanyl)oxy]propyl] amino}methyl)pyridin-2-yl]methyl})amino]propan-2-yldiphenylphosphinite (**7**)*

White viscous oily product **7** (0.11 g, 92%). Anal. Calcd for $C_{51}H_{53}N_3O_2P_2$ (%): C, 76.38; H, 6.67; N, 5.24. Found (%): C, 76.21; H, 6.48; N, 5.16. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.23–7.54 (m, 33H, aromatic protons), 4.14–4.16 (m, 2H, –C*H*CH$_3$), 3.61–3.75(m, 4H, –NCH_2Ph + –NCH_2), 2.83 (broad, 2H, –CHCH_2 (a)), 2.58 (broad, 2H, –CHCH_2 (b)), 1.26 (d, 2H, J = 6.20 Hz, –CHCH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 136.51, 142.63, 158.93 (*ipso* carbons), 120.95, 126.89, 128.17, 128.23, 128.46, 128.99, 129.06, 130.01, 130.23, 130.50, 130.70 (aromatic carbons), 75.36 (–CHCH$_3$), 60.85 (–CHCH$_2$), 59.41 (–NCH_2Ph + –NCH_2Py), 20.87 (–CHCH$_3$). ^{31}P-{^{1}H} NMR ($CDCl_3$, δ, ppm): 106.84 (s) (see supporting information, Fig. S1). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3055, 2966, 2926; ν(C=N), 1589; ν(C=C), 1494, 1479, 1453; ν(O–P), 1070.

*Synthesis of (2R)-1-[benzyl({[3-({benzyl[(2R)-2-[(diphenylphosphanyl)oxy]propyl] amino}methyl)phenyl]methyl})amino]propan-2-yl diphenylphosphinite (**8**)*

White viscous oily product **8** (0.11 g, 92%). Anal. Calcd for $C_{52}H_{54}N_2O_2P_2$ (%): C, 77.98; H, 6.81; N, 3.50. Found (%): C, 77.73; H, 6.61; N, 3.38. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.25–7.52 (m, 34H, aromatic protons), 4.21 (broad, 2H, –C*H*CH$_3$), 3.56–3.61(m, 4H, –NCH_2Ph + –NCH_2), 2.74–2.79 (m, 2H, –CHCH_2 (b)), 2.53–2.56 (m, 2H, –CHCH_2 (a)), 1.26–1.31 (m, 6H, –CHCH_3). ^{13}C NMR ($CDCl_3$, δ, ppm): 139.21, 139.44, 142.66 (*ipso* carbons), 126.81, 127.55, 128.16, 128.23, 128.34, 128.46, 128.94, 129.43, 130.05, 130.26, 130.37, 130.59 (aromatic carbons), 75.56 (d, J = 23.1 Hz, –CHCH$_3$), 60.50 (–CHCH$_2$), 59.07 (–NCH_2Ph + –NCH_2), 20.94 (–CHCH$_3$). ^{31}P-{^{1}H} NMR ($CDCl_3$, δ, ppm): 108.03 (s) (see supporting information, Fig. S1). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3054, 2926, 2904; ν(C=C), 1493, 1479, 1443; ν(O–P), 1071.

General procedure for synthesis of bis(phoshinite)–Pd(II) complexes (9–12)

$Pd(cod)Cl_2$ (1.5 mmol) and bis(phosphinite) ligands **5–8** (1.5 mol) were dissolved in 30 ml of CH_2Cl_2 under an argon atmosphere and stirred for 1 h at room temperature. The resulting yellow solution was concentrated to 2 ml under reduced pressure, and addition of petroleum ether (15 ml) caused the precipitation of a dark yellow solid. The supernatant solution was decanted, the solid was washed with hexane–diethyl ether (1:1) and dried by vacuum, yielding palladium(II) complexes **9–12**.

