JOC The Journal of Organic Chemistry

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pubs.acs.org/joc

One-Step Trimethylstannylation of Benzyl and Alkyl Halides

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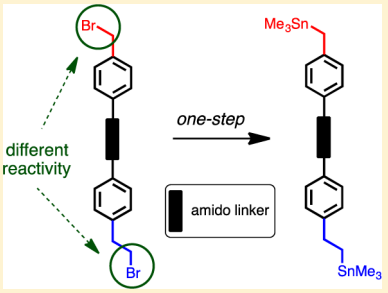
Supporting Information

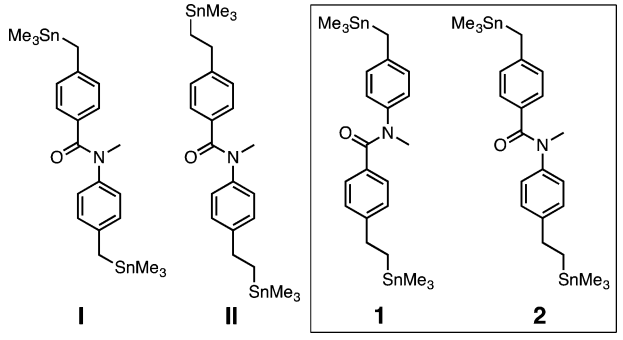
ABSTRACT: Trialkylstannanes are good leaving groups that have been used for the formation of carbon−metal bonds to electrode surfaces for analyses of single-molecule conductivity. Here, we report the multistep synthesis of two amide-containing compounds that are of interest in studies of molecular rectifiers. Each molecule has two trimethylstannyl units, one linked by a methylene and the other by an ethylene group. To account for the very different reactivities of the parent halides, a new methodology for one-step trimethylstannylation was developed and optimized.



The preparation of trialkylstannyl compounds is of broad importance due to their wide applications in organic synthesis,[1,2] their bioactivity,[3] and their surface attachment potential.[4] Trialkylstannanes are common building blocks for construction of complex compounds, as exemplified by Pd-mediated Stille coupling.[2] Trialkylstannanes are also good leaving groups that facilitate the formation of carbon−metal bonds for self-assembled surface attachment.[4−6] In single-molecule studies of molecular rectifiers between Au tips, C−Au bonds formed from trimethyltin compounds gave improved performance compared with that of traditional methods.[5,6] In order to study the affect of unsymmetrical anchoring groups, it is necessary to synthesize trialkylstannyl compounds with the SnR_3 moieties linked asymmetrically to the molecular core, such as by using a methylene linker on one end and an ethylene linker on the other (see **1** and **2** in Chart 1).

Conventional methodologies for preparing trialkylstannyl compounds include either an organotin nucleophile with an electrophilic counterpart or an organotin electrophile with a nucleophilic partner.[7−13] Great efforts have been made to modulate the nucleophilicity or electrophilicity of the trialkylstannyl unit to accommodate substrates with different reactivity.[8−12,14−16] Lipshutz et al.[15] developed a method involving trimethylstannylmethylcuprate [$Me_3Sn(Me)Cu(CN)Li_2$] which selectively delivered the trimethylstannyl moiety to a variety of substrates. Oshima et al.[14] prepared tributylstannylmanganate ($R_3SnMe_3MnLi_2$) as a trialkylstannylation reagent for several organic substrates. Uchiyama et al.[16] used a polycyclic aromatic hydrocarbon catalyzed method to prepare ambient-stable stannyl−lithium (Sn−Li) compounds from different tin sources and showed the high reactivity that resulted.

Chart 1. Amido Compounds with Two Trimethylstannyl Groups



Molecular rectifiers are organic molecules in which electron migration is favored in one direction over the other.[17] We have reported the synthesis of amide-containing compounds as molecular rectifiers with applications in solar energy conversion.[18] The rectification property measurements required the incorporation of anchoring groups into the molecules to attach them to the gold electrodes used in single-molecule break junction measurements.[17,19,20] Several anchoring groups have been reported,[17,19,20] and one attractive type is $RSnMe_3$. This transfers the R group to Au and thus leads to the covalent attachment of the R group to a gold electrode surface. To test asymmetric linkers, we needed to start from a precursor having halide groups of very different reactivity. The two reported prior cases involve symmetrical compounds (**I** and **II**, Chart 1) that contain either two benzyl or two alkyl trimethylstannyl units, with different methods being required for the synthesis of each.[18]

Here, we report the synthesis of two analogous compounds containing both a benzyl and an alkyl trimethylstannyl unit at the opposite termini of each molecule (**1** and **2**, Chart 1). Due to the unsymmetrical nature of both molecules, our synthetic

