Supporting Information

Palladium-Catalyzed Cross-Coupling of *B*-Benzyl-9-Borabicyclo[3.3.1]nonane to Furnish Methylene-Linked Biaryls

Alice Flaherty,* Amy Trunkfield and William Barton

*Medicinal Chemistry, AstraZeneca R & D Charnwood, Bakewell
Road, Loughborough, Leics, UK, LE11 5RH and Department of
Chemistry, University of Warwick, Coventry, CV4 7AL.*

Alice.Flaherty@astrazeneca.com

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General Experimental Details

B-benzyl-9-BBN (0.5 M solution in THF); THF; DMF; Pd(PPh₃)₄ and Pd(OAc)₂ were purchased from Aldrich. SPhos is commercially available from Strem. Arylhalides and triflates were commercially available unless otherwise stated. Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. Column chromatography was performed on silica cartridges. ¹H and ¹³C NMR spectra were obtained from either a 300 MHz (¹H: 300 MHz, ¹³C: 75 MHz) or 400 MHz (¹H: 400 MHz, ¹³C: 100 MHz) Varian Unity Inova spectrometer. ¹H and ¹³C shifts are given in ppm, δ scale and are measured relative to tetramethylsilane as standard. Mass spectra were recorded on a Hewlett Packard HP 6890 or HP 5973 MSD instrument.

General Coupling Procedure

K₃PO₄ (3 equiv) was added to the catalyst Pd(PPh₃)₄ or Pd(OAc)₂ and SPhos in THF or DMF (3mL/mmol). When Pd(PPh₃)₄ was used H₂O (1mL/mmol) was added. The aryl halide/triflate (1 equiv) was subsequently added along with the *B*-benzyl-9-BBN (2 equiv of a 0.5 M solution in THF). The resulting mixture was heated with stirring in a sealed tube until the reaction had reached completion, as judged by LC/MS. The crude mixture was diluted with EtOAc, the organics washed with 2M NaOH, brine, dried (MgSO₄) and concentrated *in vacuo* to yield the crude product. Purification was carried out on silica gel using pentane/ethyl acetate to give the desired methylene-linked biaryl product.

Ethyl-4-benzylbenzoate¹ (2a)

A colourless oil, **2a** (83% yield from **1a**). ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 7.98-7.95 (m, 2H, Ar-*H*), 7.31-7.15 (m, 7H, Ar-*H*), 4.35 (q, 2H, CO₂CH₂CH₃), 4.02 (s, 2H, CH₂Ph), 1.37 (t, 3H, CO₂CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 166.6, 146.4, 140.2, 129.8, 128.9, 128.6, 128.5, 128.3, 126.3, 60.8, 41.9, 14.3.

In agreement with reference 1.

4-Benzylbenzonitrile² (2b)

A colourless oil, **2b** (74% yield from **1b** or 89% yield from **1c**). ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 7.62-7.60 (m, 2H, Ar-*H*), 7.38-7.36 (m, 2H, Ar-*H*), 7.30-7.26 (m, 2H, Ar-*H*), 7.20-7.17 (m, 3H, Ar-*H*), 4.06 (s, 2H, CH₂Ph); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 148.8, 141.2, 133.4, 131.0, 130.1, 129.8, 127.6, 119.9, 110.9, 42.6; IR (cm⁻¹) 3028 ν (C-H), 2919, 2227 sharp ν (C $\equiv$ N).

In agreement with reference 2.

(1) Suh, Y. S.; Lee, J.; Kim, S.-H.; Rieke, R. D. *J. Organomet. Chem.* **2003**, 684, 20-36.

(2) Akiyama, T.; Hirofujii, H.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1992**, 65, 1932-1938.

4-Benzylbenzenesulfonamide³ (2c)

A white powdery solid, **2c** (76% yield from **1d**); mp 126-128°C; ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 7.71-7.34 (m, 2H, Ar-*H*), 7.28-7.20 (m, 2H, Ar-*H*), 7.20-7.15 (m, 2H, Ar-*H*), 7.11-7.08 (m, 3H, Ar-*H*), 4.05 (s, 2H, CH₂Ph); ¹³C NMR (75 MHz, CD₃OD): δ_{ppm} 147.9, 142.9, 141.9, 130.6, 130.1, 129.7, 127.5, 127.4, 42.5; IR (cm⁻¹) 3346 ν(N-H), 3254 ν(N-H), 2923 ν(C-H), 1596 δ(N-H), 793 ν(C-H); Elemental Analysis C: 62.81% (63.13), H: 5.50% (5.30), N: 5.72% (5.66), S: 13.02% (12.97).