*Synthesis of dichloro[(2R)-2-[benzyl({[6-{[benzyl[(2R)-1-[(diphenylphosphanyl) oxy]-3-phenylpropan-2-yl]amino}methyl)pyridin-2-yl]methyl})amino]-3-phenyl-propyldiphenyl phosphinite]palladium(II) (**9**)*

Yield 0.15 g, 88%; m.p. 130–132°C; $[\alpha]_D^{20}$ = +12.9° (c: 1, CH_2Cl_2). Anal. Calcd for $C_{63}H_{61}N_3O_2P_2PdCl_2$ (%): C, 66.88; H, 5.43; N, 3.71. Found (%): C, 66.45; H, 5.13; N, 3.51. ^{1}H NMR ($CDCl_3$, δ, ppm): 7.05–7.88 (m, 43H, aromatic protons), 4.26 (broad, 4H, –CH_2OP), 3.81 (broad, 2H, –NCH_2Py), 3.57–3.66 (m, 4H, –NCH_2Ph (a) + –NCH_2Py (b)), 3.38–3.42 (m, 2H, –NCH_2Ph), 3.10 (broad, 2H, –NCH), 2.58–2.64 (m, 2H, –CHCH_2Ph (a)), 2.38–2.42 (m, 2H, –CHCH_2Ph (b)). ^{13}C NMR ($CDCl_3$, δ, ppm): 136.40, 139.18, 139.49, 141.60, 159.43 (i-carbons), 126.10, 127.02, 127.40, 128.19, 128.33, 128.54, 129.10, 129.92, 130.93, 131.50, 131.82, 132.41, 132.47, 132.78 (aromatic carbons), 68.86 (–CH_2OP), 61.35 (–NCH), 56.05, 55.07 (–NCH_2Py + –NCH_2Ph), 34.64 (–CHCH_2Ph). ^{31}P-{^{1}H} NMR ($CDCl_3$, δ, ppm): 110.45 (s, O–*P*$(Ph)_2$) (see supporting information, Fig. S2). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3067, 3020, 2915; ν(C=N), 1640; ν(C=C), 1560, 1554, 1441; ν(O–P), 1020. *m/z*: 1132.15 [M − H$^+$] $C_{63}H_{61}N_3O_2P_2PdCl_2$ (MA: 1131.44).

*Synthesis of dichloro[(2R)-2-{benzyl[(3-{[benzyl-(2R)-1-[(diphenylphosphanyl) oxy]-3-phenylpropan-2-yl)amino]methyl}phenyl]methy}}amino]-3-phenylpropyl diphenylphosphinite]palladium(II) (**10**)*

Yield 0.14 g, 82%; m.p. 131–133°C; $[\alpha]_D^{20}$ = −59.9° (c: 1, CH_2Cl_2]. Anal. Calcd for $C_{64}H_{62}N_2O_2P_2PdCl_2$ (%): C, 68.00; H, 5.53; N, 2.48. Found (%): C, 67.75; H, 5.38; N, 2.15. ^{1}H NMR ($CDCl_3$, δ, ppm): 6.72–7.74 (m, 44H, aromatic protons), 3.64–3.68 (m, 4H, –NCH_2Ph(a) + –NCH_2(a)), 3.44–3.48 (m, 2H, NCH_2Ph(b)), 3.15–3.22 (m, 4H, –NCH_2(b) + –CH$_2$OP(a)), 3.06–3.09 (m, 2H, –CH$_2$OP (b)), 2,00 (broad, 2H, –C*H*CH$_2$Ph), 1.57–1.70 (m, 4H, –CHCH_2Ph). ^{13}C NMR ($CDCl_3$, δ, ppm): 137.94, 138.68, 141.01 (i-carbons), 125.95,

126.14, 127.12, 127.37, 127.59, 128.17, 128.60, 128.67, 129.19, 129.66, 131.01, 132.43, 132.86, 133.64 (aromatic carbons), 64.96 (–CH_2OP), 59.61 (CHCH$_2$Ph), 52.18, 55.09 (–NCH$_2$Ph + NCH$_2$), 35.39 (–CHCH$_2$Ph). ^{31}P-{^{1}H} NMR (CDCl$_3$, δ, ppm): 113.55 (s, O–*P*(Ph)$_2$) (see supporting information, Fig. S2). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3050, 3016, 2952; ν(C=C), 1430, 1450, 1427; ν(O–P): 1025.

