Selective *Ortho* and Benzylic Functionalization of Secondary and Tertiary *p*-Tolylsulfonamides. *Ipso*-Bromo Desilylation and Suzuki Cross-Coupling Reactions

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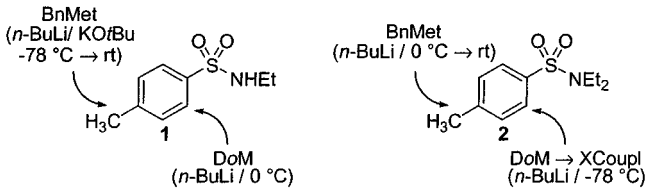
Kinetic vs thermodynamic deprotonation studies on secondary and tertiary sulfonamides **1** and **2** using *n*-BuLi have been carried out. While both **1** and **2** show kinetic *ortho*-metalation, thermodynamic conditions lead to *ortho* and benzylic deprotonation, respectively (Figures 1 and 2). Metalation of **1** using the *n*-BuLi/KO*t*Bu superbase led to regioselective benzylic metalation (Figure 4); LDA deprotonation was also briefly explored. Application of the developed conditions allows the synthesis of diverse sulfonamide products **5a**−**e**, **6a**−**e**, **7a**,**b**, and **8a**−**e**. *Ipso*-bromo desilylation reactions afford sulfonamides **9a**,**b** while Suzuki cross-coupling reactions furnish biaryl sulfonamides **11a**−**c**.

In the context of the progressive Directed *ortho*-Metalation (D*o*M) strategy,[1−3] sulfonamides constitute powerful[1,4−14] but underdeveloped Directed Metalation Groups (DMGs). Similarly, benzylic metalation studies of arylsulfonamides have been sparsely explored.[5,6] As predictable for the origin of many useful DMGs, Hauser first demonstrated metalation of secondary[4−7] and tertiary[8] arylsulfonamides and described the synthesis of heteroannelation products,[4,6−8] but this methodology has received little application. In general, few functionalized arylsulfonamides have been subjected to D*o*M. As part of our continued efforts to develop synthetically useful anionic aromatic reactions,[3] we report a systematic study of *ortho* versus benzylic metalation of secondary and tertiary *p*-tolylsulfonamides **1** and **2** as a function of conditions and describe the selective preparation of *ortho*- and benzyl-functionalized systems. Furthermore, we describe *ipso*-bromo desilylation and Suzuki−Miyaura cross-coupling reactions with arylboronic acids to yield biaryl sulfonamides.

To initiate the study, an investigation of kinetic versus thermodynamic anion formation in the secondary and tertiary *p*-tolylsulfonamides was undertaken. Thus, treatment of secondary *p*-tolylsulfonamide **1** with *n*-BuLi (2.2 equiv) at low temperature for 2.5 min followed by quench with CD_3OD resulted in selective deuterium incorporation at the *ortho*-position as observed by ^2H NMR spectroscopy (Figure 1). Likewise, tertiary *p*-tolylsulfonamide **2**, when subjected to similar *n*-BuLi (1.1 equiv) metalation−CD_3OD quench conditions, afforded only *ortho*-deuterated product. These experiments strongly suggest that *ortho*-anion formation is the kinetically controlled process for both substrates.



D*o*M: Directed *ortho* Metalation; BnMet: Benzylic Metalation; XCoupl: Cross Coupling

In contrast, results differed between secondary *p*-tolylsulfonamide **1** and tertiary *p*-tolylsulfonamide **2** when each was subjected to *n*-BuLi metalation/CD_3OD quench under conditions of thermodynamic control (Figure 2). Although the well-established lateral metalation process[15] has been reported for secondary *o*-tolylsulfonamides,[5,6] the secondary *p*-tolylsulfonamide **1** showed selective *ortho*-deuterium incorporation using conditions of metalation at 0 °C for 15 min followed by room-temperature metalation for 2 h before quenching with

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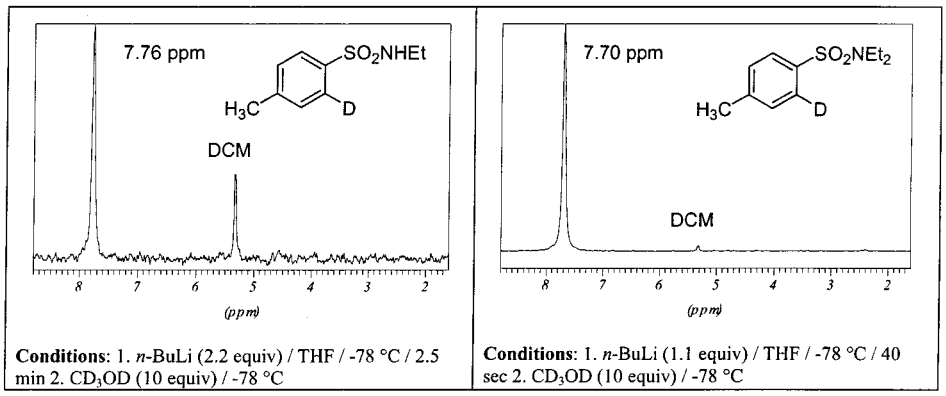


Figure 1. ^{2}H NMR spectra of products obtained from CD_3OD quench of **1** and **2** following metalation under kinetic control conditions.

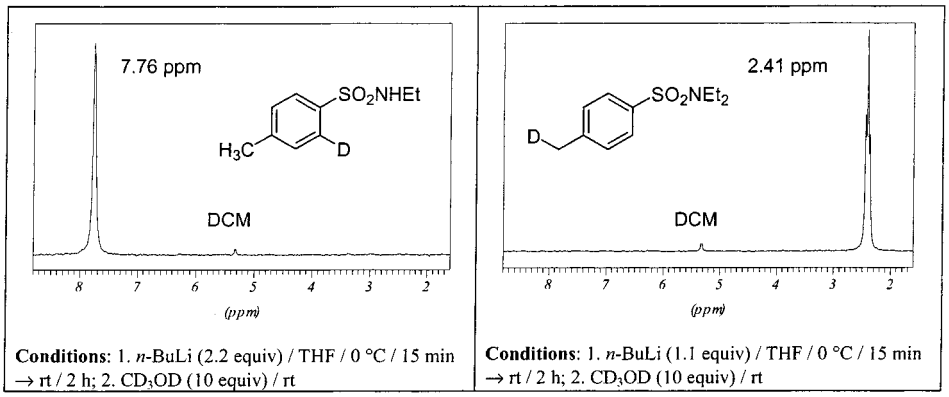
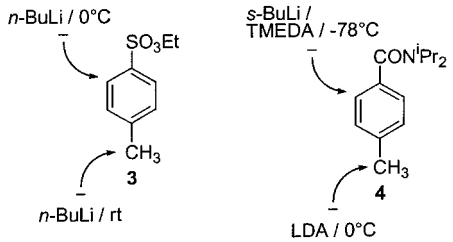


Figure 2. ^{2}H NMR spectra of products obtained from CD_3OD quench of **1** and **2** following metalation under thermodynamic control conditions.

CD_3OD. On the other hand, the tertiary *p*-tolylsulfonamide **2** showed only benzylic deuterium incorporation under the same metalation conditions. To test the effect of reaction time on the equilibration process, compound **1** was subjected to metalation under the same conditions (0 °C/15 min/CD_3OD) but stirred at room temperature for 23 h. This resulted in only *ortho*-deuterated product with no detectable benzylic deuterated material (^{2}H NMR). Furthermore, metalation of **1** at 0 °C followed by heating to reflux (67 °C/4 h/CD_3OD) failed to produce benzylic deuterated product. These experiments strongly suggest that, for **1**, the *ortho*-anion is formed under both kinetic and thermodynamic conditions.

In contrast, for **2**, selective *ortho* and benzylic deprotonation was established under kinetic and thermodynamic control conditions, respectively, and the expected equilibration was demonstrated by a series of metalation/CD_3OD quench experiments with increasing reaction times at 0 °C (Figure 3). Analogous results, with respect to kinetic versus thermodynamic deprotonation, have been observed for the *p*-tolylsulfonate **3**[16] and the tertiary *p*-toluamide **4**[17] and similarly interpreted with the appropriate caveat[17] that additional information on respective anion stabilities is required.



