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Synthesis of *P,N*-2,2′-biphenyl derivatives with central chirality

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Enantiopure 2-(dicyclohexylphosphino)-1,1′-biphenyl derivatives substituted in the 2′-position by a chiral amino group were prepared. For the compound bearing an acyclic chiral chain, the key step was a Suzuki coupling between bromobenzeneboronic acid and *N*-Boc-iodoaniline whereas an aromatic nucleophilic substitution allowed the introduction of a chiral pyrrolidine in the 2′-position of the biphenyl backbone. The efficiency of the *P,N*-biphenyl pyrrolidine derivatives as ligands in Pd-catalyzed arylaminations compares well with that of DavePhos ligand.

3-aminopyrrolidines, Suzuki coupling, biphenyls, chiral ligand, arylamination

1 Introduction

Chiral P,N compounds have been mainly prepared as asymmetric inducers owing to their steric and electronic properties [1–2]. 2,2′-Substituted biphenyls with a carbon [3] or a phosphorus [4] stereogenic center are little known, while this type of compound was widely developed in achiral transition metal mediated reactions [5–6].

Herein, we report the synthesis of two P,N-ligands containing a biphenyl moiety and for the first time a central chirality either on a flexible chain (**1**) or in a five-membered ring (**2**) (Figure 1).

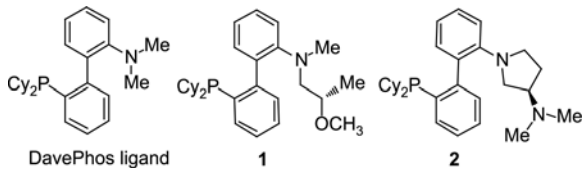

Figure 1 DavePhos ligand and target compounds.

2 Experimental

General experimental

Dichloromethane, acetonitrile, ether and toluene were dried with a PURESOLV^{TM} apparatus (Innovative Technology Inc.). THF was dried and distilled from sodium benzophenone ketyl. Hexane, 1,2-dichloroethane, benzene and chlorobenzene were distilled from calcium hydride and stored over molecular sieves 4 Å. Thin layer chromatography (TLC) was performed on Merck 60F_{254} silica gel plates and visualized with a UV lamp (254 nm). Flash column chromatography was carried out with silica gel SI 60 (0.040–0.063 mm, Merck). Uncorrected melting points were obtained using a Köfler bench apparatus. Infrared spectra (IR) were recorded with a 16 PC FT-IR spectrometer. Elementary analyses were performed on a Thermoquest apparatus. Mass and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof micro instrument. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on a Bruker Avance DPX-250. Chemical shifts are expressed in δ (ppm) units downfield from TMS. ^{31}P NMR chemical shifts are reported in ppm

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relative to H_3PO_4 (0 ppm). Optical rotations were measured at 20 °C on a Perkin-Elmer 241 LC polarimeter in a 1 dm cell. 2-Bromo and 2-aminobenzeneboronic acids, 2-iodoaniline, 2-aminobiphenyl **3** are commercially available. 2-Iodo-*N*-(*t*-butoxycarbonyl)aniline **9b** [7], 2-bromo-2′-aminobiphenyl **17** [8], dimesylate **18** [9], 3-*N,N*-dimethylaminopyrrolidine **14** [10], 1-benzyl-3-(phenylamino)pyrrolidine **26** [11] and 1-Boc-3-(phenylamino)piperidine **28** [11] are known compounds.

*1-(Biphenyl-2-yl-methylamino)-propan-2-ol (**4a**)*

To a suspension of sodium hydride (50% in mineral oil, 850 mg, 17.7 mmol) in dry THF (5 mL) was added 2-aminobiphenyl **3** (2 g, 11.8 mmol) in dry THF (10 mL) at room temperature. The mixture was stirred for 1 h and iodomethane (2 mL, 32.1 mmol) was added. After 12 h at room temperature, Et_2O (15 mL) and water (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2×15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a mixture (2.4 g) of 2-(*N*-methylamino)-1,1′-biphenyl (85%) and 2-(*N,N*-dimethylamino)-1,1′-biphenyl (15%) (The ratios were determined by ^{1}H NMR).

To the crude mixture (2.4 g) in CH_2Cl_2 (20 mL) under nitrogen was added triethylaluminium in hexanes (1 M, 15 mL, 15 mmol) at 0 °C. After 30 min, propylene oxide (850 μL, 12.1 mmol) was added and the mixture was stirred at room temperature for 3 h. Aqueous sodium hydroxide (6 N, 15 mL, 90 mmol) was carefully added at 0 °C (vigorous gas evolution). The mixture was then stirred vigorously for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (EtOAc/*n*-heptane = 20:80) afforded **4a** (1.4 g, yield: 55%) as a pale yellow oil. IR (film) 3426, 1592, 1482 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.04 (d, J = 6.1 Hz, 3H), 2.51 (s, OH), 2.60 (s, 3 H), 2.65 (dd, J = 12.6, 10.2 Hz, 1H), 2.84 (dd, J = 2.9, 12.6 Hz, 1H), 3.75 (m, 1H), 7.47–7.20 (m, 9H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 19.8, 42.4, 63.7, 64.4, 121.6, 124.1, 127.0, 128.4, 129.1, 131.1, 138.2, 140.9, 151.2 ppm.

