Metalation Chemistry of *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamides. A New Protective Group for Secondary Amides

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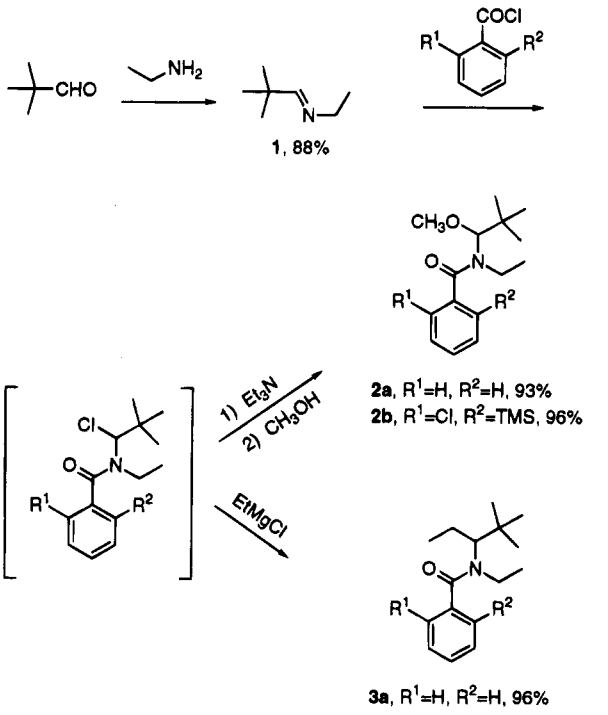
Directed ortho-metalation (DoM) chemistry has become a standard tool for functionalizing aromatic rings.[1] In particular, secondary and tertiary amides are among the most powerful of the DoM groups,[2] and they have found many applications in synthesis. The chief limitations of the DoM chemistry of tertiary benzamides include self-condensation with the ortho carbanion, typically at temperatures >−78 °C, and resistance of the amide to hydrolysis.[2b] While secondary benzamides are more easily hydrolyzed than tertiary benzamides, 2 equiv of an alkyllithium base are required for ortho-metalation, and the resulting dianions can suffer from insolubility and reduced reactivity.[2b] Others have attempted to address these limitations through the design of tertiary amide DoM groups which are more easily converted to a secondary amide after the desired metalation reaction.[3] Metalations with these DoM groups are carried out at −78 °C and require multiple steps and/or vigorous conditions to form the secondary amide. This approach could be greatly improved with a tertiary amide DoM group which undergoes clean ortho-metalation at significantly higher temperatures and converts to its secondary amide under mild conditions.

Herein we report such a solution to this problem which utilizes *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamides as protected *N*-ethylbenzamides. Ortho-substitution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide is achieved in moderate to excellent yields either through metalation at −78 °C with *sec*-butyllithium/TMEDA or at 0 °C with lithium 2,2,6,6-tetramethylpiperidide (LTMP). Subsequent low-temperature metalation reactions utilizing *sec*-butyllithium/TMEDA allow the preparation of 2,6-disubstituted and 2,3,6-trisubstituted *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamides. Hydrolysis of the protective group to the corresponding *N*-ethylbenzamides is achieved under mild acid conditions.[4]