*Synthesis of dichloro[(2R)-1-[benzyl({[6-({benzyl[(2R)-2-[(diphenylphosphanyl) oxy]propyl]amino}methyl)pyridin-2-yl]methyl})amino]propan-2-yl diphenylphosphinite]palladium(II) (**11**)*

Yield 0.12 g, 82%; m.p. 122–124°C; $[\alpha]_D^{20} = -18.8°$ (c: 0.5, CH$_2$Cl$_2$). Anal. Calcd for $C_{51}H_{53}N_3O_2P_2PdCl_2$ (%): C, 62.55; H, 5.46; N, 4.29. Found (%): C, 62.38; H, 5.30; N, 4.09. ^{1}H NMR (CDCl$_3$, δ, ppm): 7.21–7.57 (m, 33H, aromatic protons), 4.12 (m, 2H, –CHCH$_3$), 3.10–3.84 (m, 8H, –NCH$_2$Ph + –NCH$_2$), 2.55 (broad, 4H, –CHCH$_2$), 1.26 (m, 6H, –CHCH$_3$). ^{13}C NMR (CDCl$_3$, δ, ppm): 136.21, 140.63, 159.76 (*ipso* carbons), 120.65, 126.70, 127.44, 127.44, 127.76, 128.46, 128.99, 131.76, 131.98, 132.47, 132.83, 133.39 (aromatic carbons), 74,95 (–CHCH$_3$), 60.36 (–CHCH$_2$), 59.54 (–NCH$_2$Ph + –NCH$_2$Py), 19.86 (–CHCH$_3$). ^{31}P-{^{1}H} NMR (CDCl$_3$, δ, ppm): 108.20 (s) (see supporting information, Fig. S2). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3065, 2956, 2936; ν(C=N), 1579; ν(C=C), 1484, 1475, 1453; ν(O–P): 1065.

*Synthesis of dichloro[(2R)-1-[benzyl({[3-({benzyl[(2R)-2-[(diphenylphosphanyl) oxy]propyl]amino}methyl)phenyl]methyl})amino]propan-2-yl diphenylphosphinite] palladium(II) (**12**)*

Yield 0.13 g, 89%; m.p. 133–135°C; $[\alpha]_D^{20} = -20.5°$ (c: 0.5, CH$_2$Cl$_2$). Anal. Calcd for $C_{52}H_{54}N_2O_2P_2PdCl_2$ (%): C, 63.84; H, 5.56; N, 2.86. Found (%): C, 63.72; H, 5.42; N, 2.62. ^{1}H NMR (CDCl$_3$, δ, ppm): 7.20–7.58 (m, 34H, aromatic protons), 3.87 (broad, 2H, –CHCH$_3$), 3.21–3.29 (m, 8H, –NCH$_2$Ph + –NCH$_2$), 2.37–2.42 (m, 4H, –CHCH$_2$), 0.84–0.90 (m, 6H, –CHCH$_3$). ^{13}C NMR (CDCl$_3$, δ, ppm): 138.02, 138.25 (i-carbons), 127.24, 127.86, 128.37, 128.60, 128.73, 130.98, 131.69, 131.86, 132.07, 132.42, 132.72, 133.12 (aromatic carbons), 74.84 (–CHCH$_3$), 59.51 (–CHCH$_2$), 57.96 (–NCH$_2$Ph + –NCH$_2$), 19.47 (–CHCH$_3$). ^{31}P-{^{1}H} NMR (CDCl$_3$, δ, ppm): 103.76 (s) (see supporting information, Fig. S2). FT-IR (KBr pellet, cm^{-1}): ν(CH), 3064, 2936, 2924; ν(C=C), 1483, 1469, 1453; ν(O–P), 1070.

General procedure for asymmetric intermolecular Heck reactions of 2,3-dihydrofuran

A solution of the chiral bis(phosphinite)Pd(II) complexes **9–12** (0.03 mmol), organic base (3.0 mmol), phenyl triflate or iodobenzene (1.0 mmol) and 2,3-dihydrofuran (5.0 mmol) in degassed organic solvent (tetrahydrofuran (THF), benzene, toluene) (3 ml) were added to the catalyst solution. The solution was mixed until the reaction completed. Periodically a sample taken from the reaction medium was passed through an acetone silica gel column and conversion rates were observed using GC. Conversion rates were calculated based on unreacted phenyl triflate or iodobenzene.

Results and discussion

Synthesis of chiral C_2-symmetric bis(phosphinite) ligands and their Pd(II) complexes

To synthesize new chiral ligands with C_2-symmetric backbones, we were interested in chiral phosphinite ligands from chiral diols which have C_2-symmetric backbones. For this aim, initially C_2-symmetric chiral aminoalcohols **1–4** were synthesized according to a literature procedure as shown in Fig. 1.

