# Zinc Trimethylsilylamide as a Mild Ammonia Equivalent and Base for the Amination of Aryl Halides and Triflates

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## Supporting Information

**General Methods.** Most reactions were conducted using standard drybox techniques, but a procedure for conducting reactions without a drybox is also provided. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker DPX 400 MHz Spectrometer with tetramethylsilane or residual protiated solvent as a reference. GC and GC/MS analyses were conducted with an HP-1 methyl silicone column. Yields for final products in Tables 2 and 3 refer to isolated yields and are the average of at least two runs. Zinc bis[bis-(trimethylsilyl)amide],[1] (*S*)-2-(6-Methoxy-naphthalen-2-yl)-propionic acid methyl ester[2] were prepared according to the known procedures. Among aryl triflates, 3-methylphenyl trifluoromethanesulfonate, 3-methoxyphenyl trifluoromethanesulfonate, 3-(trifluoro-methyl)phenyl trifluoromethanesulfonate, 4-cyanophenyl trifluoromethanesulfonate, and 3-cyanophenyl trifluoromethanesulfonate were prepared according to the known procedure.[3] All other chemicals were used as received from commercial sources.

**Synthesis of Zinc Bis[bis(trimethylsilyl)amide].**[1] In a 150 mL Schlenck flask were placed zinc chloride (6.81 g, 50.0 mol) and sodium bis(trimethylsilylamide) (18.34 g, 100.0 mol) in a drybox. The flask was removed from the drybox, and $Et_2O$ (60 mL) was introduced via syringe under nitrogen atmosphere. The reaction mixture was stirred at 50 °C for 5 h. Cooled to ambient temperature, the flask was brought into the dry box, and the precipitate was filtered through Celite on fritted glass. The collected solid was washed with $Et_2O$ (15 mL). The combined ether filtrate was evacuated at reduced pressure, and the the resulting crude product was purified by vacuum distillation (72-74 °C at 0.4-0.5 mmHg, lit.[1] 103 °C at 2-3 mmHg) to give colorless liquid of $Zn[N(SiMe_3)_2]_2$ (13.12 g, 68%). $^{1}H$ NMR ($CDCl_3$) δ 0.10 (s); $^{13}C$ NMR ($CDCl_3$) δ 4.16.

**Synthesis of 2-(6-Methoxynaphthalen-2-yl)propionic acid methyl ester.**[2] To a 50 mL round bottom flask containing (*S*)-(+)-6-methoxy-α–methyl-2-naphthaleneacetic acid (1.10 g, 4.78 mmol) was added 50 mL of MeOH and a catalytic amount of conc. $H_2SO_4$. The reaction mixture was stirred at room temperature, and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was concentrated to half the volume in a rotary evaporator. Water (5 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (3×10 mL). The combined organic layers were washed with water (3×10 mL), brine (10 mL), and dried over $MgSO_4$. The solvent was removed in vacuo to give white solid of title compound (1.06 g, 91%) $^{1}H$ NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.70 (s, 1H), 7.67 (d, $J$ = 0.7 Hz, 1H), 7.40 (dd, $J$ = 1.6, 8.4 Hz, 1H), 7.14 (dd, $J$ = 2.4, 8.8 Hz, 1H), 7.11 (d, $J$ = 2.4 Hz, 1H), 3.91 (s, 3H), 3.86 (q, $J$ = 7.2 Hz, 1H), 3.67 (s, 3H), 1.58 (d, $J$ = 7.2 Hz, 3H); $^{13}C$ NMR ($CDCl_3$) δ 175.3, 157.8, 135.8, 133.8, 129.4, 129.1, 127.4, 126.4, 126.1, 119.2, 105.7, 55.5, 52.2, 45.5, 18.8.

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**Synthesis of Aryl Triflates.** A typical procedure[3] is given for that of 3-methylphenyl trifluoromethanesulfonate.

**3-Methylphenyl trifluoromethanesulfonate**.[4] To a cooled (0 °C) 500 mL round bottom flask containing a biphasic mixture of toluene (50 mL) and aqueous solution (50 mL) of $K_3PO_4$ (19.1 g, 0.0900 mol), and *m*-cresol (3.24 g, 0.0300 mol) was added trifluoromethanesulfonic anhydride (6.1 mL, 0.036 mol) dropwisely. The reaction mixture was allowed to warm to ambient temperature and stirred for 1 h, during which time the reaction progress was monitored by TLC. Upon completion, the layers were separated, and the toluene layer was washed with water (10 mL) and then concentrated in a rotary evaporator. The resulting crude product was further purified by column chromatography (*n*-Hexane:EtOAc = 3:1) to give yellow liquid of title compound (6.41 g, 89%). $^1$H NMR ($CDCl_3$) δ 7.11 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.88-6.86 (m, 2H), 2.19 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 149.8, 141.1, 130.0, 129.3, 121.9, 118.4, 21.3.