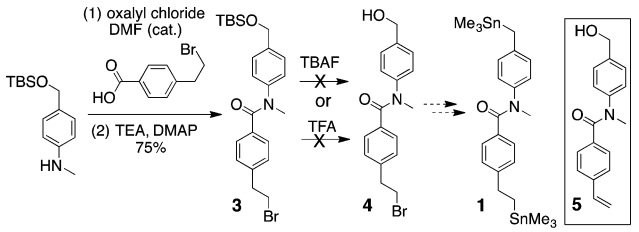
Received: August 2, 2016
Published: September 19, 2016

DOI: 10.1021/acs.joc.6b01883
J. Org. Chem. 2016, 81, 9483−9488

strategy must be totally different from the ones adopted for the two reported symmetrical counterparts **I** and **II**.[18] In the present work, the methodology for introducing two trimethylstannyl units at two sites with different reactivity (benzyl vs alkyl) was explored and optimized. The rectification efficiency of the resulting compounds will be the focus of a subsequent paper, however.

The preparation of target compound **1** was attempted using compound **4** as the key intermediate (Scheme 1). Treatment of

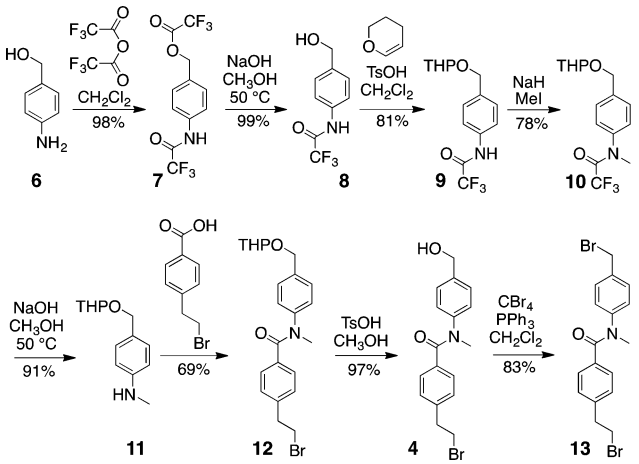
Scheme 1. Attempted Synthesis of Compound 1



para-substituted *N*-methylaniline with 4-bromoethylbenzoyl chloride, which was prepared in situ by reaction of 4-bromoethylbenzoic acid with oxalyl chloride, afforded compound **3** in 75% yield (Scheme 1). Removal of the *tert*-butyldimethylsilyl (TBS) group was achieved with tetra-*n*-butylammonium fluoride. However, the alkyl bromide was unexpectedly transformed to a styrene unit (side product **5**, Scheme 1), presumably due to the basic nature of the fluoride, which promoted the elimination of HBr. Alternative conditions were explored using trifluoroacetic acid,[21] but these failed to remove the TBS unit.

To avoid the use of the unsuitable TBS group, a synthetic strategy was adopted relying on tetrahydropyranyl (THP), instead of TBS, to protect the hydroxyl group (Scheme 2). The

Scheme 2. Synthesis of Compound 13



key intermediate **11** was prepared from 4-aminobenzyl alcohol **6** via a multistep synthesis. Reaction of **6** with trifluoroacetic anhydride in dichloromethane gave the ditrifluoroacetyl-protected compound **7**. The ester unit of **7** was selectively hydrolyzed in quantitative yield under relatively mild basic conditions that left the amide unit intact. Protection of the hydroxy group was achieved using THP in the presence of a catalytic amount of *p*-toluenesulfonic acid monohydrate (TsOH) to give compound **9**, which was methylated with methyl iodide using sodium hydride as base to give compound **10** in 78% yield. Deacetylation of **10** was achieved in methanolic NaOH solution at a modestly elevated temperature (50 °C) to give compound **11** in 91% yield. The same reaction conditions as used for the preparation of **3** were successfully used here to give compound **12** in 69% yield. The hydroxyl group was unveiled by methanolic TsOH and further converted to benzyl bromide by an Appel reaction in 83% yield.

Benzyl and alkyl halides have greatly differing reactivity in almost all of their reactions due to the special stability of the benzyl unit. Preparation of either benzyl or alkyl trialkylstannanes has been reported,[8,9,12,13] but no method is available to introduce R_3Sn on both benzyl and alkyl sites within a single molecule. Here, we explore and optimize a one-step synthesis of R_3Sn from both benzyl and alkyl halides by first forming a R_3Sn anion, followed by nucleophilic substitution. A variety of conditions (reagents, equivalents, and reaction times) were tested for optimization, as listed in Table 1.