C_2-symmetric bis(phosphinite) ligands **5–8** (Fig. 2) were prepared from the C_2-symmetric aminoalcohols **1–4** by reaction with two equivalents of Ph$_2$PCl and triethylamine in freshly distilled toluene under argon atmosphere. After 1 h stirring at room temperature, the ^{31}P NMR spectra of the reaction mixtures display the complete disappearance of the signal corresponding to Ph$_2$PCl (81.0 ppm) and the appearance of a new signal for the expected bis(phosphinites). All ligands are obtained as white viscous oil in high yields. A single resonance ranging from 106 to 114 ppm is obtained for all ligands (**5–8**) in the ^{31}P-{^{1}H} NMR spectra in line with the values previously observed for similar compounds (see supporting information, Fig. S1).[17] It is well known that phosphinites are generally unstable in the solid state and decompose rapidly on exposure to air or moisture.[19] In contrast, we observe that our phosphinite ligands are highly stable in the solid state and do not decompose in the open-air atmosphere in two weeks. Additionally, structures of **5–8** were investigated using ^{1}H NMR, ^{13}C NMR and FT-IR spectroscopies and elemental analysis, and all data are in agreement with the structures (see Experimental section).

The complexes [LPdCl$_2$], where L is **5–8**, were prepared by the addition of an equivalent of [Pd(cod)Cl$_2$] to a dry CH$_2$Cl$_2$ solution of each bis(phosphinite) ligand under argon atmosphere.

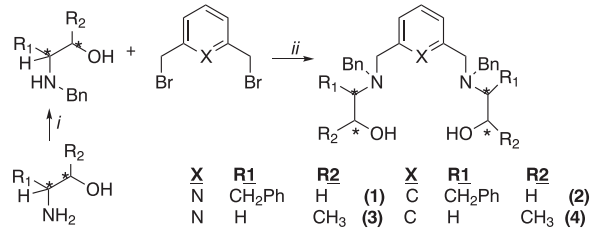


Figure 1. Synthesis of chiral C_2-symmetric amino alcohols: i, benzaldehyde, NaBH$_4$, CH$_3$OH; ii, Na$_2$CO$_3$, KI, CH$_3$CH$_2$OH.

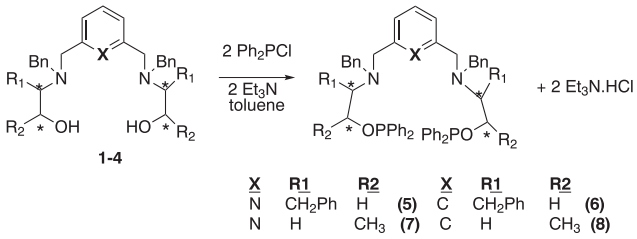


Figure 2. Synthesis of chiral C_2-symmetric bis(phosphinite) ligands.

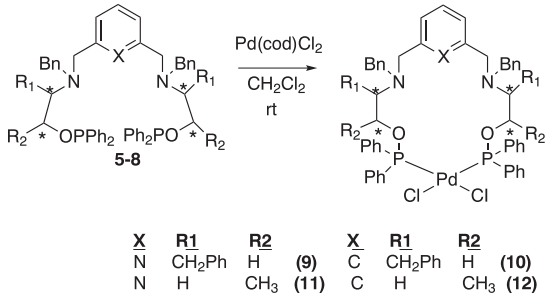


Figure 3. Synthesis of chiral C_2-symmetric bis(phosphinite)–Pd(II) complexes.

Complexation reactions were simple, with coordination to palladium(II) being carried out at room temperature, affording compounds **9–12** as air-stable dark yellow powders in high yield as shown in Fig. 3. The ^{31}P NMR spectra of palladium(II) complexes **9–12** show singlets ranging from 108 to 113 ppm for all complexes (see supporting information, Fig. S2). These spectra clearly indicate that the cod moiety has been replaced by the chelating bis (phosphinite) ligand and both phosphorus atoms are bonded to the palladium(II). The ^{1}H NMR, ^{13}C NMR, FT-IR and elemental analysis data for complexes **9–12** are consistent with the formulation of [$LPdCl_2$], and in line with the values previously observed for similar complexes[21] as detailed in the Experimental section.