In agreement with reference 3.

Methyl-4-benzylbenzoate⁴ (2d)

A colourless oil, **2d** (94% yield from **1e** and 70% yield from **1f**). ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 7.93-7.90 (m, 2H, Ar-*H*), 7.31-7.25 (m, 4H, Ar-*H*), 7.20-7.16 (m, 3H, Ar-*H*), 4.04 (s, 2H, CH₂Ph), 3.88 (s, 3H, CO₂CH₃); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 168.6, 148.7, 141.7, 130.8, 130.1, 130.0, 129.7, 129.2, 127.4, 52.5, 42.7; IR (cm⁻¹) 2951 ν(C-H), 1717 ν(C=O), 1274 ν(C-O).

In agreement with reference 4.

4-Benzylbenzaldehyde⁵ (2e)

A colourless oil, **2e** (72% yield from **1h** and 62% yield from **1g**). ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 9.92 (s, 1H, CHO), 7.83-7.80 (m, 2H, Ar-*H*), 7.41-7.36 (m, 2H, Ar-*H*), 7.31-7.24 (m, 2H, Ar-*H*), 7.21-7.17 (m, 3H, Ar-*H*), 4.05 (s, 2H, CH₂Ph); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 194.8, 150.9, 141.7, 136.4, 131.0, 130.7, 130.1, 129.7, 127.5, 42.9, IR (cm⁻¹) 3059, 3023, 2989, 2912 ν(C-H), 1678 ν(C=O).

In agreement with reference 5.

2-Benzyl-naphthalene⁶ (2f)

A colourless oil, **2f** (93% yield from **1i**). ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 7.79-7.73 (m, 3H, Ar-*H*), 7.62-7.60 (m, 1H, Ar-*H*), 7.45-7.38 (m, 2H, Ar-*H*), 7.31-7.22 (m, 6H, Ar-*H*), 4.12 (s, 2H, CH₂Ph); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 141.0, 138.6, 133.6, 132.1, 129.1, 128.5, 128.1, 127.6, 127.5, 127.1, 126.2, 125.9, 125.4, 42.1.

(3) Bordwell, F. G.; Crosby G. W. *J. Am. Chem. Soc.* **1956**, 78, 5367-5371.

(4) Smonou, I. *Synth. Commun.* **1994**, 24, 1999-2002.

(5) Gribble, G. W.; Nutaitis, C. F. *Tetrahedron Lett.* **1985**, 26, 6023-6026.

(6) Utley, J. H. P.; Rozenberg, G. G. *Tetrahedron*, **2002**, 58, 5251-5265.

In agreement with reference 6.

2-Benzylpyridine⁷ (2g)

A colourless oil, **2g** (62% yield from **1j**). ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 8.46-8.41 (m, 1H, Ar-*H*), 7.76-7.70 (m, 1H, Ar-*H*), 7.30-7.14 (m, 7H, Ar-*H*), 4.12 (s, 2H, CH₂Ph); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 162.2, 149.6, 140.7, 138.9, 130.0, 129.7, 127.6, 125.2, 123.1, 44.8.

In agreement with reference 7.

2-Benzylquinoline⁸ (2h)

A colourless oil, **2h** (76% yield from **1k**). ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 8.10 (s, 1H, Ar-*H*), 8.01 (s, 1H, Ar-*H*), 7.76-7.67 (m, 2H, Ar-*H*), 7.51-7.47 (m, 1H, Ar-*H*), 7.32-7.21 (m, 6H, Ar-*H*), 4.35 (s, 2H, CH₂Ph); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 161.2, 147.8, 139.2, 136.5, 129.5, 129.2, 129.0, 128.6, 127.5, 126.7, 126.5, 125.9, 121.5, 45.6.