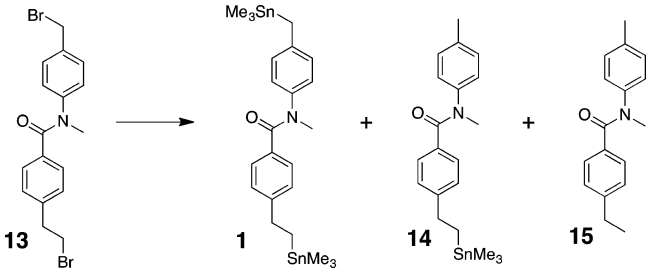
The initial conditions (entry 1 in Table 1) involved the formation of ^{n}Bu$_2$Cu(CN)Li$_2$ by mixing CuCN with 2 equiv of ^{n}BuLi, followed by addition of 1 equiv of hexamethylditin to give Me$_3$Sn(^{n}Bu)Cu(CN)Li$_2$,[15,22] which was expected to deliver the Me$_3$Sn unit both to the benzyl and the alkyl sites. However, only the monotrimethylstannylated product **14** and debrominated product **15** were observed, without detection of the desired product, **1**, as determined by high-resolution mass spectrometry (HRMS) and proton nuclear magnetic resonance (^{1}H NMR). Elimination of CuCN from entry 1 gave Me$_3$SnLi as the nucleophile, but this still failed to give any improvement, presumably due to the excess ^{n}BuLi causing lithium−halogen exchange, rendering the benzyl and alkyl sites nucleophilic and affording the debrominated products after acidic aqueous workup.

Success was finally achieved by reducing the ratio of ^{n}BuLi to hexamethylditin to 1:1 (3.3 equiv, entry 3). This at first gave the desired product in 10% yield. Further optimization raised the yield to 32% (entry 4). Finally, reducing the reaction time from 8 h to 30 min further increased the yield to 42%, implying that we are dealing with a kinetic product that decays after long reaction times. All the yields above are based on isolated products after fine silica column chromatography. Reaction yields for side products **14** and **15** were not included due to the presence of other inseparable minor impurities.

Successful introduction of the trimethylstannyl units was confirmed by HRMS, ^{1}H NMR, and ^{13}C NMR. An expanded portion of the ^{1}H NMR spectrum of compound **1** is displayed in Figure 1 and shows the expected splitting patterns from the tin isotopes. ^{119}Sn and ^{117}Sn are the most important isotopes among its three NMR active nuclei (^{115}Sn, ^{117}Sn, and ^{119}Sn, all with $I = 1/2$). The benzyl −CH$_2$− a protons were split by ^{119}Sn and ^{117}Sn, resulting in two broadened satellite peaks with a coupling constant [J(H−^{119}Sn) and J(H−^{117}Sn)] of 64 Hz (Figure 1A). A similar splitting pattern was observed for the b protons with a J value of 56 Hz. The ^{13}C NMR spectrum also shows the splitting from ^{119}Sn and ^{117}Sn. The peaks from three methyl carbons A and B attached to each Sn atom display two sets of satellite peaks with coupling constants [J(C−^{119}Sn) and J(C−^{117}Sn)] of 1100 Hz for both carbons (Figure 1B). ^{119}Sn NMR also gives two distinct peaks for the two different Sn units (Figure 1C). All coupling constants observed above are in good agreement with the reported values.[23,24] HRMS also shows characteristic isotopic distributions of the various tin isotopes. The observed spectrum is almost identical to the

DOI: 10.1021/acs.joc.6b01883
J. Org. Chem. 2016, 81, 9483−9488

Table 1. Reaction Conditions for Trimethylstannylation of Compound 13



entry	reagents (equiv)	conditions	product[b,c]
1	CuCN (3.3), ^{n}BuLi (6.6), hexamethylditin (3.3)	CuCN, ^{n}BuLi, −41 °C, 30 min → hexamethylditin, −41 °C, 1 h → **13**, −78 °C, 8 h	**14** **15**
2	^{n}BuLi (6.6), hexamethylditin (3.3)	^{n}BuLi, −41 °C, 30 min → hexamethylditin, −41 °C, 1 h → **13**, −78 °C, 8 h	**14** **15**
3	^{n}BuLi (3.3), hexamethylditin (3.3)	^{n}BuLi, hexamethylditin, −41 °C, 40 min → **13**, 8 h, 0 °C	**1** (10%) **14**
4	^{n}BuLi (2.1), hexamethylditin (2.1)	^{n}BuLi, hexamethylditin, −41 °C, 40 min → **13**, 8 h, 0 °C	**1** (32%) **14**
5	^{n}BuLi (2.1), hexamethylditin (2.1)	^{n}BuLi, hexamethylditin, −41 °C, 40 min → **13**, 30 min, 0 °C	**1** (42%) **14**

[a]All reactions were conducted in a Schlenk flask under N_2 atmosphere. [b]Products were confirmed by ^{1}H NMR and LC−MS. [c]Isolated yields in parentheses.

