Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides

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Supporting Information

I. General

The following reagents were purchased: Ni(cod)₂ (Strem), bathophenanthroline (Lancaster), KO^t-Bu (Strem), *s*-butanol (anhydrous; Aldrich), *exo*-2-bromonorbornane (*exo:endo* 115:1; Aldrich), 1-bromobenzocyclobutane (Aldrich), isopropyl bromide (Alfa-Aesar), cyclopentyl bromide (Alfa-Aesar), *trans*-2-bromo-1-hydroxylindane (Lancaster), cyclohexyl bromide (Alfa-Aesar), cyclohexyl iodide (Lancaster), *s*-butyl iodide (TCI), neopentyl iodide (Aldrich), 1-iodo-3-methylbutane (Aldrich), phenylboronic acid (Frontier Scientific), *p*-tolylboronic acid (Frontier Scientific), 4-methoxyphenylboronic acid (Frontier Scientific), 4-cyanophenylboronic acid (Frontier Scientific), 4-trifluoromethylphenylboronic acid (Frontier Scientific), 3-thiopheneboronic acid (Aldrich), *N*-methylindole-5-boronic acid (Frontier Scientific), 3-chlorophenylboronic acid (Frontier Scientific), 3,4-methylenedioxyphenylboronic acid (Frontier Scientific), *trans*- β -styreneboronic acid (Frontier Scientific), 4-methylthiophenylboronic acid (Frontier Scientific), (*E*)-1-octen-1-ylboronic acid (Aldrich). *endo*-2-Bromonorbornane [13237-87-1] (*endo:exo* 32:1) was prepared according to a literature procedure.¹ The liquid alkyl halides were purged with argon prior to use. Other reagents were used as received.

All reactions were conducted in oven-dried glassware under an inert atmosphere with magnetic stirring.

II. Preparation of Substrates

***trans*-2-Bromo-1-(*t*-butyldimethylsiloxy)indane.** Imidazole (0.96 g, 14 mmol) was added to a solution of *trans*-2-bromo-1-hydroxyindane (2.00 g, 9.4 mmol) and TBSCl (1.83 g, 12.2 mmol) in CH₂Cl₂ (50 mL) at r.t. This reaction mixture was stirred overnight, and then the resulting yellow suspension was filtered through a pad of silica gel (washed with 10:1 hexane/EtOAc). The filtrate was concentrated, and the residue was purified by flash chromatography (hexane), which provided 2.72 g (88%) of the desired product as a yellow oil.

¹H NMR (400 MHz, CDCl₃): 7.33-7.22 (m, 4H), 5.33 (d, *J* = 5.7 Hz, 1H), 4.27 (dd, *J* = 13.8, 7.4 Hz, 1H), 3.58 (dd, *J* = 16.1, 7.4 Hz, 1H), 3.22 (dd, *J* = 16.1, 7.5 Hz, 1H), 0.99 (s, 9H), 0.29 (s, 3H), 0.26 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): 143.2, 139.7, 128.6, 127.5, 124.6, 124.3, 84.0, 55.0, 40.9, 26.1, 18.4, -3.6, -4.1.

IR (thin film): 2956, 2929, 2894, 2857, 1471, 1462, 1362, 1257 cm⁻¹.

HRMS (EI): Calcd for C₁₅H₂₂BrSiO (M-H)⁺: 325.0623. Found: 325.0628.

III. Suzuki Cross-Coupling Reactions (Tables 2 and 3)

Procedure: no glove box. Ni(cod)₂ (5.6 mg, 0.020 mmol), bathophenanthroline (13.2 mg, 0.040 mmol), the arylboronic acid (0.60 mmol), and KO^t-Bu (90 mg, 0.80 mmol) were added to a vial equipped with a stir bar. The vial was evacuated/refilled with argon three times, and then *s*-butanol (3.0 mL) was added. The mixture was stirred at r.t. for 10 min, and to the resulting deep-purple solution was added the alkyl halide (0.50 mmol). The reaction mixture was stirred at 60 °C for 5 h, and then it was passed through a short pad of silica gel (to remove *s*-butanol and polar compounds). The filtrate was concentrated, and the residue was purified by flash chromatography.

Procedure: with a glove box. In a glove box, Ni(cod)₂ (5.6 mg, 0.020 mmol), bathophenanthroline (13.2 mg, 0.040 mmol), the arylboronic acid (0.60 mmol), KO^t-Bu (90 mg, 0.80 mmol), and *s*-butanol (3.0 mL) were added to a vial equipped with a stir bar. The mixture was stirred at r.t. for 10 min, and to the resulting deep-purple solution was added the alkyl halide (0.50 mmol). The vial was removed from the glove box, and the reaction mixture was stirred at 60 °C for 5 h. Then, it was passed through a short pad of silica gel (to remove *s*-butanol and polar compounds), and the filtrate was concentrated. The residue was purified by flash chromatography.

