Supporting Information for

Thiol Ester – Boronic Acid Cross-Coupling. Catalysis Using Alkylative Activation of the Palladium Thiolate Intermediate

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GENERAL METHODS

^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 MHz (300 MHz ^1H, 75 MHz ^{13}C) or Varian Inova 400 MHz (400 MHz ^1H, 100 MHz ^{13}C) spectrometer in deuteriochloroform ($CDCl_3$) or deuterioDMSO ($(CD_6)_2SO$) with either tetramethylsilane (TMS) (0.00 ppm ^1H, 0.00 ppm) or chloroform (7.26 ppm ^1H, 77.00 ppm) or DMSO (2.50 ppm, ^1H) as internal reference unless otherwise stated. Data are reported in the following order: chemical shifts are given (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), pent (pentuplet), hex (hextet), hept (heptet), m (multiplet), exch (exchangeable), app (apparent)); coupling constants, *J*, are reported (Hz); integration is provided. Infrared spectra were recorded on a Nicolet 510 FT-IR spectrometer with a resolution of 4 cm^{-1}. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (weak, 20-40 %) and br (broad). GC-MS spectra were recorded on a Shimadzu Gas Chromatograph GC-17A, Mass Spectrometer QP-5000. GC/MS analysis was carried out on a bonded 5% diphenylsiloxane capillary column (30m, 0.25mm id, 0.25 μm df). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 plates, 0.25 mm thick with F-254 indicator. Visualization was accomplished by UV light, 5% phosphomolybdic acid solution in ethanol. Flash column chromatography was performed by the method of Still with 32-63 μm silica gel (Woelm). Rotatory chromatography was performed with a Chromatotron from Harrison Research using 4 mm PF-254 silica rotors. Preparative plate chromatography was performed on Merck silica gel 60 plates, 0.5 mm thick with F-254 indicator. Solvents for extraction and chromatography were reagent grade and used as received. Dried solvents (THF, toluene, CH_3CN, benzene, DMA) used as reaction media were purchased from Aldrich and

dried over 4A molecular sieves and titrated for water level prior to use with a Fisher Coulomatic K-F titrator. Et_3N and pyridine were dried over 4Å molecular sieves. Unless otherwise noted all solvents were sparged with nitrogen for several hours. All reactions were performed under an atmosphere of dry argon in oven- and/or flame-dried glassware, except for those reactions utilizing water as a solvent, which were run under air. "Brine" refers to a saturated aqueous solution of NaCl. Unless otherwise specified, solutions of HCl, NH_4Cl, $NaHCO_3$ refer to aqueous solutions.

STARTING MATERIALS

Phenylboronic acid, thioacetamide, P(*o*-tolyl)$_3$, anhydrous K_2CO_3, NaOH, NaI, thiobenzoic acid, thiolacetic acid, 1-bromohexane, 1,4-dibromobutane, 1,2-dibromoethane, Me_2S_2, $CoCl_2$, $Pd(OAc)_2$, lauroyl chloride, *p*-toluoyl chloride, *n*-Bu_4NPF_6, activated carbon, and Zn powder were purchased from Aldrich Chemical Co. and used as received. 4-Methoxy-2-formylphenyl boronic acid, 3-methoxyphenyl boronic acid, 2-naphthalene boronic acid were obtained from Frontier Scientific. *trans*-Di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]-dipalladium(II) was prepared according to a literature procedure.[1]