*2-(Biphenyl-2-yl)-(2-methoxypropyl)methyl-amine (**4b**)*

To a suspension of sodium hydride (50% in mineral oil, 224 mg, 4.7 mmol) in dry THF (2 mL) was added amino alcohol **4a** (750 mg, 3.1 mmol) in dry THF (8 mL). The mixture was stirred at room temperature for 15 min before adding iodomethane (400 μL, 6.4 mmol). The mixture was stirred at room temperature for 2 h. Et_2O (10 mL) and water (5 mL) were then added. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (petroleum ether/EtOAc = 90:10) yielded **4b** (630 mg, yield: 80%) as a pale yellow oil. IR (film) 3022, 2972, 2930, 2878, 1594, 1500, 1482, 1452, 1434, 1102 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (d, J = 6.1 Hz, 3H), 2.68 (s, 3H), 2.79 (dd, J = 13.7, 5.3 Hz, 1H), 2.92 (dd, J = 13.7, 6.5 Hz, 1H), 3.28 (s, 3H), 3.29–3.35 (m, 1H), 7.06 (td, J = 7.4, 0.9 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.24 (dd, J = 7.5, 1.6 Hz, 1H), 7.28–7.35 (m, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 17.8, 42.6, 56.5, 60.8, 76.0, 119.8, 122.2, 126.9, 127.5, 128.4, 129.3, 129.4, 129.7, 132.0, 135.6, 142.3, 151.3 ppm.

*(2′-Bromo-biphenyl-2-yl)-carbamic acid tert-butyl ester (**7**)*

A Schlenk flask, evacuated and backfilled with nitrogen, was charged with $Pd(OAc)_2$ (196 mg, 5 mol% Pd), triphenylphosphine (945 mg, 20 mol%), dioxane/H_2O (4:1, 90 mL), 2-iodo-*N*-(*t*-butoxycarbonyl)aniline **9b** (5.6 g 17.5 mmol), 2-bromobenzeneboronic acid **10** (5.25 g, 26.5 mmol) and Na_2CO_3 (4.0 g, 38.5 mmol). The flask was evacuated and backfilled with nitrogen then capped with a rubber septum. The mixture was heated to 95 °C for 12 h. The crude product was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (*n*-hexane/EtOAc = 90:10) afforded **7** (5.0 g, yield: 82 %) as a colorless powder. Mp 66 °C; IR (film): 1724, 1584, 1516, 1444 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (s, 9H), 6.17 (br s, NH), 7.14 (d, J = 3.24 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.40–7.50 (m, 2H), 7.74 (d, J = 8.1 Hz, 1H), 8.11 (br d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.4, 80.6, 120.3, 123.0, 124.3, 128.0, 129.0, 129.8, 130.0, 130.8, 131.9, 133.3, 135.7, 138.9, 152.9 ppm; GC/MS (EI) (*m/z*) 349 (15), 347 (15), 294 (16), 293 (81), 292 (22), 291 (84), 212 (100), 213 (15), 194 (12), 168 (94), 167 (41), 166 (34), 57 (74); Anal. calcd for $C_{17}H_{18}BrNO_2$: C, 58.63; H, 5.21; N, 4.02. Found: C, 59.02; H, 5.34; N, 4.08.

*(2′-Bromo-biphenyl-2-yl)-methyl-amine (**8**) [12]*

A solution of aniline **7** (8.3 g, 23.7 mmol) in dry THF (100 mL) was added slowly at room temperature to a suspension of $LiAlH_4$ (2 g, 52.6 mmol) in dry THF (100 mL). The mixture was refluxed for 2 h under N_2, cooled to room temperature and carefully treated with water (2 mL), aqueous sodium hydroxyde (15%, 2 mL) and water (6 mL). The mixture was dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (*n*-hexane/EtOAc = 90:10) afforded **8** as a yellow oil (3.3 g, yield: 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.91 (s, 3H), 3.55 (br s, NH), 6.85 (br d, J = 7.9 Hz, 1H), 6.91 (td, J = 7.4, 1.0 Hz, 1H), 7.14 (dd, J = 7.4, 1.7 Hz, 1H), 7.34 (td, J = 7.9, 1.9 Hz, 1H), 7.42–7.51 (m, 3H), 7.83 (dd, J = 8.0, 1.1 Hz, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 30.8, 109.9, 116.6, 124.7, 126.8, 128.0, 129.3, 129.4, 129.8, 132.1, 133.2, 140.0, 146.2 ppm; GC/MS (EI) (*m/z*) 263 (97), 261 (100), 182 (96), 180 (29), 167 (63).

*(S)-1-[(2′-Bromo-biphenyl-2-yl)-methylamino]-propan-2-ol (S-**11**)*

To a solution of aniline **8** (576 mg, 2.2 mmol) in CH_2Cl_2

(5 mL) under nitrogen was added triethylaluminium in hexane (1 M, 3.1 mL, 3.1 mmol) at 0 °C. After 30 min, (*S*)-propylene oxide (170 μL, 2.43 mmol) was added and the mixture was stirred at room temperature for 2 h. Aqueous sodium hydroxide (6 N, 3 mL, 18 mmol) was carefully added (vigorous gas evolution) at 0 °C. The mixture was stirred vigorously for 1 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (*n*-heptane/EtOAc = 80:20) afforded (*S*)-**11** (430 mg, yield: 61%) as a pale yellow oil. $[\alpha]^{25}_D$: +26 (c 1.3 in $CHCl_3$); ^{1}H NMR [400 MHz, $CDCl_3$], 2 conformers A and B (A/B = 50:50), δ: 1.05 (d, J = 5.9 Hz, 0.5H), 1.07 (d, J = 5.9 Hz, 0.5H), 2.59 (s, 1.5 H_A), 2.60 (s, 1.5 H_B) 2.65 (s, OH), 2.65–2.78 (m,1H), 2.79–2,83 (m, 1H), 3.75–3.85 (m, 1H), 7.15–7.28 (m, 4H), 7.34–7.45 (m, 3H), 7.71 (s, 0.5H_A), 7.73 (s, 0.5H_B) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 20.2 and 20.3, 41.8 and 42.1, 63.8, 64.5 and 64.8,121.3, 121.8, 123.9 and 124.1, 124.3, 127.6 and 127.8, 129.3, 129.4 and 129.5, 131.9 and 132.0, 133.4 and 133.5, 137.4, 142.0 and 142.1, 151.9 and 152.1; GC/MS (EI) (*m/z*) 319 (11), 276 (100), 274 (97), 195 (85), 194 (38), 152 (6); HRMS calcd for $C_{16}H_{18}NOBr$ (MH^+): 320.0650, found: 320.0660.

