Supporting Information

Halogen and N-Haloimide Promoted Homo and Heterocoupling of α-\((N\text{-Carbamoyl})\)alkylcuprates and α-\((Alkoxy)\)alkylcuprates

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General. NMR spectra were recorded as CDCl$_3$ solutions. The $^1$H NMR chemical shifts are reported as $\delta$ values in parts per million (ppm) relative to tetramethylsilane (TMS) or CHCl$_3$ ($\delta = 7.26$ ppm) as internal standard. The $^{13}$C NMR chemical shifts are reported as $\delta$ values in parts per million (ppm) downfield from TMS and referenced with respect to the CDCl$_3$ signal (triplet, centerline $\delta = 77.0$ ppm). APT = attached proton test which refers to a DEPT experiment. Infrared spectra (IR) were recorded as neat samples (liquid films on NaCl plates) unless otherwise noted. Gas chromatography/mass spectrometry measurements were performed on a GC coupled to a mass selective detector at 70 eV. Analytical thin-layer chromatography (TLC) was performed on silica gel plates, 200 µ mesh with F-254 indicator. Visualization was accomplished by UV light (254 nm), 4% ethanol solution of phosphomolybdic acid, 5% $p$-anisaldehyde, or 5% H$_2$SO$_4$-90% EtOH solution. Flash column chromatography was performed with 200-400 µ mesh silica gel. Bulb-to-bulb distillation was performed on a Büchi micro-distillation oven model GKR-51; boiling points were recorded as the oven temperature and are not corrected. Elemental analyses were determined from doubly purified samples involving column chromatography followed by kugelrohr distillation.

Materials. Tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH$_2$Cl$_2$), $N$, $N$, $N'$, $N'$-tetramethylethylenediamine (TMEDA) and chlorotrimethylsilane were distilled from CaH$_2$ under a N$_2$ atmosphere. BF$_3$·Et$_2$O was purified by distillation. $(-)$-Sparteine was distilled via Kugelrohr distillation at 150 °C, 0.05 mm Hg. CuCN and CuCl were used without further purification. sec-BuLi (1.5 M in cyclohexane) was either purchased from FMC Corporation or prepared$^1$ from sec-BuCl and FMC's Stabi-Li-ze lithium powder and titrated using sec-BuOH and 1,10-phenanthroline monohydrate in THF. Enantiomeric ratios were determined on a Chiral Tecnologies, Inc. CHIRALCEL OD [cellulose tris(3,5-dimethylcarbamate) on a 10 µm silica-gel substrate] chiral stationary phase HPLC column (250 x 4.0 mm, L x D).

All round bottom flasks used for the preparation of the organocopper and cuprate reagents were first cleaned with 48% hydrobromic acid, followed by placement into a potassium hydroxide-isopropyl alcohol bath, rinsed with 10% hydrochloric acid, with copious amounts of water, followed by rinsing with acetone and then oven dried (100 °C). All glassware was flamed-dried under house vacuum and purged with argon and then cooled under a dry nitrogen atmosphere. The LiCl was first dried under high vacuum (0.05 mm Hg) with heat (100-110 °C) while stirring for five minutes. Then it was weighed into a flame-dried flask and flamed-dried under vacuum (0.05 mm Hg) and purged with argon and then cooled under a dry nitrogen atmosphere.

All copper reactions were conducted under a positive, dry nitrogen atmosphere in anhydrous solvents in flasks fitted with a rubber septum. The nitrogen gas was passed through concentrated sulfuric acid, potassium hydroxide, and indicating and non-indicating Drierite® before being introduced into the reaction flask. Low temperature baths (-78 °C or warmer) were prepared using shallow thermoflasks with a Neslab CC-60 II cyrocool machine, or dry ice-isopropanol slush bath mixtures. Flask to flask transfer of air and moisture sensitive
intermediates was completed using double-tipped needles (cannula) under a positive argon pressure maintained by double layered balloons filled with argon.