**3-Methoxyphenyl trifluoromethanesulfonate.**[5] From 3-methoxyphenol (3.72 g, 0.0300 mol), 6.23 g (81%) of triflate was obtained according to the general procedure. $^1$H NMR ($CDCl_3$) δ 7.34 (t, *J* = 8.3 Hz, 1H), 6. 90 (m, 2H), 6.82 (t, *J* = 2.3 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 161.1, 150.4, 130.7, 118.9 (q, *J* = 318.8 Hz), 114.3, 113.4, 107.7, 55.8.

**3-(Trifluoromethyl)phenyl trifluoromethanesulfonate.**[6] From α,α,α-trifluoro-*m*-cresol (4.86 g, 0.0300 mol), 7.58 g (86%) of triflate was obtained according to the general procedure. $^1$H NMR ($CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 149.5, 133.2 (q, *J* = 33.6 Hz), 131.3, 125.6 (q, *J* = 3.7 Hz), 125.1, 123.0 (q, *J* = 271.1 Hz), 119.0 (q, *J* = 3.7 Hz), 118.9 (q, *J* = 318.9 Hz).

**4-Cyanophenyl trifluoromethanesulfonate.**[7] From 4−cyanophenol (3.57 g, 0.0300 mmol), 7.23 g (96%) of triflate was obtained according to the general procedure. $^1$H NMR ($CDCl_3$) δ 7.78 (d, *J* = 8.9 Hz, 2H), 7.42 (d, *J* = 8.9 Hz, 2H); $^{13}$C NMR ($CDCl_3$) δ 152.0, 134.6, 122.7, 118.7 (q, *J* = 320.8 Hz), 117.2, 113.0.

**3-Cyanophenyl trifluoromethanesulfonate.**[3] From 3−cyanophenol (3.57 g, 0.0300 mol), 7.23 g (96%) of triflate was obtained according to the general procedure. $^1$H NMR ($CDCl_3$) δ 7.58 (d, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.44 (s, 1H), 7.39 (d, *J* = 8.1 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 132.6, 131.9, 126.6, 125.5, 120.6, 119.0 (q, *J* = 318.9 Hz), 117.1, 115.0.

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**General Procedure for the Coupling of Aryl Halides and $Zn[N(SiMe_3)_2]_2$.** In a screw-capped vial containing the aryl halide (0.50 mmol) were placed P(*t*-Bu)$_3$ (0.025-0.0050 mmol, a 0.25 M stock solution), Pd(dba)$_2$ (0.025-0.0050 mmol), and $Zn[N(SiMe_3)_2]_2$ (0.30 mmol), followed by solvent (1.0 mL). For the reactions in Scheme 1, DMF was used as a solvent. For the reactions in Table 2, LiCl (0.30 mmol) was added, and THF was used as a solvent. The vial was sealed with a cap fitted with a PTFE septum and removed from the drybox. The reaction mixture was stirred at the temperature stated in the table, and the reaction progress was monitored by GC analysis. Upon consumption of the aryl halide, the crude reaction mixture was diluted with $Et_2O$ (10 mL), and the silylamide was deprotected by adding one drop of aqueous 1 N HCl. The mixture was transferred to a separatory funnel and washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane:EtOAc = 1:1).

**Aniline (Scheme 1 and Table 2, entry 5).**[8] $^1$H NMR δ 7.17 (ddd, *J* = 7.4, 6.6, 0.8 Hz, 2H), 6.77 (dt, *J* = 7.4, 1.0 Hz, 1H), 6.69 (ddd, *J* = 6.6, 1.0, 0.8 Hz, 2H), 3.65 (s, 2H); $^{13}$C NMR ($CDCl_3$) δ 147.01, 129.96, 119.22, 115.77.

***p*-Toluidine (Scheme 1 and Table 2, entry 7 ).**[8] $^1$H NMR ($CDCl_3$) δ 6.99 (d, *J* = 8.3 Hz, 2H), 6.63 (d, *J* = 8.3 Hz, 2H), 3.53 (s, 2H, NH), 2.26 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 143.9, 129.9, 127.9, 115.4, 20.6.

**4-Aminobenzonitrile (Scheme 1 and Table 2, entry 1).**[9] $^1$H NMR ($CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 4.15 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 150.5, 134.0, 120.3, 114.6, 100.4.

**4-Nitroaniline (Scheme 1 and Table 2, entry 2).**[9] $^1$H NMR (DMSO) δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.71 (s, 2H, NH), 6.58 (d, *J* = 8.8 Hz, 2H); $^{13}$C NMR (DMSO) δ 155.7, 135.6, 126.4, 112.4.

