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The First Method for Achieving Palladium-Catalyzed Cross-Couplings of Simple Alkyl Chlorides: Suzuki Reactions Catalyzed by $Pd_2(dba)_3/PCy_3$

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I. General

$Pd_2(dba)_3$ (Johnson Matthey), PCy_3 (Strem), $CsOH•H_2O$ (Aldrich), KOH (Alfa Aesar; ACS grade), 9-BBN dimer (Aldrich), 9-BBN (0.5 M solution in THF; Aldrich) and anhydrous dioxane (Aldrich) were used as received. 1-Chlorododecane (Avocado), 1-chloropentane (Aldrich), 1-chloro-3-methylbutane (Alfa Aesar), 4-chlorobutyraldehyde diethyl acetal (Avocado), 7-chloroheptanenitrile (Lancaster), 1-octene (Acros), 4-allylanisole (Alfa Aesar), and 4-vinylcyclohexene (Aldrich) were sparged with argon prior to use. 5-Benzyloxypent-1-ene[1] [81518-74-3] and 1-(10-undecyl)piperidine[2] [160279-32-3] were prepared according to literature procedures. 1-(*tert*-Butyldimethylsiloxy)-6-chlorohexane [59431-24-2][3] was prepared from 6-chlorohexan-1-ol.

II. Preparation of Substrates

6-Chlorohexyl pivalate. Under argon, 6-chlorohexan-1-ol (Avocado; 2.73 g, 20.0 mmol), NEt_3 (4.22 mL, 30.0 mmol, 1.5 equiv), and DMAP (61 mg, 0.40 mmol, 2.0%) were dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. Pivaloyl chloride (2.95 mL, 24.0 mmol, 1.2 equiv) was added dropwise, leading to the formation of a white precipitate. The reaction mixture was allowed to warm to room temperature overnight, and then it was diluted with Et_2O (100 mL) and washed with water (2 ∞ 10 mL). The aqueous phase was extracted with Et_2O (10 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting orange residue was purified by flash chromatography (hexanes/EtOAc 20:1 ∅ 10:1), which afforded the title compound as a colorless liquid (3.58 g, 81%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.04 (t, *J* = 6.5 Hz, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 1.77 (tt, *J* = 7.3, 6.6 Hz, 2H), 1.63 (tt, *J* = 7.0 Hz, 6.9 Hz, 2H), 1.52-1.30 (m, 4H), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): 178.7, 64.3, 45.0, 38.8, 32.6, 28.6, 27.3, 26.6, 25.4. IR (thin film): 2958, 2938, 2869, 1728, 1540, 1480, 1461, 1398, 1365, 1285, 1157, 1034, 974, 887, 771, 730, 651 cm^{-1}. HRMS (ESI): Calcd for $C_{11}H_{21}O_2ClNa$ $(M+Na)^+$: 243.1122. Found: 243.1122.

III. Suzuki Cross-Couplings of Alkyl Chlorides (Table 2)

Cross-coupling reactions were carried out in a preheated oil bath in 3-mL vials with teflon-lined caps or teflon septum screw-caps. Each of the yields reported in Table 2 reflects the average of two runs, one with Procedure A and one with Procedure B.

Procedure A (with glove box). In a glove box, 9-BBN dimer (146 mg, 1.20 mmol, 1.20 equiv), dioxane (0.9 mL), and the olefin (1.20 mmol, 1.20 equiv) were introduced in turn into a vial equipped with a stir bar. The heterogeneous mixture was stirred for at least six hours at room temperature, during which time it became homogeneous. To a second vial equipped with a stir bar was added $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol, 5%), PCy_3 (56.0 mg, 0.200 mmol, 20%), $CsOH•H_2O$ (185 mg, 1.10 mmol, 1.10 equiv), and dioxane (0.3 mL). The alkyl-9-BBN solution was then introduced by syringe from the first vial, with dioxane washings (2 ∞ 0.3 mL). The alkyl chloride (1.00 mmol, 1.00 equiv) was added to the resulting homogeneous brown mixture, and the vial was then closed with a septum screw-cap, removed from the glove box, and stirred vigorously in an oil bath at 90 °C for 48 hours. At the conclusion of the coupling, the now-heterogeneous reaction mixture was cooled to room temperature, diluted with Et_2O (5 mL), and filtered through a short plug of silica gel with Et_2O washings (30 mL). The solvent was evaporated, and the resulting yellow residue was purified by flash chromatography.