\[ N,N'-\text{Bis(1,1-dimethylethoxy)carbonyl}]-[2,2'-\text{bipyrrolidine}]\text{-1,1'-dicarboxylic acid (1): Using 0.34 g (2.0 mmol) of N-Boc-pyrrolidine, 0.6 mL (4.0 mmol) of TMEDA, 2.0 mL of sec-BuLi (2.6 mmol, 1.3 M cyclohexane/hexane, 92/8), 6.0 mL of dry THF, 0.19 g (1.0 mmol) of purified CuI, 0.086 g (2.0 mmol) of LiCl and 0.25 g (1.0 mmol) of iodine (I\(_2\)) as substrate and reagents, 0.33 g (0.97 mmol, yield 97\%) of the coupling product was obtained as a yellowish semi-solid: IR (CDCl\(_3\)) 2975 (s), 2933 (m), 2881 (m), 1693 (vs), 1479 (w), 1455 (w), 1392 (vs), 1367 (s), 1346 (w), 1253 (w), 1165 (s), 1105 (m) cm\(^{-1}\); \(^1\)H NMR-Cosy (CDCl\(_3\)), the \(R*S*\) (meso) and the \(dl-R*R*\) (RR/SS) mixture: \(\delta\) 1.53-2.18 (br m, 8 H) correlated with 3.41-3.61 (br s, 1 H), 1.53-2.18 (br m, 8 H) correlated with 3.61-3.95 (br s, 1 H); LC-mass spectrum (FAB, \(m/z\)) at 7.51 minutes: 341.1 (25, M\(^+\) + 1), 285.1 (10), 241.1 (60), 185.1 (100); 7.91 minutes: 341.1 (30, M\(^+\) + 1), 285.1 (2), 241.1 (50), 185.1 (100); mass spectrum (FAB, \(m/z\)) 341.3 (100, M\(^+\) + 1), 285.2 (5), 241.2 (940), 185.1 (68), 170.2 (30).

When the crude product was dissolved in CH\(_2\)Cl\(_2\) and allowed to stand at room temperature for about two weeks, the \(R*S*\) (meso) diastereomer crystallized as colorless crystals. After flash chromatography (10% AcOEt/Hexane, v/v, silica gel, \(R_f = 0.63\), the \(R*S*\) (meso) diastereomer was re-crystallized from CH\(_2\)Cl\(_2\)/Et\(_2\)O/Hexane (1:1:1, v/v) as white crystals: mp 141.5 °C-142.5 °C; \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.46 (s, 18 H), 1.60-2.40 (br m, 8 H), 2.82-3.42 (m, 4 H), 3.42-3.70 (m, 1 H), 3.70-4.10 (br s, 1 H) (rotamers); \(^{13}\)C NMR (CDCl\(_3\), TMS) \(\delta\) 22.7 (23.4, Apt, down), (27.9, 28.1, 28.3) 28.5 (Apt, up), (45.5, 45.9) 46.6 (Apt, down), 59.6 (Apt, up), (78.8, 79.1, 79.4) 79.5 (Apt, down), (154.6) 155.5 (Apt, down) (rotamers); high resolution mass spectrum (FAB, \(m/z\)) 341.2441 (MH\(^+\)) (calcld. for M\(^+\) + H, \(C_{18}H_{33}N_2O_4\), 341.2440). Anal. Calcld for \(C_{18}H_{32}N_2O_4\): C, 63.50; H, 9.47; N, 8.23. Found: C, 63.64; H, 9.35; N, 8.20.

The \(dl\)-diastereomer (RR/SS) was obtained as a colorless oil by flash chromatography (10% AcOEt/Hexane, v/v, silica gel, \(R_f = 0.47\), Lit.^2): \(^1\)H NMR \(\delta\) (1.42) 1.45, (s, 18 H), 1.55-2.30 (br m, 8 H), 3.00-3.65 (m, 4 H), 3.65-4.10 (m, 2 H) (rotamers); \(^{13}\)C NMR \(\delta\) (22.4, 22.8) 23.3 (Apt, down), (27.7) 28.4 (29.0, 29.2, Apt, up), (46.5) 47.0 (Apt, down), (58.7, 59.0, 59.4) 59.6 (Apt, up), (78.4) 78.8 (79.2, Apt, down), (154.6) 155.5 (Apt, down) (rotamers).