**Ethyl 4-aminobenzoate (Table 2, entry 3).**[10] $^1$H NMR ($CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.08, 1.35 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 166.9, 151.0, 131.7, 120.0, 113.9, 60.4, 14.5.

**Methyl 4-aminobenzoate (Table 2, entry 4).**[8] $^1$H NMR ($CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 2H), 4.05 (s, 2H, NH), 3.85 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 167.3, 151.0, 131.7, 119.7, 113.9, 51.8.

**4-(Trifluoromethyl)aniline (Tables 2, entry 6).**[8] $^1$H NMR ($CDCl_3$) δ 7.44 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 3.95 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 149.6, 126.8 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 268.8 Hz), 120.0 (q, *J* = 32.4 Hz), 114.3.

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**4-Methoxyaniline (Tables 2, entry 8).**[8] $^1$H NMR ($CDCl_3$) δ 6.75 (d, $J$ = 8.9 Hz, 2H), 6.65 (d, $J$ = 8.9 Hz, 2H), 3.75 (s, 3H), 3.41 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 152.9, 140.0, 116.6, 114.9, 55.9.

**(4-Aminophenyl)(phenyl)methanone (Table 2, entry 9).**[9] $^1$H NMR ($CDCl_3$) δ 7.72 (m, 4H), 7.54 (t, $J$ = 7.4 Hz, 1H), 7.45 (t, $J$ = 7.4 Hz, 2H), 6.68 (d, $J$ = 8.6 Hz, 2H), 4.19 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 195.5, 151.0, 139.0, 133.1, 131.6, 129.7, 128.2, 127.6, 113.8.

**1-(4-Amino-phenyl)-propan-1-one (Table 2, entry 10).**[11] $^1$H NMR ($CDCl_3$) δ 7.82 (d, $J$ = 8.6 Hz, 2H), 6.64 (d, $J$ = 8.6 Hz, 2H), 4.12 (s, 2H, NH), 2.90 (q, $J$ = 7.3 Hz, 2H), 1.19 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR ($CDCl_3$) δ 119.4, 151.1, 130.6, 127.6, 113.9, 31.2, 8.8.

**3,5-Bis(trifluoromethyl)aniline (Table 2, entry 11).** $^1$H NMR ($CDCl_3$) δ 7.21 (s, 1H), 7.03 (s, 2H), 4.06 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 147.6, 132.7 (q, $J$ = 33.1 Hz), 123.6 (q, $J$ = 273.7 Hz), 114.3 (d, $J$ = 3.4 Hz), 111.7 (m). This compound is commercially available, and it was identified by the comparison of the spectra of the isolated material to the commercial sample.

**General Procedure for the Coupling of Aryl Halides and $LiN(SiMe_3)_2$ with Added Zinc Chloride.** A typical procedure is given for entry 1 in Table 1.

**4-Nitroaniline (Table 1, entry 1).** In a screw-capped vial were placed lithium bis(trimethylsilyl)amide (100.4 mg, 0.600 mmol) and zinc chloride (40.8 mg, 0.300 mmol), and these solids were dissolved in THF (0.5 mL). After stirring at room temperature for 5 min, the solution was transferred to a screw-capped vial containing 4-bromonitrobenzene (101 mg, 0.500 mmol), P(*t*-Bu)$_3$ (50 μL of a 0.50 M THF solution, 0.025 mmol), and $Pd(dba)_2$ (12 mg, 0.025 mmol). The vial was sealed with a cap fitted with a PTFE septum and removed from the drybox. The reaction mixture was stirred at room temperature, and the reaction progress was monitored by GC analysis. Upon consumption of aryl halide, the crude reaction mixture was diluted with $Et_2O$ (10 mL), and the silylamide was deprotected by adding one drop of aqueous 1 N HCl. The mixture was transferred to a separatory funel and washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane:EtOAc = 1:1) to give 65.4 mg of 4-nitroaniline (95%).

**3-Nitroaniline (Table 1, entry 3).**[9] $^1$H NMR ($CDCl_3$) δ 7.58 (dt, $J$ = 1.1, 8.1 Hz, 1H), 7.49 (t, $J$ = 2.1 Hz, 1H), 7.28 (t, $J$ = 8.1 Hz, 1H), 6.95 (dt, $J$ = 1.1, 8.1 Hz, 1H), 3.98 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 149.4, 147.6, 130.1, 120.8, 113.3, 109.2.