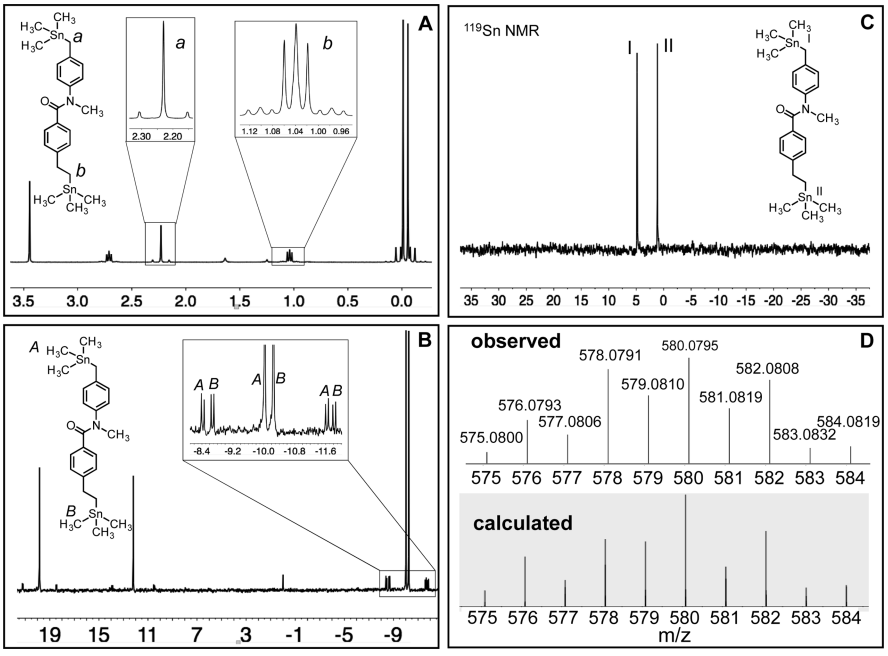
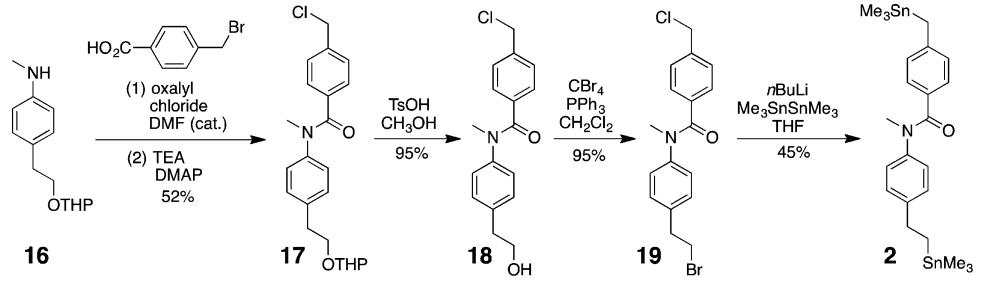


Figure 1. ^{1}H NMR (A), ^{13}C NMR (B), and ^{119}Sn NMR (C) spectra of compound **1** in $CDCl_3$. (D) HRMS spectra of compound **1**.

Scheme 3. Synthesis of Compound 2



DOI: 10.1021/acs.joc.6b01883
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simulated one, further confirming the presence of two Me_3Sn units.

The same strategy as we used for the synthesis of compound **1** was adopted to prepare compound **2** (Scheme 3). THP-protected *N*-methylanaline **16** was prepared according to a previous procedure[18] and condensed with 4-bromomethylbenzoic acid to give **17**. Unexpected benzyl halide exchange occurred in this reaction to give benzyl chloride. The chloride originated from either oxalyl chloride or sodium chloride during aqueous workup. The same THP deprotection and Appel reactions were conducted to give **18** and **19**, respectively, in 95% yield for both steps (Scheme 3). Trimethylstannylation of **19** using the optimized condition from **1** (entry 5 in Table 1) afforded **2** in 45% yield. The slightly higher yield than for compound **1** (42%) presumably originated from Cl−Br exchange, rendering the reactivity of benzyl chloride closer to that of alkyl bromide.

In conclusion, we have conducted a multistep synthesis for preparing amide-containing compounds for future studies of molecular rectifiers. In the synthesis of these compounds, we developed an approach for one-step trimethylstannylation of benzyl and alkyl halides in moderate yields. We believe this approach can be applied to other organic substrates and lead to a variety of new symmetrical or unsymmetrical trialkylstannyl compounds.