Preparation of Thiol Esters

Thiobenzoic acid *S*-(4-bromobutyl) ester, 1a.[2] Thiobenzoic acid 90% pure (18.1 g, 0.12 mol, 1.0 equiv) was added to a solution of NaOH (9.6 g, 0.24 mol, 2.0 equiv) in dry, degassed THF (150 mL) containing 1,4-dibromobutane (29.0 mL, 0.24 mol, 2 equiv). The mixture was stirred under nitrogen overnight at room temperature. After addition of Et_2O, the reaction mixture was filtered through Celite, and then concentrated to a viscous oil. The crude material was purified by silica gel chromatography (5 x 20 cm, 2:1 hexanes-Et_2O) to give **1a** (20.0 g, 56%) . TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.66) IR (neat, cm^{-1}): 1660 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, *J* = 8.0 Hz, 2 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 3.45 (t, *J* = 6.8 Hz, 2 H), 3.11 (t, *J* = 7.2 Hz, 2 H), 1.97-2.04 (m, 2 H), 1.81-1.89 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.4, 136.8, 133.2, 128.4, 127.0, 32.8, 31.5, 28.0, 27.8. MS (low resolution FAB), m/e (relative intensity) 105 (100), 193 (3), 273 (14). HRMS (FAB) Calcd for $C_{11}H_{14}BrOS$: 272.9949. Found: 272.9942.

Thioacetic acid *S*-(-4-bromobutyl) ester, 1b.[2] Following the same procedure, thiolacetic acid (7.6 g, 0.10 mol, 1.0 equiv), 1,4-dibromobutane (40.0 g, 0.18 mol, 1.8 equiv), and NaOH (4.0 g, 0.10

mol, 1.0 equiv) in THF (30 mL) gave 13.6 g (0.06 mol, 64% yield) of **1b** after distillation (Bp 82-90 °C, 1.5 mmHg). TLC (silica gel, 2:1 hexanes-Et_2O, TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.78). IR (neat, cm^{-1}): 1688 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.41 (t, J = 6.8 Hz, 2 H), 2.90 (t, J = 7.2 Hz, 2 H), 2.33 (s, 3 H), 1.89-1.95 (m, 2 H), 1.72-1.77 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.6, 32.8, 31.4, 30.5, 28.0. 28.0. Anal. Calcd for $C_6H_{11}OSBr$: C, 34.13; H, 5.25; S, 15.19; Br, 37.85; Found: C, 34.26; H, 5.37; S, 15.21; Br, 37.73.

Thiolauric acid *S*-(4-bromobutyl) ester, 1c. The procedure of Takido was followed.[3] A mixture of thioacetamide (1.00 g, 13.3 mmol, 1.0 equiv) and lauroyl choride (3.1 mL, 13.4 mmol, 1.0 equiv) in dry and degassed benzene (30.0 mL) was stirred at 30 °C for 3 h under N_2. Then, 1,4-dibromobutane (4.8 mL, 40.2 mmol, 3.0 equiv), Bu_4NPF_6 (cat.) and aqueous NaOH (1.00 g of NaOH in 10 mL of water) were added and the mixture was vigorously stirred for 5 hours at 30 °C. The organic layer was separated, washed with H_2O (3 x 50 mL), dried ($MgSO_4$), and evaporated. Recrystallization of the residue from Et_2O/hexanes gave **1c** (760 mg, 15%). TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.80). Mp 37-39 °C (Et_2O/hexanes); IR (CH_2Cl_2, KCl, cm^{-1}): 1693 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 3.41 (t, J = 6.8 Hz, 2 H), 2.89 (t, J = 7.2 Hz, 2 H), 2.54 (t, J = 7.2 Hz, 2 H), 1.92 (pent, J = 6.8 Hz, 2 H), 1.73 (pent, J = 7.2 Hz, 2 H), 1.61-1.66 (m, 2 H), 1.25-1.29 (m, 16 H), 0.87 (t, J = 6.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.4, 44.1, 32.9, 31.9, 31.5, 29.6, 29.4, 29.3, 29.2, 28.9, 28.2, 27.7, 25.6, 22.6, 14.1. MS (low resolution FAB), m/e (relative intensity) 353 (44), 351 (50), 183 (100). HRMS (FAB) Calcd for $C_{16}H_{32}BrOS$: 351.1357. Found: 351.1359.