In agreement with reference 8.

1-Benzyl-2-methyl-benzene⁹ (2i)

A colourless oil, **2i** (77% yield from **1l**). ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 7.24-7.21 (m, 2H, Ar-*H*), 7.15-7.07 (m, 7H, Ar-*H*), 4.00 (s, 2H, CH₂Ph), 2.21 (s, 3H, CH₃); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 141.9, 140.3, 137.7, 131.3, 131.1, 129.7, 129.4, 127.6, 127.0, 126.9, 40.3, 19.8; IR (cm⁻¹) 3062, 3025, 2922 ν(C-H).

In agreement with reference 9.

2-Benzyl-1,3-dimethylbenzene⁹ (2j)

A colourless oil, **2j** (80% yield from **1m**). ¹H NMR (300 MHz, CD₃OD): δ_{ppm} 7.25-7.11 (m, 3H, Ar-*H*), 7.06-7.05 (m, 3H, Ar-*H*), 7.00-6.98 (m, 2H, Ar-*H*), 4.12 (s, 2H, CH₂Ph), 2.28 (s, 6H, 2 x CH₃); ¹³C NMR (75 MHz, CD₃OD): δ_{ppm} 141.3, 138.2, 138.1, 129.4, 129.2, 128.9, 127.5, 126.8, 35.9, 20.3; IR 3062, 3023, 2923 ν(C-H).

In agreement with reference 9.

(7) Hall, S. S.; Farahat, S. E. *J. Heterocyclic. Chem.* **1987**, 24, 1205-1213.

(8) Haase, M.; Guenther, W.; Goerls, H.; Anders, E. *Synthesis*, **1999**, 12, 2071-2081.

(9) Kondo, T.; Kajiya, S.; Tantayanon, S.; Watanabe, Y. *J. Organomet. Chem.* **1995**, 489, 83-91.

2-Benzyl-1,3,5-triisopropylbenzene¹⁰ (**2k**)

A colourless oil, **2k** (52% yield from **1n**). ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 7.24-7.19 (m, 2H, Ar-*H*), 7.13 (t, 1H, Ar-*H*), 7.04-7.00 (m, 4H, Ar-*H*), 4.12 (s, 2H, CH₂Ph), 3.08-3.01 (m, 2H, CH[CH₃]₂), 2.94-2.87 (m, 1H, CH[CH₃]₂), 1.28 (d, 6H, CH[CH₃]₂), 1.13 (d, 12H, CH[CH₃]₂); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 147.4, 147.0, 141.6, 130.7, 128.2, 128.0, 127.9, 125.6, 121.0, 34.2, 33.1, 29.7, 24.2, 24.1. In agreement with reference 10.

4-Benzylphenol¹¹ (**2l**)

A white powdery solid, **2l** (83% yield from **1o**); mp 83-85°C; ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 7.29-7.25 (m, 2H, Ar-*H*), 7.20-7.16 (m, 3H, Ar-*H*), 7.07-7.03 (m, 2H, Ar-*H*), 6.77-6.73 (m, 2H, Ar-*H*), 3.91 (s, 2H, CH₂Ph); ¹³C NMR (75 MHz, CDCl₃): δ_{ppm} 153.9, 141.5, 133.3, 130.0, 128.8, 128.4, 125.9, 115.3, 40.9. In agreement with reference 11.

1-Benzyl-4-methoxybenzene¹² (**2m**)

A colourless semi-solid, **2m** (84% yield from **1r** ; 53% yield from **1q** and 95% from **1p**). ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 7.26-7.21 (m, 2H, Ar-*H*), 7.17-7.11 (m, 3H, Ar-*H*), 7.10-7.05 (m, 2H, Ar-*H*), 6.83-6.78 (m, 2H, Ar-*H*), 3.88 (s, 2H, CH₂Ph), 3.74 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 159.5, 143.2, 134.8, 130.8, 129.8, 129.4, 126.9, 114.8, 55.7, 41.9; IR (cm⁻¹) 3061, 2996, 2901 ν(C-H), 2835 ν(C-H), 1509, 1243 ν(C-O).

In agreement with reference 12.