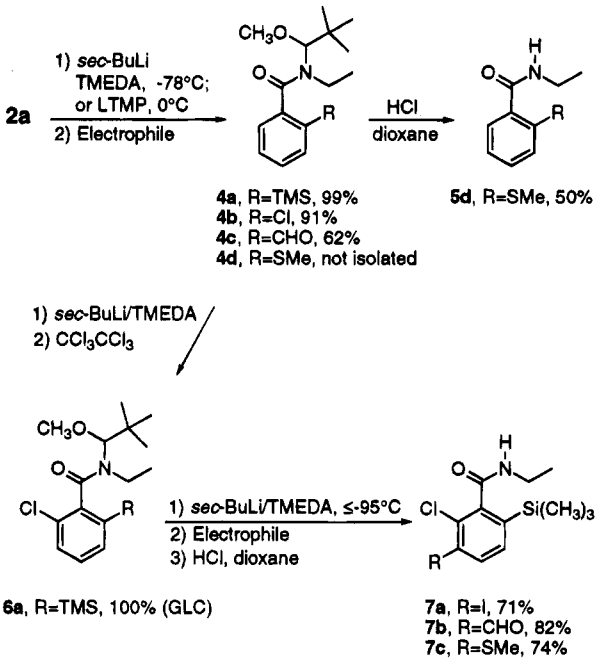
As shown in Scheme 1 this protective group was easily prepared.[5] Aqueous 70% ethylamine smoothly condensed with trimethylacetaldehyde to afford *N*-ethyltrimethylacetaldehyde imine (**1**) in 88% yield after distillation. With no α-hydrogens for aldol condensations, this imine formation proceeded very cleanly with no byproducts. Benzoyl chloride reacted exothermically with **1** to afford an α-chloro amide intermediate which reacted with methanol and triethylamine to give the α-methoxy amide **2a** and with ethylmagnesium chloride to afford **3a**. Even the very hindered 2-chloro-6-(trimethylsilyl)benzoyl chloride was smoothly converted to **2b**, demonstrating the tolerance of this chemistry to sterically hindered acid chlorides. These reactions all gave excellent yields of products.

Scheme 1



Scheme 2 shows the ortho-metalation chemistry which was carried out with *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamides. Protected benzamide **2a** was ortho-metalated under the usual conditions of *sec*-butyllithium/TMEDA at −78 °C and reacted with chlorotrimethylsilane to give **4a** in excellent yield. Ortho-metalation of **2a** was also effected with LTMP at 0 °C to afford **4b**–**d**[6] in moderate to good yields after reaction with electrophiles.

Scheme 2



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(4) These compounds were made as part of a program to control wheat take-all disease.
(5) An alternate method for the preparation of α-alkoxy amides is described in *Chem. Abstr.* **1994**, *121*, 182386c.

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In these latter reactions, a study showed that excess LTMP was required to effect complete metalation. Metalation of **2a** with 3.0 equiv of LTMP and quench of the subsequent anion into excess hexachloroethane gave a 98:2 ratio of product **4b** to starting material **2a**.[7] It is postulated that the extra 2 equiv of LTMP was required to shift the equilibrium in favor of the ortho-metalation reaction, because, under similar reaction conditions, decreasing amounts of LTMP gave lower ratios of **4b** to **2a** and 4.8 equiv of LDA afforded **4b** in less than 5% yield.

Highly hindered compound **4a** was also successfully metalated with *sec*-butyllithium/TMDEA to afford a quantitative yield of 2,6-disubstituted benzamide **6a** after reaction with hexachloroethane. In contrast, *N*-ethyl-2-(trimethylsilyl)benzamide could not be ortho-metalated under similar conditions with 2 equiv of *sec*-butyllithium, demonstrating the superiority of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamides for ortho-metalation.

The tandem metalation of **2a** gave 2,3,6-trisubstituted benzamides **7a–c** in overall yields of 70–80%. This metalation reaction required *sec*-butyllithium/TMEDA at ≤−95 °C to prevent benzyne formation and could not be achieved with *N*-ethyl-2-chloro-6-(trimethylsilyl)benzamide under similar conditions; the metalation chemistry mediated by an adjacent DoM group is complemented by this secondary amide protective group. Introduction of the electrophiles and mild removal of the protective group with aqueous HCl in dioxane at room temperature gave good yields of **7a–c**. The regiochemistry of **7c** was assigned through a NOESY spectrum.[8]

The unexpected stability of *o*-lithio **2a** at 0 °C prompted a comparative temperature study of its properties with those of three other benzamides: *N,N*-diethylbenzamide, *N*-ethylbenzamide, and the isosteric analog **3a**. *N,N*-Diethylbenzamide and *N*-ethylbenzamide were included to determine the thermal stability and the extent of LTMP metalation of simple disubstituted and monosubstituted benzamides. Compound **3a** was included to evaluate the role of the methoxy group in **2a** in the formation and/or stability of its ortho carbanion.

