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DIFLUORPHOS®, a New Electron-Poor Diphosphane : a Good Match Between Electronic and Steric Features

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General Methods : ^{1}H NMR spectra were recorded on a Bruker AC 200 at 200 MHz or on a Bruker AC 300 at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker AC 200 at 50 MHz, or on a Bruker AC 300 at 75 MHz. ^{31}P NMR and ^{19}F NMR spectra were recorded on a Avance 400 at 162 MHz and 376 MHz respectively. Chemical shifts (δ) are reported in ppm downfield relative to external Me_4Si, H_3PO_4 (85%) or $CFCl_3$ (1% in $CDCl_3$). Coupling constants (J) are reported in Hz and refer to apparent peak multiplicities. Mass spectra were determined on a Ribermag instrument. Ionization was obtained either by electronic impact (EI) or chemical ionization with ammonia (DCI/NH_3). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589 nm (sodium lamp). Melting points (m.p.) were determined on a Kofler melting point apparatus. Gas chromatographic analyses were performed on a Hewlett Packard 5890 serie II instrument connected to a Merck D-2500 or D-2000 integrator, using flame ionization detector. Enantiomeric excesses were determined on a chiral capillary column (Lipodex A). HPLC analyses of compound **4** were conducted with Waters 600 system, using Daicel chiral stationary phase column : Chiralpak AD, heptane/2-propanol (97/3). All reactions were carried out under an atmosphere of argon unless otherwise specified.

(2,2-Difluoro-1,3-benzodioxol-5-yl)diphenylphosphane oxide (2): To a solution of magnesium (10.2 g, 420 mmol) in dry THF (25 mL), 5-bromo-2,2-difluoro-1,3-benzodioxole **1** (90.1g, 380 mmol) in dry THF (168 mL) was added within 2h, at 60°C under a nitrogen stream. The resulting suspension was stirred for an additional time of 3h at room temperature. Then, chlorodiphenylphosphane oxide (90g, 381 mmol) was added dropwise within 2h at such a rate that the reaction temperature did not exceed 20°C. The solution was stirred at 20°C for an additional 19h, quenched with 27 mL of water, 135 mL of an aqueous solution of HCl 1N and extracted with 270 mL of ethyl acetate. The organic layer was separated, washed with 135 mL of an aqueous solution of HCl 1N, 135 mL of a saturated aqueous solution of potassium bicarbonate and 135 mL of water. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to give a dark brown oil. Purification on silica gel eluting with ethyl acetate / heptane (50/50 to 100/0) afforded **2** as a brown oil (90 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) : δ= 7.16 (dd, J = 2.1, 8.1 Hz, 1H), 7.37 (dd, J = 1.2, 11.3 Hz, 1H), 7.43 (dd, J = 1.4, 8.1 Hz, 1H), 7.44-7.70 (m, 10H) ; ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 109.8 (d, J = 14.3 Hz), 112.9 (d, J = 12.3 Hz), 128.7 (d, J = 12.3 Hz), 128.8 (d, J = 10.6 Hz), 131.1, 132.0 (d, J = 10.1 Hz), 132.3 (d, J = 2.8 Hz), 132.5, 143.9 (d, J = 18.6 Hz), 146.3 (d, J = 2.9 Hz), 171.1 ; MS (DCI/NH_3) : *m/z* : 359 $[M+H]^+$, 376 $[M+NH_4]^+$.

(2,2-Difluoro-4-iodo-1,3-benzodioxol-5-yl)diphenylphosphane oxide (3) : To a solution of diisopropylamine (35.5 mL, 253 mmol) in 150 mL of anhydrous THF, 96.6 mL (242 mmol) of butyllithium (2.5 M solution in hexanes) were added at 0°C within 40 min under a nitrogen stream. The resulting solution was stirred at 0°C for 15min and added within 1 h to a solution of **2** (82.5 g, 230 mmol) in 600 mL of anhydrous THF at –78°C, under a nitrogen stream. This solution was stirred at –78°C for an additional time of 50 min. A solution of diiode (60.9 g, 240 mmol) in 250 mL of anhydrous THF was then added to the previous mixture at –78°C within 1 h. The reaction temperature was slowly raised to room temperature and the solution was stirred for 20 h. After filtration at 0°C, the resulting solid was washed three times with 20 mL of THF and dried at 40°C under reduced pressure. A white solid was obtained (97.6 g, 88 %).

