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Evidence for the Structure of the Enantioactive Ligand in the Phosphine•Copper Catalyzed Addition of Diorganozinc Reagents to Imines

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General experimental procedures. Characterization data for new compounds. ^{1}H and ^{13}C NMR spectra. HPLC conditions to determine enantiomeric excess.

General: All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.[1] All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere of gas. Anhydrous solvents were obtained either by filtration through drying columns (THF, ether, CH_2Cl_2, benzene, DMF, CH_3CN, toluene, hexane, methanol) on a GlassContour system (Irvine, CA), by distillation over calcium hydride (Et_3N, $ClCH_2CH_2Cl$, pyridine, diisopropylamine, isopropanol) or by distillation over sodium/benzophenone (DME). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F_{254}). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine, or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) of the indicated solvent system according to standard technique.[2] Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR equiped with a golden gate diamond ATR with ZnSe lenses and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra (^{1}H, ^{13}C, ^{31}P) were recorded either on a Bruker AV 300, AMX 300, AV 400, ARX 400 spectrometer equiped with a QNP probe. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million with the solvent resonance as the internal standard (chloroform, δ7.26 ppm or deuteromethanol, δ3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, sp = septet, oc = octet, no = nonet m = multiplet and br = broad), coupling constant in Hz and integration. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (77.00 ppm) or deuteromethanol (49.00 ppm) as the internal standard. Chemical shifts for ^{31}P NMR spectra are recorded in parts per million from phosphoric acid. All spectra were obtained with complete proton decoupling. Optical rotations were determined with a Perkin-Elmer 341 polarimeter at 589 or 546 nm. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, Concentration (*c* in g/100 mL), and solvent. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal.

Analytical High Performance Liquid Chromatography was performed on HP 1100 Analytical Instrument equipped with a diode array UV detector. Data are reported as follows: (column type, eluent, flow rate: retention time (t_r)).

Reagents: Me-DuPHOS, CuCl, CuOAc and $Cu(OTf)_2$ were purchased from Strem Chemicals Inc. Neat diethylzinc was purchased from AkzoNobel. Potassium cyanide, $(CuOTf)_2$•toluene and all other chemical compounds were purchased from Aldrich. Unless otherwise stated, commercial reagents were used without purification.

The *N*-diphenylphosphinoylimine was prepared according to a known literature procedure[3-21]. The resulting *N*-diphenylphosphinic amide was compared to literature data[8,11,13-21]. Racemic sample for HPLC comparison was prepared by the addition of EtCuCN•ZnEt in THF to the *N*-diphenylphosphinoylimine. BozPHOS (**2**) was prepared according to a known literature procedure.[22] $(CuOTf)_2$•benzene was prepared according to a known literature procedure. [23]

Degassed solvents and glassware: Solvents were degassed by distillation under argon followed by bubbling argon into them for 4 hours (the grade of argon used was 99.998% and contained less than 5 ppm of oxygen according to Praxair analysis). The reaction vessels were heated to 120 °C for a minimum of 12h in an oven and cooled under vacuum (glove-box antechamber) before use in a glove-box containing less than 1 ppm of oxygen and water.