EXPERIMENTAL SECTION

General Information. All chemicals and solvents were commercially available and used as obtained, without further purification. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, and ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. Chemical shifts are reported as parts per million from the internal reference tetramethylsilane. HRMS was performed on a Q-TOF LC−MS with API by direct injection of a methanolic solution at ∼0.5 mg/mL concentration. NMR spectra are available in the Supporting Information.

Synthesis. *4-(2-Bromoethyl)-N-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)-N-methylbenzamide (**3**).* To a suspension of 4-bromoethylbenzoic acid (1.54 g, 6.74 mmol) in a solvent mixture of CH_2Cl_2 (6.0 mL) and benzene (6.0 mL) were added oxalyl chloride (723 μL, 8.43 mmol) and DMF (10 μL, 0.77 mmol). The reaction mixture was stirred for 2 h under nitrogen atmosphere. The solvent was removed under vacuum to give a yellow residue, which was redissolved in benzene (6.0 mL). A solution of 4-(((*tert*-butyldimethylsilyl)oxy)methyl)-*N*-methylaniline (1.41 g, 5.62 mmol), triethylamine (2.35 mL, 16.9 mmol), and DMAP (35 mg, 0.29 mmol) in CH_2Cl_2 (6.0 mL) was then added to the benzene solution. The combined mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction residue was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, and chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to afford a colorless oil (2.18 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 4.0 Hz, 2H), 6.97 (d, J = 4.0 Hz, 2H), 4.66 (s, 2H), 3.47 (s, 3H), 3.45 (t, J = 4.0 Hz, 2H), 3.05 (t, J = 4.0 Hz, 2H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 143.6, 140.4, 139.8, 134.5, 129.1, 128.1, 126.9, 126.6, 64.4, 39.0, 38.5, 32.2, 25.9, 18.4, −5.25; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{23}H_{33}BrNO_2Si$ 462.1458, found 462.1438.

*4-(2,2,2-Trifluoroacetamido)benzyl 2′,2′,2′-trifluoroacetate (**7**).* To a solution of 4-aminobenzyl alcohol (1.23 g, 10 mmol) in anhydrous CH_2Cl_2 (250 mL) were added K_2CO_3 (6.91 g, 50 mmol) and trifluoroacetic anhydride (4.24 mL, 30 mmol), and the mixture was stirred at room temperature under nitrogen for 1 h. The reaction mixture was washed with water and extracted with CH_2Cl_2. The combined organic extract was dried over Na_2SO_4, and the solvent was evaporated to yield a yellow-brown solid (3.09 g, 98%). The compound was used for the next step without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 7.69 (d, J = 12 Hz, 2H), 7.48 (d, J = 12 Hz, 2H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 135.9, 131.3, 129.9, 120.7, 115.0, 68.8; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{11}H_7F_6NO_3Na$ 338.0222, found 338.0233.

*2,2,2-Trifluoro-N-(4-(hydroxymethyl)phenyl)acetamide (**8**).* To a solution of **7** (2.28 g, 7.23 mmol) in methanol (190 mL) was added a 2.0 M aqueous solution of potassium hydroxide (36 μL, 72 μmol), and the mixture was stirred at 50 °C under nitrogen for 1 h. The solution was cooled to room temperature, and the solvent was evaporated under reduced pressure to yield the desired product as a brown solid (1.58 g, 99%). It was used for the next reaction without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 5.18 (t, J = 8.0 Hz, 1H), 4.46 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$ + CD_3OD) δ 142.7, 139.0, 131.5, 124.8, 121.3, 118.4, 67.8, 3.7; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_9H_8F_3NO_2Na$ 242.0399, found 242.0402.

*2,2,2-Trifluoro-N-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-phenyl)acetamide (**9**).* To a solution of **8** (1.4 g, 6.39 mmol) in anhydrous dichloromethane (128 mL) were added 3,4-dihydro-2*H*-pyran (641 μL, 7.03 mmol) and TsOH (60.7 mg, 0.32 mmol). The mixture was stirred under nitrogen at room temperature for 4 h. The mixture was washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extract was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography [(silica, CH_2Cl_2/EtOAc (9:1)] to yield the desired compound as a colorless oil (1.57 g, 81%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 4.77 (d, J = 12 Hz, 1H), 4.69 (t, J = 4.0 Hz, 1H), 4.49 (d, J = 12 Hz, 1H), 3.87−3.93 (m, 1H), 3.52−3.57 (m, 1H), 1.52−1.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.3, 128.7, 120.4, 117.1, 114.2, 97.8, 68.1, 62.2, 30.5, 25.4, 19.3; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{14}H_{16}F_3NO_3Na$ 326.0974, found 326.0955.