Metalation regioselectivity is influenced by additives[18] and by variation of metalating agent.[17] To explore the effect of additive, **1** was treated with *n*-BuLi/TMEDA (1:1; 2.2 equiv/THF/0 °C/15 min) followed by CD_3OD quench to afford only *ortho*-deuterated product (^{2}H NMR). To explore the effect of amide base, **1** was metalated with LDA (2.2 equiv/THF/0 °C/15 min) followed by warming to room temperature over 20 h. Aliquots were quenched at 0 °C and room temperature during the course of the reaction by addition to neat CD_3OD. Assessment of deuterium incorporation (^{2}H NMR; see Supporting Information) showed only benzylic deuterated product. However, use of TMSCl quench, a much less reactive electrophile, at several temperatures furnished a mixture of products of *ortho*, benzylic, and simultaneous *ortho* and benzylic silylation.[19] A number of factors, including the compatibility of LDA with TMSCl[20] complicates the interpretation of this result.

The deprotonation regioselectivity for **1** as a function of base was tested using the Lochmann−Schlosser superbase, *n*-BuLi/KO*t*Bu[18] (1:1; 2.2 equiv / −78 °C/30 min

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(19) Reactions were carried out at −78 °C, 0 °C, and room temperature, and products were analyzed by ^{1}H NMR and GC/MS examination of crude materials.
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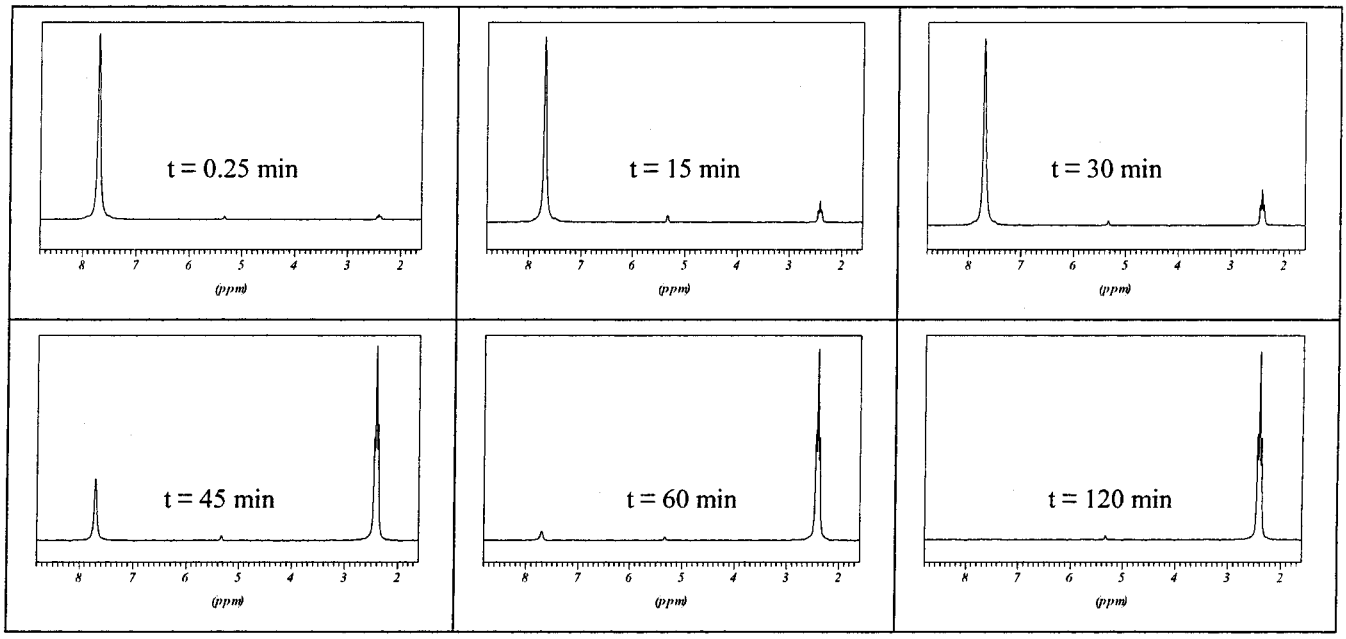


Figure 3. ^{2}H NMR spectra of products obtained from metalation (*n*-BuLi (1.1 equiv)/THF/0 °C)/CD_3OD quench (10 equiv/0 °C) of **2** as a function of metalation time (*t*).

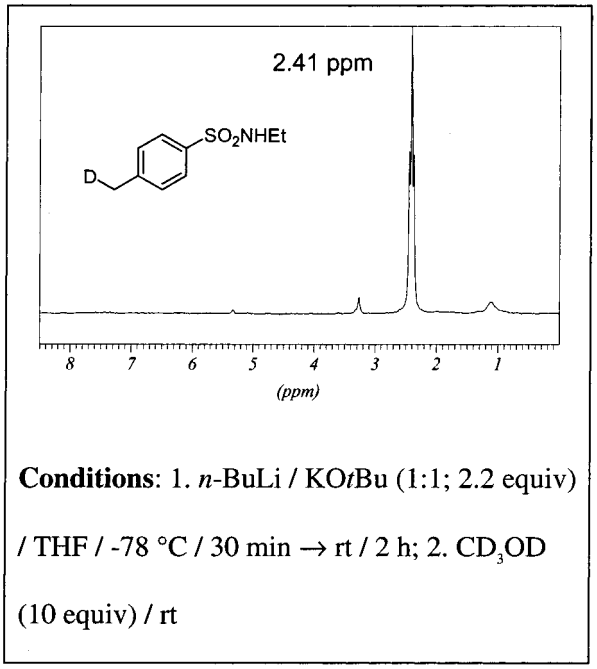
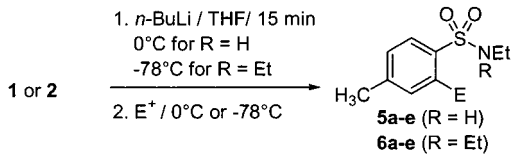


Figure 4. ^{2}H NMR spectrum of product obtained from CD_3OD quench of **1** following metalation with *n*-BuLi/KO*t*Bu (1:1; 2.2 equiv)/THF at −78 °C (30 min) then rt (2 h).

→ rt/2 h/CD_3OD) (Figure 4), yielding a product of regioselective benzylic deuteration, presumably a result of a noncoordinating deprotonation mechanism.[18]

The established kinetic metalation conditions led to the development of synthetically useful reactions (Table 1). Thus, when **1** was treated with *n*-BuLi (2.2 equiv) in THF at 0 °C for 15 min followed by electrophile quench at 0 °C, *ortho*-functionalized sulfonamides **5a**−**e** were obtained in high yields. For the I_2 quench (entry 5, R = H), it was necessary to cool to −78 °C in order to achieve a clean reaction. Likewise, metalation of **2** with *n*-BuLi (1.1 equiv) in THF at −78 °C for 15 min and quench with electrophiles afforded products **6a**−**e** in excellent yields.

Table 1. Syntheses of *N*-Ethyl- and *N*,*N*-Diethyl-2-substituted-4-methylbenzenesulfonamides (5 and 6)



E^+	Product	Yield, %
CD_3OD	**5a**	94
	6a	>99
TMSCl	**5b**	96
	6b	86
MeI	**5c**	92
	6c	92
PhCHO	**5d**	96
	6d	93
I_2	**5e**	78[a]
	6e	92

[a] Quenched at −78 °C.

Synthetic utility of benzylic metalation was demonstrated for **1** and **2** by incorporation of a number of electrophiles to give products **7a**,**b** and **8a**−**e**, respectively, in reasonable yields (Table 2). Interestingly, attempts to effect bromination and iodination of **2** led to the dimeric product **8e**[21,22] while condensation of **1** with benzaldehyde resulted in a mixture of the desired alcohol **7b** and the corresponding ketone[23] which was treated with $NaBH_4$ to give **7b** in 76% yield (see Experimental Section).

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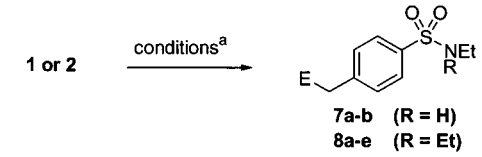
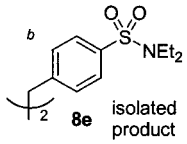
(22) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117−2188.

(23) Benzyl alcohol was also present in the reaction mixture according to GC analysis of the crude material; for precedents, see Swain, C. G.; Powell, A. L.; Lynch, T. J.; Alpha, S. R.; Dunlap, R. P. *J. Am. Chem. Soc.* **1979**, *101*, 3584−3587; Majewski, M.; Mpango, G. B.; Thomas, M. T.; Wu, A.; Snieckus, V. *J. Org. Chem.* **1981**, *46*, 6 (10), 2029−2045.