***exo*-2-Phenylnorbornane [52752-81-5] (Table 2, entry 1).** *exo*-2-Bromonorbornane (88 mg, 0.50 mmol; *exo*:*endo* 115:1) and phenylboronic acid (74 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 64 mg, 74%; glove box: 63 mg, 73%). ¹H NMR revealed a product *exo*:*endo* ratio of >50:1. The assignment of product stereochemistry is based on comparison with reported ¹H and ¹³C NMR spectra.²

¹H NMR (400 MHz, CDCl₃): 7.34-7.31 (m, 2H), 7.28-7.26 (m, 2H), 7.21-7.18 (m, 1H), 2.79 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.40 (d, *J* = 3.1 Hz, 2H), 1.85-1.79 (m, 1H), 1.74-1.68 (m, 1H), 1.65-1.57 (m, 3H), 1.43-1.30 (m, 2H), 1.23 (dd, *J* = 8.2 Hz, 1.5 Hz, 1H).

¹³C NMR (400 MHz, CDCl₃): 147.8, 128.4, 127.3, 125.6, 47.5, 43.1, 39.3, 37.0, 36.3, 30.8, 29.1.

***exo*-2-Phenylnorbornane [52752-81-5] (Table 2, entry 2).** *endo*-2-Bromonorbornane (88 mg, 0.50 mmol; *endo*:*exo* 32:1) and phenylboronic acid (74 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 62 mg, 71%; glove box: 64 mg, 74%). ¹H NMR revealed a product *exo*:*endo* ratio of >50:1. The assignment of product stereochemistry is based on comparison with reported ¹H and ¹³C NMR spectra.²

1-*p*-Tolylbenzocyclobutene (Table 2, entry 3). 1-Bromobenzocyclobutane (92 mg, 0.50 mmol) and *p*-tolylboronic acid (81 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 87 mg, 90%; glove box: 82 mg, 84%).

¹H NMR (400 MHz, CDCl₃): 7.36-7.31 (m, 2H), 7.24-7.17 (m, 6H), 4.73 (dd, *J* = 5.5, 2.6 Hz, 1H), 3.77 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.13 (dd, *J* = 13.9, 2.6 Hz, 1H), 2.40 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): 148.1, 144.4, 140.0, 136.1, 129.3, 127.7, 127.3, 127.0, 123.4, 122.9, 47.4, 40.3, 21.3.

IR (thin film): 3021, 2921, 1661, 1513, 1459 cm⁻¹.

HRMS (EI): Calcd for C₁₅H₁₄ (M⁺): 194.1090. Found: 194.1090.

4-Isopropylanisole [4132-48-3] (Table 2, entry 4). Isopropyl bromide (62 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (99 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 51 mg, 68%; glove box: 50 mg, 67%).

¹H NMR (400 MHz, CDCl₃): 7.25-7.21 (m, 2H), 6.94-6.90 (m, 2H), 3.87 (s, 3H), 2.94 (heptet, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H).

¹³C NMR (400 MHz, CDCl₃): 157.8, 141.3, 127.5, 113.9, 55.5, 33.5, 24.4.

3-Cyclopentylbenzonitrile (Table 2, entry 5). Cyclopentyl bromide (76 mg, 0.50 mmol) and 3-cyanophenylboronic acid (89 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 38 mg, 44%; glove box: 40 mg, 47%).

¹H NMR (400 MHz, CDCl₃): 7.54 (s, 1H), 7.50-7.48 (m, 2H), 7.41-7.37 (m, 1H), 3.03 (m, 1H), 2.15-2.08 (m, 2H), 1.88-1.80 (m, 2H), 1.78-1.69 (m, 2H), 1.63-1.53 (m, 2H).

¹³C NMR (400 MHz, CDCl₃): 148.1, 132.0, 130.9, 129.6, 129.2, 119.4, 112.3, 45.6, 34.6, 25.6.

IR (thin film): 2955, 2869, 2228, 1483 cm⁻¹.

HRMS (EI): Calcd for C₁₂H₁₃N (M⁺): 171.1043. Found: 171.1035.