**Procedure for the Coupling of Aryl Halides and $LiN(SiMe_3)_2$ with Zinc Chloride without a Drybox.** A 1.0 M stock solution (1.0 mL) of $LiN(SiMe_3)_2$ (167.3 mg) and

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$ZnCl_2$ (68.1 mg) in 1.0 mL of THF was prepared. This solution need not be used immediately, and was equally active after two days at room temperature. To a screw-capped vial containing 4-bromonitrobenzene (101 mg, 0.500 mmol), P(*t*-Bu)$_3$ (0.025 mmol, 50 μL of a 0.50 M solution in THF), and $Pd(dba)_2$ (12 mg, 0.025 mmol), was added 0.6 mL of the 1.0 M stock solution of lithium bis(trimethylsilyl)amide and zinc chloride via syringe. The reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was diluted with $Et_2O$ (10 mL), and the silylamide was deprotected by adding one drop of aqueous 1 N HCl. The mixture was transferred to a separatory funel and washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane:EtOAc = 1:1) to give 60.0 mg of 4-nitroaniline (87%).

**A Procedure using Commercially Available Stock Solutions.** To a screw-capped vial were added lithium bis(trimethylsilyl)amide (0.6 mL of a 1.0 M solution in THF, 0.6 mmol) and zinc chloride (0.6 mL of a 0.5M solution in THF, 0.3 mmol) via syringe. After stirring at room temperature for 5 min, the solution was transferred via syringe to a screw-capped vial containing 4-bromonitrobenzene (101 mg, 0.500 mmol), P(*t*-Bu)$_3$ (50 μL of a 0.50 M THF solution, 0.025 mmol), and $Pd(dba)_2$ (12 mg, 0.025 mmol). The reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was diluted with $Et_2O$ (10 mL), and the silylamide was deprotected by adding one drop of aqueous 1 N HCl. The mixture was transferred to a separatory funel and washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane:EtOAc = 1:1) to give 56.5 mg of 4-nitroaniline (82%).

**General Procedure for the Coupling of Aryl Triflates and $Zn[N(SiMe_3)_2]_2$.** A typical procedure is given for entry 4 in Table 3.

***m*-Toluidine (Tables 3, entry 4 and 5).**[8] In a screw-capped vial containing m-tolyl triflate (0.50 mmol) were placed P(*t*-Bu)$_3$ (60 μL of a 0.25 M stock solution in THF, 0.015 mmol), $Pd(dba)_2$ (8.6 mg, 0.015 mmol), $Zn[N(SiMe_3)_2]_2$ (116 mg, 0.30 mmol), and tetrabutylammonium bromide (322 mg, 1.00 mmol), followed by THF (1.0 mL). The vial was sealed with a cap fitted with a PTFE septum and removed from the drybox. The reaction mixture was stirred at 50 °C, and the reaction progress was monitored by GC analysis. Upon consumption of aryl halide, the crude reaction mixture was diluted with $Et_2O$ (10 mL), and the silylamide was deprotected by adding one drop of aqueous 1 N HCl. The mixture was transferred to a separatory funel and washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane : EtOAc = 1 : 1) to give 48.3 mg of *m*-toluidine (90%). $^1$H NMR ($CDCl_3$) δ 7.08 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 6.54-6.52 (m, 2H), 3.58 (s, 2H), 2.30 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 146.96, 139.76, 129.80, 120.08, 116.55, 112.88, 22.08.

**2-Naphthylamine (Tables 3, entry 6-8).**[8] $^1$H NMR ($CDCl_3$) δ 7.68 (m, 2H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 1H), 6.95 (dd, *J* = 1.9, 8.7 Hz, 1H), 3.84 (s, 2H, NH). $^{13}$C NMR ($CDCl_3$) δ 144.3, 135.0, 129.4, 128.1,

127.9, 126.5, 126.0, 122.6, 118.4, 108.7.

**3-Methoxyaniline (Tables 3, entry 10 and 11).**[8] $^1$H NMR ($CDCl_3$) δ 7.08 (t, *J* = 8.0 Hz, 1H), 6.33 (m, 2H), 6.26 (t, *J* = 2.2, 1H), 3.77 (s, 3H), 3.64 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 160.8, 147.9, 130.2, 108.0, 104.0, 101.1, 55.2.

**3-(Trifluoromethyl)aniline (Tables 3, entry 12).**[8] $^1$H NMR ($CDCl_3$) δ 7.24 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.98 (dd, *J* = 7.6, 0.4 Hz, 1H), 6.89 (broad s ,1H), 6.81 (dd, *J* = 8.0, 0.4 Hz, 1H), 3.84 (s, 2H); $^{13}$C NMR ($CDCl_3$) δ: 146.58, 131.35 (q, *J*=22.2Hz), 129.60, 124.07 (q, *J*=272.2Hz), 117.82, 114.87 (q, *J*=3.9Hz), 111.17 (q, *J*=3.5Hz).

**3-Aminobenzonitrile (Table 3, entry 14).**[9] $^1$H NMR ($CDCl_3$) δ 7.20 (t, *J* = 7.9Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.89 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.92 (s, 2H, NH); $^{13}$C NMR ($CDCl_3$) δ 147.1, 131.2, 122.0, 119.4, 119.3, 117.5, 112.9.