In this study,[7] 2.2 equiv of LTMP was used to metalate each of these four benzamides. Small aliquots of each reaction mixture were added to excess hexachloroethane in THF to determine the extent of ortho-metalation at various temperatures. Small portions of each reaction mixture were also quenched in aqueous HCl to determine the relative stability of each carbanion by measuring the ratio of starting material to 2-benzoylbenzamides which formed at various temperatures. Thus, *o*-lithio **2a** was found to be completely stable at room temperature for at least 30 min without any formation of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-benzoylbenzamide. Pure **2a** was recovered from this reaction in 86% yield. Not surprisingly, *N*-ethylbenzamide did not undergo any ortho-lithiation even at ambient temperature, and although *N,N*-diethylbenzamide did undergo ortho-lithiation at −45 °C, *N,N*-diethyl-2-benzoylbenzamide formed over 30 min in 25% yield. Warming this reaction to 0 °C led to the formation of *N,N*-diethyl-2-benzoylbenzamide in >90% yield over 30 min. The metalation of **3a** was very similar to the metalation of **2a**. Its ortho carbanion was also found to be completely stable at room temperature for 30 min with no formation of any *N*-ethyl-*N*-(1-ethyl-2,2-dimethylpropyl)-2-benzoylbenzamide. Pure **3a** was recovered from this reaction in 93% yield. These results suggest that the stability of *o*-lithio **2a** is primarily due to steric hindrance and not to any intramolecular chelation of lithium with the methoxy group.

This chemistry should be generally applicable to the synthesis and metalation of other *N*-substituted-*N*-(1-methoxy-2,2-dimethylpropyl)arylamides, which should allow the preparation of compounds not obtainable by direct metalation of the corresponding secondary arylamides. Large scale synthesis should also be greatly simplified with this robust DoM chemistry since carbanion formation proceeds smoothly at 0 °C with LTMP.[9]

Experimental Section

General. Anhydrous reactions were performed under an atmosphere of nitrogen. Ether and THF were distilled from sodium benzophenone ketyl when used as reaction solvents. All other reagents and solvents were used without additional purification. ^{1}H NMR were conducted at 300 or 400 MHz in $CDCl_3$. Benchtop GC-MS were carried out using an HP 5790A gas chromatograph equipped with an HP 5970A series mass selective detector using a 12.5 m, 0.2 mm cross-linked methyl silicone gum column. Radial chromatography used EtOAc/hexanes gradient elution of a 4 mm silica plate on a Harrison Research Model 7924 chromatotron. Melting points are uncorrected and elemental analyses were performed by Atlantic Microlab Inc, Norcross, GA. Kugelrohr distillation was conducted at 2–5 Torr. The preparation of 2-chloro-6-(trimethylsilyl)benzoyl chloride is described elsewhere.[10]

***N*-Ethyltrimethylacetaldehyde Imine (1).** An aqueous solution of 70% ethyl amine (20.00 g, 310 mmol) was added to trimethylacetaldehyde (24.35 g, 283 mmol) with occasional ice-water cooling to control the mild exotherm. The resulting two-phase mixture was stirred at rt and monitored to completion by ^{1}H NMR, through loss of the aldehyde hydrogen and formation of the imine hydrogen. The layers were separated and the organic phase was distilled from CaH_2 to afford 28.30 g (88% yield) of *N*-ethyltrimethylacetaldehyde imine as a colorless oil: bp 96–98 °C; ^{1}H NMR δ 7.49 (t, J = 1.1 Hz, 1H), 3.36 (d of q, J = 7.3, 1.1 Hz, 2H), 1.14 (t, J = 7.3 Hz, 3H), 1.04 (s, 9H). Anal. Calcd for $C_7H_{15}N_1 \cdot 0.13H_2O$: C, 72.80; H, 13.31; N, 12.13. Found: C, 72.81; H, 13.07; N, 12.12.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide (2a).** A solution of *N*-ethyltrimethylacetaldehyde imine (30.00 g, 265 mmol) in CH_2Cl_2 (60 mL) was added rapidly dropwise to an ice-water-cooled solution of benzoyl chloride (36.00 g, 256 mmol) in CH_2Cl_2 (190 mL). With a mild exotherm the reaction was stirred at rt for 1 h; then the resulting solution of the α-chloro amide intermediate was cooled with an ice-water bath and triethylamine (26.60 g, 263 mmol) was added with no apparent exotherm. This was followed by the dropwise addition of methanol (15.30 g, 478 mmol) at a rate which allowed the internal reaction temperature to be maintained below 15 °C. The resulting slurry was stirred at rt for 30 min, diluted with ether, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to afford 61.23 g (96% yield) of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide as a colorless oil: ^{1}H NMR (2 rotamers) δ 7.37 (m, 5H), 5.02 (s) and 4.39 (s) [1H combined], 3.57–3.34 (m, 5H), 1.32 (t, J = 6.9 Hz) and 1.03 (s) and 0.87 (m) [12H combined]; GC-MS m/z 234 ($M^+ - CH_3$). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.36; H, 9.24; N, 5.70.