***trans*-1-*t*-Butyldimethylsiloxy-2-(4-trifluoromethylphenyl)indane (Table 2, entry 6).** *trans*-2-Bromo-1-*t*-butyldimethylsiloxyindane (164 mg, 0.50 mmol) and 4-trifluoromethylphenylboronic acid (114 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 123 mg, 63%; glove box: 118 mg, 60%). ¹H NMR revealed a product *trans*:*cis* ratio of >50:1.³

¹H NMR (400 MHz, CDCl₃): 7.62 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.33-7.25 (m, 4H), 5.29 (d, *J* = 7.7 Hz, 1H), 3.50 (dd, *J* = 17.8, 8.2 Hz, 1H), 3.36 (dd, *J* = 15.7, 8.2 Hz, 1H), 3.08 (dd, *J* = 15.6, 9.9 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 3H), -0.35 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): 147.2, 144.7, 140.5, 129.1, 128.7, 128.3, 127.3, 125.61, 125.57, 124.8, 124.1, 83.9, 57.3, 38.3, 25.9, 18.2, -4.3, -4.7.

¹⁹F NMR (400 MHz, CDCl₃): -62.6.

IR (thin film): 2955, 2930, 2858, 1620, 1326 cm⁻¹.

HRMS (EI): Calcd for C₁₈H₁₈SiOF₃ (M-C₄H₉)⁺: 335.1074. Found: 335.1075.

3-Cyclohexylthiophene [120659-34-9] (Table 2, entry 7). Cyclohexyl bromide (82 mg, 0.50 mmol) and 3-thiopheneboronic acid (77 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 52 mg, 63%; glove box: 51 mg, 61%).

¹H NMR (400 MHz, CDCl₃): 7.27 (dd, *J* = 5.7, 3.7 Hz, 1H), 7.02 (d, *J* = 4.9 Hz, 1H), 6.96 (d, *J* = 2.1 Hz, 1H), 2.67-2.62 (m, 1H), 2.05-2.00 (m, 2H), 1.86-1.84 (m, 2H), 1.81-1.74 (m, 1H), 1.47-1.35 (m, 4H), 1.32-1.24 (m, 1H).

¹³C NMR (400 MHz, CDCl₃): 149.3, 127.2, 125.1, 118.5, 39.7, 34.4, 26.8, 26.4.

***N*-Methyl-5-cyclohexylindole (Table 2, entry 8).** Cyclohexyl bromide (82 mg, 0.50 mmol) and *N*-methylindole-5-boronic acid (105 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Yellow solid (no glove box: 71 mg, 67%; glove box: 69 mg, 65%).

¹H NMR (400 MHz, CDCl₃): 7.51 (t, *J* = 0.8 Hz, 1H), 7.29 (d, *J* = 11.3 Hz, 1H), 7.16 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.06 (d, *J* = 3.1 Hz, 1H), 6.48 (d, *J* = 3.1 Hz, 1H), 3.81 (s, 3H), 2.68-2.61 (m, 1H), 1.98 (d, *J* = 11.9 Hz, 2H), 1.91 (d, *J* = 12.2 Hz, 2H), 1.84-1.80 (m, 1H), 1.60-1.42 (m, 4H), 1.39-1.32 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3): 139.5, 135.6, 129.0, 128.7, 121.4, 118.4, 109.1, 100.7, 44.9, 35.4, 33.0, 27.4, 26.5.

IR (KBr pellet): 2921, 2849, 1511, 1490, 1446, 1424 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{N}$ (M^+): 213.1512. Found: 213.1509.

3-Cyclohexyl-1-chlorobenzene [27163-66-2] (Table 2, entry 9). Cyclohexyl bromide (82 mg, 0.50 mmol) and 3-chlorophenylboronic acid (94 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 71 mg, 75%; glove box: 68 mg, 70%).

^1H NMR (400 MHz, CDCl_3): 7.26-7.22 (m, 2H), 7.19-7.16 (m, 1H), 7.12-7.10 (m, 1H), 2.54-2.48 (m, 1H), 1.89-1.86 (m, 4H), 1.80-1.76 (m, 1H), 1.47-1.35 (m, 4H), 1.31-1.25 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3): 150.3, 134.2, 129.7, 127.2, 126.1, 125.3, 44.5, 34.5, 27.0, 26.2.

Formaldedehyde 4-cyclohexyl-1,2-catechol acetal (Table 3, entry 1). Cyclohexyl iodide (106 mg, 0.50 mmol) and 3,4-methylenedioxyphenylboronic acid (100 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 63 mg, 62%; glove box: 61 mg, 60%).

^1H NMR (400 MHz, CDCl_3): 6.77-6.75 (m, 2H), 6.68 (dd, $J = 8.0, 1.6$ Hz, 1H), 5.94 (s, 2H), 2.48-2.43 (m, 1H), 1.87-1.85 (m, 4H), 1.81-1.75 (m, 1H), 1.45-1.33 (m, 4H), 1.30-1.23 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3): 147.6, 145.6, 142.5, 119.7, 108.2, 107.5, 100.9, 44.6, 35.0, 27.1, 26.3.

