Room temperature Negishi cross-coupling of unactivated alkyl bromides with alkyl organozinc reagents utilizing a Pd-N-Heterocyclic carbene catalyst

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General Experimental

All reactions were carried out under an atmosphere of argon using Schlenk techniques in screw-cap threaded vials (caps attached, 17 × 60 mm). All reagents and solvents were purchased from commercial sources and were used without further purification, unless indicated otherwise. Dry NMP, DMI and DME (stored over 4Å molecular sieves) were purchased from Fluka and handled under argon; THF was dried under argon over sodium-benzophenone; CH₂Cl₂ was dried under argon over CaH₂; dry DMA was handled under argon; DMF was vacuum distilled over anhydrous MgSO₄, stored over 4Å molecular sieves and handled under argon. All alkylzinc reagents were products of Rieke Metals, Inc. 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl, **1**),¹ 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (SIPr·HCl, **2**),¹ 1,3-bis(2,6-diethylphenyl)imidazolium chloride (IEt·HCl, **3**),¹ 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes·HCl, **5**),¹ 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride (SIMes·HCl, **6**),¹ and 1,3-bis(1-adamantyl)benzimidazolium chloride (**8**)² were prepared according to published procedures. 1,3-bis(1-adamantyl)imidazolium chloride (**7**) was purchased from Strem Chemicals. Thin layer chromatography (TLC) was performed on Whatman 60 F₂₅₄ glass plates and were visualized using UV light (254 nm), potassium permanganate or phosphomolybdic acid stains. Column chromatography purifications were carried out using the flash technique on Silicycle silica gel 60 (230-400 mesh). The NMR chemical shifts (δ) for ¹H are given in ppm referenced to the residual proton signal of the deuterated solvent (commercial CDCl₃, CD₂Cl₂ or CD₃OD). The chemical shifts (δ) for ¹³C are referenced relative to the signal from the carbon of the deuterated solvent and ¹⁹F relative to neat TFA as an external standard.

Imidazolium salts and Pd precursors for catalyst preparation (Table 1-4) were weighed in a glovebox under an atmosphere of dry Ar.

Synthetic Procedures

NHC ligand precursor synthesis

***N,N'*-bis(2,6-diethylphenyl)oxalamide (4a).** To a cooled solution (0 °C) of 2,6-diethylaniline (17.3 mL, 15.67 g, 105 mmol, 2.1 equiv) and triethylamine (15.3 mL, 11.13 g, 110 mmol, 2.2 equiv) in dry CH₂Cl₂ (150 mL), oxalyl chloride (4.4 mL, 6.35 g, 50 mmol, 1.0 equiv) was added dropwise. The reaction mixture was warmed up to rt with stirring over 18 h. The solvent was removed on a rotary evaporator, water (150 mL) was added and the precipitated product was filtered, washed with water, diethyl ether and dried in high vacuum over P₂O₅. **4a** (16.53 g, 95 %) was obtained as a white solid, mp = 225-227 °C. ¹H NMR (400 MHz, CDCl₃): δ 10.36 (broad s, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 7.15 (d, *J* = 7.5 Hz, 4H), 2.55 (q, *J* = 7.5 Hz, 8H), 1.14 (d, *J* = 7.5 Hz, 12H). ¹³C NMR (100 MHz, CDCl₃): δ 162.5, 159.1, 155.9, 146.4, 131.5, 129.4, 125.0, 90.9, 90.9, 56.4, 55.8, 53.7, 51.4, 28.9, 23.5. Anal. Calcd. for C₂₂H₂₈N₂O₂: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.89; H, 7.85; N, 8.08.

1,3-bis(2,6-diethylphenyl)-4,5-dihydroimidazolium chloride (SI^{Et}-HCl, 4). To **4a** (4.33 g 12.5 mmol, 1.0 equiv), placed in a vacuum-dried round-bottomed flask equipped with a reflux condenser, 1M BH₃·THF solution (100 mL, 100 mmol, 8.0 equiv) was added via cannulated under Ar. The resultant solution was refluxed with stirring over 18 h, cooled to rt and the excess borane