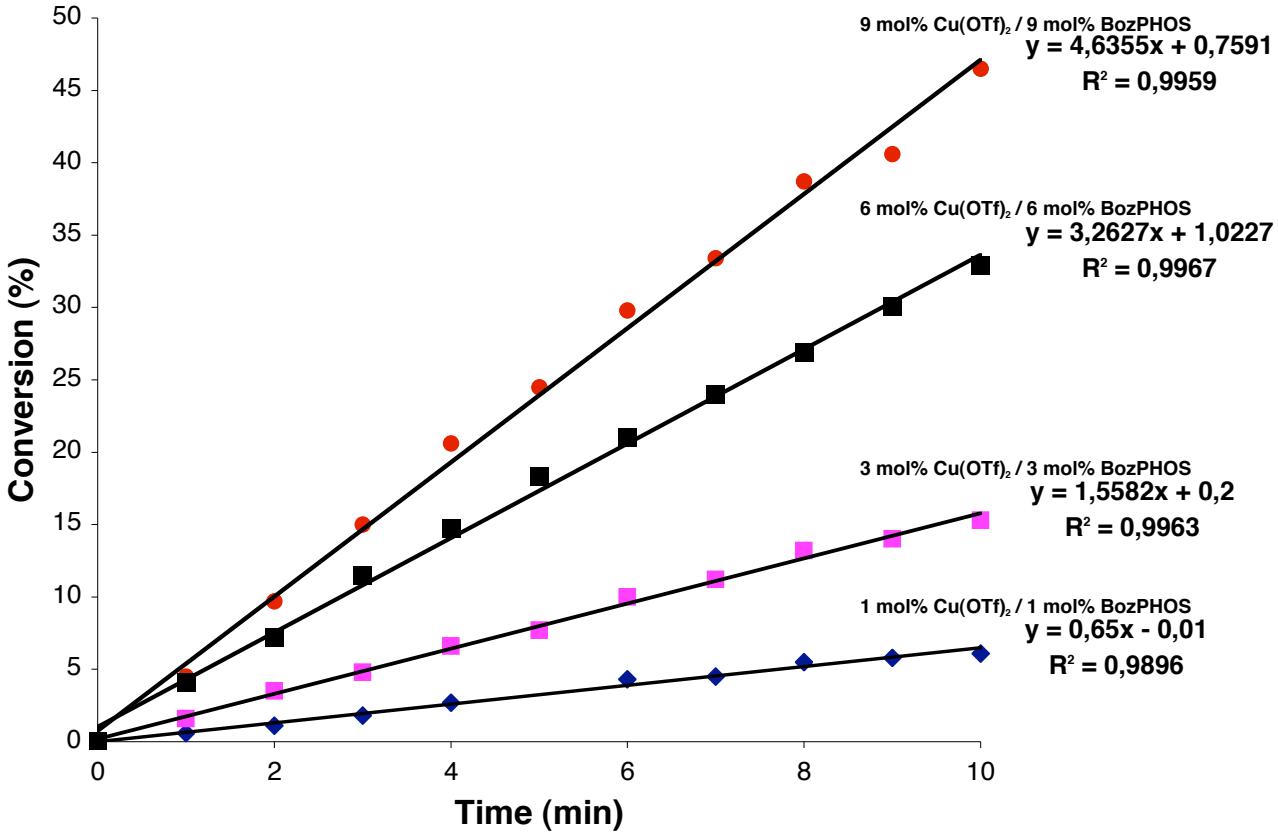
General procedure for quantification of ligand oxidation in non oxidative conditions (control experiment). To a 10 mL flask containing a heterogeneous solution of CuX (2 equiv.) in toluene (1 mL) at -40 °C (acetonitrile/dry ice bath), neat diethylzinc (10 equiv.) was added (CAUTION: DIETHYLZINC IS PYROPHORIC). After 15 min, the ligand **1**, **2** or **3** (20 mg, 1 equiv.) in toluene (1 mL + 1 mL to rinse flask) was added at -40 °C to the heterogeneous solution. The reaction was stirred an additional 15 min at -40 °C and warmed to room temperature for the next 60 min. The reaction was quenched with degassed H_2O (1 mL) and stirred for 5 min. Freshly prepared and degassed saturated aqueous KCN solution (6 mL) was added and the heterogeneous solution was stirred vigorously for 20 h under argon. The aqueous solution was extracted with degassed EtOAc (2 X 20 mL), the organic layers were combined, dried over Na_2SO_4 and quickly evaporated. The mixture was immediately analyzed by quantitative ^{31}P NMR in C_6D_6 as solvent. Chemical shifts are 3.4 ppm for **1**, 8.7 and 65.7 ppm for **2** and 69.7 ppm for **3**. ^{31}P NMR parameters: 30 sec *relaxation time*, ZGIG *pulse program*, QNP *probe*. The control experiment starting with a determined mixture of **1**, **2** and **3** led typically to the same final ratio under those conditions ($PH_3P=O$ was used as internal standard in this control experiment). The mass recovery was higher than 70%.

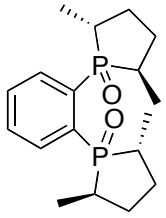
General procedure for quantification of ligand oxidation in oxidative conditions. In a 10 mL flask, ligand **1, 2** or **3** (20 mg, 1 equiv) and CuX (2 equiv) were dissolved in toluene (3 mL) under argon. The resulting heterogeneous solution was stirred for 1 h at room temperature. Neat diethylzinc (10 equiv) was added at room temperature and the resulting dark red suspension was stirred for 30 min at room temperature (CAUTION: DIETHYLZINC IS PYROPHORIC). The reaction was quenched with degassed H_2O (1 mL) and stirred for 5 min. Freshly prepared and degassed saturated aqueous KCN solution (6 mL) was added and the heterogeneous solution was stirred vigorously 20 h under argon. The aqueous solution was extracted with degassed EtOAc (2 X 20 mL), the organic layers were combined, dried over Na_2SO_4 and quickly evaporated. The mixture was immediately analyzed by quantitative ^{31}P NMR in C_6D_6 as solvent. Chemical shifts are 3.4 ppm for **1**, 8.7 and 65.7 ppm for **2** and 69.7 ppm for **3**. ^{31}P NMR parameters: 30 sec *relaxation time*, ZGIG *pulse program*, QNP *probe*. The mass recovery was higher than 70%.