*2,2,2-Trifluoro-N-methyl-N-(4-(((tetrahydro-2H-pyran-2-yl)oxy)-methyl)phenyl)acetamide (**10**).* To a solution of **9** (1.28 g, 4.23 mmol) in anhydrous THF (53 mL) under nitrogen were added sodium hydride (60 wt % dispersion in mineral oil, 194 mg, 4.85 mmol) and methyl iodide (395 μL, 6.35 mmol), and the reaction mixture was stirred under nitrogen at 45 °C for 2 h. The mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were combined, dried over Na_2SO_4, and filtered. The filtrate was evaporated under reduced pressure. Column chromatography [silica, CH_2Cl_2/EtOAc (19:1)] yielded the desired compound as a colorless oil (1.05 g, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.81 (d, J = 12 Hz, 1H), 4.72 (t, J = 4.0 Hz, 1H), 4.52 (d, J = 12 Hz, 1H), 3.86−3.92 (m, 1H), 3.52−3.58 (m, 1H), 3.3 (s, 3H), 1.53−1.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 136.6, 134.3, 128.7, 120.4, 115.6, 97.8, 68.0, 62.2, 30.5, 25.5, 19.3; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{15}H_{19}F_3NO_3$ 318.1312, found 318.1308.

*N-Methyl-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)aniline (**11**).* To a solution of **10** (1.06 g, 3.33 mmol) in methanol (50 mL) was added KOH (559 mg, 9.98 mmol), and the mixture was stirred at room temperature under nitrogen for 3 h. The solvent was evaporated. The residue was washed with water and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4, and the solvent was evaporated to yield a colorless oil (0.67 g, 91%). The obtained compound was used without further purification in the following step: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 6.59 (d, J = 8.0 Hz, 2H), 4.68 (t, J = 4.0 Hz, 1H), 4.67 (d, J = 12 Hz, 1H), 4.40 (d, J = 12 Hz, 1H), 3.91−3.97 (m, 1H), 3.73 (br, 1H), 3.51−3.57 (m, 1H), 1.53−1.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 129.7, 112.2, 97.2, 68.8, 62.2, 30.65, 30.78, 25.6, 19.5; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{13}H_{20}NO_2$ 222.1489, found 222.1477.

*4-(2-Bromoethyl)-N-methyl-N-(4-(((tetrahydro-2H-pyran-2-yl)-oxy)methyl)phenyl)benzamide (**12**).* To a suspension of 4-bromoethylbenzoic acid (1.16 g, 5.04 mmol) in benzene (30 mL) were added oxalyl chloride (520 μL, 6.05 mmol) and DMF (8 μL, 0.62 mmol).

DOI: 10.1021/acs.joc.6b01883
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The reaction mixture was stirred for 2 h under nitrogen atmosphere. The solvent was removed under vacuum to give a yellow residue, which was redissolved in benzene (6.0 mL). A solution of **11** (744 mg, 3.36 mmol), triethylamine (1.4 mL, 10.1 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (6.0 mL) was then added to the benzene solution. The combined mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction residue was diluted with CH_2Cl_2, washed with brine, and extracted with CH_2Cl_2. The organic extracts were combined, dried over Na_2SO_4, and chromatographed [silica, CH_2Cl_2/ethyl acetate (19:1)] to afford a colorless oil (1.5 g, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 4H), 4.71 (d, J = 12 Hz, 1H), 4.64 (t, J = 4.0 Hz, 1H), 4.42 (d, J = 12 Hz, 1H), 3.83−3.89 (m, 1H), 3.44−3.54 (m, 6H), 3.06 (t, J = 8.0 Hz, 2H), 1.51−1.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.1, 140.5, 136.7, 134.5, 129.1, 128.4, 128.0, 126.7, 97.9, 68.1, 62.2, 39.0, 32.1, 30.5, 25.4, 19.4; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{22}H_{27}BrNO_3$ 432.1169, found 432.1139.

*4-(2-Bromoethyl)-N-(4-(hydroxymethyl)phenyl)-N-methylbenzamide (**4**).* To a solution of **12** (210 mg, 0.486 mmol) in methanol (2.43 mL) was added TsOH (9.2 mg, 48.6 μmol). The resulting mixture was stirred at room temperature under nitrogen for 3 h. Aqueous $NaHCO_3$ was added to the reaction mixture, and the resulting solution was extracted by CH_2Cl_2. The organic extract was combined, dried, and chromatographed [silica, CH_2Cl_2/ethyl acetate (7:3)] to afford a colorless oil (164 mg, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.24 (m, 4H), 6.99−7.02 (m, 4H), 4.63 (s, 2H), 3.47 (s, 3H), 3.46 (t, J = 8.0 Hz, 2H), 3.06 (t, J = 8.0 Hz, 2H), 1.76 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 144.1, 140.5, 139.2, 134.4, 129.1, 128.1, 127.6, 126.9, 64.5, 39.0, 38.5, 32.3, 29.7; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{17}H_{18}BrNO_2$ 348.0594, found 348.0583.