destroyed with methanol. Conc. HCl (2 mL) was added and most of the organic solvents removed on a rotary evaporator. The crude product was partitioned between 1M NaOH (100mL) and diethyl ether (50 mL) and the organic layer separated. The aqueous layer was extracted with diethyl ether (2 x 25 mL), the organic layers were combined, washed with water (2 x 100 mL), brine (30 mL), dried (Na_2SO_4) and evaporated. The diamine intermediate was dissolved under Ar in $\text{HC}(\text{OEt})_3$ (75 mL), conc. HCl (1.1 mL) added and the septum was removed. The mixture was heated at 120 °C over 2h with vigorous stirring. After cooling to rt, the mixture was diluted with diethyl ether (75 mL), the solid was filtered, washed with small portions of diethyl ether and dried in vacuum. **4** (2.61 g, 56 %) was obtained as a white solid, mp = 266-267 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ 10.19 (s, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 7.6 Hz, 4H), 4.53 (s, 4H), 2.81-2.70 (m, 8H), 1.34 (t, J = 7.4 Hz, 12H). ^{13}C NMR (100 MHz, CD_2Cl_2): δ 160.7, 141.4, 131.6, 130.7, 127.2, 53.0, 24.3, 14.8. Anal. Calcd. for $\text{C}_{23}\text{H}_{31}\text{ClN}_2$: C, 74.47; H, 8.42; N, 7.55. Found: C, 74.50; H, 8.33; N, 7.50.

Chloroformyl-N-(2,6-diisopropylphenyl)formamide (12a). In a flame dried, round-bottomed flask, **12** (2.49 g, 10.0 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (50 mL). Oxalylchloride

(0.96 mL, 1.40 g, 11.0 mmol, 1.1 equiv) was added, followed by DMF (25 μ L). The solution was stirred for 4 h, then the solvent was removed and the solid **12a** obtained was used directly for the next step after drying in high vacuum and back-filling the flask with Ar.

***N*-(2,6-diisopropylphenyl)-*N'*-(2,6-diethylphenyl)oxalamide (13).** To a cooled solution (0 °C) of **12a** in dry CH₂Cl₂ (30 mL), a mixture of 2,6-diethylaniline (1.98 mL, 1.79 g, 12.0 mmol, 1.2 equiv) and triethylamine (1.95 mL, 1.42 g, 14.0 mmol, 1.4 equiv) was added dropwise with vigorous stirring. The reaction mixture was warmed to rt and stirred for a further 18 h. The solvent was removed on a rotary evaporator; the product was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with 5 % H₂SO₄ (50 mL), saturated. NaHCO₃ solution (50 mL), brine (20 mL), dried (MgSO₄) and the solvent removed. The crude product was treated with pentane (10 mL), filtered, and washed with a small volume of pentane. **13** (2.71 g, 71 %) was obtained as a white solid, mp = 261-263 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.97 (broad s, 1H), 8.87 (broad s, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 3.09 (m, 2H), 2.63 (q, *J* = 7.6 Hz, 4H), 1.24 (d, *J* = 6.7 Hz, 12H), 1.23 (t, *J* = 7.6 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 159.4, 159.0, 145.8, 141.0, 131.2, 129.7, 128.9, 128.5, 126.6, 123.7, 29.0, 25.0, 23.6, 14.4. Anal. Calcd. for C₂₄H₃₂N₂O₂: C, 75.75; H, 8.48; N, 7.36. Found: C, 76.10; H, 8.32; N, 7.75.

***N*-(2,6-diisopropylphenyl)-*N'*-(2,4,6-trimethylphenyl)oxalamide (14).** To a cooled solution (0 °C) of **12a** in dry CH₂Cl₂ (30 mL), a mixture of 2,4,6-trimethylaniline (1.68 mL, 1.62 g, 12.0 mmol, 1.2 equiv) and triethylamine (1.95 mL, 1.42 g, 14.0 mmol, 1.4 equiv) was added dropwise with vigorous stirring. The reaction mixture was warmed to rt and stirred for a further 18 h. The solvent was removed on a rotary evaporator, water (50 mL) was added and the precipitated

product was filtered, washed with water, diethyl ether and dried in high vacuum over P₂O₅. **14** (3.49 g, 95 %) was obtained as a white solid, mp = 214-216 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.87 (broad s, 1H), 8.82 (broad s, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 2H), 6.98 (s, 2H), 3.08 (m, 2H), 2.32 (s, 3H), 2.27 (s, 6H), 1.25 (d, *J* = 6.9 Hz, 12H). ¹³C NMR (76 MHz, CDCl₃): δ 159.4, 158.3, 145.8, 137.6, 134.6, 129.7, 129.1, 128.7, 123.7, 123.7, 29.0, 23.6, 20.9, 18.3. Anal. Calcd. for C₂₃H₃₀N₂O₂: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.80; H, 7.67; N, 6.59.