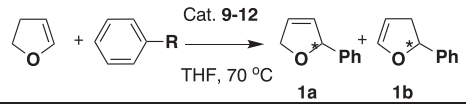
Catalytic asymmetric intermolecular Heck reactions

The palladium-catalysed asymmetric intermolecular Heck reaction has received increasing attention in the last decade, as it is a selective method for the formation of new chiral ligands in a single operational step.[22,23] The reaction is appealing because of its tolerance of nearly any solvent and functional group on the substrates, its high selectivity and its moderate toxicity.[24,25] The activity of palladium(II) complexes bearing various chiral phosphorus moieties is well known in this catalytic reaction.[26] To the best of our knowledge, in this study the C_2-symmetric chiral bis(phosphinite)–Pd(II) complexes were used for the first time in asymmetric intermolecular Heck reactions. We report the use of C_2-symmetric chiral bis(phosphinite)–Pd(II) complexes **9–12** in the palladium-catalysed asymmetric Heck reaction of 2,3-dihydrofuran using iodobenzene or phenyl triflate. Generally, reaction of 2,3-dihydrofuran and phenyl triflate has been used to study the asymmetric intermolecular Heck reaction since the first report by Hayashi and co-workers.[9]

A set of optimal catalytic conditions experiments was carried out to discover a suitable reaction medium. The results are summarized in Table 1. Initially, we studied the effect of various solvents including polar (THF) and non-polar (benzene, toluene) media, organic (*N*,*N*-diisopropylethylamine (DIPEA), proton sponge) and inorganic (Ag_2CO_3) bases, and temperature (room temperature or reflux). For instance, there is no conversion reaction of 2,3-dihydrofuran with phenyl triflate when THF, benzene or toluene is used as solvent and DIPEA or proton sponge is used as organic base at room temperature or reflux conditions in 10 days. However, there is low conversion (<10%) when Ag_2CO_3 is used as inorganic base in the reaction of 2,3-dihydrofuran with phenyl triflate under reflux conditions in 10 days when THF is used as the polar solvent. At room temperature no appreciable formation of **1a** or **1b** is observed in all reactions. The best activity and regio- or enantioselectivity are achieved with iodobenzene as substrate, THF as polar solvent and Ag_2CO_3 as inorganic base under reflux conditions. For these optimized conditions conversion is high (<95%) but enantioselectivities (<28%) and regioselectivities (<74%) are moderate for the phenylation of 2,3-dihydrofuran. In another test reaction, the use of THF as polar organic solvent and DIPEA or proton sponge as organic base does not give improved conversion. Each catalytic reaction was carried out three times to examine reproducibility.

Considering the number of reports that have dealt with the preparation of efficient chiral palladium catalyst systems for the asymmetric Heck reaction, they indicated that either activity or selectivity is affected by the ligand structure.[8] In this study, ligand structure was studied with C_2-symmetric bis(phosphinites) **5–8**. The highest enantio- and regioselectivity is obtained from complex **12**, which bears ligand **8**. The results clearly indicate that when the chiral centre is present near the metal centre, high enantio- and regioselectivity is observed.

Table 1. Palladium-catalysed enantioselective phenylation of 2,3-dihydrofuran using C_2-symmetric chiral bis(phosphinite)–Pd(II) complexes (**9–12**)



Catalyst	R	Base	Time (h)	Conversion (%)[a]	**1a**/**1b**	ee (%)[b] (**1a**)	ee (%)[c] (**1b**)
9	I	DIPEA	240	<10	—	—	—
10	I	DIPEA	240	<10	—	—	—
11	I	DIPEA	240	<10	—	—	—
12	I	DIPEA	240	<10	—	—	—
9	I	Proton sponge	240	<10	—	—	—
10	I	Proton sponge	240	<10	—	—	—
11	I	Proton sponge	240	<10	—	—	—
12	I	Proton sponge	240	<10	—	—	—
9	I	Ag_2CO_3	24	97	68/32	20(*S*)	12(*S*)
10	I	Ag_2CO_3	24	98	72/28	23(*S*)	10(*S*)
11	I	Ag_2CO_3	48	95	70/30	27(*S*)	15(*S*)
12	I	Ag_2CO_3	72	97	74/26	28(*S*)	13(*S*)
9	OTf	Ag_2CO_3	240	<10	—	—	—
10	OTf	Ag_2CO_3	240	<15	—	—	—
11	OTf	Ag_2CO_3	240	<10	—	—	—
12	OTf	Ag_2CO_3	240	<10	—	—	—

[a]Catalyst **9–12** (0.03 mmol), organic solvent (THF) (3 ml), base (3 mmol), phenyl triflate or iodobenzene (1 mmol), 2,3-dihydrofuran (5 mmol).
[b]Determined by GC (three independent catalytic experiments).
[c]Ratios determined by GC with Chiraldex G-TA 30 M column at 70°C.

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