IR (thin film): 2925, 2851, 1503, 1490, 1441, 1247 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ (M^+): 204.1145. Found: 204.1143.

(E)-3-Methyl-1-phenyl-1-pentene [15325-63-0] (Table 3, entry 2). *s*-Butyl iodide (92 mg, 0.50 mmol) and *trans*- β -styreneboronic acid (89 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 52 mg, 65%; glove box: 49 mg, 61%).

^1H NMR (400 MHz, CDCl_3): 7.39-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.23-7.19 (m, 1H), 6.36 (d, $J = 15.9$ Hz, 1H), 6.12 (dd, $J = 15.9, 7.9$ Hz, 1H), 2.22 (m, 1H), 1.43 (quintet, $J = 8.2$ Hz, 2H), 1.10 (d, $J = 6.7$ Hz, 3H), 0.93 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (400 MHz, CDCl_3): 138.2, 137.0, 128.7, 128.3, 126.9, 126.2, 39.1, 30.0, 20.4, 12.1.

Methyl 4-neopentylphenyl thioether (Table 3, entry 3). Neopentyl iodide (100 mg, 0.50 mmol) and 4-methylthiophenylboronic acid (101 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:3. Colorless oil (no glove box: 73 mg, 75%; glove box: 68 mg, 70%).

^1H NMR (400 MHz, CDCl_3): 7.21-7.19 (m, 2H), 7.08-7.06 (m, 2H), 2.50 (s, 3H), 2.47 (s, 2H), 0.91 (s, 9H).

^{13}C NMR (400 MHz, CDCl_3): 137.1, 135.3, 131.2, 126.5, 49.9, 32.0, 29.5, 16.4.

IR (thin film): 2920, 2864, 1495, 1476, 1363 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{18}\text{S}$ (M^+): 194.1124. Found: 194.1119.

(E)-2-Methyl-5-dodecene [112197-48-5] (Table 3, entry 4). 1-Iodo-3-methylbutane (100 mg, 0.50 mmol) and (*E*)-1-octen-1-ylboronic acid (94 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 57 mg, 63%; glove box: 56 mg, 61%).

^1H NMR (400 MHz, CDCl_3): 5.42-5.40 (m, 2H), 1.20 (br s, 4H), 1.57 (heptet, $J = 6.6$ Hz, 1H), 1.35-1.22 (m, 10H), 0.92-0.89 (m, 9H).

^{13}C NMR (400 MHz, CDCl_3): 130.7, 130.4, 39.1, 32.9, 32.0, 30.7, 29.9, 29.1, 27.7, 22.9, 22.7, 14.3.

References

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- (2) (a) *exo*-2-Phenylnorbornane: Brunel, J. M.; Heumann, A.; Buono, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1946-1949; Namyslo, J. C.; Kaufmann, D. E. *Chem. Ber.* **1997**, *130*, 1327-1331. (b) *endo*-2-Phenylnorbornane: Tateiwa, J.-i., Aoki, I.; Suama, M.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1170-1177.
- (3) *trans*-1-*t*-Butyldimethylsiloxy-2-phenylindane was synthesized via hydroboration/oxidation of commercially available 2-phenylindene, followed by silylation of the secondary alcohol. The coupling patterns for the protons at C₂ and C₃ are essentially identical to those for the reaction product of Table 2, entry 6.

61312

7.327
7.318
7.305
7.296
7.286
7.283
7.277
7.226
7.217

5.336
5.321
4.302
4.287
4.284
4.269
4.250
3.612
3.593
3.571
3.553
3.254
3.235
3.213
3.194

1.568
1.291
1.037
0.991
0.987
0.945
0.919
0.909
0.893
0.287
0.255
0.097

trans-2-Bromo-1-*t*-butyldimethylsiloxyindane

6269e

Table 2, entry 1

6269e

Table 2, entry 1

6269g

Table 2, entry 2

62.6c

Table 2, entry 2

6169f

Table 2, entry 3

6277h

7.324
7.247
7.239
7.234
7.223
7.218
7.210
6.939
6.931
6.926
6.915
6.910
6.902

3.888
3.865

2.976
2.959
2.942
2.924
2.907

1.314
1.296

Table 2, entry 4

Table 2, entry 5

6271e2

Table 2, entry 6

6277e

Table 2, entry 7

6277br

Table 2, entry 8

6277F

Table 2, entry 9

6277c1r

Table 3, entry 1

Table 3, entry 2

6281br

7.284
7.211
7.206
7.195
7.190
7.185
7.084
7.063

Table 3, entry 3

6275b

Table 3, entry 4