\[ \text{Bis(1,1-dimethylethyl)ester \ [2,2'-bipiperidine]-1,1'-dicarboxylic acid (3a): This compound was prepared by the homocoupling of the lithium dialkylcuprate derived from N-Boc-\(\alpha\)-lithiopiperidine (2b-Li) using General Procedure A. From 0.74 g (4.0 mmol) of N-Boc-piperidine (2b), 0.6 mL of TMEDA, 4.5 mL of sec-BuLi (4.7 mmol, 1.05 M cyclohexane/hexane, 92/8, Acros), 8 mL of dry Et\(_2\)O (for carbanion generation) and 12.0 mL of dry THF (for cuprate formation), 0.38 g (2.0 mmol) of purified CuI, 0.164 g (4.0 mmol) of LiCl and 1.02 g (4.1 mmol) of iodine (I\(_2\)), 0.63 g (1.71 mmol, yield 85\%) of the coupling product 3a was obtained as a colorless oil (10% AcOEt/Hexane, v/v, silica gel, two diastereomers, \(R_f = 0.29\) and \(R_f = 0.13\)): IR (CDCl\(_3\), \(cm^{-1}\)
1) 2978 (m), 2937 (m), 2866 (w), 1677 (vs), 1477 (m), 1423 (s), 1388 (m), 1275 (m), 1158 (s), 1110 (m), 1031 (m); \( ^1\)H NMR \( \delta \) (CDCl\(_3\)) 1.40 (1.44) (s, 20 H), 1.50-2.00 (broad m, 10 H), 2.40-3.40 (m, 2 H), 3.70-4.50 (m, 2 H), 4.45 (s, 1 H), 4.7 (s, 1 H) (rotamers or diastereomers); \( ^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 19.0 (19.4) (Apt, down), 25.3 (25.8) (Apt, down), 26.5 (26.6) (Apt, down), 28.5 (Apt, up), 38.8 (40.0) (Apt, up), 47.3 (48.7) (Apt, down), 78.8 (79.2) (Apt, down), 153.9 (154.2) (Apt, down) (rotamers or diastereomers); LC-mass spectrum (FAB, \( m/z \)) at 5.56 minutes: 369.1 (5, M\(^+\) + 1), 269.1 (50), 213.1 (75), 169.1 (100); MS (FAB, \( m/z \)) 369.5 (100, M\(^+\)) + 1), 269.3 (75); high resolution mass spectrum (FAB, \( m/z \)) 369.2759 (MH\(^+\)) (calcd. for M\(^+\) + H, C\(_{20}\)H\(_{37}\)N\(_2\)O\(_4\), 369.2753).

**Bis(1,1-dimethylethyl)ester [1,2-ethylenediamine]-1,1’-dicarboxylic acid (3b):** This compound was prepared by the homocoupling of the lithium dialkylcuprate derived from N-Boc-\( \alpha \)-lithio-dimethylamine (2c-Li) using the General Procedure A. From 0.58 g (4.0 mmol) of N-Boc-dimethylamine (2c), 1.2 mL of TMEDA, 6.0 mL of sec-BuLi (6.3 mmol, 1.05 M cyclohexane/hexane, 92/8, Acros), 8.0 mL of dry THF, 0.38 g (2.0 mmol) of purified CuI, 0.164 g (4.0 mmol) of LiCl and 1.02 g (4.1 mmol) of iodine (I\(_2\)), 0.46 g (1.6 mmol, yield 80% based on 2c, 97% after subtraction of the coupling product with sec-BuLi formed as a by-product) of the coupling product 3b was obtained as a yellowish oil (Lit.\(^3\) 10% AcOEt/Hexane, v/v, silica gel, \( R_f = 0.18 \)); IR (neat) 3002 (m), 2956 (s), 2936 (m), 2872 (m), 1683 (vs), 1480 (s), 1435 (s), 1397 (s), 1364 (m), 1297 (m), 1225 (m), 1164 (s), 1131 (m), 1051 (w) cm\(^{-1}\); \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.45 (s, 18 H), 2.87 (s, 6 H), 3.33 (s, 4 H); \( ^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 27.6 (27.9), 34.0 (34.8), 46.1 (46.5), 79.0, 155.0; mass spectrum (FAB, \( m/z \)) 289.1 (30, M\(^+\) + 1), 233.0 (28), 189.0 (45), 145.0 (90), 133.0 (100); high resolution mass spectrum (FAB, \( m/z \)) 289.2126 (MH\(^+\)) (calcd. for M\(^+\) + H, C\(_{14}\)H\(_{29}\)N\(_2\)O\(_4\), 289.2127). Anal. Calcd for C\(_{14}\)H\(_{28}\)N\(_2\)O\(_4\): C, 58.30; H, 9.79; N, 9.71. Found: C, 58.30; H, 9.49; N, 9.81.