Thiobenzoic acid S-(4-iodobutyl) ester, 2. The thiol ester **1a** (185 mg, 0.68 mmol, 1.0 equiv) was stirred overnight at room temperature in dry and degassed CH_3CN (2 mL) in the presence of NaI (327 mg, 2.19 mmol, 3.2 equiv). The solid (NaBr) was filtered and washed with CH_3CN. Dichloromethane was added to the filtrate and excess NaI was filtered off. After concentration, 210 mg (96%) of **2** as a brown oil was obtained. TLC (silica gel, hexanes-Et_2O 2:1, R_f = 0.64). IR (neat, cm^{-1}): 1662 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (d, J = 6.8 Hz, 2 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 3.21 (t, J = 6.8 Hz, 2 H), 3.09 (t, J = 7.2 Hz, 2 H), 1.92-1.99 (m, 2 H), 1.76-1.83 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 191.6, 136.9, 133.3, 128.5, 127.1, 32.3, 30.4, 27.7, 5.8.

MS (low resolution FAB), m/e (relative intensity) 321 (70), 183 (36), 105 (100). HRMS (FAB) Calcd for $C_{11}H_{14}IOS$: 320.9810. Found: 320.9810.

4-Methylthiobenzoic acid *S*-methyl ester, 3.[4] The procedure of Roy was followed.[5] To a solution of $CoCl_2$ (119 mg, 0.9 mmol, 5%) in dry and degassed CH_3CN (20 mL) under nitrogen at room temperature was added dimethyldisulfide (0.72 mL, 8.0 mmol, 1.0 equiv). The reaction mixture turned dark blue. Zinc powder (850 mg, 13.0 mmol, 1.6 equiv) was then added followed by the dropwise addition of *p*-toluoyl chloride (2.2 mL, 16.6 mmol, 2.1 equiv) over 15 minutes. The reaction mixture, which rapidly turned black, was stirred overnight at room temperature. Et_2O (50 mL) was added and the organic layer was extracted with 2N HCl (60 mL), $NaHCO_3$ (30 mL), brine (30 mL), dried ($MgSO_4$) and treated with activated carbon. After filtration of $MgSO_4$ and concentration, product **3** (1.35 g, 51%) was obtained as a light yellow oil. TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.71). IR (neat, NaCl, cm^{-1}): 1662 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, J = 8.0 Hz, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 2.46 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.0, 144.0, 134.5, 129.2, 127.1, 21.6, 11.6.

Dodecanethioic acid *S*-ethyl ester, 4.[6] Lauroyl chloride (5.80 g, 26.5 mmol, 1.0 equiv) was added to a solution of Et_3N (4.90 mL, 35.0 mmol, 1.3 equiv) and ethanethiol (3.50 g, 56.1 mmol, 2.1 equiv) in dry and degassed THF (100 mL). The reaction mixture was stirred under nitrogen overnight. The white precipitate was filtered and the organic layer concentrated to give **4** (6.10 g. 94%) as a yellow oil. TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.84). IR (neat, NaCl, cm^{-1}): 1693 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 2.86 (q, J = 14.8, 7.6 Hz, 2 H), 2.52 (t, J = 7.6 Hz, 2 H), 1.64 (pent, J = 7.6 Hz, 2 H), 1.22-1.32 (m, 20 H), 0.87 (t, J = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.6, 44.0, 31.8, 29.5, 29.3, 29.3, 29.2, 28.9, 25.6, 23.1, 22.6, 14.7, 14.0. MS (low resolution FAB), m/e (relative intensity) 245 (100), 183 (70). HRMS (FAB) Calcd for $C_{14}H_{28}OS$: 245.1933. Found: 245.1939.

Typical procedure for the cross-coupling reaction of the 4-bromothiol ester derivatives with boronic acids.

Under argon in a 25 mL Schlenk tube, a solution of *trans*-di(u-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]-dipalladium(II) (5-10%), K_2CO_3 (4.0 –6.0 equiv), NaI (20-45%), and boronic acid (1.1-1.5 equiv) in 2 mL of dry, degassed dimethylacetamide (DMA) was treated with (1.0 equiv) of thiol ester. The reaction was stirred overnight (12-24 h) at 90-95 °C. After

adding Et_2O (~15 mL), the organic layer was washed with either saturated NH_4Cl or 2N HCl (~15 mL). The aqueous phase was extracted once with Et_2O (5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a viscous yellow oil or solid. Preparative thin layer chromatography (1:2 Et_2O/hexanes) or radial chromatography (Chromatotron, trace amounts of Et_2O in hexanes) provided the desired product, some being further recrystallized.