1-Benzyl-2-methoxybenzene¹³ (**2n**)

A colourless semi-solid, **2n** (43% yield from **1s**). ¹H NMR (300 MHz, CD₃OD): δ_{ppm} 7.22-6.72 (m, 9H, Ar-*H*), 3.71 (s, 2H, CH₂Ph), 3.64 (s, 3H, OCH₃); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 157.4, 141.1, 130.3, 129.7, 128.9, 128.3, 127.4, 125.8, 120.5,

(10) Montaudou, G.; Finocchiaro, P. *Tetrahedron Lett.* **1972**, 13, 3429-3432.

(11) Kaye, I. A.; Klein, H. C.; Burlant, W. J. *J. Am. Chem. Soc.* **1953**, 75, 745-746.

(12) (a) Mayr, H.; Lang, G.; Ofial, A. R. *J. Am. Chem. Soc.* **2002**, 124, 4076. (b) Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, 40, 271-275.

(13) Darbeau, R. W.; White, E. H.; Song, F.; Darbeau, N. R.; Chou, J. *J. Org. Chem.* **1999**, 64, 5966-5978.

110.4, 55.4, 35.9; IR (cm⁻¹) 3061, 3026, 2965, 2930 ν(C-H), 2837 ν(C-H), 1590, 1236 ν(C-O).

In agreement with reference 13.

2-Benzyl-1-isopropyl-5-methoxy-3-methylbenzene (2o)

5-Isopropyl-3-methylanisole¹⁴

5-Isopropyl-3-methylphenol (6.74 g, 0.045 mol) in sodium hydroxide (1 M, 45 mL) was cooled in an ice-bath and dimethylsulfate (5.10 mL, 0.054 mol) was added slowly. The ice-bath was removed, the cloudy solution was allowed to warm to room temperature and heated under reflux for 1.5 h. The mixture was subsequently allowed to cool, adjusted to pH 10 with sodium hydroxide (1 M) and extracted with diethyl ether (x 2), the organics were combined, washed with brine, dried (MgSO₄) and evaporated to dryness. The resultant oil was purified by column chromatography (silica, 20:1 hexanes:ethyl acetate) affording 5-isopropyl-3-methylanisole (5.10 g, 69%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 6.64 (s, 1H), 6.59 (s, 1H), 6.54 (s, 1H), 3.77 (s, 3H), 2.86-2.79 (m, 1H), 2.31 (s, 3H), 1.23 (d, 6H); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 159.7, 150.5, 139.2, 119.8, 111.7, 109.4, 55.1, 34.2, 23.9, 23.8, 21.6.

In agreement with reference 14.

4-Bromo-5-isopropyl-3-methylanisole (1t)

N-Bromosuccinimide (1.08 g, 6.07 mmol) in acetonitrile (9 mL) was added dropwise to a cold (ice-bath) solution of 5-isopropyl-3-methylanisole (1.05 g, 6.39 mmol) in acetonitrile (1.2 mL). The solution was allowed to warm to room temperature and stirred for 6 h, quenched with water and extracted with diethyl ether (x 2). The combined organics were dried and evaporated to dryness. The reaction mixture was purified by column chromatography (hexanes) to afford 4-bromo-5-isopropyl-3-methylanisole (0.62 g, 42%) as a colourless oil. ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 6.69 (d, 1H), 6.65 (d, 1H), 3.78 (s, 3H), 3.46-3.39 (m, 1H), 2.40 (s, 3H), 1.22 (d, 6H); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 158.5, 148.8, 139.2, 117.6, 113.4, 110.2, 55.3, 33.3, 24.6, 22.8. Elemental Analysis C: 54.04% (54.34), H: 6.26% (6.22).