**1,1-Dimethylethyl-2-[(N-tert-butoxycarbonyl-N-methylamino)methyl]pyrrolidine-1-carboxylate (3c):** Lithium N-Boc-2-pyrrolidinyl(cyano)cuprate 2a-Cu (L = CN) was prepared as described above in General procedure A. N-Boc-N-methyl-N-lithiomethylamine (2c-Li) was similarly prepared in a separate flask as described in General Procedure A. The THF solution containing 2c-Li was added quickly to the solution of 2a-Cu (L = CN) at -78 °C via syringe, and the reaction mixture was stirred for 15 minutes at -78°C. An I\(_2\) solution (dry Et\(_2\)O) was added dropwise into the stirred cuprate solution at -78°C. The reaction mixture was stirred at -78°C for another hour then warmed up to room temperature over 12 hours. The reaction mixture was diluted with Et\(_2\)O and the organic phase was washed with saturated NH\(_4\)Cl solution, followed by concentration in vacuo to afford the crude product. Pure compound was obtained as a colorless oil (flash column chromatography, 50% AcOEt/Hexane, silica gel, v/v, \( R_f = 0.73 \)); IR (neat) 2977 (s), 2932 (m), 2884 (m), 1680 (vs), 1479 (s), 1454 (m), 1406 (s), 1367 (s), 1252 (s), 1164 (vs), 1119 (s), 1031 (m), 910 (s), 880 (w), 772 (w) cm\(^{-1}\); \( ^1\)H NMR (CDCl\(_3\), TMS) \( \delta \) 1.47 (s, 18 H), 1.75-2.15 (m, 4 H), 3.10-3.80 (br s, 1 H), 4.70-5.10 (m, 3 H); \( ^{13}\)C NMR (CDCl\(_3\), TMS) \( \delta \) (22.3) 22.8, 27.8 (27.9), 45.8, 46.8, 48.5, 56.1, (69.8)
General Procedure B: Oxidative Heterocouplings Of Mixed Lithium Dialkylcuprates Derived from \(N\)-Boc-2-pyrrolidinylithium and ArLi, \(n\)-Bu-, \(s\)-Bu or \(t\)-BuLi. At room temperature, \(N\)-Boc-pyrrolidine (2a) was mixed with TMEDA (2.0 equiv) under argon and the mixture was dissolved in dry THF to form a homogeneous clear solution. The mixture was cooled to -78°C and stirred for 10 minutes. Then sec-BuLi (1.2 equiv) was added dropwise, whereupon the solution became a bright yellow color. The yellow solution was stirred at -78°C for an additional hour. The copper salt (CuX, X = CN, Br, or I; 1.0 equiv) and lithium chloride (2.0 equiv per CuX) were flame dried under a dry argon atmosphere and then allowed to cool to room temperature. Dry THF was added and the mixture was stirred at room temperature for 30 minutes until a homogeneous solution was achieved. At room temperature, the premixed CuX-2LiCl solution was added dropwise into the solution containing the \(\alpha\)-(N-carbomoyl)alkyllithium reagent. The solution was then stirred at -78°C for 1.0 hour. The lithium reagent (PhLi, \(p\)-MeOC\(_{6}\)H\(_{4}\)Li, \(n\)-BuLi, \(s\)-BuLi, or \(t\)-BuLi; 1.1 equiv) was added dropwise to the reaction mixture at -78°C, and the solution was then stirred for 15 minutes at -78°C. The I\(_2\) (dry Et\(_2\)O) was added dropwise into the stirred cuprate solution at -78°C. The reaction mixture was stirred at -78°C for another hour and then warmed up to room temperature over twelve hours. The reaction mixture was extracted with Et\(_2\)O (3 x 10 mL) and the organic phase was washed with saturated NH\(_4\)Cl solution, followed by concentration in \textit{vacuo} to afford the crude product. Pure product was obtained from flash column chromatography.