**The Coupling of Bromobenzene with $Zn[N(SiMe_3)_2]_2$ in the Presence of (*S*)-Naproxen Methyl Ester (Scheme 3).** In a screw-capped vial containing bromobenzene (78.5 mg, 0.500 mmol) were placed P(*t*-Bu)$_3$ (40 μL of a 0.25 M stock solution in THF, 0.010 mmol), $Pd(dba)_2$ (5.7 mg, 0.010 mmol), (*S*)-Naproxen methyl ester (122 mg, 0.500 mmol), LiCl (12.1 mg, 0.300 mmol), and $Zn[N(SiMe_3)_2]_2$ (116 mg, 0.300 mmol), followed by THF (1.0 mL). The vial was sealed with a cap fitted with a PTFE septum and removed from the drybox. The reaction mixture was stirred at 50 °C, and the reaction progress was monitored by GC analysis. Upon consumption of aryl halide, the crude reaction mixture was diluted with $Et_2O$ (10 mL), and the silylamide was deprotected by adding one drop of aqueous 1 N HCl. The mixture was transferred to a separatory funel and washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane:EtOAc = 1:1) to give 39.7 mg of aniline (85%). HPLC analysis of the recovered (S)-Naproxen methyl ester (105 mg, 86%) indicated an enantiomeric excess of 98% [Chiralcel® OD-H column, eluting with *n*-hexane:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm; (*R*) enantiomer(minor) tR, 7.0, (*S*) enantiomer(major) tR 7.9 min].

**General Procedure for the Amination of Bromobenzene with Amines in the Presence of (*S*)-Naproxen Methyl Ester (Table 4).** A typical procedure is given for entry 1 in Table 4.

**Reaction of Bromobenzene with Aniline and added (*S*)-Naproxen Methyl Ester using $Zn[N(SiMe_3)_2]_2$ as a Base (Table 4, entry 1).** In a screw-capped vial containing bromobenzene (78.5 mg, 0.500 mmol) were placed P(*t*-Bu)$_3$ (40 μL of a 0.25 M stock solution in THF, 0.010 mmol), $Pd(dba)_2$ (5.7 mg, 0.010 mmol), (*S*)-Naproxen methyl ester (122 mg, 0.500 mmol), aniline (51.2 mg, 0.550 mmol), LiCl (12.1 mg, 0.300 mmol), and $Zn[N(SiMe_3)_2]_2$ (116 mg, 0.300 mmol), followed by THF (1.0 mL). The vial was sealed with a cap fitted with a PTFE septum and removed from the drybox. The reaction mixture was stirred at 50 °C or at 85 °C, and the reaction progress was monitored by GC analysis. Upon consumption of aryl halide, the crude reaction mixture was diluted with $Et_2O$ (10 mL), and the mixture was transferred to a separatory funel and

washed with aqueous 1 N NaOH (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (*n*-Hexane:EtOAc = 4:1). The reaction at 50 °C for 2 h give 74.6 mg of diphenylamine (88%) and the reaction at 85 °C for 20 min gave 77.1 mg of diphenylamine (91%).[12] $^1$H NMR ($CDCl_3$) δ 7.30 (m, 4H), 7.11 (m, 4H), 6.97 (m, 2H), 5.73 (s, 1H, NH); $^{13}$C NMR ($CDCl_3$) δ 143.2, 129.5, 121.1, 117.9. HPLC analysis of the recovered (*S*)-Naproxen methyl ester (118 mg, 97% at 50 °C, 119 mg, 98% at 85 °C) indicated an enantiomeric excess of 94% for the reaction at 50 °C for 2 h and 99% for the reaction at 85 °C for 20 min [Chiralcel® OD-H column, eluting with *n*-hexane:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm; (*R*) enantiomer(minor) tR, 7.0, (*S*) enantiomer(major) tR 7.9 min].

**Reaction of Bromobenzene with Aniline and added (*S*)-Naproxen Methyl Ester using $K_3PO_4$ as a Base (Table 4, entry 2).** The general procedure described above was followed using $K_3PO_4$ (265 mg, 1.25 mmol), instead of $Zn[N(SiMe_3)_2]_2$ as a base. The reaction was conducted at 85 °C to give 88.4 mg of diphenylamine (99%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (110 mg, 90%) indicated an enantiomeric excess of 97%.

**Reaction of Bromobenzene with Aniline and added (*S*)-Naproxen Methyl Ester using $Cs_2CO_3$ as a Base (Table 4, entry 3).** The general procedure described above was followed using $Cs_2CO_3$ (407 mg, 1.25 mmol), instead of $Zn[N(SiMe_3)_2]_2$ as a base. The reaction was conducted at 85 °C to give 77.8 mg of diphenylamine (92%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (119 mg, 98%) indicated an enantiomeric excess of 25%.

