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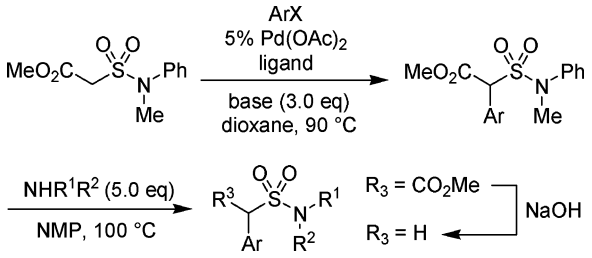
A New Strategy for the Synthesis of Benzylic Sulfonamides: Palladium-Catalyzed Arylation and Sulfonamide Metathesis

Jonathan B. Grimm, Matthew H. Katcher, David J. Witter, and Alan B. Northrup*

Department of Drug Design and Optimization, Merck Research Laboratories, Boston, Massachusetts 02115

alan_northrup@merck.com

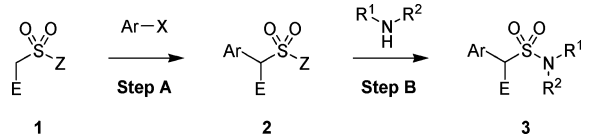
Received July 2, 2007



An efficient two-step strategy has been developed to access diversely functionalized benzylic sulfonamides. Execution of this strategy required the development of two reaction methods: the palladium-catalyzed cross-coupling of aryl halides with CH-acidic methanesulfonamides and a metathesis reaction between the resulting α-arylated sulfonamides and diverse amines. The broad scope of the cross-coupling process combined with a versatile sulfonamide metathesis constitutes an efficient strategy for the synthesis of various benzylic sulfonamides.

The sulfonamide is a key functional group in organic chemistry that is present both in the structures of natural products and also in marketed therapeutics such as Celecoxib for pain and inflammation,[1] Tipranavir for HIV/AIDS,[2] and Zonisamide for seizure.[3] During the course of two distinct medicinal chemistry programs we required access to diversely substituted benzylic sulfonamides. To enable rapid exploration of structure/activity relationships, we searched the literature for a strategy to build benzylic sulfonamides that met three essential requirements: (1) the sulfonamide moiety must be introduced at a late stage of the syntheses in the presence of sensitive functionality; (2) removable functional handles must be present to allow diversification of substituents on both the carbon and the nitrogen atoms bonded to sulfur as a final step of the synthesis; and (3) the diversification steps must be sufficiently mild and generally applicable to allow for incorporation of a range of sterically and electronically diverse substituents. As conventional approaches to preparing benzylic sulfonamides typically rely on free-radical processes, harsh oxidation conditions, and unstable sulfonyl chloride intermediates,[4] we decided to devise a new strategy for their construction. As shown in Scheme 1, our strategy required the development of the two new procedures that are the subject of this communication—a cross-coupling between an α-C−H activated, yet hydrolytically stable, sulfonyl chloride equivalent **1** and aryl halides (Step A) and a method for converting stable sulfonyl chloride equivalent **2** to the desired sulfonamides **3** (Step B).

SCHEME 1. Strategy for Preparing Benzylic Sulfonamides



The central C−C bond-forming event in our strategy relies on extending the scope of the palladium-catalyzed α-arylation of carbonyl compounds[5] to include substrates, such as **1**, containing a removable activating group, E, and a stable sulfonyl chloride equivalent (SO_2Z). The early, pioneering efforts of Buchwald, Hartwig and others focused largely on the arylation of ketones.[6] Since that time, the α-arylation chemistry has been expanded to include esters,[7] amides,[8] aldehydes,[9] nitriles,[10] nitroalkanes,[11] malonates,[12] sulfones,[13] and sulfoximines.[14] There are even two reports concerning sulfonamide *C*-arylations.

(1) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C *J. Med. Chem.* **1997**, *40*, 1347.

(2) Thaisrivongs, S.; Skulnick, H. I.; Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Johnson, P. D.; Aristoff, P. A.; Judge, T. M.; Gammill, R. B.; Morris, J. K.; Romines, K. R.; Chrusciel, R. A.; Hinshaw, R. R.; Chong, K.-T.; Tarpley, W. G.; Poppe, S. M.; Slade, D. E.; Lynn, J. C.; Horng, M.-M.; Tomich, P. K.; Seest, E. P.; Dolak, L. A.; Howe, W. J.; Howard, G. M.; Schwende, F. J.; Toth, L. N.; Padbury, G. E.; Wilson, G. J.; Shiou, L.; Zipp, G. L.; Wilkinson, K. F.; Rush, B. D.; Ruwart, M. J.; Koeplinger, K. A.; Zhao, Z.; Cole, S.; Zaya, R. M.; Kakuk, T. J.; Janakiraman, M. N.; Watenpaugh, K. D. *J. Med. Chem.* **1996**, *39*, 4349.

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(4) (a) Hill, B.; Liu, Y.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 4285. (b) Abdellaoui, H.; Depreux, P.; Lesieur, D.; Pfeiffer, B.; Bontempelli, P. *Synth. Commun.* **1995**, *25*, 1301. (c) Anderson, K. K. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: Oxford, 1979; Vol. 3, p 345. (d) For a creative and useful strategy limited to ammonia-derived benzylic and alkyl sulfonamides, see: Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002**, *43*, 8479.

(5) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234.

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(7) (a) Moradi, W. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7996. (b) Lee, S.; Beare, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8410. (c) Jørgensen, M.; Lee, S.; Liu, X.; Wolkowski, J. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 12557.