*(S)-(2′-Bromo-biphenyl-2-yl)-(2-methoxy propyl)methylamine (S-**12**)*

To a suspension of sodium hydride (50% in mineral oil, 50 mg, 0.84 mmol) in dry THF (2 mL) was added (*S*)-**11** (180 mg, 0.56 mmol) in dry THF (2 mL). The mixture was stirred at room temperature for 1 h before adding iodomethane (39 μL, 0.62 mmol). The mixture was stirred for 12 h, and then diluted with Et_2O (10 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (2×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (*n*-heptane/EtOAc = 85:15) afforded (*S*)-**12** (156 mg, yield: 83%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$), 2 conformers A and B (A/B = 53:47), δ: 0.83 [d, J = 6.2 Hz, 3H (A, B)], 2.65–2.70 [m, 1H, (A, B)], 2.71 [s, 3H (A, B)], 2.80 [dd, J = 13.2, 5.9 Hz, 0.53 H_A] and 2.89 (dd, J = 13.2, 5.9 Hz, 0.47 H_B), 2.99–3.05 [m, 1H (A or B)], 3.18–3.22 [m, 1H (A or B)], 3.22 and 3.23 [s, 3H (A, B)], 7.00–7.08 [m, 1H (A, B)], 7.12–7.20 [m, 3H (A, B)], 7.30–7.38 [m, 3H (A, B)], 7.65 (0.53H_A) and 7.67 (0.47 H_B) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 17.5 and 17.6, 42.02 and 42.06, 56.7, 61.4 and 61.8, 76.3 and 76.7, 119.7 and 120.1, 121.6 and 121.8, 124.4 and 124.5, 127.5, 128.7, 129.1, 132.2, 132.7 and 132.5, 133.35 and 133.30, 135.0 and 134.8, 143.0 and 142.7, 151.7 and 152.1 ppm.

*(S)-(2′-(Dicyclohexylphosphanyl-biphenyl-2-yl)-(2-methoxy-propyl)-methyl-amine (S-**1**)*

To (*S*)-**12** (436 mg, 1.3 mmol) in dry THF (3 mL) was added dropwise *n*-BuLi (1.6 M in hexane, 900 μL, 1.4 mmol) at −78 °C. The yellow solution was stirred at −78 °C for 20 min before adding $ClPCy_2$ (350 μL, 1.6 mmol). The mixture was stirred for 12 h with gradual warming to room temperature. The reaction mixture was quenched with NH_4Cl (saturated solution) and diluted with Et_2O. The organic layer was separated, washed with brine (saturated), dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (*n*-heptane/EtOAc = 90:10) afforded (*S*)-**1** (250 mg, yield: 42%) as a colorless oil. $[\alpha]^{25}_D$: −2.0 (c 5.5 in $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$), 2 conformers A and B (A/B = 58/42), δ: 0.71 and 0.73 [d, J = 6.2 Hz, 3H (A, B)], 1.00–2.10 (m, 22H), 2.48–2.55 [m, 1H (A, B)], 2.55–2.70 [m, 1H (A, B)], 2.78 (s, 1.36, 3H_B), 2.92 (s, 1.74 3H_A), 3.16 (s, 1.36 3H_B), 3.18 [s, 1.74 3H_A], 6.90–7.10 (m, 3H), 7.30–7.40 (m, 4H), 7.58 (bs, 1H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ: 17.3, 26.9, 27.5, 27.9, 28.1, 29.0, 30.2, 30.4, 30.6, 31.1, 33.6, 36.9, 42.4, 41.5, 62.3, 59.9, 119.3, 120.5, 121.3, 126.3, 128.4, 128.8, 130.4, 131.1, 132.8, 133.1, 135.7, 150.0, 152.3 ppm (observed complexity due to P-C splitting); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ: −8.8 and −9.0; MS (CI) (*m/z*) 452 (100) (MH^+) 435 (5), 420 (9), 349 (38); HRMS calcd for $C_{29}H_{42}NOP$ (MH^+): 452.3082, found: 452.3091.