***N*-(2,6-diisopropylphenyl)-*N'*-(2,4,6-trifluorophenyl)oxalamide (15).** The acyl chloride **12a** was prepared as described above from **12** (3.74 g, 15.0 mmol, 1.0 equiv) and oxalylchloride (1.4 mL, 2.00 g, 15.75 mmol, 1.05 equiv). From **12a**, 2,4,6-trifluoroaniline (2.21 g, 15.0 mmol, 1 equiv) and triethylamine (2.1 mL, 1.52 g, 15.00 mmol, 1.0 equiv), **15** (5.14 g, 90 %) was obtained as a white solid following the procedure for compound **14**, mp = 229-230 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.98 (broad s, 1H), 8.83 (broad s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 2H), 6.82 (t, ³*J*_{C-F} = 7.9 Hz, 2H), 3.05 (m, 2H), 1.22 (d, *J* = 6.8 Hz, 12H). ¹³C NMR (76 MHz, CDCl₃): δ 161.3 (dt, ¹*J*_{C-F} = 250.5, ³*J*_{C-F} = 14.5 Hz), 158.5, 158.2, 157.8 (ddd, ¹*J*_{C-F} = 253.9, ³*J*_{C-F} = 14.8 Hz, ³*J*_{C-F} = 6.8 Hz), 145.8, 129.2, 129.0, 124.0, 109.1 (td, ³*J*_{C-F} = 25.6, ³*J*_{C-F} = 3.2 Hz), 100.9 (dt, ³*J*_{C-F} = 16.6, ³*J*_{C-F} = 5.1 Hz), 28.9, 23.8. ¹⁹F NMR (282 MHz, CDCl₃) δ -94.64 (1F, ⁴*J*_{F-F} = 6.0 Hz), -100.40 (1F, ⁴*J*_{F-F} = 6.0 Hz). Anal. Calcd. for C₂₀H₂₁F₃N₂O₂: C, 63.48; H, 5.59; N, 7.40. Found: C, 63.72; H, 5.93; N, 7.38.

***N*-(2,6-diisopropylphenyl)-*N'*-(2,4,6-trimethoxyphenyl)oxalamide (16).** To a cooled solution (0 °C) of **12a** in dry CH₂Cl₂ (30 mL), a mixture of 2,4,6-trimethylaniline (1.68 mL, 1.62 g, 12.0 mmol, 1.2 equiv) and triethylamine (1.95 mL, 1.42 g, 14.0 mmol, 1.4 equiv) was added dropwise with vigorous stirring. The reaction mixture was warmed up to rt and stirred for a further 18 h. The solvent was removed on a rotary evaporator, water (50 mL) was added and the precipitated

product was filtered, washed with water, diethyl ether and dried in high vacuum over P₂O₅. **16** (3.48 g, 84 %) was obtained as a white solid, mp = 172-173 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.88 (broad s, 1H), 8.61 (broad s, 1H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 6.21 (s, 2H), 3.86 (s, 3H), 3.85 (s, 6H), 3.11 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 12H). ¹³C NMR (76 MHz, CDCl₃): δ 159.4, 158.4, 155.9, 145.8, 129.9, 128.6, 123.6, 125.0, 91.0, 91.0, 56.4, 55.5, 28.8, 23.6. Anal. Calcd. for C₂₃H₃₀N₂O₅: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.80; H, 7.67; N, 6.59.

1-(2,6-diisopropylphenyl)-3-(2,6-diethylphenyl)-4,5-dihydroimidazolium chloride (SIPr-Et·HCl, 17). From **13** (4.20 g, 11.0 mmol, 1.0 equiv), reduced with 1M BH₃·THF solution (88 mL, 88.0 mmol, 8.0 equiv), the imidazolidinium chloride **17** (3.41 g, 78 %) was obtained as off-white solid using the procedure for compound **4**, mp = 274-275 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.61 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 4.85-4.78 (m, 4H), 3.04 (m, 2H), 2.75 (q, *J* = 7.6 Hz, 4H), 1.39 (d, *J* = 6.8 Hz, 6H), 1.33 (t, *J* = 7.6 Hz, 6H), 1.28 (d, *J* = 6.9 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 158.5, 146.1, 141.1, 131.5, 131.1, 131.1, 129.3, 127.5, 124.9, 55.0, 54.0, 29.0, 25.2, 24.3, 23.8, 15.3. Anal. Calcd. for C₂₅H₃₅ClN₂: C, 75.25; H, 8.84; N, 7.02. Found: C, 74.79; H, 8.55; N, 6.79.