Procedure B (without glove box). A vial equipped with a

septum screw-cap and a stir bar was purged with argon. The olefin (1.20 mmol, 1.20 equiv) and then a solution of 9-BBN (0.50 M in THF; 2.40 mL, 1.20 mmol, 1.20 equiv) were introduced to the vial, and the resulting homogeneous solution was stirred for at least 6 hours at room temperature. After that time, the THF was removed under vacuum and replaced with dioxane (0.9 mL).[4] In air, a stir bar, $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol, 5%), PCy_3 (56.0 mg, 0.200 mmol, 20%), and $CsOH•H_2O$ (185 mg, 1.10 mmol, 1.10 equiv) were placed into a second vial, which was then capped with a septum screw-cap and purged with argon for 10 minutes. Dioxane (0.3 mL) was added by syringe, and then the solution of the alkyl-9-BBN was added via cannula (complete transfer of the alkyl-9-BBN was achieved by rinsing the first vial with dioxane (2 ∞ 0.3 mL)). The alkyl chloride (1.00 mmol, 1.00 equiv) was introduced to this homogeneous brown solution, and the resulting mixture was stirred vigorously under argon for 48 hours at 90 °C. At the conclusion of the coupling, the now-heterogeneous reaction mixture was cooled to room temperature, diluted with Et_2O (5 mL), and filtered through a short plug of silica gel with Et_2O washings (30 mL). The solvent was evaporated, and the resulting yellow residue was purified by flash chromatography.

***n*-Eicosane [112-95-8] (Table 2, entry 1).** Solvent for chromatography: hexanes. White solid (Procedure A: 230 mg, 81%; Procedure B: 239 mg, 85%), identical to an authentic sample (Alfa Aesar) with respect to ^1H NMR, ^{13}C NMR, GC, and melting point.

1-(4-Methoxyphenyl)octane[5] [3307-19-5] (Table 2, entry 2). Solvent for chromatography: hexanes/EtOAc 75:1. Colorless oil

(Procedure A: 180 mg, 82%; Procedure B: 181 mg, 82%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.15 (ddd, *J* = 8.8, 2.8, 2.2 Hz, 2H), 6.88 (ddd, *J* = 8.8, 2.8, 2.2 Hz, 2H), 3.83 (s, 3H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.63 (m, 2H), 1.45-1.26 (m, 10H), 0.94 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 157.8, 135.2, 129.4, 113.8, 55.4, 35.3, 32.1, 32.0, 29.7, 29.5 (2 coincident resonances), 22.9, 14.3.

Benzyl(8-methylnonyl)ether (Table 2, entry 3). Solvent for chromatography: hexanes/EtOAc 35:1. Pale-yellow oil (Procedure A: 181 mg, 73%; Procedure B: 184 mg, 74%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40-7.28 (m, 5H), 4.53 (s, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 1.65 (m, 2H), 1.54 (septet, *J* = 6.6 Hz, 1H), 1.45-1.26 (m, 8H), 1.18 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.9, 128.5, 127.8, 127.7, 73.0, 70.7, 39.2, 30.1, 30.0, 29.7, 28.2, 27.6, 26.4, 22.9. IR (thin film): 3088, 3064, 3030, 2953, 2927, 2854, 1723, 1495, 1466, 1454, 1383, 1364, 1307, 1272, 1203, 1103, 1028, 732, 696 cm^{-1}. HRMS (ESI): Calcd for $C_{17}H_{28}ONa$ $(M+Na)^{+}$: 271.2032. Found: 271.2036.

1-(9,9-Diethoxynonyloxymethyl)benzene (Table 2, entry 4). Solvent for chromatography: hexanes/EtOAc 20:1 to 10:1. Pale-yellow oil (Procedure A: 220 mg, 68%; Procedure B: 231 mg, 72%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40-7.26 (m, 5H), 4.52 (s, 2H), 4.50 (t, *J* = 5.8 Hz, 1H), 3.66 (m, 2H), 3.52 (q, *J* = 7.2 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 1.63 (m, 4H), 1.47-1.28 (m, 10H), 1.22 (t, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 128.5, 127.8, 127.6, 103.1, 73.0, 70.6, 60.9, 33.7, 29.9, 29.7, 29.6, 29.5, 26.3, 24.9, 15.5. IR (thin film): 3030, 2974, 2929, 2856,

1653, 1558, 1540, 1496, 1455, 1372, 1114, 1062, 999, 734, 697 cm^{-1}. HRMS (ESI): Calcd for $C_{20}H_{34}O_3Na$ $(M+Na)^+$: 345.2400. Found: 345.2394.