Benzophenone, 5.[7] Following the typical procedure, a solution of 6% Pd cat. (7 mg, 0.01 mmol), K_2CO_3 (130 mg, 0.94 mmol, 4.1 equiv), 32 % NaI (11 mg, 0.07 mmol), phenylboronic acid (30 mg, 0.24 mmol, 1.1 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **1a** (63 mg, 0.23 mmol, 1.0 equiv) at 95 °C for 20 h; product **5** (37 mg, 0.20 mmol, 88%) was obtained. TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.53). Mp 48-49 °C (Et_2O/hexanes; lit. mp 48 °C[8]); IR (CH_2Cl_2, KCl, cm^{-1}): 1662 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, J = 7.2 Hz, 4 H), 7.59 (d, J = 7.2 Hz, 2 H), 7.49 (t, J = 7.2 Hz, 4 H).

***m*-Methoxybenzophenone, 6.**[9] Following the typical procedure, a solution of 6% Pd cat. (15 mg, 0.03 mmol), K_2CO_3 (314 mg, 2.27 mmol, 4.4 equiv), 36% NaI (28 mg, 0.19 mmol), and 3-methoxyphenylboronic acid (92 mg, 0.75 mmol, 1.4 equiv) in dry and degassed DMA (2 mL) was treated with 143 mg (0.52 mmol, 1 equiv) of thiol ester **1a** at 95 °C for 18 h; product **6** (64 mg, 0.30 mmol, 57%) was obtained. TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.56). Mp 36-38 °C (Et_2O/hexanes, lit. mp 37-38 °C[10]); IR (CH_2Cl_2, KCl, cm^{-1}): 1660 (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, J = 8.1 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.32-7.50 (m, 5 H), 7.13 (d, J = 7.5 Hz, 1 H), 3.86 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.5, 159.5, 138.8, 137.5, 132.4, 130.0, 129.2, 128.2, 122.8, 118.8, 114.2, 55.4.

2-Benzoyl-4-methoxybenzaldehyde, 7. A solution of 6% Pd cat. (14 mg, 0.03 mmol), K_2CO_3 (313 mg, 2.27 mmol, 4.3 equiv), 33% NaI (26 mg, 0.17 mmol), and 4-methoxy-2-formylphenylboronic acid (113 mg, 0.62 mmol, 1.2 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **1a** (142 mg, 0.52 mmol, 1.0 equiv) at 95 °C for 17 h. After adding Et_2O (15 mL) the organic layer was extracted with 2N HCl (15 mL) and the aqueous layer was washed once with Et_2O (5 mL). After drying the combined organic layers over $MgSO_4$, filtering and evaporating, the crude material was

subjected to radial chromatography (Chromatotron, 4 mm PF-254 silica rotors; hexanes as eluent). Recrystallization with Et_2O/hexanes afforded **7** (98 mg, 0.41 mmol, 78%) as white needles. TLC (silica gel, 2:1 hexanes-Et_2O, $R_f = 0.25$). IR (CH_2Cl_2, NaCl, cm^{-1}): 1696 (s); 1654 (s); 1598 (s). Mp 82-84 °C (Et_2O-hexanes). ^1H NMR ($CDCl_3$, 400 MHz): δ 10.08 (s, 1 H), 7.80 (dd, J = 6.8, 1.6 Hz, 2 H), 7.60 (dt, J = 7.6, 1.6 Hz, 1 H), 7.45-7.53 (m, 4 H), 7.13 (dd, J = 8.4, 2.4 Hz, 1 H), 3.92 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 195.4, 190.7, 161.7, 138.5, 137.6, 133.6, 133.3, 132.1, 130.1, 128.5, 118.8, 112.7, 55.7. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; O, 19.98; Found: C, 75.08; H, 5.10; O, 19.98.