(6) Compound **4d** was directly hydrolyzed and isolated as **5d**.

(7) Compound identification and quantitation were determined with the benchtop GC-MS described in the experimental section using a temperature gradient from 100 to 275 °C at 30 °C/min.

(8) The spectrum showed one cross peak between the SMe and just one aromatic hydrogen at 7.12 ppm and a second cross peak between the $SiMe_3$ and the other aromatic hydrogen at 7.42 ppm.

(9) Lithium dialkylamides more basic than LTMP should greatly improve the ortho-metalation equilibrium. See: (a) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442. (b) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790.

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***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide (2b).** Thionyl chloride (18.9 mL, 259 mmol) was carefully added to a solution of 2-chloro-6-(trimethylsilyl)benzoic acid (48.85 g, 216 mmol) in CH_2Cl_2 (250 mL). The resulting solution was stirred at rt for 18 h, then was concentrated, diluted with toluene, and concentrated again under vacuum to remove the excess thionyl chloride. The crude acid chloride was dissolved in toluene (500 mL); then *N*-ethyltrimethylacetaldehyde imine (48.54 g, 430 mmol) and 4-DMAP (1.32 g, 11 mmol) were added. This solution was heated at 135 °C for 6 h and then was cooled to 80 °C; dry triethylamine (45.0 mL, 0.323 mol) was added, followed by the addition of methanol (26.2 mL, 650 mol). A precipitate formed, and the suspension was stirred at 80 °C for 1.5 h and then at rt overnight. The resulting mixture was diluted with water and extracted with ether. The organic solution was washed sequentially with 1 N aqueous HCl, aqueous $NaHCO_3$, and brine and then was dried ($MgSO_4$) and concentrated to afford 73.45 g (96%) of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide as an off-white solid: mp 82–83 °C; ^{1}H NMR δ 7.27–7.54 (m, 3H), 5.42 (s, 1H), 3.60 (s, 3H), 3.39 (m, 2H), 1.07 (s, 9H), 0.88 (t, J = 7.1 Hz, 3H), 0.38 (s, 9H); GC-MS m/z 340 ($M^+ - CH_3$). Anal. Calcd for $C_{18}H_{30}ClNO_2$: C, 60.73; H, 8.49; N, 3.93. Found: C, 60.58; H, 8.60; N, 3.95.