2-Benzyl-1-isopropyl-5-methoxy-3-methylbenzene (2o)

A colourless oil, **2o** (80% yield from **1t**). ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 7.15-7.12 (m, 2H, Ar-*H*), 7.05 (t, 1H, Ar-*H*), 6.91 (d, 2H, Ar-*H*), 6.67 (d, 1H, Ar-*H*), 6.54 (d, 1H, Ar-*H*), 3.96 (s, 2H, CH₂Ph), 3.72 (s, 3H, OCH₃), 3.01-2.95 (m, 1H, CH(CH₃)₂), 2.12 (s, 3H), 1.04 (d, 6H, CH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 158.2, 149.2, 140.9, 138.6, 128.3, 128.2, 127.9, 127.5, 125.7, 112.9, 109.1, 55.0, 33.5, 29.6, 24.0, 20.9. Elemental Analysis C: 84.70% (84.90), H: 8.69% (8.72).

(14) Demerseman, P.; Raynaud, R.; Lechartier, J. P.; Pene, C.; Cheutin, A.; Royer, R.; Rumpf, P. *Bull. Soc. Chim.* **1966**, *10*, 3328-3334.

1-Methoxy-2,4-bis(4-methoxy-benzyl)-benzene (4)

B-(4-Methoxy-benzyl)-9-BBN* (5 equiv.), 2,4-dibromoanisole (1.0 equiv.), SPhos (0.03 equiv.), palladium(II) acetate (0.015 equiv.), 20 h at 100 °C. A colourless oil, **4** (39% yield from **3**). MS(APCI -ve) 347 (M-H). ¹H NMR (400 MHz, CDCl₃): δ_{ppm} 7.09 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 7.05 (d, 2H, *J* = 8.7 Hz, Ar-*H*), 6.94 (dd, 1H, *J* = 8.2, 2.3 Hz, Ar-*H*), 6.90 (d, 1H, *J* = 2.3 Hz, Ar-*H*), 6.81 (d, 2H, *J* = 3.1 Hz, Ar-*H*), 6.78 (d, 2H, *J* = 3.1 Hz, Ar-*H*), 6.75 (d, 1H, *J* = 8.2 Hz, Ar-*H*), 3.86 (s, 2H, CH₂), 3.80 (s, 2H, CH₂), 3.76 (s, 9H, 3 x OCH₃); ¹³C NMR (100 MHz, CDCl₃): δ_{ppm} 157.8, 157.7, 155.7, 133.8, 133.4, 133.2, 130.8, 129.9, 129.8, 129.7, 127.4, 113.8, 113.6, 110.5, 55.5, 55.2, 55.2, 40.1, 35.0.

* Prepared as follows: 4-Methoxybenzylmagnesium chloride (8 mL, 0.25 M in THF) was added dropwise to a cold (-78 °C) solution of *B*-methoxy-9-BBN (2.0 mL, 1 M in hexanes), stirred for 15 min and allowed to warm to room temperature. After 1 h at room temperature the solution was used directly in the coupling reaction.

2,4-Bis(4-Hydroxybenzyl)-phenol¹⁵ (5)

Boron tribromide (0.94 mL, 1.0 M in DCM) was added dropwise to a cold (0 °C) solution of 1-methoxy-2,4-bis(4-methoxy-benzyl)-benzene (41 mg, 0.118 mmol) in DCM (2.2 mL), warmed slowly to room temperature and stirred overnight. The reaction mixture was quenched with water and extracted with ethyl acetate (x 3), the combined organics were evaporated to dryness and purified by preparative HPLC to afford 2,4-bis(4-hydroxybenzyl)-phenol (30 mg, 83%) as a colourless oil. ¹H NMR (400 MHz, CD₃OD): δ_{ppm} 6.99 (dd, 2H, *J* = 6.4, 2.0 Hz, Ar-*H*), 6.92 (dd, 2H, *J* = 6.4, 2.0 Hz, Ar-*H*), 6.79-6.76 (m, 2H, Ar-*H*), 6.66-6.63 (m, 5H, Ar-*H*), 3.77 (s, 2H, ArCH₂) 3.69 (s, 2H, ArCH₂); ¹³C NMR (100 MHz, CD₃OD): δ_{ppm} 156.4, 156.3,

(15) Noda, N.; Kobayashi, Y.; Miyahara, K.; Fukahori, S. *Phytochemistry*, **1995**, 39, 1247-1248.

154.2, 134.4, 134.1, 133.7, 131.9, 130.8, 130.7, 129.5, 128.3, 116.0, 115.9, 41.2, 35.8.
In agreement with reference 15.