*4-(2-Bromoethyl)-N-(4-(bromomethyl)phenyl)-N-methylbenzamide (**13**).* To a solution of **4** (82 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (2.35 mL) were added carbon tetrabromide (117 mg, 0.35 mmol) and triphenylphosphine (92.6 mg, 0.35 mmol), and the mixture was stirred at 0 °C under nitrogen. The mixture was further stirred at room temperature for 4 h. The reaction mixture was chromatographed [silica, CH_2Cl_2/ethyl acetate (9:1)] to yield the desired product as a colorless oil (80 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.26 (m, 4H), 6.98−7.03 (m, 4H), 4.41 (s, 2H), 3.48 (s, 3H), 3.47 (t, J = 8.0 Hz, 2H), 3.07 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.8, 140.7, 135.9, 134.2, 129.9, 129.1, 128.2, 127.0, 39.0, 38.4, 32.6, 32.3; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_{17}H_{17}Br_2NONa$ 431.9569, found 431.9540.

*N-Methyl-4-(2-(trimethylstannyl)ethyl)-N-(4-((trimethylstannyl)methyl)phenyl)benzamide (**1**).* A solution of hexamethylditin (171 μL, 0.823 mmol) in anhydrous THF (3.0 mL) was purged with nitrogen and cooled to −40 °C using an acetonitrile/dry ice cooling bath. *n*-Butyllithium (293 μL, 2.2 M in hexanes, 0.778 mmol) was added dropwise to the suspension, and the mixture was stirred at −40 °C for 40 min under nitrogen. A solution of **13** (94 mg, 0.229 mmol) in anhydrous THF (3.0 mL) was added dropwise, and the mixture was further stirred at −40 °C for 30 min under nitrogen. The reaction was quenched with a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, the organic phase was dried over Na_2SO_4, and the solvent was evaporated. The crude residue was purified by column chromatography [silica, hexanes/ethyl acetate (17:3)] to yield the desired compound as a colorless oil (55.6 mg, 42%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.77−6.83 (m, 4H), 3.44 (s, 3H), 2.71 (d, J = 8.0 Hz, 2H), 2.23 (s, 2H), 1.04 (d, J = 8.0 Hz, 2H), −0.01 (s, 9H), −0.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 146.8, 141.8, 140.4, 133.3, 129.0, 127.1, 127.0, 126.9, 38.4, 32.3, 19.8, 12.2, 10.0, 10.3; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{23}H_{36}NOSn_2$ 582.0835, found 582.0810. Compounds **14** and **15** were also isolated on the same column chromatography. The yields are not reported here due to the presence of minor impurities in each sample. Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 2H), 7.0 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 3.45 (s, 3H), 2.75 (t, J = 8.0 Hz, 2H), 2.27 (s, 3H), 1.08 (t, J = 8.0 Hz, 2H), −0.08 (s, 9H); HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{20}H_{28}NOSn$ 418.1187, found 418.1205. Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.0 Hz, 2H), 3.45 (s, 3H), 2.55 (q, J = 8.0 Hz, 2H), 2.28 (s, 3H), 1.15 (t, J = 8.0 Hz, 3H); HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{17}H_{20}NO$ 254.1539, found 254.1555.

*4-(Chloromethyl)-N-methyl-N-(4-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)phenyl)benzamide (**17**).* To a suspension of 4-bromomethylbenzoic acid (1.08 g, 5.04 mmol) in CH_2Cl_2 (8.0 mL) was added oxalyl chloride (780 μL, 9.08 mmol) and DMF (20 μL, 1.54 mmol). The reaction mixture was stirred for 3 h under nitrogen atmosphere to give a yellow suspension. Benzene (8.0 mL) was added, and the mixture was stirred for another 2 h. The solvent was removed under vacuum to give a yellow residue, which was redissolved in benzene (6.0 mL). A solution of **16** (791 mg, 3.36 mmol), triethylamine (1.4 mL, 10.1 mmol), and DMAP (20 mg, 0.16 mmol) in CH_2Cl_2 (6.0 mL) was then added to the benzene solution. The combined mixture was stirred at room temperature for 16 h under nitrogen atmosphere. The reaction residue was diluted with CH_2Cl_2, washed with brine, and extracted with CH_2Cl_2. The organic extract was combined, dried over Na_2SO_4, and chromatographed [silica, CH_2Cl_2/ethyl acetate (19:1)] to afford a colorless oil (678 mg, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 4.54 (t, J = 4.0 Hz, 1H), 4.47 (s, 2H), 3.85−3.91 (m, 1H), 3.67−3.73 (m, 1H), 3.51−3.57 (m, 1H), 3.34−3.46 (m, 4H), 2.83 (d, J = 8.0 Hz, 2H), 1.44−1.80 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 142.8, 138.6, 137.8, 135.9, 129.8, 129.1, 127.8, 126.6, 98.7, 67.9, 63.3, 45.5, 35.7, 30.6, 25.4, 19.4; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{22}H_{27}ClNO_3$ 388.1674, found 388.1643.