1-(2,6-diisopropylphenyl)-3-(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium chloride (SIPr-Mes·HCl, 18). From **14** (2.29 g, 6.25 mmol, 1.0 equiv), reduced with 1M BH₃·THF solution (50 mL, 50.0 mmol, 8.0 equiv), **18** (1.26 g, 52 %) was obtained as off-white solid using the procedure for compound **4**, mp = 324-326 °C. ¹H NMR (300 MHz, CDCl₃): δ 8.98 (s, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 2H), 4.67 (broad s, 4H), 2.99 (m, 2H), 2.34 (s, 3H), 2.28 (s, 6H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.23 (d, *J* = 6.6 Hz, 6H). ¹³C NMR (76 MHz, CDCl₃): δ 159.0, 146.1, 140.6, 134.8, 131.3, 130.0, 129.6, 129.6, 124.8, 54.7, 52.5, 29.0, 25.2,

28.8, 23.7, 21.0, 17.7. Anal. Calcd. for $C_{24}H_{33}ClN_2$: C, 74.87; H, 8.64; N, 7.28. Found: C, 74.60; H, 8.72; N, 7.23.

1-(2,6-diisopropylphenyl)-3-(2,4,6-trifluorophenyl)-4,5-dihydroimidazolium chloride (SIPr- $F_3 \cdot HCl$, **19).** To **15** (3.03 g, 8.00 mmol, 1.0 equiv), placed in a vacuum-dried round-bottomed flask equipped with a reflux condenser, 1M $BH_3 \cdot THF$ solution (64 mL, 64.0 mmol, 8.0 equiv) was added via cannula under Ar. The solution formed was refluxed with stirring over 24 h. After cooling to rt, the excess borane was destroyed with methanol. Conc. HCl (2.45 mL) was added and the organic solvents were removed on a rotary evaporator. The solid was co-evaporated with methanol (3 x 15 mL) to remove the boric acid formed and dried in high vacuum. The white solid obtained was dispersed in $HC(OEt)_3$ (25 mL) and the mixture was heated with vigorous stirring for 2 h. After cooling to rt, the mixture was diluted with diethyl ether (25 mL), the solid was filtered, washed with small portions of diethyl ether and dried in vacuum. The imidazolidinium chloride **19** (2.60 g, 82 %) was obtained as off-white solid, mp = 318-319 °C. 1H NMR (300 MHz, CD_3OD): δ 9.50 (s, 1H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.42 (d, $J = 7.8$ Hz, 2H), 7.28 (t, $^3J_{C-F} = 8.4$ Hz, 2H), 4.75 (m, 2H), 4.53 (m, 2H), 3.09 (m, 2H) 1.38 (d, $J = 6.9$ Hz, 6H), 1.30 (d, $J = 6.6$ Hz, 6H). ^{13}C NMR (76 MHz, CD_3OD): d 164.3 (dd, $^1J_{C-F} = 253.0$ Hz, $^4J_{C-F} = 15.4$ Hz), 159.3 (ddd, $^1J_{C-F} = 253.0$ Hz, $^4J_{C-F} = 15.4$ Hz, $^4J_{C-F} = 5.7$ Hz), 147.8, 133.0, 131.0, 126.4, 112.0 (m, $^2J_{C-F} = 15.7$ Hz, $^4J_{C-F} = 5.7$ Hz), 103.2 (m, $^2J_{C-F} = 15.1$ Hz, $^4J_{C-F} = 3.6$ Hz), 55.7, 53.1, 30.1, 25.2, 24.3. ^{19}F NMR (282 MHz, CD_3OD) d -91.61 (1F, $^4J_{F-F} = 6.7$ Hz), -104.53 (1F, $^4J_{F-F} = 6.7$ Hz). Anal. Calcd. for $C_{21}H_{24}ClF_3N_2$: C, 63.55; H, 6.10; N, 7.06. Found: C, 63.41; H, 6.30; N, 7.00.