1,1-Dimethylethyl 2-(phenyl)-1-pyrrolidinecarboxylate (4b): Pure compound was obtained as a colorless oil (120-130°C/0.3-0.5 mmHg, Lit.\(^4\)); IR (neat) 3003 (w), 2926 (s), 2883 (m), 1699 (vs), 1401 (vs), 1171 (s), 1120 (s), 745 (m), 703 (s) cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), TMS) \(\delta\) 1.18 (1.47) (s, 9 H), 1.75-2.10 (m, 3 H), 2.20-2.45 (m, 1 H), 3.40-3.70 (m, 2 H), 4.75 (4.95) (br. s, 1 H), 7.10-7.40 (m, 5 H) (rotamer); \(^{13}\)C NMR (CDCl\(_3\), TMS) \(\delta\) 23.2 (Apt, down), 28.1 (28.5, Apt, up), 34.8 (36.0, Apt, down), 47.1 (Apt, down), (60.6) 61.3 (Apt, up), 79.2 (Apt, down), 125.5 (Apt, up), 126.5 (Apt, up), 128.1 (Apt, up), 145.3 (Apt, down), 154.6 (Apt, down) (rotamers); mass spectrum \(m/z\) (intensity) EI 247 (5, M\(^+\)), 191 (85, M\(^+\) - C\(_4\)H\(_9\)), 146 (90, M\(^+\) - BuCO\(_2\)), 57 (100, C\(_4\)H\(_9\)).

\(N\)[1,1-dimethylethoxy]carbonyl]-2-[1-(2-methoxyphenyl)pyrrolidine (4c). IR (neat) 2980 (w), 2888 (w), 1695 (vs), 1495 (s), 1408 (vs), 1239 (s), 1162 (s), 1119 (s), 760 (s) cm\(^{-1}\); \(^1\)H NMR \(\delta\) 1.16 (s, 6 H), 1.43 (s, 3 H), 1.63-1.81 (m, 3 H), 2.10-2.30 (m, 1 H), 3.46-3.59 (m, 2 H), 3.80 (s, 3 H), 5.06-5.20 (m, 1 H), 6.80-6.88 (m, 2 H), 7.01-7.04 (m, 1 H), 7.16 (m, 1 H); \(^{13}\)C NMR \(\delta\) 23.1, 28.1 (28.2), (32.5) 33.8, 46.8 (46.9), (55.3) 56.0, 78.8, 110.2, 120.1, 125.2, 125.9, 127.3, 154.7, 156.1 (rotamers); mass spectrum, \(m/z\) (intensity) EI 277 (10, M\(^+\)), 220 (25, M\(^+\) - C\(_4\)H\(_9\)), 204 (20, M\(^+\) - C\(_4\)H\(_9\)O), 176 (100, M\(^+\) - C\(_4\)H\(_9\)CO\(_2\)), 161 (10, M\(^+\) - C\(_4\)H\(_9\)CO\(_2\)CH\(_3\)), 91 (25, C\(_6\)H\(_4\)CH\(_3\)\(^+\)), 57 (45, C\(_4\)H\(_9\)).
1,1-Dimethylethyl 2-(1-butyl)-1-pyrrolidinecarboxylate (4d). IR (neat) 2957 (s), 2931 (s), 2871 (s), 1692 (vs), 1398 (vs), 1185 (s), 1102 (s) cm⁻¹; ¹H NMR δ 0.86 (t, J = 5.20 Hz, 3 H), 1.21-1.27 (m, 4 H), 1.43 (s, 9 H), 1.72-1.83 (m, 4 H), 3.27 (br s, 2 H), 3.68 (br s, 1 H); ¹³C NMR δ 14.1, 22.7, 23.3, 28.5, 30.2, 34.1, 46.2, 57.3, 78.7, 154.6; mass spectrum, m/z (intensity) EI 227 (5, M⁺), 170 (15, M⁺ - C₄H₉), 114 (100, M⁺ - C₈H₁₇), 70 (90, M⁺ - C₈H₁₇CO₂), 57 (75, C₄H₉⁺); high resolution mass spectrum m/z 227.1879 (M⁺) (calcd. for C₁₃H₂₅NO₂ 227.1885).