Table 2. Syntheses of 4-Functionalized *N*-Ethyl-4-methylbenzenesulfonamides (7) and 4-Functionalized *N,N*-Diethyl-4-methylbenzenesulfonamides (8)

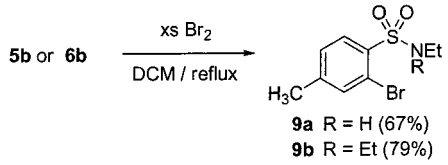


E^+	Product	Yield, %
D_2O	**8a**	68
TMSCl	**8b**	64
	7a	73
MeI	**8c**	83
PhCHO	**8d**	56
	7b	76
I_2	**8e**	56[b]
$BrCH_2CH_2Br$	**8e**	77[b,c]



[a] For **1**: 1. *n*-BuLi / KO*t*Bu / THF / -78 °C / 30 min. 2. -78 °C → rt. 3. E^+ / rt; For **2**: 1. *n*-BuLi / THF / 0 °C / 15 min. 2. 0 °C → rt. 3. E^+ / rt. [c] quenched at -78°C

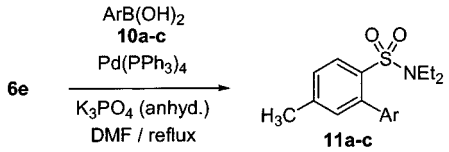
To further enhance synthetic utility of this metalaton chemistry, a study of *ipso*-bromodesilylation of **5b** and **6b**, a reaction of some synthetic utility for *N*,*N*-diethyl *ortho*-silyl benzamides,[24] was conducted. In the event, bromination of **5b** and **6b** under standard conditions afforded satisfactory yields of products **9a** and **9b**, neither of which are readily attainable by direct bromination of corresponding *ortho*-lithiated intermediates.[25]

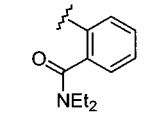
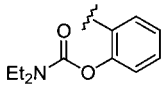


The availability of the iodo sulfonamides (via D*o*M reactions) invited an excursion into a further link of D*o*M to Suzuki−Miyaura cross-coupling chemistry.[26,27] Thus, using selected examples of aryl boronic acid cross-coupling partners, biaryl sulfonamides **11a**−**c** were, with the exception of **11c** (in part, unusual carbamoyl hydrolysis, see Experimental Section), uneventfully prepared in high yields (Table 3).[28]

In conclusion, a systematic study has provided conditions for selective *ortho* and benzylic metalation of secondary sulfonamide **1** and tertiary sulfonamide **2**. Synthetic utility has been demonstrated by the provision of functionalized derivatives **5a**−**e, 6a**−**e, 7a**,**b**, and **8a**−**e**. Use of an *ipso*-desilylative regimen allows the preparation of bromosulfonamides **9a** and **9b** from **5b** and **6b**, respectively. These products are otherwise difficult to obtain by direct D*o*M-Br^+ electrophile quench. The iodide **6e**, prepared by D*o*M, serves effectively for Suzuki−Miyaura cross-coupling reactions with phenylboronic acid and D*o*M-derived arylboronic acids **10b** and **10c** to afford biarylsulfonamides **11a**−**c**, compounds of potential interest for further metalation chemistry. The current pharmaceutical interest in the sulfonamide functionality in context of aryl and biaryl frameworks[32] may trigger application and further exploration of these results.

Table 3. Syntheses of Biaryl Sulfonamides (11) by Suzuki Cross-Coupling Reactions



Ar	Product	Yield, %
Ph	**11a**	95
	**11b**	92
	**11c**	87

Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded neat or as thin films. ^1H (300 or 400 MHz) and ^{13}C (75.43 or 100.57 MHz) NMR spectra were obtained in $CDCl_3$ using either TMS (for ^1H) or $CDCl_3$ (for ^{13}C) as the internal standard. ^2H NMR (61.40 MHz) spectra were obtained in CH_2Cl_2 using residual CD_2Cl_2 as an internal standard. All dry solvents used were purified according to Perrin.[33] THF was freshly distilled from sodium benzophenone ketyl under nitrogen, CH_2Cl_2 was freshly distilled from CaH_2 under nitrogen, and *N*,*N*-dimethylformamide was distilled from CaH_2 and stored over 4 Å molecular sieves prior to use. *n*-Butyllithium was purchased from Aldrich as a solution in hexanes, stored in a resealable container, and titrated periodically against *sec*-butanol.[34] All experiments were carried out under argon in dried glassware, using syringe-septum cap

(24) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372−4385.

(25) For example, metalation of **5b** followed by quench with $BrCH_2CH_2Br$ led to mixtures of **9a** and starting material which were very difficult to separate by column chromatography.

(26) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(27) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 49−97.

(28) In consonance with a previous report,[29] albeit with the boronic acid and aryl halide coupling partners reversed, secondary sulfonamide **5e** behaved sluggishly in Suzuki cross-coupling attempts. Thus, reactions of **5e** with the $PhB(OH)_2$ under several sets of conditions [$Pd(PPh_3)_4$ (5 mol %), Na_2CO_3 (aq), DME, 85 °C;[30] $Pd(PPh_3)_4$ (3.7 mol %), CsF, DME, 85 °C;[31] $Pd(PPh_3)_4$ (5.5 mol %), NaOH (aq), toluene/EtOH[29]] led to a comparable yield (81%) of the corresponding cross-coupling product only under one set of conditions[30] but required >120 h for completion.

(29) Chang, L. L.; Ashton, W. T.; Flanagan, K. L.; Chen, T.-B.; O'Malley, S. S.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S.; Lotti, V. J.; Chang, R. S. L.; Greenlee, W. J. *J. Med. Chem.* **1995**, *38*, 3741−3758.

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(32) See, inter alia, *Annu. Rept. Med. Chem.* **1999**, *34*, pp 7, 38, 46−47, 72, 74, 77−78, 84−85, 92−94, 114, 116, 133, 145, 185, 277−278, 318, 331; Chambers, M. S.; Hobbs, S. C.; Graham, M. I.; Watt, A. P.; Fletcher, S. R.; Baker, R.; Freedman, S. B.; Patel, S.; Smith, A. J.; Matassa, V. G. *Bioorg. Med. Chem. Lett.* **1995**, *20*, 2308 and references therein; Rice, W. G.; Supko, J. G.; Malspeis, L.; Buckheit, R. W., Jr.; Clanton, D.; Bu, M.; Graham, L.; Schaeffer, C. A.; Turpin, J. A.; Domagala, J.; Gogliotti, R.; Bader, J. P.; Halliday, S. M.; Coren, L.; Sowder, R. C., II; Arthur, L. O.; Henderson, L. E. *Science*, **1995**, *270*, 1194−1197.

(33) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: Oxford, 1980.

(34) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165−168.

techniques. The −78 °C and 0 °C external bath temperatures designated are approximate as achieved by a dry ice−acetone or ice-salt bath, respectively. Flash column chromatography was carried out using Merck kieselgel 60 silica gel (particle size: 32−63) with EtOAc:hexanes as eluent.

CD_3OD Quench Experiments.

Kinetic Conditions. General Procedure. A solution of **1**[35] or **2**[36] in THF (0.5 M) was cooled to −78 °C under an Ar atmosphere and treated with *n*-BuLi in hexanes (2.1 and 1.2 equiv, respectively). Following metalation (2.5 min for **1**, 40 s for **2**), the reaction mixture was quenched with CD_3OD (10.0 equiv), precooled to −78 °C, via cannula addition. The resulting solution was stirred for 1 h and quenched with a satd aq NH_4Cl solution (5 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 2 mL), and the extract was dried (Na_2SO_4), subjected to filtration, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes).

For 1. Use of the general procedure with the following materials [**1** (0.1154 g, 0.58 mmol), *n*-BuLi (0.45 mL, 2.70 M, 1.2 mmol), CD_3OD (0.24 mL, 5.9 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow oil (0.1137 g, 98%); ^1H NMR (300 MHz, $CDCl_3$) 7.76 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.37 (bs, 1H), 3.05−2.96 (m, 2H), 2.43 (s, 3H), 1.10 (t, J = 7.3 Hz, 3H); ^2H NMR (61 MHz, CH_2Cl_2) 7.76 (s).

For 2. Use of the general procedure with the following materials [**2** (0.1021 g, 0.45 mmol), *n*-BuLi (0.22 mL, 2.50 M, 0.55 mmol), CD_3OD (0.18 mL, 4.4 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded a colorless solid (0.1022 g, 99%); ^1H NMR (300 MHz, $CDCl_3$) 7.69 (d, J = 8.4 Hz, 1H), 7.30−7.28 (m, 2H), 3.22 (q, J = 7.1 Hz, 4H), 2.42 (s, 3H), 1.12 (t, J = 7.1 Hz, 6H); ^2H NMR (61 MHz, CH_2Cl_2) 7.70 (s).