1-(2,6-diisopropylphenyl)-3-(2,4,6-trimethoxyphenyl)-4,5-dihydroimidazolium hexafluorophosphate (SIPr-(MeO) $_3$ HPF $_6$, **20).** To **16** (2.26 g, 5.45 mmol, 1.0 equiv), placed in a vacuum-

dried round-bottomed flask equipped with a reflux condenser, 1M BH₃·THF solution (44 mL, 44.0 mmol, 8.0 equiv) was added via cannula under Ar. The resultant solution was refluxed with stirring over 24 h, then a second portion of 1M BH₃·THF solution (22 mL, 22.0 mmol, 4 equiv.) was added. After refluxing for additional 24 h, the solution was cooled to rt and the excess borane was destroyed with methanol. Conc. HCl (2 mL) were added and most of the organic solvents were removed on a rotary evaporator. The crude product was partitioned between 1M NaOH (100mL) and diethyl ether (50 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 x 25 mL), the organic layers were combined, washed with water (2 x 100 mL), brine (30 mL), dried (Na₂SO₄) and evaporated. The diamine intermediate was dissolved under Ar in dry THF (13.5 mL). HC(OEt)₃ (1.81 mL, 1.62 g, 10.9 mmol, 2.0 equiv) and solid NH₄PF₆ (0.89 g, 5.45 mmol, 1.0 equiv) were added and the mixture was heated at 80 °C over 18h with vigorous stirring. After cooling to rt, the organic solvents were removed on a rotary evaporator, the crude product was redissolved in a small volume of CH₂Cl₂ and passed through a short pad of Celite with CH₂Cl₂. **20** (1.10 g, 37 %) was obtained as off-white solid after column chromatography on silicagel (CH₂Cl₂:ethyl acetate = 100:1; *R_f* = 0.22), mp = 268-269 °C. ¹H NMR (300 MHz, CD₂Cl₂): δ 7.81 (s, 1H), 7.56 (t, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 2H), 6.28 (s, 2H), 4.59 (m, 2H), 4.38 (m, 2H), 3.94 (s, 6H), 3.90 (s, 3H), 3.04 (m, 2H), 1.39 (d, *J* = 6.8 Hz, 6H), 1.31 (d, *J* = 6.8 Hz, 6H). ¹³C NMR (400 MHz, CD₂Cl₂): δ 162.5, 159.1, 155.9, 146.4, 131.5, 129.4, 125.0, 90.9, 90.9, 56.4, 55.8, 53.7, 51.4, 28.8, 24.6, 23.8. Anal. Calcd. for C₂₄H₃₃F₆N₂O₃P: C, 53.14; H, 6.13; N, 5.16. Found: C, 53.56; H, 6.45; N, 5.25.

Negishi alkyl-alkyl cross-coupling reactions

Representative procedure for Table 1 (entry 5, out of the glovebox). A vial was charged with Pd(OAc)₂ (8.8 mg, 0.040 mmol), IPr·HCl (**1**) (34 mg, 0.080 mmol) and a stirbar in air. The vial was sealed with a septum and backfilled with Ar. Dry THF (0.60 mL) and dry NMP (1.60 mL) were added via syringe. After stirring for 5-10 min at rt, *n*-butylzinc bromide (2.60 mL of a 0.5 M THF solution, 1.30 mmol) was added and the reaction mixture was stirred at rt for additional 1 h. 1-bromo-3-phenylpropane (199 mg, 152 μL, 1.00 mmol) and *n*-undecane (GC internal standard, 100 μL) were added, the septum was replaced with a Teflon®-line screw cap under an inert atmosphere² and the reaction mixture was stirred for 24 h at rt, diluted with hexane and analyzed by GC/MS after passing through a short pad of silica gel. The GC retention time and EI fragmentation pattern were identical to commercially available material (Aldrich).