General procedure for diethylzinc addition to diphenylphosphinoylimine (kinetic study of ligands 1, 2 and 3). To a 25 mL flask containing a heterogeneous solution of $Cu(OTf)_2$ (0.12 mmol, 0.06 equiv) in toluene (3 mL) at -40 °C (acetonitrile/dry ice bath), neat diethylzinc (410 μL, 4.00 mmol, 2.00 equiv) was added (CAUTION: DIETHYLZINC IS PYROPHORIC). After 15 min, the ligand **1, 2** or **3** (0.06 mmol, 0.03 equiv) in toluene (3 mL + 3 mL to rinse flask) was added at -40 °C to the heterogeneous yellow solution. The reaction was stirred an additional 15 min at -40°C and warmed to room temperature for 50 min. At this moment, the dark red suspension was cooled at 0 °C for 10 min. A cold (0 °C) suspension of (610 mg, 2.00 mmol, 1.00 equiv) in toluene (11 mL) was quickly transferred (Teflon cannula) to the catalyst solution and the reaction time was started. Typically, aliquots (300 μL) were taken at 5 min, 10 min, 20 min, 30 min, 45 min, 60 min, 90 min, 120 min, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h and 14

h. Each aliquots were quickly diluted in CH_2Cl_2 (3 mL) at -78 °C and quenched with MeOH (1 mL) at -78 °C and stirred for 1 min. Saturated NH_4Cl solution (4 mL) was added and the aqueous layer was extracted rapidly with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried over Na_2SO_4. Aliquots conversions were determined by integrating peaks at 26.1, 23.9 and 23.5 ppm ($CDCl_3$) in quantitative ^{31}P NMR analysis. These peaks correspond respectively to, *N*-diphenylphosphinic amide and $NH_2P(O)Ph_2$ [$NH_2P(O)Ph_2$ results from hydrolysis of *N*-diphenylphosphinoylimine]. ^{31}P NMR parameters: 5 sec *relaxation time*, ZGIG *pulse program*, QNP *probe*.

Data obtained for first order plot. The kinetic curves obtained for 1 mol%, 3 mol%, 6 mol% and 9 mol% of catalyst are illustrated below. The first order plot illustrates the relation between the slope and the catalyst loading for each curves.