Thermodynamic Conditions Using *n*-BuLi. General Procedure. A solution of **1** or **2** in THF (0.5−0.6 M) was cooled to 0 °C under an Ar atmosphere and treated with *n*-BuLi in hexanes (2.1 and 1.2 equiv, respectively). Following stirring at 0 °C for 15 min, the reaction mixture was warmed quickly to room temperature and stirred for an additional 2 h prior to quench with CD_3OD (10.0 equiv). The resulting solution was stirred for 1 h and quenched with a satd NH_4Cl solution (5 mL). The aqueous portion was extracted with CH_2Cl_2 (3 × 2 mL), and the extract was dried (Na_2SO_4), subjected to filtration, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes).

For 1. Use of the general procedure with the following materials [**1** (0.1168 g, 0.59 mmol), *n*-BuLi (0.46 mL, 2.70 M, 1.2 mmol), CD_3OD (0.24 mL, 5.9 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow solid (0.1153 g, 98%); ^1H NMR (300 MHz, $CDCl_3$) 7.75 (d, J = 8.4 Hz, 2H), 7.32−7.30 (m, 2H), 4.39 (bs, 1H), 3.05−2.96 (m, 2H), 2.43 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^2H NMR (61 MHz, CH_2Cl_2) 7.76 (s).

For 2. Using the general procedure with the following materials [**2** (0.1151 g, 0.51 mmol), *n*-BuLi (0.24 mL, 2.50 M, 0.60 mmol), CD_3OD (0.21 mL, 5.2 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow solid (0.0708 g, 61%); ^1H NMR (300 MHz, $CDCl_3$) 7.69 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 3.22 (q, J = 7.1 Hz, 4H), 2.40 (t, J = 2.0 Hz, 2H), 1.12 (t, J = 7.1 Hz, 6H); ^2H NMR (61 MHz, CH_2Cl_2) 2.41 (t, J = 2.1 Hz).

Metalation of 1 with LDA. A solution of **1** in THF (0.1 M) was cooled to 0 °C under an Ar atmosphere and treated with LDA [2.2 equiv; prepared by dropwise addition of *n*-BuLi to a solution of HN*i*Pr$_2$ in THF (1 M) precooled to 0 °C under an Ar atmosphere]. Immediately following addition of LDA, a 5 mL aliquot was quenched by addition to neat CD_3OD precooled to 0 °C under an Ar atmosphere. The reaction mixture was stirred at 0 °C for 15 min at which point a second 5 mL aliquot was quenched. Following warming to room temperature, 5 mL aliquots were sequentially quenched at <2 min, 15 min, 30 min, 2, 4, 6, 8, and 20 h. Each aliquot was extracted into CH_2Cl_2 (3 × 2 mL), and the extracts were dried (Na_2SO_4), subjected to filtration, concentrated, and purified by passing through short pads of silica (EtOAc eluent). The samples were analyzed by ^2H NMR (CH_2Cl_2 solvent; see Supporting Information).

Metalation of 1 with *n*-BuLi/KO*t*Bu. *n*-BuLi (2.2 equiv) was added dropwise via syringe to a slurry of KO*t*Bu (2.2 equiv) in THF (1 mL) precooled to −78 °C under an Ar atmosphere. Following stirring at −78 °C for 30 min, the slurry was treated with a solution of **1** (1 equiv) in THF (9 mL), precooled to −78 °C under an Ar atmosphere. The resulting bright yellow solution was stirred at −78 °C for 30 min and then warmed to room temperature and stirred for 2 h prior to quenching by addition to neat CD_3OD (10 equiv). The reaction mixture was stirred for 25 min then quenched with satd aq NH_4Cl (5 mL). Extraction with CH_2Cl_2 (3 × 10 mL) followed by drying (Na_2SO_4), filtration, concentration and purification by passing through a short pad of silica (EtOAc eluent) yielded an orange oil (0.2271 g, >95%). ^2H NMR analysis yielded the spectrum displayed in Figure 4.

Kinetic to Thermodynamic Anion Equilibration for 2. General Procedure. A solution of **2** in THF (0.09 M) was cooled to 0 °C under an Ar atmosphere and treated with *n*-BuLi in hexanes (1.2 equiv). Following stirring at 0 °C for the time indicated, the reaction mixture was quenched with CD_3OD (10.0 equiv). The resulting solution was stirred for 1 h and quenched with a satd aq NH_4Cl solution (5 mL). The aqueous portion was extracted with Et_2O (3 × 2 mL), and the extract was dried (Na_2SO_4), subjected to filtration, and concentrated. The residue was purified by flash column chromatography (EtOAc/hexanes).

(1**)** Using the general procedure with the following materials [**2** (0.1105 g, 0.49 mmol), *n*-BuLi (0.23 mL, 2.50 M, 0.58 mmol), CD_3OD (0.20 mL, 4.9 mmol) in THF (5 mL)] and a 0.25 min metalation, followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow solid (0.1114 g, >99%); ^2H NMR (61 MHz, CH_2Cl_2) 7.70 (s), 2.42 (t, J = 2.2 Hz) (ratio by integration 45:1).

(2) Using the general procedure with the following materials [**2** (0.1006 g, 0.44 mmol), *n*-BuLi (0.21 mL, 2.50 M, 0.52 mmol), CD_3OD (0.18 mL, 4.4 mmol) in THF (5 mL)] and a 15 min metalation time, followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow solid (0.0945 g, 94%); ^2H NMR (61 MHz, CH_2Cl_2) 7.70 (s), 2.42 (t, J = 2.2 Hz) (ratio by integration 11:1).

(3) Using the general procedure with the following materials [**2** (0.1000 g, 0.44 mmol), *n*-BuLi (0.21 mL, 2.50 M, 0.52 mmol), CD_3OD (0.18 mL, 4.4 mmol) in THF (5 mL)] and a 30 min metalation time, followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow solid (0.0911 g, 91%); ^2H NMR (61 MHz, CH_2Cl_2) 7.70 (s), 2.42 (t, J = 2.2 Hz) (ratio by integration 6:1).

(4) Using the general procedure with the following materials [**2** (0.1040 g, 0.46 mmol), *n*-BuLi (0.22 mL, 2.50 M, 0.55 mmol), CD_3OD (0.19 mL, 4.7 mmol) in THF (5 mL)] and a 45 min metalation time, followed by flash column chromatography (20% EtOAc/hexanes) afforded a colorless liquid (0.0710 g, 68%); ^2H NMR (61 MHz, CH_2Cl_2) 7.71 (s), 2.42 (t, J = 2.2 Hz) (ratio by integration 1:3).

(5) Using the general procedure with the following materials [**2** (0.1020 g, 0.45 mmol), *n*-BuLi (0.22 mL, 2.50 M, 0.55 mmol), CD_3OD (0.18 mL, 4.4 mmol) in THF (5 mL)] and a 1 h metalation time, followed by flash column chromatography (20% EtOAc/hexanes) afforded a light yellow solid (0.0808 g, 79%); ^2H NMR (61 MHz, CH_2Cl_2) 7.71 (s), 2.42 (t, J = 2.2 Hz) (ratio by integration 1:20)

(6) Using the general procedure with the following materials [**2** (0.1066 g, 0.47 mmol), *n*-BuLi (0.23 mL, 2.50 M, 0.58 mmol), CD_3OD (0.19 mL, 4.7 mmol) in THF (5 mL)] and a 2 h metalation time, followed by flash column chromatography (20% EtOAc/hexanes) afforded a colorless oil (0.0801 g, 75%); ^2H NMR (61 MHz, CH_2Cl_2) 2.42 (t, J = 2.2 Hz).

Syntheses of *N*-Ethyl-2-substituted-4-tolylsulfonamides (5). General Procedure. A solution of **1** in THF (0.1

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M), precooled to 0 °C under an Ar atmosphere, was treated dropwise with *n*-BuLi in hexanes (2.2 equiv). The resulting bright yellow solution was stirred at 0 °C for 30 min prior to quenching with the appropriate electrophile (1.2 equiv, unless otherwise stated). Following stirring at 0 °C for 1 h, the reaction mixture was quenched with a satd aq NH_4Cl solution (5 mL), and the reaction mixture was extracted with Et_2O (3 × 5 mL). The ether extract was dried (Na_2SO_4), subjected to filtration, and concentrated, and the resulting residue was purified by flash column chromatography (EtOAc/hexanes).