***N*-Ethyl-*N*-(1-ethyl-2,2-dimethylpropyl)benzamide (3a).** *N*-Ethyltrimethylacetaldehyde imine (5.62 g, 49.7 mmol) was added to a solution of benzoyl chloride (5.00 g, 35.6 mmol) in THF (36 mL). The resulting solution was stirred at rt for 80 min and then was cooled with a dry ice/acetonitrile bath while a 2.0 M solution of ethyl magnesium chloride in THF (20.0 mL, 40 mmol) was added dropwise, maintaining the internal reaction temperature at −15 °C. After addition, the cold bath was replaced with a dry ice/CCl_4 bath and the reaction monitored by GC-MS to completion over 3 h. The resulting mixture was diluted with ether and washed with aqueous 10% HCl followed by aqueous saturated $NaHCO_3$ and then was dried ($MgSO_4$), concentrated, and Kugelrohr distilled to afford 8.46 g (96% yield) of *N*-ethyl-*N*-(1-ethyl-2,2-dimethylpropyl)benzamide as a colorless oil: ^{1}H NMR δ 7.36–7.34 (m, 5H), 4.63–4.59 (m) and 3.67–3.58 (m) and 3.39–3.36 (m) and 3.32–3.22 (m) [3H combined], 1.75–1.48 (m), 1.31 (t, J = 6.9 Hz) and 1.06–0.99 (m) and 0.85 (s) [17H combined]; GC-MS m/z 232 ($M^+ - CH_3$). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.41; H, 10.17; N, 5.70.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-(trimethylsilyl)benzamide (4a).** A 1.3 M solution of *sec*-butyllithium in cyclohexane (140.6 mL, 182.8 mmol) was added dropwise to a dry ice/acetone cooled solution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide (35.00 g, 141 mmol) and TMEDA (25.4 mL, 169 mmol) in THF (280 mL), maintaining the internal reaction temperature ≤−60 °C. The resulting yellow solution was stirred at −78 °C for 1 h and then was cannulated into a dry ice/acetone cooled solution of trimethylsilyl chloride (26.7 mL, 211 mmol) in THF (140 mL) at a rate which maintained the internal reaction temperature ≤−55 °C during the addition. The yellow solution was warmed to 0 °C and diluted with ether; then it was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), concentrated, and Kugelrohr distilled to afford 44.80 g (99% yield) of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-(trimethylsilyl)benzamide as a colorless oil: ^{1}H NMR δ 7.65 (m, 1H), 7.36–7.33 (m, 3H), 5.55 (s, 1H), 3.50 (s, 3H), 3.46 (q, J = 7.1 Hz, 2H), 1.03 (s, 9H), 0.82 (t, J = 7.1 Hz, 3H), 0.33 (s, 9H); GC-MS m/z 306 ($M^+ - CH_3$). Anal. Calcd for $C_{18}H_{31}NO_2Si$: C, 67.24; H, 9.72. Found: C, 67.13; H, 9.77.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chlorobenzamide (4b).** A 1.6 M solution of *n*-butyllithium in hexanes (7.5 mL, 12.0 mmol) was added dropwise to an ice–water-cooled solution of 2,2,6,6-tetramethylpiperidine (2.2 mL, 12.8 mmol) in THF (20 mL). After stirring at 0 °C for 15 min, an ice–water-cooled solution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-benzamide (1.00 g, 4.0 mmol) in THF (10 mL) was cannulated into this solution of lithium tetramethylpiperidide. The resulting tannish-yellow solution was stirred at 0 °C for 30 min and then was cannulated into a 0 °C solution of hexachloroethane (3.41 g, 14.4 mmol) in THF (20 mL). The resulting mixture was stirred at 0 °C for 30 min and then was poured into a stirred mixture of aqueous saturated NH_4Cl and ether. The aqueous layer was extracted with additional ether, and the combined organic layers were washed with aqueous sodium metabisulfite, 0.2 N HCl, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford 1.03 g (91% yield) of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chlorobenzamide as a light yellow oil: ^{1}H NMR δ 7.24–7.45 (m, 4H), 5.50 (br s, 1H), 3.20–3.58 (series of m, 5H), 1.06 (s, 9H), 0.94 (m, 3H); GC-MS m/z 268 ($M^+ - CH_3$). Anal. Calcd for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.81; N, 4.94. Found: C, 63.23; H, 7.92; N, 4.76.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-formylbenzamide (4c).** A 1.6 M solution of *n*-butyllithium in hexanes (7.5 mL, 12.0 mmol) was added dropwise to an ice–water-cooled solution of 2,2,6,6-tetramethylpiperidine (2.2 mL, 12.8 mmol) in THF (20 mL). After stirring at 0 °C for 15 min, an ice–water-cooled solution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-benzamide (1.00 g, 4.0 mmol) in THF (10 mL) was cannulated into this solution of lithium tetramethylpiperidide. The resulting tannish-yellow solution was stirred at 0 °C for 30 min and then was cooled to −78 °C, and DMF (0.93 mL, 12 mmol) was slowly added. The resulting mixture was allowed to warm to −30 °C and then was poured into a stirred mixture of 0.2 N HCl and ether. The aqueous layer was extracted with additional ether, and the combined organic layers were washed with aqueous 0.2 N HCl, aqueous $NaHCO_3$, and brine and then dried ($MgSO_4$), concentrated, and purified by radial chromatography to afford 0.69 g (62% yield) of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-formylbenzamide as a colorless oil: ^{1}H NMR δ 9.46, 10.10, and 10.13 (3 s) [1H combined], 7.35–8.02 (series of m, 4H), 5.56 (s, 1H), 3.27–3.57 (m, 5H), 1.23–1.41 (series of m, 1H), 1.06 (s, 7H), 0.83–0.87 (m, 4H); GC-MS m/z 262 ($M^+ - CH_3$). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.12; H, 8.35; N, 5.03.