**Reaction of Bromobenzene with Aniline and added (*S*)-Naproxen Methyl Ester using NaO*t*-Bu as a Base (Table 4, entry 4).** The general procedure described above was followed using NaO*t*-Bu (57.7 mg, 0.600 mmol), instead of $Zn[N(SiMe_3)_2]_2$ as a base. The reaction was conducted at 50 °C to give 27.1 mg of diphenylamine (32%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (77 mg, 98%) indicated an enantiomeric excess of 25%.

**Reaction of Bromobenzene with Morpholine and added (*S*)-Naproxen Methyl Ester using $Zn[N(SiMe_3)_2]_2$ as a Base (Table 4, entry 5).** The general procedure described above was followed with morpholine (47.9 mg, 0.550 mmol) and with $Zn[N(SiMe_3)_2]_2$ (116 mg, 0.300 mmol) as a base. The reaction was conducted at 50 °C to give 67.7 mg of 4-phenylmorpholine (83%) and also at 85 °C to give 70.7 of 4-phenylmorpholine (87%).[13] $^1$H NMR ($CDCl_3$) δ 7.31 (m, 2H), 6.94 (m, 3H), 3.89 (t, $J$ = 4.8 Hz, 4H), 3.19 (t, $J$ = 4.8 Hz, 4H); $^{13}$C NMR ($CDCl_3$) δ 151.4, 129.4, 120.2, 115.9, 67.1, 49.5. HPLC analysis of the recovered (*S*)-Naproxen methyl ester (111 mg, 98% at 50 °C and 108 mg, 95% at 85 °C) indicated an enantiomeric excess of 98% in both cases.

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[12] Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575-5580.

[13] Kuwano, R.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 6479-6486.

**Reaction of Bromobenzene with Morpholine and added (*S*)-Naproxen Methyl Ester using $K_3PO_4$ as a Base (Table 4, entry 6).** The general procedure described above was followed with morpholine (47.9 mg, 0.550 mmol) and with $K_3PO_4$ (265 mg, 1.25 mmol), instead of $Zn[N(SiMe_3)_2]_2$, as base. The reaction was conducted at 85 °C to give 71.4 mg of 4-phenylmorpholine (87%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (110 mg, 98%) indicated an enantiomeric excess of 87%.

**Reaction of Bromobenzene with Morpholine and added (*S*)-Naproxen Methyl Ester using $Cs_2CO_3$ as a Base (Table 4, entry 7).** The general procedure described above was followed with morpholine (47.9 mg, 0.550 mmol) and with $Cs_2CO_3$ (407 mg, 1.25 mmol), instead of $Zn[N(SiMe_3)_2]_2$, as base. The reaction was conducted at 85 °C to give 71.9 mg of 4-phenylmorpholine (87%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (93 mg, 76%) indicated an enantiomeric excess of 6%.

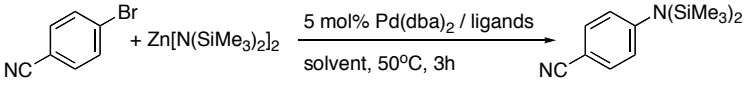
**Reaction of Bromobenzene with Dibutylamine and added (*S*)-Naproxen Methyl Ester using $Zn[N(SiMe_3)_2]_2$ as a Base (Table 4, entry 8).** The general procedure described above was followed with dibutylamine (71.1 mg, 0.550 mmol) and with $Zn[N(SiMe_3)_2]_2$ (116 mg, 0.300 mmol) as base. A 3 mol% quantity of P(*t*-Bu)$_3$ (60 μL of a 0.25 M stock solution in THF, 0.015 mmol) and $Pd(dba)_2$ (8.6 mg, 0.015 mmol) was used. The reaction was conducted at 50 °C to give 79.8 mg of *N*,*N*-dibutylaniline (78%) and also at 85 °C to give 85.0 mg of *N*,*N*-dibutylaniline (83%) .[13] $^1$H NMR ($CDCl_3$) δ 7.18 (m, 2H), 6.62 (m, 3H), 3.24 (t, *J* = 7.7 Hz, 4H), 1.55 (m, 4H), 1.34 (m, 4H), 0.94 (t, *J* = 7.4 Hz, 6H); $^{13}$C NMR ($CDCl_3$) δ 148.3, 129.3, 115.2, 11.8, 50.9, 29.5, 20.5, 14.2. HPLC analysis of the recovered (*S*)-Naproxen methyl ester (107 mg, 88% at 50 °C and 118 mg, 97% at 85 °C) indicated an enantiomeric excess of 97% from the reaction at 50 °C and 94% from the reaction at 85 °C.