2-Naphthyl phenyl ketone, 8.[7] A solution of 6% Pd cat. (13 mg, 0.03 mmol), K_2CO_3 (307 mg, 2.22 mmol, 4.3 equiv), 35% NaI (27 mg, 0.18 mmol), and naphthalene-2-boronic acid (104 mg, 0.60 mmol, 1.2 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **1a** (138 mg, 0.51 mmol, 1.0 equiv) at 90 °C for 17 h; product **8** (90 mg, 0.38 mmol, 76%) was obtained. TLC (silica gel, hexanes-Et_2O 2:1, $R_f = 0.40$). Mp 78-80 °C (Et_2O/hexanes; lit mp 82 °C[11]); IR (CH_2Cl_2, KCl, cm^{-1}): 1659 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1 H), 7.85-7.96 (m, 6 H), 7.50-7.65 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 196.7, 137.8, 135.2, 134.7, 132.3, 132.2, 131.8, 130.1, 129.4, 128.5, 123.3, 127.8, 127.2, 126.8, 125.7.

Acetophenone, 9.[7] A solution of 7% Pd cat. (12 mg, 0.03 mmol), K_2CO_3 (206 mg, 1.49 mmol, 4.0 equiv), 20% NaI (12 mg, 0.08 mmol), and phenylboronic acid (65 mg, 0.53 mmol, 1.4 equiv) in dry and degassed DMA (2 mL) was treated with 80 mg (0.38 mmol, 1.0 equiv) of thiol ester **1b** for 18 h at 90 °C. TLC (silica gel, 2:1 hexanes-Et_2O, $R_f = 0.40$). According to GC/MS, 100% of acetophenone (with *n*-decane, 55 mg, 0.39 mmol, as internal standard) was obtained while all of the starting material was consumed. GC/MS data for acetophenone were consistent with an authentic sample purchased from Aldrich.

2-Acetonaphthone, 10.[7] A solution of 6% Pd cat. (16 mg, 0.03 mmol), K_2CO_3 (307 mg, 2.22 mmol, 3.9 equiv), 30% NaI (26 mg, 0.17 mmol), and naphthalene-2-boronic acid (108 mg, 0.62 mmol, 1.1 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **1b** (119 mg, 0.56 mmol, 1.0 equiv) at 90 °C for 17 h; product **10** (66 mg, 0.39 mmol, 70%) was obtained. TLC (silica gel, 2:1 hexanes-Et_2O, $R_f = 0.39$). Mp 52-54 °C (Et_2O/hexanes; lit mp 53-55 °C[7]); IR (CH_2Cl_2, KCl, cm^{-1}):

1680 (s). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46 (s, 1 H), 8.03 (d, J = 8.4 Hz, 1 H), 7.96 (d, J = 8.0 Hz, 1 H), 7.88 (t, J = 8.0 Hz, 2 H), 7.53-7.62 (m, 2 H), 2.73 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.1, 135.5, 134.4, 132.4, 130.2, 129.5, 128.4, 128.4, 127.7, 126.7, 123.8, 26.7.

1-Phenyl-dodecan-1-one, 11.[7,12] A solution of 6% Pd cat. (8 mg, 0.02 mmol), K_2CO_3 (160 mg, 1.16 mmol, 4.1 equiv), 45% NaI (19 mg, 0.13 mmol), and phenylboronic acid (40 mg, 0.33 mmol, 1.2 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **1c** (98 mg, 0.28 mmol, 1.0 equiv) at 90 °C for 23 h; product **11** (58 mg, 0.22 mmol, 80%) was obtained. TLC (silica gel, hexanes-Et_2O 2:1, R_f = 0.68). Mp 42-44 °C (Et_2O/hexanes; lit. mp 43-45 °C[13]); IR (CH_2Cl_2, KCl, cm^{-1}): 1684 (s). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.96 (td, J = 7.2, 1.2 Hz, 2 H), 7.55 (tt, J = 7.2, 1.2 Hz, 2 H), 7.46 (tt, J = 7.2, 1.6 Hz, 1 H), 2.96 (t, J = 7.2 Hz, 2 H), 1.73 (pent, J = 7.2 Hz, 2 H), 1.20-1.34 (m, 16 H), 0.88 (t, J = 6.8 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.6, 137.0, 132.8, 128.5, 128.0, 38.6, 31.9, 29.6, 29.5, 29.4, 29.3, 24.4, 22.7, 14.1.