*(±)-[1-(2-Bromo-phenyl)-pyrrolidin-3-yl]dimethylamine (**13a**)*

In a Schlenk tube under an argon atmosphere, Pd_2dba_3 (4.42 mg, 0.005 mmol, 0.005 equiv), BINAP (9.34 mg, 0.015 mmol, 0.015 equiv) and *t*-BuONa (300 mg, 3.1 mmol, 3.1 equiv) were dissolved in degassed toluene (5 mL). Dihydrochloride of pyrrolidine **14** (187 mg, 1.0 mmol) and dibromobenzene **15a** (96 μL, 0.8 mmol, 0.8 equiv) were added and the mixture was heated to 105 °C for 24 h. An aqueous solution of ammonia (14%, 10 mL) was added and the aqueous layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude product was purified by column chromatography [CH_2Cl_2/MeOH/NH_4OH (28%) = 95:5:1] to afford pyrrolidine **13a** as a colorless oil (172 mg, yield: 80%). IR (film): 2948, 2816, 2770, 1586, 1474, 1336, 1154, 1042, 1022, 746 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.87 (m, 1H), 2.11–2.25 (m, 1H), 2.32 (s, 6H), 2.87 (quint, J = 7.6 Hz, 1H), 3.25 (td, J = 8.7, 3.6 Hz, 1H), 3.35–3.47 (m, 2H), 3.62 (dt, J = 8.7, 7.2 Hz, 1H), 6.78 (dt, J = 7.6, 1.5 Hz, 1H), 6.93 (dd, J = 8.0, 1.5 Hz, 1H), 7.21 (dt, J = 7.6, 1.5 Hz, 1H), 7.51 (dd, J = 8.0, 1.5 Hz, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 29.6, 44.0, 50.3, 55.6, 65.4, 114.4, 118.2, 121.9, 127.8, 134.5, 148.1 ppm; MS (EI) (*m/z*) 269 (100, M+H^+), 268 (60, M+H^+), 225 (6), 169 (4), 145 (4), 84 (60), 70 (30).

*(±)-[1-(2-Iodo-phenyl)-pyrrolidin-3-yl]-dimethylamine (**13b**)*

Using the same procedure as for **13a**, diamine **13b** was obtained as a colorless oil (215 mg, yield: 85%). IR (film) 2952, 2820, 2775, 1580, 1469, 1264, 1212, 737 cm^{-1}; ^{1}H

NMR (250 MHz, $CDCl_3$) δ: 1.87 (dq, J = 12.1, 7.9 Hz, 1H), 2.11–2.24 (m, 1H), 2.31 (s, 6H), 2.90 (quint, J = 7.5 Hz, 1H), 3.17 (td, J = 8.8, 4.5 Hz, 1 H), 3.25–3.39 (m, 2H), 3.53 (dt, J = 9.1, 7.5 Hz, 1H), 6.70 (dt, J = 7.5, 1.4 Hz, 1H), 6.98 (dd, J = 8.0, 1.4 Hz, 1H), 7.26 (dt, J = 7.5, 1.4 Hz, 1H), 7.82 (dd, J = 8.0, 1.4 Hz, 1H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.8, 43.2, 50.4, 55.4, 64.7, 91.4, 118.4, 123.0, 128.1, 140.1, 150.7 ppm; MS (EI) *m/z*: 317 (100, M+H$^+$), 316 (13), 271(19), 146 (3), 84 (16).

*(1R)-(3-Bromo-1-bromomethyl-propyl)-carbamic acid tert-butyl ester (**19**)*

To the dimesylate (*S*)-**18** (480 mg, 1.33 mmol) was added LiBr (690 mg, 7.84 mmol, 5.9 equiv) in dry acetone (10 mL). The mixture was heated to 45 °C for 24 h, filtered and the acetone was removed. An aqueous solution of ammonia (28%) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give compound (*S*)-**19** as a colorless solid (255 mg, 58%). Mp 68 °C; IR (film): 3431, 2251, 1708, 1499, 1367, 1243, 1163, 907, 731, 650 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 2.08–2.20 (m, 2H), 3.40–3.50 (m, 2H), 3.50–3.64 (m, 2H), 4.00–4.12 (m, 1H), 4.73 (m, 1H) ppm.^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 28.3, 29.0, 36.4, 37.9, 49.2, 80.1, 155.0 ppm.

*2'-Bromo-2-fluoro-5-nitro-1,1'-biphenyl (**20**)*

$Pd(OAc)_2$ (112 mg, 0.5 mmol, 0.05 equiv) and PPh_3 (540 mg, 2.0 mmol, 0.2 equiv) were dissolved in degassed dioxane (30 mL). Fluorobenzene **21** (2.67 g, 10.0 mmol), 2-bromobenzeneboronic acid **10** (2.00 g, 10 mmol, 1.0 equiv) and CsF (2.70 g, 18 mmol, 1.8 equiv) were added. The mixture was heated to 120 °C in a sealed tube for 24 h. After cooling, water (15 mL) was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (pentane/EtOAc = 98:2) afforded biphenyl **20** as a colorless solid (2.40 g, yield: 81%). Mp 73 °C; IR (film): 3100, 1626, 1578, 1562, 1527, 1492, 1469, 1434, 1344, 1248, 1102, 744 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.12–7.26 (m, 3H), 7.28–7.38 (m, 1H), 7.60–7.64 (m, 1H), 8.14–8.31 (m, 2H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 116.8 (d, $J_{C\text{-}F}$ = 24.9 Hz), 123.3, 125.7 (d, $J_{C\text{-}F}$ = 10.1 Hz), 127.5, 127.6, 129.9 (d, $J_{C\text{-}F}$ = 18.6 Hz), 130.5, 131.3, 133.0, 134.6, 143.9 (d, $J_{C\text{-}F}$ = 2.8 Hz), 163.0 (d, $J_{C\text{-}F}$ = 258.5 Hz). HRMS (M+H$^+$): calcd for $C_{12}H_8BrFNO_2$: 295.9722, found 295.9727.