Representative procedure for Table 2 (entry 6). A vial was charged with Pd₂(dba)₃ (4.4 mg, 0.0050 mmol), SIPr·HCl (**2**) (8.5 mg, 0.020 mmol) in a glovebox. The vial was sealed with a septum and removed from the glovebox. Dry THF (0.15 mL) and dry NMP (0.40 mL) were added via syringe. After stirring for 5-10 min at rt, *n*-butylzinc bromide (0.65 mL of a 0.5 M THF solution, 0.325 mmol) was added and the reaction mixture was stirred at rt for additional 1 h. 1-Bromo-3-phenylpropane (49.8 mg, 38 μL, 0.25 mmol) and *n*-undecane (GC internal standard, 25 μL) were added, the septum was replaced with a Teflon®-lined screw cap under an inert atmosphere² and the reaction mixture was stirred for 24 h at rt, diluted with hexane and analyzed by GC/MS after passing through a short pad of silica gel. The ¹H-NMR, GC retention time and EI fragmentation pattern were identical to commercially available material (Aldrich).

General Procedure for Table 4: A vial equipped with a stirbar was charged with Pd₂(dba)₃ (9.2 mg, 0.010 mmol) and IPr·HCl (17 mg, 0.040 mmol) in a glove box and the vial was capped with

a septum. The vial was removed from the glove box and 0.3 mL of dry THF and 0.8 mL of dry NMP were added via syringe. After stirring for 5-10 min at rt, *n*-butylzinc bromide (12.14 mg, 0.12 mL of a 0.5 M THF solution, 0.06 mmol) was added and the reaction mixture was stirred for 1 h at rt, after which the alkylzinc reagent (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and the alkyl bromide (0.50 mmol) were added. The septum was replaced with a Teflon®-line screw cap under an inert atmosphere² and the solution stirred at rt for 24 h. The reaction mixture was then transferred to a separatory funnel with diethyl ether (10 mL) and the organic layer successively washed with 1 M Na₃EDTA solution (prepared from EDTA and 3 eq. NaOH), water, and brine. After drying over anhydrous MgSO₄, the solution was filtered and concentrated and the residue purified by flash chromatography.

Ethyl octanoate (21) CAS # [106-32-1]

(Table 4, entry 1). Following the general procedure, *n*-butylzinc bromide (1.30 mL of a 0.5 M THF solution, 0.65 mmol) and ethyl 4-bromobutyrate (97.5 mg, 71 μ L, 0.50 mmol) provided 79 mg of **21**, 92 % yield.

(Table 4, entry 4). Following the general procedure, 4-ethoxy-4-oxobutylzinc bromide (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and 1-bromobutane (68.5 mg, 53 μ L, 0.50 mmol) provided 79 mg of **21**, 92 % yield.

Preparation without *n*-butylzinc bromide activation: A vial equipped with a stirbar was charged with Pd₂(dba)₃ (9.2 mg, 0.010 mmol) and IPr-HCl (17 mg, 0.040 mmol) in a glove box and the vial was capped with a septum. The vial was removed from the glove box and 0.3 mL of

dry THF and 0.8 mL of dry NMP added via syringe. After stirring for 5-10 min at rt, 4-ethoxy-4-oxobutylzinc bromide (1.3 mL of a 0.5 M THF solution, 0.65 mmol) was added and the reaction mixture was stirred for 1 h at rt, followed by addition of 1-bromobutane (68.5 mg, 53 μ L, 0.5 mmol). From this point, the general procedure was followed. Provided 75 mg of **21**, 87 % yield. The ^1H NMR spectrum was identical to the spectrum included in the Aldrich database.

***n*-Decanenitrile (22) CAS # [1975-78-6]**

(Table 4, entry 2). Following the general procedure, *n*-butylzinc bromide (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and 6-bromohexanenitrile (88.0 mg, 66 μ L, 0.5 mmol) provided 70 mg of **22**, 92 % yield. The ^1H NMR spectrum was identical to the spectrum included in the Aldrich database.

***N*-octylphthalimide (23) CAS # [59333-62-9]**

(Table 4, entry 3). Following the general procedure, *n*-butylzinc bromide (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and *N*-(4-bromobutyl)phthalimide (141.0 mg, 0.5 mmol) provided 84 mg of **23**,⁴ 65 % yield after column chromatography (hexane:ethyl acetate = 8:1; *R*_f = 0.22). The ^1H and ^{13}C NMR spectra were identical to the spectra previously reported.