^{1}H NMR (300 MHz, $CDCl_3$) : δ= 7.01 (dd, J = 8.2, 23.5 Hz, 1H), 7.03 (t, J = 8.4 Hz, 1H), 7.48-7.54 (m, 4 H), 7.58-7.63 (m, 2H), 7.67-7.74 (m, 4H) ; ^{13}C NMR (75 MHz, $CDCl_3$) : δ= 108.5 (d, J = 13.7 Hz), 128.7 (d, J = 12.3 Hz), 130.2, 130.6, 131.9, 132.0 (d, J = 9.3 Hz), 132.3 (d, J = 2.8 Hz), 132.3 (d, J = 9.6 Hz), 144.1, 147.6 ; ^{31}P NMR (162 MHz, $CDCl_3$) : δ = 35.6 ; ^{19}F NMR (376 MHz, $CDCl_3$) : δ = -49.6 ; MS (EI) : *m/z* : 484 $[M^{\cdot+}]$; HRMS : calculated for $C_{19}H_{13}F_2I\,O_3P$ [M+H] 484.9615, found 484.9612.

(*R,S*)-[4,4’-bi(2,2-difluoro-1,3-benzodioxol)-5,5’-diyl]bis(diphenylphosphane oxide) (4) : A mixture of **3** (30 g, 62 mmol) and activated copper (11.8 g, 185 mmol) in anhydrous DMF (150 mL) was heated at 130°C for 4h. The solvent was evaporated and the residue was treated for 5 min. with hot CH_2Cl_2 (300 mL). The solids were filtered and washed with CH_2Cl_2 (50 mL). The filtrate was washed with a saturated aqueous NH_4Cl solution (100 mL), dried over $MgSO_4$ and concentrated. The solid residue was recrystallized in MeOH (250 mL) at 0°C and a white solid was obtained (15.2 g, 69%).

m.p. > 260°C ; ^{1}H NMR (300 MHz, $CDCl_3$) : δ= 7.01 (dd, J = 8.3, 14.1 Hz, 2H), 7.04 (s, 2H), 7.27 (td, J = 3.1, 7.6 Hz, 4H), 7.37 (dd, J = 1.4, 7.5 Hz, 2H), 7.39-7.44 (m, 2H), 7.46 (dd, *J* = 3.0, 7.5 Hz, 2H), 7.54 (dd, *J* = 1.5, 12.4 Hz, 2H), 7.56 (dd, *J* = 1.2, 12.3 Hz, 2H), 7.63 (dd, *J* = 1.5, 11.9 Hz, 2H), 7.66 (dd, *J* = 1.2, 11.9 Hz, 4H) ; ^{13}C NMR (50 MHz, $CDCl_3$) : δ = 109.0 (d, *J* = 14.9 Hz), 125.5, 127.6, 128.2 (d, *J* = 12.3 Hz), 128.3 (d, *J* = 12 Hz), 129.6 (d, *J* = 13 Hz), 131.2, 131.7 (d, *J* = 7.5 Hz), 131.9 (d, *J* = 9.6 Hz), 132.4 (d, *J* = 10.5 Hz), 134.4 (d, *J* = 31.1 Hz), 143.2 (d, *J* = 15.8 Hz), 145.1 ; ^{31}P NMR (162 MHz, $CDCl_3$) : δ = 31.17 ; ^{19}F NMR (376 MHz, $CDCl_3$) : δ = -49.50 (dd, *J* = 110.3, 91.9 Hz) ; MS (DCI/NH_3) : *m/z* : 715 $[M+H]^+$; HRMS : calculated for $C_{38}H_{25}F_4O_6P_2$ [M+H] 715.1063, found 715.1069 ; Chiral HPLC : Chiralpak AD Column, heptane/*i*PrOH (97/3), Flow : 1 mL/min, λ = 254 nm, t_R (*R*) = 30.29 min, t_R (*S*) = 30.94 min.

Resolution of racemic 4 [(-)-(*S*)-4 and (+)-(*R*)-4] :

Racemic **4** was resolved by preparative HPLC, using a chiral stationary phase (Chirose® C3). All analytical data were identical to the corresponding spectra of racemic **4**.