*(R)-[1-(2'-Bromo-5-nitro-biphenyl-2-yl)-pyrrolidin-3-yl]-dimethyl-amine (**22**)*

To compound **20** (1.40 g, 4.72 mmol) in DMF (8 mL) were added K_2CO_3 (2.93 g, 21.24 mmol, 4.5 equiv) and dimethylaminopyrrolidine (*R*)-**14** (1.33 mg, 7.08 mmol, 1.5 equiv). The mixture was heated to 110 °C for 4 h. After cooling, the aqueous layer was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 98:2) to afford (*R*)-**22** as a yellow oil (1.40 g, yield: 76%). $[\alpha]_D$ = +34.6 (*c* 0.7 in $CHCl_3$); IR (film): 2951, 2868, 2776, 2420, 1598, 1571, 1469, 1302, 1268, 1108, 727 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$), 2 conformers A and B (A/B = 50:50), δ: 1.65–1.80 (m, 1H), 1.99–2.11 (m, 1H), 2.13 (s, 3H), 2.14 (s, 3H), 2.52–2.68 (m, 1H), 2.77 (t, J = 9.1 Hz, 0.5H), 2.91 (t, J = 9.1 Hz, 0.5H), 3.06–3.32 (m, 3H), 6.64 (d, J = 7.6 Hz, 0.5H), 6.68 (d, J = 7.6 Hz, 0.5H), 7.18–7.26 (m, 1.5H), 7.28–7.34 (m, 0.5H), 7.37 (dd, J = 7.4, 1.2 Hz, 0.5H), 7.45 (dd, J = 7.6, 1.8 Hz, 0.5H), 7.58 (dd, J = 8.0, 1.2 Hz, 0.5H), 7.63–7.69 (m, 0.5H), 7.95 (d, J = 2.8 Hz, 0.5H), 7.97 (d, J = 3.5 Hz, 0.5H), 8.10 (t, J = 3.5 Hz, 0.5H), 8.14 (t, J = 2.8 Hz, 0.5H); ^{13}C NMR (62.9 MHz, $CDCl_3$), 2 conformers, δ: 30.2, 30.3, 44.2, 44.3, 49.7, 49.8, 55.2, 55.3, 65.2, 65.3, 112.4, 113.0, 124.7, 124.9, 125.0, 125.2, 125.3, 125.4, 127.0, 127.1, 129.0, 129.3, 129.4, 131.9, 132.9, 132.3, 132.7, 136.8, 137.1, 141.5, 142.0, 150.8, 151.1; MS (ESI) (*m/z*) 390 (27, M+H$^+$), 362 (80), 345 (97), 266 (46), 265 (100), 226 (36), 225 (15); HRMS (M+H$^+$): calcd for $C_{18}H_{21}N_3O_2Br$: 390.0793, found: 390.0802.

*(R)-[1-(2'-Bromo-5-amino-biphenyl-2-yl)-pyrrolidin-3-yl]-dimethyl-amine (**23**)*

To compound (*R*)-**22** (100 mg, 0.26 mmol) in ethanol (5 mL) were added zinc powder (336 mg, 5.13 mmol, 19.7 equiv) and calcium chloride (43 mg, 0.39 mmol, 1.5 equiv). The reaction mixture was heated under reflux for 16 h. The reaction mixture was filtered and the filtrate was diluted with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over $MgSO_4$, filtered and evaporated to afford (*R*)-**23** as a brown oil (85 mg, yield: 91%) which required no purification. $[\alpha]_D$ = +40.1 (*c* 0.8 in $CHCl_3$); IR (film): 3332, 3206, 2949, 2818, 1621, 1505, 1468, 1315, 1156, 1018, 807, 733 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$), (2 conformers 50:50), δ: 1.54–1.72 (m, 1H), 1.82–1.98 (m, 1H), 2.10 (s, 6H), 2.53–2.76 (m, 2H), 2.77–3.00 (m, 3H), 3.30 (br s, 2H), 6.50 (dd, J = 8.3, 2.8 Hz, 1H), 6.64 (dd, J = 4.2, 2.9 Hz, 0.5 H), 6.70 (dd, J = 3.9, 2.8 Hz, 0.5H), 6.72–6.78 (m, 1H), 7.08–7.16 (m, 1H), 7.21–7.26 (m, 1H), 7.27–7.39 (m, 1H), 7.58 (dd, J = 7.8, 1.1 Hz, 0.5H), 7.63 (br d, J = 7.8 Hz, 0.5H) ppm; ^{13}C NMR (62.9 MHz, $CDCl_3$), 2 conformers, δ: 29.4, 29.8, 43.6, 43.8, 49.9, 50.5, 55.0, 55.3, 65.2, 65.4, 115.9, 116.0, 116.2, 116.5, 119.0, 119.5, 124.0, 124.4, 126.8, 127.0, 128.0, 128.2, 131.3, 131.9, 131.7, 132.3, 132.2, 132.7, 138.4, 138.6, 140.4, 140.7, 142.9, 143.3 ppm; MS (ESI) (*m/z*) 360 (24, M+H$^+$), 315 (96), 287 (52), 275 (11), 261 (11), 236 (32), 235 (100), 208 (11), 196 (17), 182 (9); HRMS (M+H$^+$): calcd for $C_{18}H_{23}N_3Br$: 360.1075, found: 360.1068.

*(R)-[1-(2'-Bromo-biphenyl-2-yl)-pyrrolidin-3-yl]-dimethyl-amine (**24**)*

To compound (*R*)-**23** (400 mg, 1.16 mmol) in THF/H_2O (1:1, 10 mL) were added H_3PO_2 (50% aqueous solution, 450 μL, 8.1 mmol, 7.0 equiv), then Cu_2O (20.2 mg, 0.14 mmol, 0.12 equiv) and $NaNO_2$ (104 mg, 1.51 mmol, 1.3 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of Na_2CO_3 was added and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography (pentane/EtOAc = 80:20) to afford (*R*)-**24** (280 mg, yield: 70%) as a colorless oil. $[\alpha]_D = +62.2$ (*c* 1.15 in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$), 2 conformers A and B (A/B = 50:50), δ: 1.58–1.76 (m, 1H), 1.89–2.03 (m, 1H), 2.13 (s, 3H), 2.14 (s, 3H), 2.52–2.74 (m, 1.5H), 2.80 (t, J = 8.5 Hz, 0.5H), 2.92–3.12 (m, 3H), 6.77–6.87 (m, 2H), 7.01–7.20 (m, 2H), 7.23–7.36 (m, 2.5H), 7.42 (dd, J = 7.6, 1.8 Hz, 0.5H), 7.63 (dd, J = 7.9, 1.2 Hz, 0.5H), 7.68 (d, J = 7.9 Hz, 0.5H).