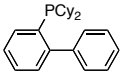
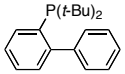
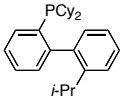
**Reaction of Bromobenzene with Dibutylamine and added (*S*)-Naproxen Methyl Ester using $K_3PO_4$ as a Base (Table 4, entry 9).** The general procedure described above was followed with dibutylamine (71.1 mg, 0.550 mmol) and with $K_3PO_4$ (265 mg, 1.25 mmol), instead of $Zn[N(SiMe_3)_2]_2$ as base. A 3 mol% quantity of P(*t*-Bu)$_3$ (60 μL of a 0.25 M stock solution in THF, 0.015 mmol) and $Pd(dba)_2$ (8.6 mg, 0.015 mmol) was used. The reaction was conducted at 85 °C to give 92.6 mg of *N*,*N*-dibutylaniline (90%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (112 mg, 92%) indicated an enantiomeric excess of 88%.

**Reaction of Bromobenzene with Dibutylamine and added (*S*)-Naproxen Methyl Ester using $Cs_2CO_3$ as a Base (Table 4, entry 10).** The general procedure described above was followed with dibutylamine (71.1 mg, 0.550 mmol) and with $Cs_2CO_3$ (407 mg, 1.25 mmol), instead of $Zn[N(SiMe_3)_2]_2$ as base. The reaction was conducted at 85 °C to give 92.4 mg of *N*,*N*-dibutylaniline (90%). HPLC analysis of the recovered (*S*)-Naproxen methyl ester (114 mg, 93%) indicated an enantiomeric excess of 27%.

**Screening of Ligands and Solvents for the Coupling of Aryl Bromides and $Zn[N(SiMe_3)_2]_2$.** The results of reactions of 4-bromobenzonitrile and $Zn[N(SiMe_3)_2]_2$ in the presence of several solvents (entries 1-5) and ligands (entries 6-16) are summarized in Table S1. In the solvents examined, the reaction was fastest in DMF. The reactions were less facile in cyclic ethers such as THF and 1,4-dioxane. Little reaction occurred in toluene or DME (entry 1-5). Among the ligands examined, the reactions in DMF with P(*t*-Bu)$_3$ occurred with the highest conversion. Other monodendate trialkylphosphines, ferrocene-based bidendate ligands, the ferrocenyl ligand Q-Phos, and several 2-phosphinobiphenyl ligands were not as effective as P(*t*-Bu)$_3$.

**Table S1.** Results from Studies on the effect of Ligand and Solvent on the Coupling of 4-Bromobenzonitrile with $Zn[N(SiMe_3)_2]_2$.[a]




| entry | solvent | ligand | conversion[b] |
|---|---|---|---|
| 1 | THF | P(*t*-Bu)$_3$ | 51% |
| 2 | DME | | 29% |
| 3 | 1,4-dioxane | | 66% |
| 4 | toluene | | 21% |
| 5 | DMF | | 81% |
| 6 | | $PAd_2$(t-Bu) | 55% |
| 7 | | PCy3 | 8% |
| 8 | | P(*p*-tol)$_3$ | 10% |
| 9 | | DPPF | 9% |
| 10 | |  | 11% |
| 11 | | DtBPF | 9% |
| 12 | | Q-Phos | 28% |
| 13 | | BINAP | 7% |
| 14 | |  | 35% |
| 15 | |  | 11% |
| 16 | |  | 4% |

[a] Reaction condition: 4-Bromobenzonitrile (0.25 mmol), $Zn[N(SiMe_3)_2]_2$ (0.15 mmol), $Pd(dba)_2$ (0.0125 mmol), ligand (0.0125 mmol), solvent (0.7 mL). [b] Conversion was determined by GC analysis using dodecane as internal standard.

**The Effect of Lithium Halide in the Coupling of Aryl Halides and $Zn[N(SiMe_3)_2]_2$.** To examine the effect of added LiCl, reactions of 4-bromobenzonitrile and $Zn[N(SiMe_3)_2]_2$ were performed in the presence of $Pd(dba)_2$ and P(*t*-Bu)$_3$ as catalyst with and without added LiCl. As shown in Figure S1, the reactions with 0.6 equiv of added LiCl were faster than the reaction performed without additive. The rate was further improved by using THF, instead of DMF, as solvent. In THF, the reaction was complete in 45 min at 50 °C, while in DMF under the same conditions the reaction was only 90% complete in 12 h.