Ethyl 9-cyanononanoate (24) CAS # [133309-93-0]

(Table 4, entry 5). Following the general procedure, 4-ethoxy-4-oxobutylzinc bromide (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and 6-bromohexanonitrile (88.0 mg, 66 μ L, 0.5 mmol) provided 66 mg of **24**,⁵ 62 % yield after column chromatography (pentane:ethyl acetate = 20:1; R_f = 0.1). ¹H NMR (CDCl₃, 400 MHz) δ 4.12 (q, J = 7.2 Hz, 2H), 2.34 (t, J = 7.1 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 1.65 (m, 4H), 1.44 (t, J = 6.1 Hz, 2H), 1.33 (m, 6H), 1.25 (t, J = 7.2 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 177.8, 119.8, 60.2, 34.2, 28.9 (2C), 28.6 (2C), 25.3, 24.9, 17.1, 14.3.

Ethyl 7-phenylheptanoate (25) [134511-26-5]

(Table 4, entry 6). Following the general procedure, 4-ethoxy-4-oxobutylzinc bromide (1.3 mL of a 0.5 M THF solution, 0.65 mmol) and 3-bromopropylbenzene (99.5 mg, 76 μ L, 0.5 mmol) provided 89 mg of **25**,⁶ 76 % yield after column chromatography (pentane:ethyl acetate = 20:1; R_f = 0.25). The ¹H and ¹³C NMR spectra were identical to the spectra previously reported.

2-Undecanyl-1,3-dioxolane (26) CAS # [5735-88-6]

(Table 4, entry 7). Following the general procedure, [2-(1,3-dioxolan-2-yl)]-ethylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and *n*-nonylbromide (103.6 mg, 95 μ L, 0.5 mmol) provided 75 mg of **26**,⁷ 66 % yield after column chromatography (pentane:diethyl ether = 95:5; R_f = 0.25). The ¹H and ¹³C NMR spectra were identical to the spectra previously reported.

2-(5-phenylpentyl)-1,3-dioxolane (27)

(Table 4, entry 8). Following the general procedure, [2-(1,3-dioxolan-2-yl)]-ethylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and 3-bromopropylbenzene (99.5 mg, 76 μ L, 0.5 mmol) provided 77 mg of **27**, 70 % yield after column chromatography (pentane:diethyl ether = 9:1; R_f = 0.32). ^1H NMR (CDCl_3 , 400 MHz): δ 7.32-7.19 (m, 5H), 4.87 (t, J = 3.6 Hz, 1H), 4.01-3.98 (m, 2H), 3.88-3.85 (m, 2H), 2.64 (t, J = 7.5 Hz, 2H), 1.68-1.63 (m, 4H), 1.50-1.41 (m, 4H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 142.7, 128.4, 128.2, 125.6, 104.6, 64.8, 35.8, 33.8, 31.4, 29.2, 23.9. Anal. Calcd. For $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33; H, 9.15. Found C, 76.46; H, 9.47.

(6-(1, 3-dioxolan-2-yl) hex-1-ynyl)trimethylsilane (28)

(Table 4, entry 9). Following the general procedure, [2-(1,3-dioxolan-2-yl)]-ethylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and 4-trimethylsilyl-1-bromobut-3-yne (105 mg, 0.5 mmol) provided 69 mg of **28**, 61 % yield after column chromatography (pentane:diethyl ether = 19:1; R_f = 0.1). ^1H NMR (CDCl_3 , 400 MHz): δ 4.87 (t, J = 4.6 Hz, 1H), 4.00-3.97 (m, 2H), 3.88-3.85 (m, 2H), 2.25 (t, J = 6.7 Hz, 2H), 1.71-1.67 (m, 2H), 1.61-1.51 (m, 4H) 0.16 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 107.3, 104.5, 84.5, 64.9, 33.3, 28.5, 23.3, 19.8, 0.17. Anal. Calcd. For $\text{C}_{12}\text{H}_{22}\text{O}_2\text{Si}$: C, 63.66; H, 9.80. Found C, 63.51; H, 10.18.