1-(3-Methoxy-phenyl)-dodecan-1-one, 12.[14] A solution of 6% Pd cat. (8 mg, 0.02 mmol), K_2CO_3 (147 mg, 1.06 mmol, 3.8 equiv), 24% NaI (10 mg, 0.07 mmol), and 3-methoxyphenylboronic acid (54 mg, 0.34 mmol, 1.2 equiv) in dry and degassed DMA (1.5 mL) was treated with thiol ester **1c** (100 mg, 0.28 mmol, 1.0 equiv) at 95 °C for 16 h; product **12** (41 mg, 0.14 mmol, 50%) was obtained. TLC (silica gel, 2:1 hexanes-Et_2O, R_f = 0.60). IR (CH_2Cl_2, KCl, cm^{-1}): 1683 (s). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.54 (td, J = 7.5, 1.5 Hz, 1 H), 7.49 (dd, J = 2.7, 1.5 Hz, 1 H), 7.36 (t, J = 8.1 Hz, 1 H), 7.09 (ddd, J = 8.1, 3.6, 1.2 Hz, 1 H), 3.86 (s, 3 H), 2.94 (t, J = 7.2 Hz, 2 H), 1.72 (pent, J = 7.5 Hz, 2 H), 1.25-1.33 (m, 16 H), 0.88 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.4, 159.8, 138.4, 129.5, 120.7, 119.3, 112.3, 55.4, 38.7, 31.9, 29.6, 29.5, 29.5, 29.3, 29.3, 24.4, 22.7, 14.1. MS (low resolution FAB), m/e (relative intensity) 291 (100), 290 (11), 207 (11), 183 (11), 163 (14), 150 (41), 135 (69), 147 (31). HRMS (FAB) Calcd for $C_{19}H_{31}O_2$: 291.2324. Found: 291.2337.

Intermolecular Alkylative Activation

1-Phenyl-dodecan-1-one, 11.[12] A solution of 6% Pd cat. (17 mg, 0.04 mmol), K_2CO_3 (337 mg, 2.44 mmol, 4.1 equiv), 30% NaI (30 mg, 0.20 mmol), and phenylboronic acid (87 mg, 0.71 mmol, 1.1 equiv) in dry and degassed DMA (2 mL), treated with ethylthiol ester **4** (148 mg, 0.60 mmol, 1.0 equiv) and 1,4-dibromobutane (0.10 mL, 0.84 mmol, 1.3 equiv) for 18 h at 90 °C. Ketone **11** (75 mg,

0.29 mmol, 48%) was obtained and thiol ester **4** (22 mg, 0.09 mmol, 15%) was recovered. TLC (silica gel, hexanes-Et_2O 2:1, $R_f = 0.68$). Mp 42-44 °C (Et_2O/hexanes; lit. mp 43-45 °C[13]); IR (CH_2Cl_2, KCl, cm^{-1}): 1684 (s). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.96 (td, $J = 7.2$, 1.2 Hz, 2 H), 7.55 (tt, $J = 7.2$, 1.2 Hz, 2 H), 7.46 (tt, $J = 7.2$, 1.6 Hz, 1 H), 2.96 (t, $J = 7.2$ Hz, 2 H), 1.73 (pent, $J = 7.2$ Hz, 2 H), 1.20-1.34 (m, 16 H), 0.88 (t, $J = 6.8$ Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.6, 137.0, 132.8, 128.5, 128.0, 38.6, 31.9, 29.6, 29.5, 29.4, 29.3, 24.4, 22.7, 14.1.

Control Experiments.