*(R)-[1-(2'-Dicyclohexyphosphanyl)-biphenyl-2-yl]-pyrrolidin-3-yl]-dimethyl-amine (**2**)*

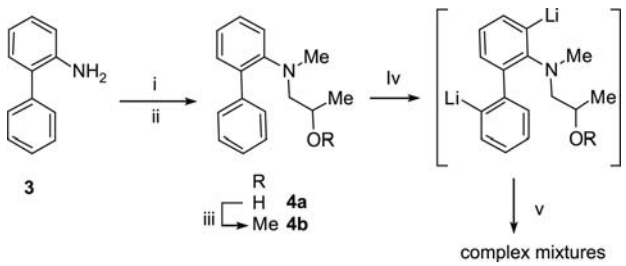
To compound (*R*)-**24** (120 mg, 0.35 mmol) in dry THF (2 mL) was added dropwise *n*-BuLi (2.5 M in hexane, 155 μL, 0.38 mmol, 1.1 equiv) at −78 °C. The yellow solution was stirred at −78 °C for 20 min. Then $ClP(Cy)_2$ (94 μL, 0.45 mmol, 1.3 equiv) was added and the mixture was stirred for 12 h with gradual warming to room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and diluted with Et_2O. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH = 99:1) to afford (*R*)-**2** as a colorless oil (104 mg, yield: 64%). $[\alpha]_D$ = +51.3 (*c* 2.0 in $CHCl_3$); IR (film): 3049, 2923, 2850, 1595, 1567, 1496, 1481, 1462, 1446, 1160, 726 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), 2 conformers A and B (A/B = 60:40), δ: 0.80–2.00 (m, 23H), 2.01–2.06 (m, 1H), 2.07 (s, 2.4H_B), 2.13 (s, 3.6H_A), 2.45–2.56 (m, 1H), 2.64 (t, J = 8.9 Hz, 0.4H_B), 2.69 (t, J = 8.9 Hz, 0.6H_A), 2.79 (dt, J = 9.8, 6.7 Hz, 0.6H_A), 2.91 (dt, J = 9.1, 1.8 Hz, 0.6H_A), 2.96 (dd, J = 9.1, 7.2 Hz, 0.4H_B), 3.06 (dt, J = 9.1, 6.9 Hz, 0.4H_B), 3.12 (dd, J = 8.1, 7.3 Hz, 0.6H_A), 3.15 (dt, J = 9.0, 3.1 Hz, 0.4H_B), 6.75–6.84 (m, 2H), 6.99 (m, 1H), 7.20–7.40 (m, 4H), 7.47–7.52 (m, 0.6H_A), 7.52–7.57 (m, 0.4H_B) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 26.4–28.4 (6 C), 29.5–30.9 (6 C), 32.5, 33.9, 35.7, 36.3, 44.0, 44.2, 49.4, 49.9, 55.1, 55.3, 65.5, 65.7, 113.6, 114.2, 116.6, 117.5, 125.9, 126.0, 127.8, 127.9, 128.0, 128.2, 129.5, 129.6, 130.7, 130.8, 131.3, 131.4, 131.5, 132.0, 132.1, 132.4, 132.5, 132.6, 133.6, 133.7, 135.3, 135.6, 135.8, 136.1, 146.8, 148.0, 150.0, 150.5 ppm (observed complexity due to P–C splitting and conformers; definitive assignments have not yet been made); ^{31}P NMR (101.2 MHz, $CDCl_3$), δ: −9.52 (A), −10.75 (B) ppm; MS (ESI) (*m/z*) 463 (49, M+H^+), 435 (40), 418 (43), 390 (23), 378 (66), 349 (100), 336 (30), 308 (60), 267 (30), 226 (25), 221 (29), 220 (99), 214 (25), 185 (27), 115 (37); HRMS (M+H^+): calcd for $C_{30}H_{44}N_2P$ 463.3242, found 463.3239.

3 Results and discussion

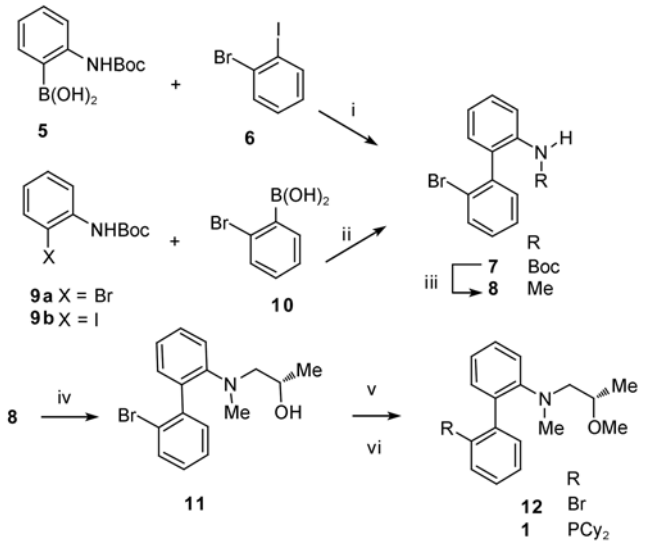
The functionalization of aminobiphenyls **4** (Scheme 1) was the first strategy we envisaged to prepare compound **1**. We assumed that an aminoethanol or ether moiety could direct a remote lithiation of the biphenyl backbone [13, 14]. In order to test this hypothesis and to know the potential sites of deprotonation, we treated the alcohol **4a** and the ether **4b** easily prepared from aminobiphenyl with an alkyllithium. The reaction mixture was then allowed to react with chlorotrimethylsilane. With **4a**, the complex mixtures of products were formed including the trimethylsilyl protected alcohol. No reaction took place under the same conditions with the ether **4b**.