8-(1, 3-dioxolan-2-yl)-2,2-dimethyl octanenitrile (29)

(Table 4, entry 10). Following the general procedure, [2-(1,3-dioxolan-2-yl)]-ethylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and 6-bromo-2,2-dimethylhexanenitrile (102.0 mg, 85 μ L, 0.5 mmol) provided 84.6 mg of **29**, 75 % yield after column chromatography (pentane-diethyl ether = 4:1; R_f = 0.18). ^1H NMR (CDCl_3 , 400 MHz): δ 4.86 (t, J = 4.8 Hz, 1H), 4.00-3.97 (m, 2H), 3.91-3.85 (m, 2H), 1.70-1.65 (m, 2H), 1.45-1.29 (m, 10H), 1.27 (s, 6H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 125.3, 104.6, 64.9, 41.0, 33.8, 32.4, 29.5, 29.3, 26.7, 25.2, 24.0. Anal. Calcd. For $\text{C}_{13}\text{H}_{23}\text{NO}_2$: C, 69.29; H, 10.29; N, 6.22. Found C, 69.67; H, 10.40; N, 5.91.

12-chloro-2,2-dimethyldodecanitrile (30)

(Table 4, entry 11). Following the general procedure, 5-cyano-5-methylhexylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and 1-bromo-6-chlorohexane (100 mg, 75 μ L, 0.5 mmol) provided 98.5 mg of **30**, 81 % yield after column chromatography (3 vol. % diethyl ether in pentane; R_f = 0.18). ^1H NMR (CDCl_3 , 300 MHz): δ 3.55 (t, J = 6.8 Hz, 2H), 1.77 (m, 2H), 1.55-1.39 (m, 4H), 1.35 (s, 6H), 1.34-1.27 (m, 12H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 125.3, 53.5, 45.2, 41.1, 32.6, 32.4, 29.6, 29.4, 29.4, 28.8, 26.9, 26.7, 25.3. Anal. Calcd. For $\text{C}_{14}\text{H}_{26}\text{ClN}$: C, 68.97; H, 10.75; N, 5.74. Found C, 69.34; H, 11.01; N, 5.40.

7-cyclohexyl-2,2-dimethylheptanenitrile (31)

(Table 4, entry 12). Following the general procedure, 5-cyano-5-methylhexylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and bromomethylcyclohexane (88.5 mg, 69 μ L, 0.5 mmol) provided 69.5 mg of **31**, 63 % yield after column chromatography (3 vol. % diethyl ether in pentane; R_f = 0.15). ^1H NMR (CDCl_3 , 400 MHz): δ 1.72-1.67 (m, 5H), 1.53-1.45 (m, 4H), 1.34 (s, 6H), 1.32-1.29 (m, 6H), 1.27-1.16 (m, 6H), 0.98-0.80 (m, 2H). ^{13}C NMR (CDCl_3 , 100 MHz): δ 125.2, 41.1, 37.6, 37.3, 33.4, 29.9, 26.7, 26.6, 26.5, 26.4, 25.2. Anal. Calcd. for $\text{C}_{15}\text{H}_{27}\text{N}$: C, 81.38; H, 12.29; N, 6.33. Found C, 81.77; H, 12.01; N, 5.96.

(Table 4, entry 13). Following the general procedure, cyclohexylmethylzinc bromide (1.3 mL of a 0.5 M THF solution; 0.65 mmol) and 5-cyano-5-methyl-1-bromohexane (1.2 mg, 85 μ L, 0.5 mmol) provided 94 mg of **31**, 84 % yield after column chromatography (conditions as above).

Spectral Data

References.

1. Arduengo, III, A. J.; Krafczyk, R.; Schutzler, R *Tetrahedron* **1999**, *55*, 14523-14534.
2. Hadei, N, Kantchev, E. A. B., O'Brien, C. J., Organ, M. G. *Org. Lett.* **2005**, *7*, 1991-1994.
3. Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*, 2nd ed; Blackie Academic & Professional: Oxford, 1995; pp 96-97.
4. Martin, B.; Sekljic, H.; Chassaing, C. *Org. Lett.* **2003**, *5*, 1851-1853
5. Yoshida, H.; Kakeya, N.; Kashiwagi, M. Preparation of α -(ω -cyanoalkanoyl)- γ -butyrolactones. Eur. Pat. Appl. 0402063, Dec 12, 1990.
6. Labaudiniere, R.; Hilboll, G.; Leon-Lomeli, A.; Lautenschläger, H-H.; Parnham, M.; Kuhl, P., Dereu, N. *J. Med. Chem.* **1992**, *35*, 3156-3169.
7. Arterburn, J. B.; Perry, M. C. *Org. Lett.* **1999**, *1*, 769-771.