Typical Procedure. Under argon in a 25 mL Schlenk tube a solution of 5-9% *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]-dipalladium(II), K_2CO_3 (4.0-6.0 equiv), NaI (20-45%), and boronic acid (1.1-1.5 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester (0.55 mmol) and the alkyl halide or alkyl dihalide (1.1-1.5 equiv). The reaction was stirred overnight (12-24 h) at 90-95 °C. After adding Et_2O (~15 mL), the organic layer was washed with saturated NH_4Cl or 2N HCl (~ 15mL). The aqueous phase was extracted once with Et_2O (5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to a viscous yellow oil. Preparative thin layer chromatography (1/2 Et_2O/hexanes) or radial chromatography (Chromatotron, drops of Et_2O in hexanes) provided the desired product. The remaining starting material could also be recovered.

Cross-coupling of bromobutyl thiol ester ***1a*** *in the absence of NaI.* A solution of 8% Pd cat. (13 mg, 0.03 mmol), K_2CO_3 (170 mg, 1.23 mmol, 6.1 equiv), and phenylboronic acid (43 mg, 0.35 mmol, 1.7 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **1a** (55 mg, 0.20 mmol, 1.0 equiv). The reaction was stirred for 22 h at 95 °C. TLC (silica gel, hexanes-Et_2O 2:1, $R_f = 0.53$). Traces of product were observed by GC/MS (*n*-decane (30 mg, 0.21 mmol) was used as internal standard).

Cross-coupling of iodobutyl thiol ester ***2*** *in the absence of NaI.* A solution of 9% Pd cat. (9 mg, 0.02 mmol), K_2CO_3 (177 mg, 1.3 mmol, 6.1 equiv), phenylboronic acid (40 mg, 0.32 mmol, 1.6 equiv) in dry and degassed DMA (2 mL) was treated with thiol ester **2** (67 mg, 0.21 mmol, 1.0 equiv). The reaction was stirred for 18 h at 90 °C. After usual work up, benzophenone (21 mg, 0.12 mmol, 56%) was obtained

Cross-coupling of p-tolylmethylthiol ester 3 in the absence of alkylhalide. A solution of 7% Pd cat. (20 mg, 0.04 mmol), K_2CO_3 (362 mg, 2.6 mmol, 4.6 equiv), phenylboronic acid (83 mg, 0.68 mmol, 1.2 equiv), 36% NaI (31 mg, 0.20 mmol) in dry and degassed DMA (2 mL) was treated with *p*-tolylmethylthiol ester **3** (95 mg, 0.57 mmol, 1.0 equiv). The reaction was stirred for 18 h at 95 °C. Traces of product were observed by GC/MS (*n*-decane (80 mg, 0.56 mmol) was used as internal standard).

References

(1) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1844-1847.

(2) Gol'dfarb, Y. L.; Ispiryan, R. M.; Belen'kii, L. I. *Dokl. Akad. Nauk. SSSR* **1967**, *173*, 97-100.

(3) Takido, T.; Toriyama, M.; Itabashi, K. *Synthesis* **1988**, 404-406.

(4) Olah, G. A.; Bruce, M. R.; Clouet, F. L. *J. Org. Chem.* **1981**, *46*, 438-442.

(5) Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1997**, *38*, 2149-2152.

(6) Ralston, A. W.; Segebrecht, E. W.; Bauer, S. T. *J. Org. Chem.* **1939**, *4*, 502-505.

(7) Commercial product purchased from Aldrich Chemical Company or Acros.

(8) Futami, Y.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3567-3571.

(9) Morley, J. A.; Woolsey, N. F. *J. Org. Chem.* **1992**, *57*, 6487-6495.

(10) Friedrich, S. S.; Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1970**, *35*, 944-948.

(11) Cheng, C. L.; Le Fevre, J. W.; Ritchie, G. L. D. *J. Chem. Soc. B* **1971**, 1579-1581.

(12) Negoro, K.; Yamada, M. *Nippon Kagaku Kaishi* **1978**, 597-610.

(13) Hegedus, L. S.; Kendall, S. M.; Lo, S. M.; Sheats, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 5448-5451.

(14) Marei, A.; Kassem, T. M.; Gebril, B. A. *Egypt. J. Chem.* **1977**, *20*, 85-100.