2-Deutero-*N*-ethyl-4-methylbenzenesulfonamide (5a). Use of the general procedure with the following materials [**1** (0.1056 g, 0.53 mmol), *n*-BuLi (0.43 mL, 2.70 M, 1.2 mmol), and CD_3OD (0.22 mL, 5.4 mmol, precooled to 0 °C) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **5a** as a colorless oil (0.0996 g, 94%); ^{1}H NMR (300 MHz, $CDCl_3$) 7.75 (d, J = 8.4 Hz, 1H), 7.32−7.30 (m, 2H), 4.39 (bs, 1H), 3.05−2.96 (m, 2H), 2.43 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{2}H NMR (61 MHz, CH_2Cl_2) 7.76 (s); ^{13}C NMR (75 MHz, $CDCl_3$) 143.2, 136.8, 129.6, 129.4, 127.0, 126.7 (t, J = 24.7 Hz), 38.1, 21.4, 14.8; IR (cm^{-1}) 3261, 1324, 1174; MS (EI) (*m*/*e*) 200 (M^+, 2), 185 (24), 156 (50), 92 (100); HRMS calculated for $C_9DH_{12}NSO_2$ 200.0730, found 200.0731.

***N*-Ethyl-4-methyl-2-trimethylsilylbenzenesulfonamide (5b)**. Use of the general procedure with the following materials [**1** (1.01 g, 5.07 mmol), *n*-BuLi (4.36 mL, 2.56 M, 11.2 mmol), and TMSCl (2.57 mL, 20.2 mmol) in THF (50 mL)], followed by flash column chromatography (10% EtOAc/hexanes) afforded **5b** (1.32 g, 96%) as a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.84 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 1.1 Hz, 1H), 7.31 (dd, J = 1.1, 8.1 Hz, 1H), 4.43 (t, J = 5.8 Hz, 1H), 3.04−2.95 (m, 2H), 2.43 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H), 0.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.4, 142.1, 139.8, 137.8, 130.3, 129.0, 38.6, 22.0, 15.5, 1.5; IR (cm^{-1}) 3292, 1424, S1321, 1160; MS (FAB) (*m*/*e*) 272 (MH^+, 100), 256 (16); HRMS calculated for $C_{11}H_{18}NSO_2Si$ (M^+ − 15) 256.0844, found 256.0857.

***N*-Ethyl-2,4-dimethylbenzenesulfonamide (5c)**. Using the general procedure with the following materials [**1** (0.1084 g, 0.54 mmol), *n*-BuLi (0.46 mL, 2.58 M, 1.2 mmol), and MeI (0.04 mL, 0.6 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **5c** (0.1055 g, 92%) as a light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.86 (d, J = 8.4 Hz, 1H), 7.12−7.10 (m, 2H), 4.37 (bs, 1H), 3.03−2.94 (m, 2H), 2.61 (s, 3H), 2.37 (s, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.2, 136.8, 134.9, 133.1, 129.6, 126.6, 37.8, 21.1, 20.1, 15.0; IR (cm^{-1}) 3301, 1452, 1421, 1318, 1154, 1062; MS (EI) (*m*/*e*) 213 (M^+, 5), 198 (4), 169 (22), 105 (100), 91 (18), 77 (51); HRMS calculated for $C_{10}H_{15}NSO_2$ 213.0824, found 213.0821.

***N*-Ethyl-2-(hydroxyphenylmethyl)-4-methylbenzenesulfonamide (5d)**. Using the general procedure with the following materials [**1** (0.1090 g, 0.55 mmol), *n*-BuLi (0.47 mL, 2.58 M, 1.2 mmol), and benzaldehyde (0.06 mL, 0.6 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **5d** (0.1607 g, 96%) as a light yellow solid. Recrystallization from EtOAc/hexanes afforded **5d** as colorless crystals; mp 152.5−153.0 °C (EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 7.88 (d, J = 8.0 Hz, 1H), 7.40−7.34 (m, 6H), 7.26−7.22 (m, 1H), 6.57 (s, 1H), 3.62 (bs, 1H− exchanges with D_2O), 3.40 (bs, 1H− exchanges with D_2O), 2.67 (bd, J = 6.5 Hz, 2H), 2.40 (s, 3H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.7, 142.0, 141.5, 133.8, 130.8, 130.3, 128.4, 128.2, 127.7, 126.9, 71.6, 38.0, 21.4, 14.4; IR (cm^{-1}) 3434, 3203, 1293, 1148, 1063; MS (CI) (*m*/*e*) 305 (M^+, 2), 288 (100); HRMS calculated for $C_{16}H_{17}NSO_2$ ($M^+ - H_2O$) 287.0980, found 287.0972.

***N*-Ethyl-2-iodo-4-methyl-benzenesulfonamide (5e)**. Use of the general procedure with the following materials [**1** (0.4585 g, 2.30 mmol), *n*-BuLi (2.39 mL, 2.02 M, 4.83 mmol), and I_2 (0.6670 g, 2.63 mmol) in THF (5 mL)] and the following modifications [metalation at 0 °C for 30 min followed by warming to room temperature and cooling to −78 °C prior to I_2 quench; removal of excess I_2 with a satd aqueous solution of $Na_2S_2O_3$ (10 mL) prior to NH_4Cl quench], followed by flash column chromatography (20% EtOAc/hexanes) afforded **5e** (0.5801 g, 78%) as a light yellow solid. Recrystallization from CH_2Cl_2/hexanes afforded **5e** as fine colorless crystals; mp 71.0−73.0 °C (CH_2Cl_2/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 8.04 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.28 (dd, J = 2.0, 8.2 Hz, 1H), 5.14 (s, 1H), 2.98−2.89 (m, 2H), 2.37 (s, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 144.4, 142.6, 138.9, 131.2, 129.2, 92.1, 38.2, 20.7, 14.9; IR (cm^{-1}) 3304, 1630, 1585, 1314, 1154; MS (EI) (*m*/*e*) 325 (M^+, 63), 310 (82), 281 (97), 217 (100), 155 (22), 118 (34), 110 (20), 104 (29); HRMS calculated for $C_9H_{12}NSO_2I$ 324.9634, found 324.9639.

Syntheses of *N*,*N*-Diethyl-2-substituted-4-tolylsulfonamides (6). General Procedure. A solution of **2** in THF (0.1 M), precooled to −78 °C under Ar atmosphere, was treated dropwise with *n*-BuLi in hexanes (1.2 equiv). The resulting bright yellow solution was stirred at −78 °C for 30 min, unless otherwise stated, prior to quenching with the appropriate electrophile (1.1−1.2 equiv). Following stirring at −78 °C for 1 h, the reaction mixture was quenched with a satd aq NH_4Cl solution (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The ether extract was dried (Na_2SO_4), subjected to filtration, and concentrated, and the residue was purified by flash column chromatography (EtOAc/hexanes or CH_2Cl_2/hexanes).

2-Deutero-*N*,*N*-diethyl-4-methylbenzenesulfonamide (6a). Using the general procedure with the following materials [**2** (0.1021 g, 0.45 mmol), *n*-BuLi (0.22 mL, 2.50 M, 0.55 mmol), and CD_3OD (0.18 mL, 4.4 mmol, precooled to 0 °C) in THF (5 mL)] and the following modification [metalation at −78 °C for 40 s], followed by flash column chromatography (20% EtOAc/hexanes) afforded **6a** as a light yellow solid (0.1024 g, >99%). Recrystallization from EtOH/H_2O gave **6a** as colorless needles: mp 40.5−41.0 °C (EtOH/H_2O); ^{1}H NMR (300 MHz, $CDCl_3$) 7.69 (d, J = 8.4 Hz, 1H), 7.30−7.27 (m, 2H), 3.22 (q, J = 7.1 Hz, 4H), 2.42 (s, 3H), 1.12 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.8, 137.1, 129.5, 129.4, 126.9, 126.6 (t, J = 25.0 Hz), 41.9, 21.3, 14.0; IR (cm^{-1}) 1636, 1334, 1160; MS (EI) (*m*/*e*) 228 (M^+, 6), 213 (63), 156 (93), 92 (100); HRMS calculated for $C_{11}DH_{16}NSO_2$ 228.1060, found 228.1061.