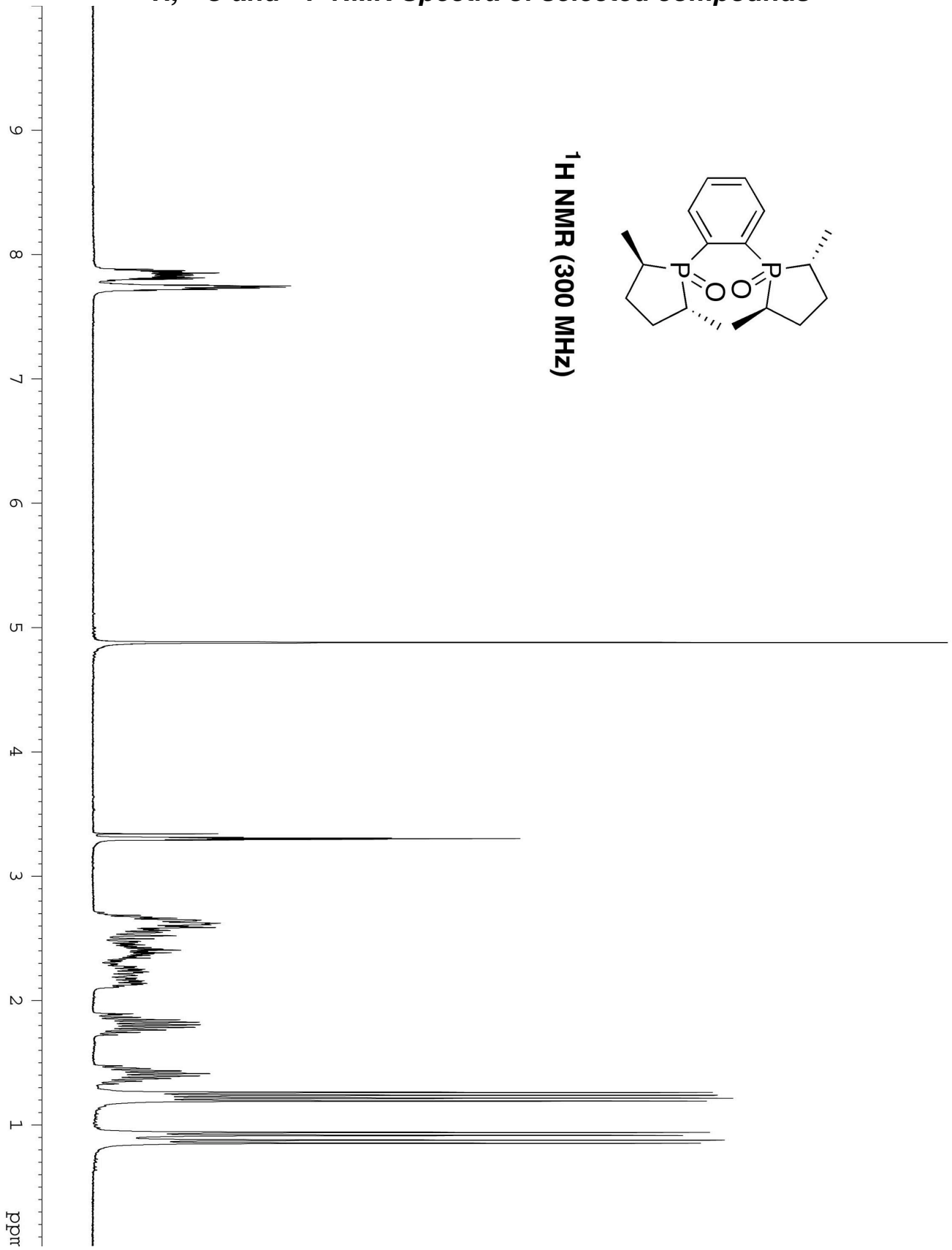


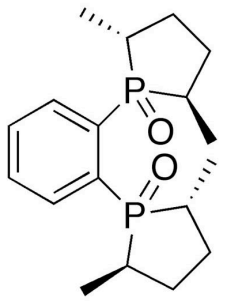


3

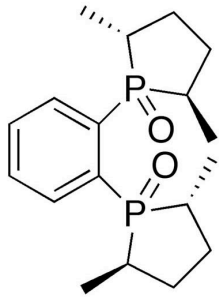
(2*R*,5*R*)-1-{2-[(2*R*,5*R*)-2,5-dimethyl-1-oxidophospholan-1-yl]phenyl}-2,5-dimethylphospholane 1-oxide (Me-DuPHOS bisoxide) (3). To a solution of (*R,R*)-Me-DUPHOS (500 mg, 1.63 mmol, 1.00 equiv) in THF (16 mL, 0.1 M) was added H_2O_2 (30% (v/v) 1.0 mL, 9.78 mmol, 6.00 equiv) at 0 °C. The mixture was stirred 45 min at this temperature and quenched slowly with saturated Na_2SO_3 at 0 °C. Aqueous layer was extracted with AcOEt (3 x 50 mL) and the combined organic layers were dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified on silica gel (95:5 to 90:10 AcOEt:MeOH) affording a white air-stable solid (519 mg, 94%): mp 223-225 ºC; R_f 0.38 (80:20 AcOEt:MeOH); $[\alpha]_D^{22}$ -160 (*c* 1.36, CD_3OD); ^{1}H NMR (300 MHz, CD_3OD) δ 7.89-7.78 (m, 2H), 7.77-7.70 (m, 2H), 2.71-2.46 (m, 4H), 2.46-2.30 (m, 2H), 230-2.09 (m, 2H), 1.81 (no, *J* = 6.1 Hz, 2H), 1.41 (oc, *J* = 6.1 Hz, 2H), 1.22 (dd, *J* = 14.0, 7.0 Hz, 6H), 0.89 (dd, *J* = 18.9, 7.4 Hz, 6H); ^{13}C NMR (75 MHz, CD_3OD) δ 135.7 (dd, $J_{C\text{-}P}$ = 83.4, 5.9 Hz), 134.1 (dd, $J_{C\text{-}P}$ = 10.6, 10.6 Hz), 132.7 (dd, $J_{C\text{-}P}$ = 10.6, 10.6 Hz), 132.7 (d, $J_{C\text{-}P}$ = 8.6 Hz), 37.4 (d, $J_{C\text{-}P}$ = 69.5 Hz), 32.8 (d, $J_{C\text{-}P}$ = 69.7 Hz), 32.6 (m), 31.9 (m), 18.0, 11.0; ^{31}P NMR (162 MHz, CD_3OD) δ 72.3; IR (Neat) 3497, 3418, 2939, 2866, 1633, 1456, 11645, 1127, 998, 750, 682, 637 cm^{-1}. Elemental Analysis calcd for $C_{19}H_{29}O_2P_2$: C, 63.89; H, 8.34 found: C, 63.82; H, 8.52.

^{1}H, ^{13}C and ^{31}P NMR Spectra of selected compounds





^{13}C NMR (75 MHz)



^{31}P NMR (162 MHz)

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