(*S*) enantiomer : $[\alpha]_D^{20}$ = -60 (c = 1 in $CHCl_3$)

(*R*) enantiomer : $[\alpha]_D^{20}$ = +60 (c = 1 in $CHCl_3$)

(+)-(*S*)-[4,4'-bi(2,2-difluoro-1,3-benzodioxol)-5,5'-diyl]bis(diphenylphosphane), (+)-(*S*)-DIFLUORPHOS® (5) :

To a suspension of (-)-(*S*)-**4** (1 g, 1.40 mmol) in dry xylene (10 mL) were added tributylamine (3.98 mL, 16.18 mmol) and trichlorosilane (1.46 mL, 14 mmol). The resulting mixture was heated at 140°C overnight. After cooling to room temperature, 10 mL of degassed 4N aqueous NaOH were added dropwise and the mixture was stirred for 30 min. Dry CH_2Cl_2 (30 mL) was then added, the organic layer was washed with degassed distilled water (10 mL), degassed brine (10 mL) and concentrated under vacuum. MeOH (20 mL) was then added and a white precipitate formed. The solids were filtered under argon and dried under vacuum for 3 h to afford (+)-(*S*)-DIFLUORPHOS® **5** (900 mg, 91%) as a white solid.

m.p. > 260°C ; ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 6.89 (dt, *J* = 1.5, 8.2 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 7.10-7.22 (m, 8H), 7.23-7.35 (m, 12H).; ^{31}P NMR (162 MHz, $CDCl_3$) : δ = -12.23 ; ^{19}F NMR (376 MHz, $CDCl_3$) : δ = -49.90 (dd, *J* = 160.8, 93.4 Hz); MS (EI) : *m/z* : 683 $[M+H]^+$; HRMS : calculated for $C_{38}H_{25}F_4O_4P_2$ [M+H] 683.1164, found 683.1147 ; $[\alpha]_D^{20}$ = +20 (c = 0.1 in benzene). An analogous reduction of (+)-(*R*)-**4** afforded (-)-(*R*)-DIFLUORPHOS® **5** in 91% yield as a white solid. All analytical datas were identical to the corresponding spectra of (+)-(*S*)-**5**. (*R*) enantiomer : $[\alpha]_D^{20}$ = -20 (c = 0.1 in benzene).

Diphosphane diselenides (compounds A) :

^{31}P NMR (162 MHz, $CDCl_3$) : (BINAP)Se_2 : δ = 34.86, (MeO-BIPHEP)Se_2 : δ = 33.65, (SYNPHOS$^{®}$)Se_2 : δ = 32.66, (SEGPHOS)Se_2 : δ = 34.48, (DIFLUORPHOS$^{®}$)Se_2 : δ = 33.92.

Compounds B :

RhCl(BINAP)(CO) : ^{31}P NMR (162 MHz, $CDCl_3$) : δ= 25.2 (dd, *J* = 42, 127 Hz), 46.7 (dd, *J* = 42, 164 Hz); IR($CHCl_3$) : ν = 2017 (C=O). **RhCl(MeO-BIPHEP)(CO) :** ^{31}P NMR (162 MHz, $CDCl_3$) : δ= 24.0 (dd, *J* = 45, 128 Hz), 45.0 (dd, *J* = 45, 162 Hz); IR($CHCl_3$) : ν = 2014 (C=O). **RhCl(SYNPHOS$^{®}$)(CO) :** ^{31}P NMR (162 MHz, $CDCl_3$) : δ= 23.4 (dd, *J* = 46, 129 Hz), 44.9 (dd, *J* = 46, 163 Hz); IR($CHCl_3$) : ν = 2012 (C=O). **RhCl(SEGPHOS)(CO) :** ^{31}P NMR (162 MHz, $CDCl_3$) : δ = 24.1 (dd, *J* = 46, 131 Hz), 44.4 (dd, *J* = 46, 164 Hz); IR($CHCl_3$) : ν = 2016 (C=O). **RhCl(DIFLUORPHOS$^{®}$)(CO) :** ^{31}P NMR (162 MHz, $CDCl_3$) : δ= 25.3 (dd, *J* = 46, 129 Hz), 44.4 (dd, *J* = 46, 162 Hz); IR($CHCl_3$) : ν = 2023 (C=O).