***N*-Ethyl-2-(methylthio)benzamide (5d).** A 1.6 M solution of *n*-butyllithium in hexanes (7.5 mL, 12.0 mmol) was added dropwise to an ice–water-cooled solution of 2,2,6,6-tetramethylpiperidine (2.2 mL, 12.8 mmol) in THF (20 mL). After stirring at 0 °C for 15 min, an ice–water-cooled solution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)benzamide (1.00 g, 4.0 mmol) in THF (10 mL) was cannulated into this solution of lithium tetramethylpiperidide. The resulting tannish-yellow solution was stirred at 0 °C for 30 min and then was cannulated into a 0 °C solution of methyl methanethiosulfonate (1.85 mL, 12 mmol) in THF (20 mL). The resulting mixture was stirred at 0 °C for 30 min and then was poured into a stirred mixture of aqueous 0.2 N HCl and ether. The aqueous layer was extracted with additional ether, and the combined organic layers were washed with aqueous 0.2 N HCl, aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to afford the crude protected amide. This material was deprotected in a mixture of dioxane (30 mL) and concentrated aqueous HCl (10 mL) over 2.5 h at rt. The resulting mixture was diluted with CH_2Cl_2 and washed with brine, followed with aqueous $NaHCO_3$, then was dried ($MgSO_4$), concentrated, and recrystallized from ether/hexanes to give 0.286 g of desired product as off-white crystals. The mother liquors were purified by radial chromatography to give an additional 0.101 g of product to afford a total of 0.387 g (50% yield) of pure *N*-ethyl-2-(methylthio)benzamide: mp 92–94 °C; ^{1}H NMR δ 7.55 (dd, J = 1.4, 7.6 Hz, 1H), 7.30–7.39 (m, 2H), 7.19 (d of t, J = 1.4, 5.6 Hz, 1H), 6.35 (br s, 1H), 3.51 (d of q, J = 5.7, 7.3 Hz, 2H), 2.46 (s, 3H), 1.26 (t, J = 7.3 Hz, 3H). Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.61; H, 6.75; N,7.07.

***N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide (6a).** A 1.3 M solution of *sec*-butyllithium in cyclohexane (15.6 mL, 20.3 mmol) was added dropwise to a dry ice/acetone cooled solution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-(trimethylsilyl)benzamide (5.00 g, 15.6 mmol) and TMEDA (3.1 mL, 20.3 mmol) in ether (32 mL), maintaining the internal reaction temperature ≤−60 °C. The resulting amber solution was warmed to −24 °C and maintained at that temperature for 1 h with a dry ice/CCl_4 bath. This was then cannulated into a dry ice/acetone cooled slurry of hexachloroethane (7.38 g, 31.2 mmol) in ether (32 mL) at a rate which maintained the internal reaction temperature ≤−50 °C during the addition. The yellow solution was warmed to 0 °C and washed with aqueous 10% HCl followed with aqueous $NaHCO_3$, then dried ($MgSO_4$), and concentrated to afford crude *N*-ethyl-

N-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)-benzamide as an amber oil which was identical to compound **2b**. GLC analysis showed that the chlorination was quantitative.