***N*,*N*-Diethyl-4-methyl-2-trimethylsilylbenzenesulfonamide (6b)**. Using the general procedure with the following materials [**2** (1.0219 g, 4.50 mmol), *n*-BuLi (2.02 mL, 2.67 M, 5.39 mmol), and TMSCl (1.14 mL, 8.98 mmol) in THF (40 mL)] and the following modification [metalation at −78 °C for 1 h], followed by flash column chromatography (50% CH_2Cl_2/hexanes) afforded **6b** (1.1601 g, 86%) as a light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) 7.58−7.53 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 3.31 (q, J = 7.1 Hz, 4H), 2.38 (s, 3H), 1.16 (t, J = 7.1 Hz, 6H), 0.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.2, 140.9, 139.6, 136.8, 129.7, 126.7, 41.7, 21.2, 14.1, 1.0; IR (cm^{-1}) 1321, 1147; MS (EI) (*m*/*e*) 299 (M^+, 1), 284 (100); HRMS calculated for $C_{14}H_{25}NSO_2Si$ 299.1375, found 299.1378.

***N*,*N*-Diethyl-2,4-dimethylbenzenesulfonamide (6c)**. Using the general procedure with the following materials [**2** (0.1076 g, 0.47 mmol), *n*-BuLi (0.23 mL, 2.50 M, 0.58 mmol), and MeI (0.04 mL, 0.6 mmol) in THF (5 mL)], followed by flash column chromatography (10% EtOAc/hexanes) afforded **6c** (0.1045 g, 92%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) 7.80 (d, J = 8.4 Hz, 1H), 7.10−7.07 (m, 2H), 3.30 (q, J = 7.1 Hz, 4H), 2.55 (s, 3H), 2.36 (s, 3H), 1.12 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.9, 137.4, 135.3, 133.2, 129.7, 126.4, 40.5, 21.1, 20.1, 13.6; IR (cm^{-1}) 1456, 1378, 1314, 1134; MS (EI) (*m*/*e*) 241 (M^+, 2), 226 (25), 169 (47), 105 (100); HRMS calculated for $C_{12}H_{19}NO_2S$ 241.1137, found 241.1133.

***N*,*N*-Diethyl-2-(hydroxyphenylmethyl)-4-methylbenzenesulfonamide (6d)**. Using the general procedure with the following materials [**2** (0.1096 g, 0.48 mmol), *n*-BuLi (0.23 mL, 2.50 M, 0.58 mmol), and benzaldehyde (0.07 mL, 0.7 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **6d** (0.1490 g, 93%) as a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) 7.77 (d, J = 8.1 Hz, 1H), 7.44−7.30 (m, 5H), 7.17 (d, J = 8.1 Hz, 1H), 7.05 (s, 1H), 6.68 (s, 1H), 3.45−3.25 (m, 5H), 3.29 (s, 3H), 1.18 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.7, 143.3, 141.8, 135.1, 131.2, 128.9, 128.2, 128.1, 127.1, 126.4, 69.8, 41.1, 21.4, 13.7;

IR (cm^{-1}) 3498, 1456, 1314, 1154; MS (EI) (*m*/*e*) 334 (MH^+, 2), 333 (M^+, 0.36), 316 (100), 228 (14), 181 (12); HRMS calculated for $C_{18}H_{23}NO_3S$ (MH^+) 334.1477, found 334.1478.

***N,N*-Diethyl-2-iodo-4-methylbenzenesulfonamide (6e)**. Using the general procedure with the following materials [**2** (1.0175 g, 4.48 mmol), *n*-BuLi (2.44 mL, 2.02 M, 4.93 mmol), and I_2 (1.2625 g, 4.97 mmol) in THF (50 mL)] and the following modification [removal of excess I_2 with a satd aqueous solution of $Na_2S_2O_3$ (10 mL) prior to NH_4Cl quench], followed by flash column chromatography (20% EtOAc/hexanes) afforded **6e** (1.46 g, 92%) as a light yellow oil (**6e**:**2** = 96:4 by ^1H NMR); ^1H NMR (300 MHz, $CDCl_3$) 8.01 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.30−7.24 (m, 1H), 3.37 (q, J = 7.1 Hz, 4H), 2.35 (s, 3H), 1.13 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.6, 142.7, 138.9, 130.7, 128.4, 92.0, 40.6, 20.1, 13.0; IR (cm^{-1}) 1636, 1585, 1321, 1147; MS (EI) (*m*/*e*) 353 (M^+, 28), 338 (100), 281 (66), 217 (69), 155 (19); HRMS calculated for $C_{11}H_{16}NSO_2I$ 352.9947, found 352.9941.

Syntheses of 4-Functionalized *N*-Ethyl-4-methylbenzenesulfonamides (7). General Procedure. A solution of **1** in THF (0.1 M), precooled to −78 °C under an Ar atmosphere, was added dropwise to a slurry of *n*-BuLi/KO*t*Bu (1:1; 2.2 equiv) in THF (2 M), precooled to −78 °C under an Ar atmosphere. The resulting solution was stirred at −78 °C for 30 min and then warmed to room temperature and stirred for 2 h prior to quench with the appropriate electrophile. Following stirring at room temperature for 1 h, the reaction mixture was quenched with a satd aq NH_4Cl (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic extract was dried (Na_2SO_4), subjected to filtration, and concentrated, and the resulting crude residue was purified by flash column chromatography (EtOAc/hexanes).

***N*-Ethyl-4-trimethylsilylmethylbenzenesulfonamide (7a)**. Using the general procedure with the following materials [**1** (0.1976 g, 0.99 mmol), *n*-BuLi (0.86 mL, 2.55 M, 2.19 mmol), KO*t*Bu (0.2445 g, 2.18 mmol), and TMSCl (0.63 mL, 4.96 mmol) in THF (10 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **7a** (0.1957 g, 73%) as a yellow oil; ^1H NMR (300 MHz, $CDCl_3$) 7.70 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 4.35 (t, J = 5.9 Hz, 1H), 3.05−2.96 (m, 2H), 2.18 (s, 2H), 1.09 (t, J = 7.2 Hz, 3H), 0.005 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.7, 135.3, 128.4, 127.2, 38.2, 27.8, 15.0, −1.9; IR (cm^{-1}) 3285; MS (EI) (*m*/*e*) 271 (M^+, 100), 256 (10), 227 (2), 163 (3); HRMS calculated for $C_{12}H_{21}NSO_2Si$ 271.1062, found 271.1070.

***N*-Ethyl-4-(2-hydroxy-2-phenylethyl)benzenesulfonamide (7b)**. Using the general procedure with the following materials [**1** (0.4009 g, 2.01 mmol), *n*-BuLi (1.74 mL, 2.55 M, 4.44 mmol), KO*t*Bu (0.5032 g, 4.48 mmol) and benzaldehyde (0.29 mL, 2.85 mmol) in THF (20 mL)], a crude yellow solid was obtained. The crude material was treated with $NaBH_4$ (0.0789 g, 2.01 mmol) in MeOH (50 mL) at 0 °C for 15 min and room temperature for 30 min. Dilution with water (20 mL), addition of dil HCl to pH 3−4, and extraction with CH_2Cl_2 followed by drying (Na_2SO_4), filtration, concentration, and flash column chromatography (20% → 40% EtOAc/hexanes) afforded **7b** (0.4663 g, 76%) as a colorless solid. Recrystallization from aq MeOH afforded **7b** as colorless crystals; mp 140.0−142.0 °C; ^1H NMR (400 MHz, DMSO-d_6) 7.64 (d, J = 8.1 Hz, 2H), 7.46 (t, J = 5.7 Hz, 1H, D_2O-exchangeable), 7.38 (d, J = 8.1 Hz, 2H), 7.32−7.27 (m, 4H), 7.21 (t, J = 6.5 Hz, 1H), 5.39 (d, J = 4.6 Hz, 1H, D_2O-exchangeable), 4.81−4.77 (m, 1H), 2.95 (d, J = 6.6 Hz, 2H), 2.77−2.71 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) 145.4, 144.0, 138.1, 130.2, 128.0, 126.9, 126.2, 126.0, 73.3, 45.3, 37.6, 14.7; IR (cm^{-1}) 3489, 3215, 1306, 1154; MS (CI) (*m*/*e*) 323 $((M + NH_4)^+$, 7), 306 (MH^+, 100), 290 (10), 288 (27), 107 (10); HRMS calculated for $C_{16}H_{20}NO_2S$ (MH^+) 306.1164, found 306.1149.