*4-(Chloromethyl)-N-(4-(2-hydroxyethyl)phenyl)-N-methylbenzamide (**18**).* To a solution of **17** (110 mg, 0.248 mmol) in methanol (1.42 mL) was added TsOH (5.5 mg, 28.4 μmol). The resulting mixture was stirred at room temperature under nitrogen for 2 h. Aqueous $NaHCO_3$ was added to the reaction mixture, and the resulting solution was extracted by CH_2Cl_2. The organic extract was combined and dried over Na_2SO_4 to afford a colorless oil (82 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 4.46 (s, 2H), 3.77 (t, J = 8.0 Hz, 2H), 3.45 (s, 3H), 2.77 (t, J = 8.0 Hz, 2H), 1.88 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 142.9, 138.7, 137.3, 135.9, 129.8, 129.1, 127.9, 126.9, 63.3, 45.5, 38.5, 29.7; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{17}H_{19}ClNO_2$ 304.1099, found 304.1070.

*N-(4-(2-Bromoethyl)phenyl)-4-(chloromethyl)-N-methylbenzamide (**19**).* To a solution of **18** (87 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (2.87 mL) were added carbon tetrabromide (143 mg, 0.43 mmol) and triphenylphosphine (113 mg, 0.43 mmol), and the mixture was stirred at 0 °C under nitrogen. The mixture was further stirred at room temperature for 3.5 h. The reaction mixture was chromatographed [silica, CH_2Cl_2/ethyl acetate (19:1)] to yield the desired product as a colorless oil (100 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 2H), 4.48 (s, 2H), 3.50 (d, J = 8.0 Hz, 2H), 3.48 (s, 3H), 3.09 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 143.4, 138.8, 137.3, 135.8, 129.5, 129.1, 127.9, 126.9, 45.5, 38.5, 38.4, 32.6; HRMS (ESI) m/z (M + H)$^+$ calcd for $C_{17}H_{18}BrClNO$ 366.0333, found 366.0348.

*N-Methyl-N-(4-(2-(trimethylstannyl)ethyl)phenyl)-4-((trimethylstannyl)methyl)benzamide (**2**).* A solution of hexamethylditin (140 μL, 0.676 mmol) anhydrous THF (3.2 mL) was purged with nitrogen and cooled to −40 °C using an acetonitrile/dry ice cooling bath. *n*-Butyllithium (255 μL, 2.2 M in hexanes, 0.676 mmol) was added dropwise to the suspension, and the mixture was stirred at −40 °C for 40 min under nitrogen. A solution of **19** (118 mg, 0.322 mmol) in anhydrous THF (3.2 mL) was added dropwise, and the mixture was further stirred at −40 °C for 30 min under nitrogen. The cooling bath was then removed, and the reaction mixture was then slowly allowed to warm to room temperature and stirred for 45 min. The reaction was

DOI: 10.1021/acs.joc.6b01883
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quenched with a saturated aqueous ammonium chloride solution. The mixture was extracted with ethyl acetate, the organic phase was dried over Na_2SO_4, and the solvent was evaporated. The crude residue was purified by column chromatography [silica, hexanes/ethyl acetate (17:3)] to yield the desired compound as a colorless oil (83.9 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 3.45 (s, 3H), 2.74 (t, J = 8.0 Hz, 2H), 2.22 (s, 2H), 1.08 (t, J = 8.0 Hz, 2H), −0.02 (s, 9H), −0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 145.5, 143.3, 143.0, 130.5, 129.2, 128.4, 126.6, 125.7, 38.5, 32.0, 20.6, 12.3, −10.0, −10.2; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{23}H_{36}NOSn_2$ 582.0835, found 582.0818.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01883.

NMR spectra of compounds **1**−**4**, **7**−**13**, and **17**−**19** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant from the U.S. Department of Energy (DE-FG02-07ER15909) and a generous grant from the TomKat Foundation. We would like to thank Terence Wu and Mousumi Ghosh of the Yale West Campus Analytical Core staff for help with instrumentation.

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DOI: 10.1021/acs.joc.6b01883
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