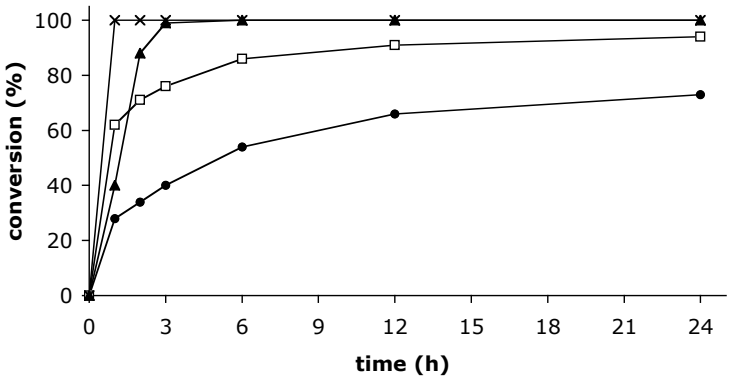
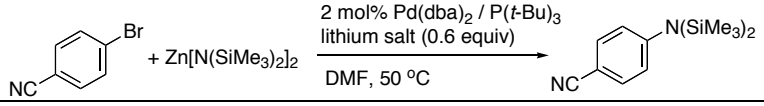



**Figure S1.** The effect of LiCl in the reaction of 4-bromobenzonitrile and $Zn[N(SiMe_3)_2]_2$ (0.6 equiv) in the presence of 2 mol% of $Pd(dba)_2$ and P(*t*-Bu)$_3$ as catalyst. ● = without any additive (50 °C in DMF) ,□ = with LiCl (0.6 equiv, 50 °C in DMF), × = with LiCl (0.6 equiv, 50 °C in THF), ▲= with LiCl (0.6 equiv, room temperature in THF).

We examined the effect of various lithium salts on the reaction in DMF. As shown in Table S2, the conversions were highest with LiCl (entry 2). Other lithium salts, such as LiF and LiBr, were less effective than LiCl, and reactions with these additives proceeded to only 49% and 45% conversion after 18 h at 50 °C (entry 1 and 3). The reactions in the presence of LiI and Li(acac) gave little product after 18 h (entry 4, 5).

**Table S2.** The Coupling of 4-Bromobenzonitrile and $Zn[N(SiMe_3)_2]_2$ with Lithium Salts[a]

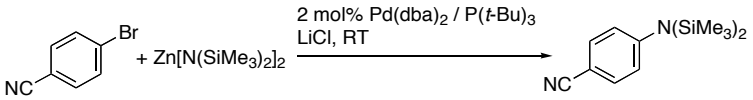



| entry | Lithium salt | conversion (%)[b] | | |
|---|---|---|---|---|
| | | 1 h | 6 h | 18 h |
| 1 | LiF | 38 | 47 | 49 |
| 2 | LiCl | 62 | 86 | 92 |
| 3 | LiBr | 25 | 43 | 45 |
| 4 | LiI | 0 | 0 | 0 |
| 5 | Li(acac) | 3 | 5 | 5 |

[a] 4-Bromobenzonitrile (0.50 mmol), $Zn[N(SiMe_3)_2]_2$ (0.30 mmol), $Pd(dba)_2$ (0.010 mmol), P(*t*-Bu)$_3$ (0.010 mmol), DMF (1.0 mL). [b] Conversion was determined by GC analysis using dodecane as internal standard.

We also tested the effect of varying the reaction solvent and the amount of added LiCl. As shown in Table S3, reactions in ether solvents occurred to higher conversions than reactions in DMF. This result contrasts with the higher conversions of reations without added halide in DMF than in THF. The optimal amount of LiCl was found to be an equimolar amount (0.6 equiv) to $Zn[N(SiMe_3)_2]_2$

**Table S3.** The Coupling of 4-Bromobenzonitrile and $Zn[N(SiMe_3)_2]_2$ Varying Solvents and the Amount of LiCl[a]




| entry | solvent | amount of LiCl | conversion (%)[b] | | | |
|---|---|---|---|---|---|---|
| | | | 1 h | 2 h | 3 h | 9 h |
| 1 | THF | 0.6 equiv | 40 | 88 | 99 | - |
| 2 | Toluene | 0.6 equiv | 7 | 9 | 14 | 29 |
| 3 | DME | 0.6 equiv | 73 | 80 | 84 | 90 |
| 4 | 1,4-dioxane | 0.6 equiv | 36 | 52 | 63 | 99 |
| 5 | DMF | 0.6 equiv | 30 | 45 | 53 | 72 |
| 6 | THF | No LiCl | 0 | 0 | 0 | 0 |
| 7 | | 0.2 equiv | 37 | 47 | 57 | 88 |
| 8 | | 0.4 equiv | 62 | 78 | 87 | 100 |
| 9 | | 0.6 equiv | 88 | 99 | 100 | - |
| 10 | | 1.0 equiv | 64 | 78 | 87 | 100 |
| 11 | | 1.2 equiv | 64 | 77 | 85 | 100 |

[a] 4-Bromobenzonitrile (0.50 mmol), $Zn[N(SiMe_3)_2]_2$ (0.30 mmol), $Pd(dba)_2$ (0.010 mmol), P(*t*-Bu)$_3$ (0.010 mmol), solvent (1.0 mL). [b] Conversion was determined by GC analysis using dodecane as internal standard.