1,1-Dimethylethyl 2-[1-(1-methyl)propyl]pyrrolidinecarboxylate (4e). IR (neat) 2965 (s), 2872 (s), 1691 (vs), 1390 (vs), 1166 (vs), 1102 (s) cm⁻¹; ¹H NMR δ 0.70 (m, 1 H), 0.78-0.90 (m, 6 H), 1.06-1.13 (m, 2 H), 1.40 (s, 9 H), 1.63-1.89 (m, 4 H), 3.20-3.61 (m, 2 H), 3.66-3.69 (m, 1 H); ¹³C NMR δ 12.1, 15.9, 23.9, 26.7, 28.5, 37.9 (40.1), 46.8 (br), (60.8) 62.0, 78.8, 155.0; mass spectrum, m/z (intensity) EI 227 (5, M⁺), 170 (20, M⁺ - C₄H₉), 114 (100, M⁺ - C₈H₁₇), 70 (92, M⁺ - C₈H₁₇CO₂), 57 (60, C₄H₉).

1,1-Dimethylethyl 2-[1-(1,1-dimethyl)ethyl]pyrrolidinecarboxylate (4f). IR (neat) 2971 (s), 2868 (s), 1702 (vs), 1376 (vs), 1170 (vs), 1110 (s) cm⁻¹; ¹H NMR δ 0.85 (s, 9 H), 1.43 (s, 9 H), 1.51-1.80 (m, 4 H), 3.10-3.16 (m, 1 H), 3.69-3.75 (m, 2 H); ¹³C NMR δ 24.5, 26.5, 27.2, 28.5, 36.5, 47.6, 65.3, 79.1, 156.3; mass spectrum, m/z (intensity) EI 170 (16, M⁺ - C₄H₉), 114 (84, M⁺ - C₈H₁₇), 70 (100, M⁺ - C₈H₁₇CO₂), 57 (80, C₄H₉).

3,4-bis(methoxymethyloxy)-1,6-diphenylhexane (5). Mixture of diastereomers: IR (neat) 2933 (w), 1721 (s), 1496 (s), 1448 (s), 1145 (s), 1120 (s), 1005 (w), 744 (s), 696 (s) cm⁻¹; ¹H NMR δ 1.92-1.99 (m, 4 H), 2.66-2.76 (m, 4 H), 3.35 (s, 6 H), 4.57-4.60 (m, 2 H), 4.65-4.80 (m, 4 H), 7.71-7.26 (m, 10 H); ¹³C NMR δ 28.1, 31.1, 36.5, 44.6, 54.1, 56.4, 93.4, 102.5, 126.3, 128.3, 128.6, 141.8, 143.1; mass spectrum m/z(intensity) EI 327 (2, M⁺ - CH₃O), 281 (3, M⁺ - C₆H₅), 148 (75, M⁺ - C₆H₅CH₂CH₂C₆H₅CH₂CH₂), 91 (100, C₆H₅CH₃).

References