4-[8-(*tert*-Butyldimethylsiloxy)octyl]-1-cyclohexene (Table 2, entry 5). Solvent for chromatography: hexanes ∅ hexanes/EtOAc 50:1. Colorless oil (Procedure A: 242 mg, 74%; Procedure B: 232 mg, 71%).

^1H NMR ($CDCl_3$, 300 MHz): δ 5.67 (m, 1H), 5.66 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 2.14 (m, 1H), 2.04 (m, 2H), 1.79-1.42 (m, 6H), 1.38-1.10 (m, 12H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 127.2, 127.0, 63.5, 37.0, 33.7, 33.1, 32.2, 30.1, 29.9, 29.7, 29.3, 27.1, 26.2, 26.0, 25.6, 18.6, –5.1. IR (thin film): 3022, 2927, 2855, 1653, 1558, 1540, 1472, 1387, 1361, 1254, 1100, 835, 774, 653 cm^{-1}. HRMS (ESI): Calcd for $C_{20}H_{40}OSiNa$ $(M+Na)^+$: 347.2741. Found: 347.2746.

1-[17-(*tert*-Butyldimethylsiloxy)heptadecyl)piperidine (Table 2, entry 6). Solvent for chromatography: CH_2Cl_2/MeOH 20:1, 1% NEt_3. Yellow oil (Procedure A: 335 mg, 74%; Procedure B: 325 mg, 72%).

^1H NMR ($CDCl_3$, 500 MHz): δ 3.57 (t, *J* = 6.6 Hz, 2H), 2.37 (br s, 4H), 2.27 (m, 2H), 1.58 (tt, *J* = 5.8, 5.5 Hz, 4H), 1.47 (m, 4H), 1.41 (m, 2H), 1.31-1.19 (m, 26H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 63.5, 59.8, 54.7, 33.1, 29.85 (3 coincident resonances), 29.84 (2 coincident resonances), 29.82 (2 coincident resonances), 29.77 (2 coincident resonances), 29.76 (2 coincident resonances), 29.6, 27.9, 27.0, 26.1, 26.0, 24.6, 18.5, –5.1. IR (thin film): 2926, 2854, 2800, 2726, 2494, 1469, 1387,

1360, 1306, 1255, 1155, 1102, 1040, 1005, 938, 836, 812, 775, 736, 661 cm^{-1}. HRMS (ESI): Calcd for $C_{28}H_{60}NOSi$ $(M+H)^+$: 454.4439. Found: 454.4431.

Pentadecanonitrile[6] [18300-91-9] (Table 2, entry 7). Solvent for chromatography: hexanes/EtOAc 20:1. Colorless oil (Procedure A: 165 mg, 74%; Procedure B: 154 mg, 69%).

^1H NMR ($CDCl_3$, 300 MHz): δ 2.32 (t, *J* = 7.0 Hz, 2H), 1.64 (apparent quintet, *J* = 7.3 Hz, 2H), 1.43 (m, 2H), 1.36-1.21 (m, 20H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 120.0, 32.1, 29.81, 29.78 (2 coincident resonances), 29.74, 29.6, 29.50, 29.45, 28.9, 28.8, 25.5, 22.8, 17.2, 14.3.

11-Benzyloxyundecyl pivalate (Table 2, entry 8). KOH was used instead of $CsOH•H_2O$. Solvent for chromatography: hexanes/EtOAc 50:1 ∅ 20:1. Colorless oil (Procedure A: 238 mg, 66%; Procedure B: 232 mg, 64 %).

^1H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.24 (m, 5H), 4.53 (s, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 3.47 (t, *J* = 6.6 Hz, 2H), 1.62 (m, 4H), 1.43-1.26 (m, 14H), 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 178.7, 138.8, 128.4, 127.7, 127.6, 73.0, 70.6, 64.6, 38.8, 29.9, 29.7, 29.61(2 coincident resonances), 29.60, 29.3, 28.7, 27.3, 26.3, 26.0. IR (thin film): 3438, 3064, 3030, 2929, 2855, 1729, 1605, 1495, 1480, 1454, 1397, 1364, 1284, 1156, 1102, 1029, 771, 734, 697 cm^{-1}. HRMS (ESI): Calcd for $C_{23}H_{38}O_3Na$ $(M+Na)^+$: 385.2713. Found: 385.2704.

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If desired, the synthesis of the alkyl-9-BBN can be conducted directly in dioxane by hydroborating the olefin with solid 9-BBN dimer, rather than a solution of 9-BBN in THF (both are commercially available).

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