Palladium mediated Suzuki-coupling has been widely developed for the synthesis of biaryls [15, 16], we thus examined the cross-coupling of *o*-bromoiodobenzene **6** and boronic acid **5** (Scheme 2). The reaction [$Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%) in DMF/H_2O or DME/H_2O/EtOH and K_3PO_4 or Na_2CO_3, under reflux] between these partners led to biphenyl **7** in low yields (26%–30%). Conversely, the coupling between bromobenzeneboronic acid **10** and *N*-Boc iodoaniline **9b** under identical catalytic conditions afforded the expected compound **7** in 82% yield after optimization.

It is noteworthy that no Suzuki coupling occurred with *N*-Boc-bromoaniline **9a**. Introduction of the chiral lateral chain was performed by ring opening of the (*S*)-propylene oxide in the presence of triethylaluminium [17]. The alcohol function was then transformed into ether and a halogen-metal exchange followed by reaction with chlorodicyclohexylphosphane led to the chiral biphenyl. Unexpectedly, the ^{1}H NMR spectra of alcohol **11**, ether **12** and target



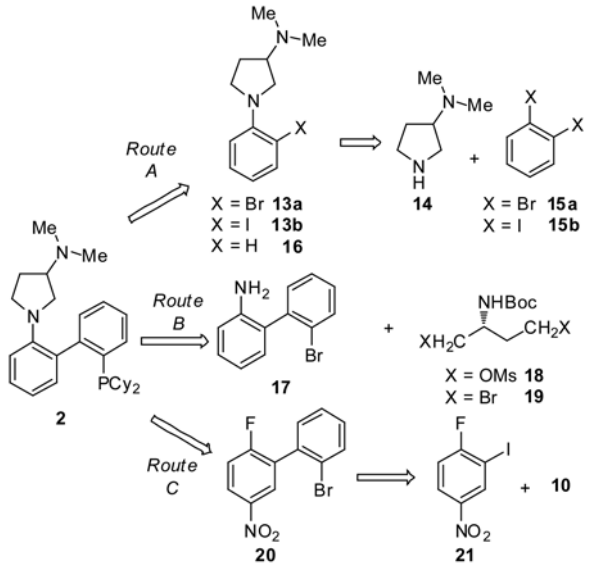
Scheme 1 Synthesis of biphenyls **4a** and **4b**. Reagents and conditions: (i) NaH, THF, 1 h then MeI, THF, RT 12 h; (ii) $AlEt_3$ in hexanes, CH_2Cl_2, 0 °C, 30 min then propylene oxide, RT, 3 h, 55% for (i) and (ii); (iii) NaH, THF, rt, 15 min then MeI, RT, 2 h 80%; (iv) *t*-Bu-Li (3 equiv), THF, −78 °C (or −20 °C or 0 °C) ; (v) Me_3SiCl (3 equiv), 2 h.



Scheme 2 Synthesis of compound **1.** Reagents and conditions: (i) Na_2CO_3, DME/H_2O/EtOH (4/1/0.1), PPh_3 (20 mol%), $Pd(OAc)_2$ (5 mol%), 85 °C, 12 h, **7**: 30%; (ii) the same as (i) but dioxane/H_2O (4:1), 95 °C, **7**: 82%; (iii) $LiAlH_4$ (2 equiv), THF, reflux, 2 h, **8** [12]: 53%; (iv) (*S*)-propylene oxide, $AlEt_3$, CH_2Cl_2, RT, 1 h, **11**: 52%; (v) NaH, THF, RT, 1 h, then MeI, rt, 12 h, **12**: 85%; (vi) *n*-BuLi, THF, –78 °C, then $ClPCy_2$, THF, –78 °C to RT, 12 h, **1**: 42%.

compound **1** show the formation of two conformers.

The synthesis of compound **2** was envisaged according to three routes summarized in Scheme 3. The first one was based on a coupling reaction between *ortho*-halogenoaniline **13** and dihalogenobenzene, whereas in the second and third approaches, the pyrrolidine moiety was built on preformed biphenyl derivatives **17** or **20**. Reaction of a slight excess of *N,N*-dimethylaminopyrrolidine dihydrochloride **14**·2HCl and dibromo or diiodobenzene **15a** or **15b** in toluene at 100 °C in the presence of *t*-BuONa, Pd_2dba_3 (3 mol%), and a ligand (4.5 mol%, BINAP for X = Br and Xantphos for X = I) afforded aminopyrrolidine **13a** and **13b** in 80% and 85% yields, respectively. A Suzuki coupling of these pyrrolidines **13a** and **13b** was attempted under different conditions (Pd_2dba_3 or $Pd(OAc)_2$, Na_2CO_3 or K_3PO_4, dioxane/H_2O, toluene or dioxane, and ligands [18, 19], 95–110 °C). When a reaction occurred, either a complex mixture of products or the dehalogeno derivative **16** was formed.