Syntheses of 4-Functionalized *N,N*-Diethyl-4-methylbenzenesulfonamides (8). General Procedure. A solution of **2** in THF (0.1 M), precooled to 0 °C under an Ar atmosphere, was treated dropwise with *n*-BuLi in hexanes (1.2 equiv). The resulting bright yellow solution was stirred at 0 °C for 15 min, warmed to room temperature, and stirred for an additional 30 min. After being recooled to 0 °C, the reaction mixture was quenched with the appropriate electrophile (1.4 equiv, unless otherwise stated). Following stirring at 0 °C for 1 h, the reaction mixture was quenched with a satd aq NH_4Cl solution (5 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic extract was dried (Na_2SO_4), subjected to filtration, and concentrated, and the resulting crude residue was purified by flash column chromatography (EtOAc/hexanes).

***N,N*-Diethyl-4-deuteriomethylbenzenesulfonamide (8a)**. Using the general procedure with the following materials [**2** (0.1250 g, 0.55 mmol), *n*-BuLi (0.27 mL, 2.50 M, 0.68 mmol), and D_2O (0.10 mL, 5.5 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **8a** as a colorless oil which solidified on standing (86 mg, 68%). Recrystallization from hexanes afforded **8a** as colorless crystals; mp 40.5−41.5 °C; ^1H NMR (300 MHz, $CDCl_3$) 7.69 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 3.22 (q, J = 7.1 Hz, 4H), 2.40 (t, J = 2.0 Hz, 2H), 1.12 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 142.8, 137.3, 129.5, 126.9, 41.9, 21.1 (t, J = 19.6 Hz), 14.0; IR (cm^{-1}) 1636, 1334, 1147; MS (EI) (*m*/*e*) 228 (M^+, 9), 213 (55), 156 (100); HRMS calculated for $C_{11}DH_{16}NSO_2$ 228.1043, found 228.1047.

***N,N*-Diethyl-4-trimethylsilylmethylbenzenesulfonamide (8b)**. Using the general procedure with the following materials [**2** (0.1082 g, 0.48 mmol), *n*-BuLi (0.23 mL, 2.50 M, 0.58 mmol), and TMSCl (0.08 mL, 0.6 mmol) in THF (5 mL)], followed by flash column chromatography (10% EtOAc/hexanes) afforded **8b** (93 mg, 64%) as a colorless oil which solidified on standing. Recrystallization from MeOH/H_2O afforded **8b** as colorless needles; mp 53.0−54.0 °C (MeOH/H_2O); ^1H NMR (300 MHz, $CDCl_3$) 7.65 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 3.23 (q, J = 7.2 Hz, 4H), 2.17 (s, 2H), 1.11 (t, J = 7.2 Hz, 6H), −0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.5, 136.0, 128.6, 127.3, 42.3, 27.9, 14.4, −1.7; IR (cm^{-1}) 1334, 1154; MS (EI) (*m*/*e*) 299 (M^+, 100), 284 (13), 227 (24), 179 (72), 148 (39), 121 (21); HRMS calculated for $C_{14}H_{25}NSO_2Si$ 299.1380, found 299.1367.

***4,N,N*-Triethylbenzenesulfonamide (8c)**. Using the general procedure with the following materials [**2** (0.1186 g, 0.52 mmol), *n*-BuLi (0.24 mL, 2.50 M, 0.60 mmol), and MeI (0.05 mL, 0.8 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **8c** (104 mg, 83%) as a colorless oil; [lit.[37] mp 52.5−53 °C (petroleum ether)]; ^1H NMR (300 MHz, $CDCl_3$) 7.72 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 3.23 (q, J = 7.2 Hz, 4H), 2.71 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.6 Hz, 3H), 1.13 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 149.0, 137.4, 128.3, 127.0, 41.9, 28.6, 15.0, 14.1; IR (cm^{-1}) 1463, 1340, 1160; MS (EI) (*m*/*e*) 241 (M^+, 1), 226 (28), 169 (51), 105 (100); HRMS calculated for $C_{12}H_{19}NO_2S$ 241.1136, found 241.1131.

***N,N*-Diethyl-4-(2-hydroxy-2-phenylethyl)benzenesulfonamide (8d)**. Using the general procedure with the following materials [**2** (0.1216 g, 0.53 mmol), *n*-BuLi (0.26 mL, 2.50 M, 0.65 mmol) and benzaldehyde (0.08 mL, 0.8 mmol) in THF (5 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **8d** (0.0997 g, 56%) as a light yellow solid. Recrystallization from EtOAc/hexanes afforded **8d** as colorless crystals; mp 72.0−73.5 °C (EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) 7.67 (d, J = 8.2 Hz, 2H), 7.34−7.24 (m, 7H), 4.90 (m, 1H), 3.21 (q, J = 7.2 Hz, 4H), 3.14−3.00 (m, 2H), 1.10 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 143.3, 143.0, 138.3, 130.1, 128.4, 127.8, 126.9, 125.8, 74.9, 45.4, 41.9, 14.0; IR (cm^{-1}) 3491, 1597, 1494, 1469, 1385, 1327, 1147; MS (CI) (*m*/*e*) 334 (MH^+, 100), 316 (41), 227 (29), 181 (48), 107 (45); HRMS calculated for $C_{18}H_{21}NSO_2$ ($M^+ - 18$) 315.1310, found 315.1310.

4,4′-(1,2-Ethanediyl)bis[*N,N*-diethylbenzenesulfonamide] (8e). Method A. Using the general procedure with the following materials [**2** (0.1150 g, 0.51 mmol), *n*-BuLi (0.24 mL, 2.50 M, 0.60 mmol), and I_2 (0.1885 g, 0.74 mmol) in THF (5 mL)] and the following modification [removal of excess I_2 with a satd aqueous solution of $Na_2S_2O_3$ (10 mL) prior to NH_4Cl quench], followed by flash column chromatography (EtOAc/

(37) Wiley: R. H.; Ketterer, C. C.; Reed, S. F. *J. Am. Chem. Soc.* **1954**, *74*, 4996−4997.

hexanes gradient [0% → 10% → 20% → 30%]) afforded **8e** (0.0646 g, 56%) as a yellow solid. Recrystallization from MeOH afforded **8e** as colorless crystals. **Method B**. Using the general procedure with the following materials [**2** (0.2028 g, 0.89 mmol), *n*-BuLi (0.42 mL, 2.56 M, 1.1 mmol), and 1,2-dibromoethane (0.10 mL, 1.1 mmol) in THF (8 mL)] and the following modification [electrophile quench at −78 °C], followed by flash column chromatography (30% EtOAc/hexanes) afforded **8e** (0.1551 g, 77%) as a light yellow solid. Recrystallization from MeOH afforded **8e** as colorless crystals; mp 111.5−113.0 °C [lit.[38] mp 114 °C (MeOH)]; ^{1}H NMR (300 MHz, $CDCl_3$) 7.66 (d, J = 8.2 Hz, 4H), 7.21 (d, J = 8.2 Hz, 4H), 3.20 (q, J = 7.1 Hz, 8H), 2.98 (s, 4H), 1.09 (t, J = 7.1 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 146.0, 138.6, 129.5, 127.5, 42.4, 37.4, 14.5.

***Ipso*-Bromo Desilylation Reactions. General Procedure.** To a solution of **5b** or **6b** in CH_2Cl_2 (0.09 M) at room temperature under Ar atmosphere was added Br_2 (10 equiv). The resulting dark red solution was heated to reflux (40 °C) and stirred for 3 h. The reaction mixture was cooled to room temperature and decolorized with $Na_2S_2O_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the organic extract was dried (Na_2SO_4), subjected to filtration, and concentrated in vacuo. The crude residue was purified by flash column chromatography using EtOAc/hexanes.

2-Bromo-*N*-ethyl-4-methyl-benzenesulfonamide (9a). Using the general procedure with the following materials [**5b** (0.5058 g, 1.86 mmol), Br_2 (0.96 mL, 19 mmol) in CH_2Cl_2 (20 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **9a** (0.2181 g, 67%) as a colorless solid. Recrystallization from CH_2Cl_2/hexanes afforded **9a** as colorless needles; mp 99.0−101.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.01 (d, J = 8.1 Hz, 1H), 7.55 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 5.08 (bs, 1H), 3.00−2.91 (m, 2H), 2.40 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 144.7, 135.6, 135.2, 131.2, 128.2, 119.2, 38.1, 20.7, 14.7; IR (cm^{-1}) 3311, 1321, 1160; MS (EI) (*m*/*e*) 279 (M^+ + 2, 25), 277 (M^+, 25), 264 (84), 262 (76), 235 (80), 233 (73), 209 (33), 171 (100), 169 (96); HRMS calculated for $C_9H_{12}NSO_2Br$ 276.9770, found 276.9781.