General Procedure for Metalation of 2b and Introduction of Electrophiles at C-3. A 1.3 M solution of *sec*-butyllithium in cyclohexane (2.0−2.2 equiv) was added dropwise to an ether/liquid nitrogen cooled solution of *N*-ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide (1 equiv) and TMEDA (1 equiv) in 1:1 THF/ether, maintaining the internal reaction temperature ≤−95 °C. The reaction was stirred at −100 °C for 30 min, then the electrophile (2.0−2.3 equiv) was added, and the mixture was allowed to warm to −30 °C and worked up in the usual manner. Concentrated aqueous HCl (2.5 mL/mmol) was added to a solution of this material in dioxane (7.5 mL/mmol) and stirred at rt for 1.5 h to hydrolyze the amide protective group. The resulting mixture was diluted with ether, washed with aqueous saturated $NaHCO_3$ and brine, then dried (MgSO4), concentrated, and purified by recrystallization or chromatography.

***N*-Ethyl-2-chloro-3-iodo-6-(trimethylsilyl)benzamide (7a).** *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide (3.56 g, 10 mmol) was metalated and reacted with 1,2-diiodoethane (2.3 equiv) using the General Procedure. Flash chromatography (ethyl acetate/hexanes) followed by recrystallization from aqueous methanol afforded 2.72 g (71% yield) of *N*-ethyl-2-chloro-3-iodo-6-(trimethylsilyl)benzamide as white crystals: mp 128−130 °C; ^{1}H NMR δ 7.84 (d, J = 7.9 Hz, 1H), 7.12 (d, J = 7.9 Hz, 1H), 5.60 (br s, 1H), 3.49 (d of q, J = 5.7, 7.3 Hz, 2H), 1.26 (t, J = 7.3 Hz, 3H), 0.29 (s, 9H); GC-MS m/z 366 ($M^+ - CH_3$). Anal. Calcd for $C_{12}H_{17}ClINOSi$: C, 37.76; H, 4.49; N, 3.67. Found: C, 37.85; H, 4.46; N, 3.58.

***N*-Ethyl-2-chloro-3-formyl-6-(trimethylsilyl)benzamide (7b).** *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide (1.78 g, 5 mmol) was metalated and reacted with DMF (2 equiv) using the General Procedure. Recrystallization from ethyl acetate/hexanes afforded 1.16 g (82% yield) of *N*-ethyl-2-chloro-3-formyl-6-(trimethylsilyl)-benzamide as white crystals: mp 140−142 °C; ^{1}H NMR δ 10.48 (d, J = 0.8 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.59 (dd, J = 0.8, 7.7 Hz, 1H), 5.73 (br s, 1H), 3.53 (d of q, J = 5.7, 7.3 Hz, 2H), 1.30 (t, J = 7.3 Hz, 3H), 0.34 (s, 9H); CI-MS m/z 284 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{18}ClNO_2Si$: C, 55.01; H, 6.39; N, 4.93. Found: C, 54.90; H, 6.41; N, 4.89.

***N*-Ethyl-2-chloro-3-(methylthio)-6-(trimethylsilyl)-benzamide (7c).** *N*-Ethyl-*N*-(1-methoxy-2,2-dimethylpropyl)-2-chloro-6-(trimethylsilyl)benzamide (1.78 g, 5 mmol) was metalated and reacted with methyl methanethiosulfonate (2.2 equiv) using the General Procedure. Recrystallization from ethyl acetate/hexanes afforded 1.12 g (74% yield) of *N*-ethyl-2-chloro-3-(methylthio)-6-(trimethylsilyl)benzamide as white needles: mp 137−139 °C; ^{1}H NMR δ 7.42 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 5.63 (br s, 1H), 3.50 (d of q, J = 5.7, 7.3 Hz, 2H), 2.47 (s, 3H), 1.27 (t, J = 7.3 Hz, 3H), 0.30 (s, 9H). NOESY NMR showed a cross peak between the SMe group (2.47 ppm) and only the aromatic proton at 7.12 ppm and a second cross peak between the trimethylsilyl group (0.30 ppm) and the other aromatic proton at 7.42 ppm confirming the structure. GC-MS: m/z 286 ($M^+ - CH_3$). Anal. Calcd for $C_{13}H_{20}ClNOSSi$: C, 51.72; H, 6.68; N, 4.64. Found: C, 51.72; H, 6.70; N, 4.58.

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