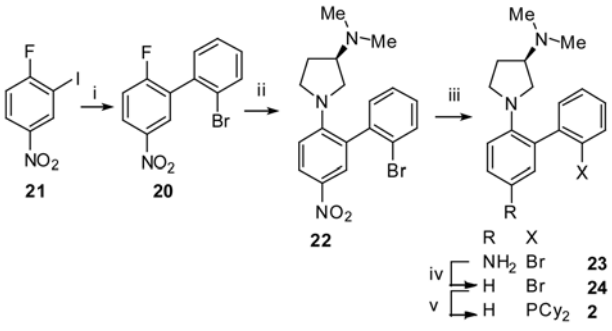
Scheme 3 Retrosynthetic analysis of compound **2**.

All the attempts to transform the bromo derivative **13a** into a boronate, a trimethylstannyl or an organozinc derivative failed. The only product isolated was the phenylpyrrolidine **16**.

The difficulties encountered to introduce a phenyl ring in the *ortho*-position to the pyrrolidine led us to study the route B in which the pyrrolidine ring could be appended to the biphenyl backbone. Reaction of aniline **17** and dimesylate **18** at 45 °C in THF in the presence of HNa for 48 h yielded the expected compound in poor yield (14%). This poor reactivity may be due to the *ortho*-substitution of the aniline and the instability of the reagents. Attempts to use the dibromide **19** failed, and a complex mixture was formed. The route C was thus studied.

A Suzuki coupling between 2-iodo 4-nitro fluorobenzene [20] and boronic acid **10** yielded the biaryl **20** in 81% yield. Aromatic nucleophilic substitution of the fluorine atom by (*R*)-(3-*N,N*-dimethylamino)pyrrolidine (*R*)-**14** afforded compound **22** in a satisfactory yield. Reduction of the nitro group followed by diazotation in the presence of a reducing agent, bromine-lithium exchange and reaction with chlorodicyclohexylphosphane led to the expected compound **2** as two conformers in six steps and 18% overall yield from 4-fluoronitrobenzene.

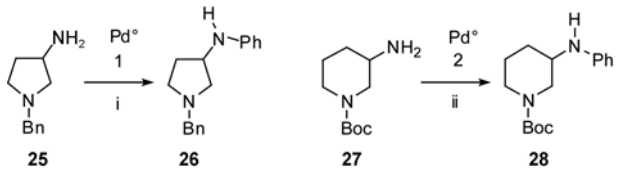
Palladium catalyzed amination of a dibromo cyclophane [21] and arylation of binaphthyl(di)amines [22, 23] have previously shown the possibility of a kinetic resolution in palladium mediated reactions. The synthesized compounds were thus evaluated in palladium mediated arylaminations. Aminopyrrolidine **25** and bromobenzene in the presence of



Scheme 4 Synthesis of compound **2.** Reagents and conditions: (i) $Pd(OAc)_2$ (5 mol%), Ph_3P (0.2 equiv), **10** (1 equiv), CsF (1.8 equiv), dioxane, 120 °C, sealed tube, 24 h, 81%; (ii) 3-(*R*)-(*N,N*-dimethylamino)pyrrolidine dihydrochloride, DMF, K_2CO_3 (4 equiv), 110 °C, 4 h, 76%; (iii) Zn (22 equiv), $CaCl_2$ (1.5 equiv), EtOH, 80 °C, 16 h, 91%; (iv) $NaNO_2$ (1.3 equiv), Cu_2O (0.12 equiv), H_3PO_2 (7 equiv), THF/H_2O (1:1), 70%; (v) *n*-BuLi (1.1 equiv), $ClPCy_2$ (1.3 equiv), THF, –78 °C, 64%.

Pd_2dba_3 and ligand **1** under the conditions shown in Scheme 5 gave no reaction. However, chlorobenzene under the same catalytic conditions afforded *N*-arylpyrrolidine **26** in 54% yield. Compared to DavePhos (Figure 1), the cross-coupling was slightly less efficient (yield with DavePhos: 80%). It is noteworthy that using $Pd(OAc)_2$ as a source of Pd, only traces of the coupled product **26** were formed. Ligand **2** was tested in the palladium mediated reaction of bromobenzene with *N*-Boc-3-aminopiperidine **27**. The expected arylamine **28** was formed in 88% yield, a value which compares well with that obtained when ligand DavePhos was used (90 % yield under the same conditions).

These results are encouraging in view of undertaking arylation of racemic amines **25** and **27** under kinetic resolution conditions.



Scheme 5 Evaluation of ligands **1** and **2**. (i) PhCl (1 mmol), **25** (1.2 mmol), *t*-BuONa (1.4 mmol), Pd_2dba_3 (1 mol%), **1** (1.5 mol%), toluene, 95 °C, 24 h, 54%; (ii) PhBr (1 mmol), **27** (1.2 mmol), *t*-BuONa (1.4 mmol), Pd_2dba_3 (1 mol%), **2** (1.5 mol%), toluene, 110 °C, 24 h, 88%.

4 Conclusions

In summary, we have synthesized the first 2,2′ biphenyl P,N compounds bearing central chirality. The study demonstrated the good reactivity of 2-bromoboronic acid compared to that of 2-N-Boc aminoboronic acid in the Suzuki coupling with 2-iodosubstituted benzene. A bulky pyrrolidine was introduced in the 2-position of 2′-substituted biphenyl via an aromatic nucleophilic substitution. Preliminary experiments have shown that these ligands, in the presence of a palladium source, are able to catalyze arylaminations efficiently, with the best results obtained with the more rigid compound **2**.

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