2-Bromo-*N*,*N*-diethyl-4-methyl-benzenesulfonamide (9b). Using the general procedure with the following materials [**6b** (0.5039 g, 1.68 mmol), Br_2 (0.87 mL, 17 mmol) in CH_2Cl_2 (20 mL)], followed by flash column chromatography (20% EtOAc/hexanes) afforded **9b** (0.4066 g, 79%) as a yellow liquid (**9b**:**6b** = 98:2 by ^{1}H NMR); ^{1}H NMR (300 MHz, $CDCl_3$) 8.00 (d, J = 8.1 Hz, 1H), 7.54 (s, 1H), 7.21 (d, J = 8.1 Hz, 1H), 3.37 (q, J = 7.1 Hz, 4H), 2.38 (s, 3H), 1.12 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 144.2, 136.5, 135.7, 131.6, 127.9, 119.7, 40.9, 20.6, 13.4; IR (cm^{-1}) 1321, 1154; MS (EI) (*m*/*e*) 307 (M^+ + 2, 15), 305 (M^+, 14), 292 (100), 290 (100), 235 (93), 233 (87), 171 (73), 169 (72); HRMS calculated for $C_{11}H_{16}NSO_2Br$ 305.0085, found 305.0084.

Suzuki Reactions. General Procedure. A flame-dried round-bottom flask equipped with a reflux condenser was charged with **6e**, aryl boronic acid (2.2−3.0 equiv), K_3PO_4 (2.1−2.2 equiv), and DMF (0.2−0.3 M), and the mixture was degassed by bubbling Ar through the solution for 15 min. Pd(PPh_3)$_4$ (5 mol %), dispensed in a glovebag, was added, and the system was purged with Ar for an additional 15 min. The reaction mixture was heated to reflux (bath temp: 100−120 °C) for the time indicated, cooled to room temperature, and poured into H_2O (50 mL). The aqueous was extracted with EtOAc (3 × 20 mL), and the organic extract was washed (10% HCl, 3 × 10 mL), dried (Na_2SO_4), subjected to filtration, and concentrated. The crude residue was purified by flash column chromatography (EtOAc/hexanes).

5-Methylbiphenyl-2-sulfonic Acid Diethylamide (11a). Using the general procedure with the following materials [**6e** (0.2036 g, 0.58 mmol), **10a** (0.1530 g, 1.25 mmol), K_3PO_4 (0.2559 g, 1.21 mmol), Pd(PPh_3)$_4$ (0.0355 g, 5.3 mol %) in DMF (25 mL); reflux for 24 h], followed by flash column chromatography (10% EtOAc/hexanes) afforded **11a** (0.1675 g, 95%) as a light yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) 8.00 (d, J = 8.1 Hz, 1H), 7.39 (bs, 5H), 7.27−7.24 (m, 1H), 7.10 (s, 1H), 2.75 (q, J = 7.1 Hz, 4H), 2.42 (s, 3H), 0.93 (t, J = 7.1 Hz, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) 141.2, 139.9, 138.3, 134.9, 132.2, 128.7, 128.4, 126.6, 126.3, 126.1, 39.5, 19.8, 12.7; IR (cm^{-1}) 1321, 1141; MS (EI) (*m*/*e*) 303 (M^+, 19), 288 (32), 231 (46), 167 (53), 165 (89), 152 (100), 115 (22); HRMS calculated for $C_{17}H_{21}NSO_2$ 303.1293, found 303.1293.

2′-Diethylsulfamoyl-5′-methylbiphenyl-2-carboxylic Acid Diethylamide (11b). Using the general procedure with the following materials [**6e** (0.2020 g, 0.57 mmol), **10b**[39] (0.3790 g, 1.71 mmol), K_3PO_4 (0.2656 g, 1.25 mmol), Pd(PPh_3)$_4$ (0.0334 g, 5.1 mol %) in DMF (20 mL); reflux for 26 h], followed by flash column chromatography (EtOAc/hexanes gradient: 10% → 20% → 30%) afforded **11b** (0.2119 g, 92%) as an opaque yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) 7.81 (bs, 1H), 7.53 (bs, 1H), 7.40−7.31 (m, 4H), 7.21 (d, J = 7.6 Hz, 1H), 3.47 (bs, 2H), 3.10 (bs, 6H), 2.37 (s, 3H), 1.11−1.04 (m, 9H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 169.5, 141.6, 138.2, 136.6, 136.4, 136.2, 128.9, 128.2, 128.0, 127.44, 127.36, 126.1, 125.6, 42.6, 41.6, 38.0, 21.1, 14.4, 13.8, 11.7; IR (cm^{-1}) 1629, 1459, 1430, 1324, 1145; MS (EI) (*m*/*e*) 403 (MH^+, 0.07), 330 (11), 266 (100), 194 (69), 165 (90), 136 (61); HRMS calculated for $C_{18}H_{20}NSO_3$ (M^+ − 72) 330.1181, found 330.1176.

Diethylcarbamoyl Acid 2′-diethylsulfamoyl-5′-methylbiphenyl-2-yl Ester (11c) and 2′-Hydroxy-5-methylbiphenyl-2-sulfonic Acid Diethylamide. Using the general procedure with the following materials [**2** (0.5069 g, 1.44 mmol), **10c** (0.6888 g, 2.91 mmol), K_3PO_4 (0.6306 g, 2.97 mmol), Pd(PPh_3)$_4$ (0.0831 g, 5.0 mol %) in DMF (60 mL); reflux for 42.5 h], flash column chromatography (5% EtOAc/hexanes) afforded **11c** (0.2887 g, 42%) as a clear oil and *N*,*N*-diethyl 2′-hydroxy-5-methylbiphenyl-2-sulfonamide (0.0877 g, 19%) as a clear oil; **11c**: ^{1}H NMR (300 MHz, $CDCl_3$) 8.00 (d, J = 8.1 Hz, 1H), 7.40−7.35 (m, 2H), 7.30−7.20 (m, 3H), 7.13 (s, 1H), 3.24−3.07 (m, 3H), 2.98−2.91 (m, 1H), 2.77 (q, J = 7.1 Hz, 4H), 2.37 (s, 3H), 1.05 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.1 Hz, 6H), 0.70 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 153.6, 148.7, 142.0, 136.5, 136.2, 133.1, 131.7, 131.2, 129.8, 128.7, 128.0, 124.0, 122.5, 41.9, 41.4, 41.1, 20.9, 14.3, 13.2, 13.1; IR (cm^{-1}) 1717, 1464, 1323, 1206, 1150; MS (CI) (*m*/*e*) 420 (M^+ + 2, 44), 419 (M^++1, 100), 346 (56), 100 (52); HRMS calculated for $C_{22}H_{31}N_2SO_4$ (MH^+) 419.2005, found 419.1992; 2′-hydroxy-5-methylbiphenyl-2-sulfonic acid diethylamide: ^{1}H NMR (300 MHz, $CDCl_3$) 8.03 (d, J = 8.1 Hz, 1H), 7.32−7.30 (m, 2H), 7.11−6.97 (m, 4H), 5.74 (bs, 1H), 2.90−2.66 (m, 4H), 2.42 (s, 3H), 0.97 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, acetone-d_6) 155.6, 143.5, 138.9, 138.8, 135.4, 133.0, 131.2, 130.3, 129.2, 128.3, 119.9, 116.9, 42.5, 21.5, 15.3; IR (cm^{-1}) 3409, 1451, 1312, 1199, 1138; MS (EI) (*m*/*e*) 319 (M^+, 8), 247 (24), 182 (33), 181 (96), 168 (100), 153 (43); HRMS calculated for $C_{17}H_{21}NSO_3$ 319.1242, found 319.1247. **Modified Procedure**. Using the general procedure with the following materials [**2** (0.2132 g, 0.60 mmol), **10c** (0.2868 g, 1.30 mmol), K_3PO_4 (0.2880 g, 1.36 mmol), Pd(PPh_3)$_4$ (0.0367 g, 5.3 mol %) in DMF (25 mL); reflux for 15 h] and the following modification [the residue from standard workup was dissolved in MeCN (20 mL), treated with K_2CO_3 (0.1165 g, 0.84 mmol) and $ClCONEt_2$ (0.11 Ml, 0.87 mmol), and heated to 100 °C for 20 h. The solution was cooled to room temperature, concentrated, and extracted into Et_2O, and the extract was dried (Na_2SO_4), subjected to filtration, and concentrated] followed by flash column chromatography (20% EtOAc/hexanes) afforded **11c** (0.2024 g, 87%) as a light yellow oil displaying spectroscopic data consistent with that presented above.

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Supporting Information Available: ^{13}C NMR spectra of all new compounds and ^{2}H NMR spectra for LDA metalation/CD_3OD quench experiments of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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