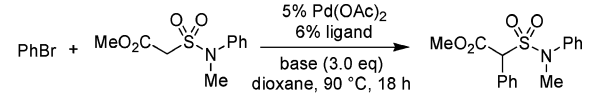
(8) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. (b) Cossy, J.; de Filippis, A.; Pardo, D. G. *Org. Lett.* **2003**, *5*, 3037.

(9) (a) Terao, Y.; Fukuoka, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 101. (b) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783.

(10) (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (b) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051. (c) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003. (d) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

10.1021/jo701431j CCC: $37.00
Published on Web 09/20/2007

TABLE 1. Optimization of Sulfonamide Arylation with PhBr



4 (1.0 eq) **5** (1.0 eq) **6**

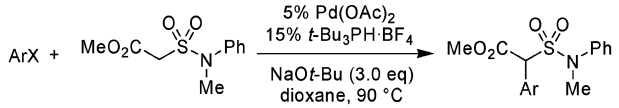
entry	ligand[a]	base	yield[b] (%)
1	*t*-$Bu_3PH{\cdot}BF_4$	NaO*t*-Bu	23
2	*t*-$Bu_3PH{\cdot}BF_4$	NaH	11
3	PCy_3	NaO*t*-Bu	31
4	PCy_3	NaH	36
5	dppf	NaO*t*-Bu	27
6	dppf	NaH	42
7	BINAP	NaO*t*-Bu	28
8	BINAP	NaH	15
9	PPh_3	NaO*t*-Bu	58
10	PPh_3	NaH	76

[a] Similar results were obtained with 15 mol % ligand. [b] Isolated yield of chromatographically pure **6**.

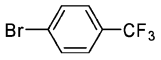
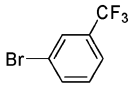
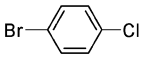
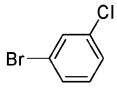
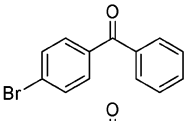
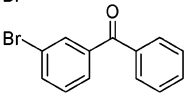
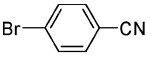
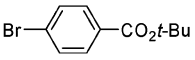
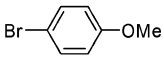
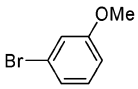
Middleton et al. described in the patent literature a single example of coupling an α-cyanosulfonamide to an aryl iodide.[15] More recently, Parkinson et al. reported the arylation of simple methanesulfonamides lacking activating substituents (e.g., CN, CO_2R, and $CONR_2$).[16] Neither example afforded the necessary synthetic flexibility we desired, so we sought to develop sulfonamide **5** as a novel substrate in this process (E = CO_2Me, Z = NMePh). We considered the methyl ester to be an ideal activating group due to the ease of its removal via decarboxylation and the rich chemistry of esters. The choice of *N*-methylaniline as a chloride surrogate relied on the hypothesis that the increased acidity of an aniline relative to that of an alkyl amine would render it a more suitable leaving group in a seldom-used sulfonamide metathesis reaction (Step B, vide infra).

The equimolar coupling between bromobenzene and sulfonamide **5** was employed as a model system to optimize this cross-coupling process. While other palladium precatalysts (such as Pd_2dba_3) were evaluated, uniformly higher yields were obtained when utilizing $Pd(OAc)_2$ with dioxane as solvent. A representative set of five ligands (*t*-$Bu_3PH{\cdot}BF_4$, PCy_3, DPPF, BINAP, and PPh_3) and two bases (NaO*t*-Bu and NaH) were then selected for investigation under those conditions (Table 1). An excess of a strong base (≥2.0 eq) was required for deprotonation of sulfonamide **5** and promotion of the catalytic cycle, as the arylation product **6** is presumably more acidic than either starting material. Optimal yield was achieved with PPh_3 as ligand and NaH as base to provide a 76% yield of **6**, although reaction with PPh_3 and NaO*t*-Bu also provided a reasonable yield (58%, entry 9). In all cases, the yields of **6** were reduced by undesired side reactions including biphenyl formation, hydrodehalogenation of bromobenzene, and decarboxylation of product **6** to form an unsubstituted benzylic sulfonamide.

TABLE 2. Sulfonamide Arylation Reaction Scope



7a-m (1.0 eq) **5** (1.0 eq) **8a-m**

entry	ArX		time	yield
1		**7a**	15 min	74%
2		**7b**	45 min	75%
3		**7c**	30 min	72%[a]
4		**7d**	45 min	70%[a]
5		**7e**	15 min	81%
6		**7f**	1 h	82%
7		**7g**	15 min	85%
8		**7h**	15 min	77%
9		**7i**	18 h[b]	39%
10		**7j**	18 h[b]	7%
11		**7k**	1 h[c]	53%
12		**7l**	1 h[c]	45%
13		**7m**	5 h[c]	53%

[a] Product resulted exclusively from coupling at position with bromine. [b] Performed at 120 °C. [c] Performed at 80 °C with 6 mol % PCy_3 as ligand.

With these results in mind, the newly optimized sulfonamide arylation conditions were applied to various substituted aryl halides (Table 2); however, conditions ideal for bromobenzene consistently resulted in poor conversions and low yields for a number of other substrates—particularly those with electron-withdrawing groups (e.g., aryl halides **7a**−**h**). It was quickly established that bulky trialkylphosphine ligands, in particular *t*-Bu_3P, led to increased conversions by reducing the propensity

(11) Vogl, E. M.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 106.
(12) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.
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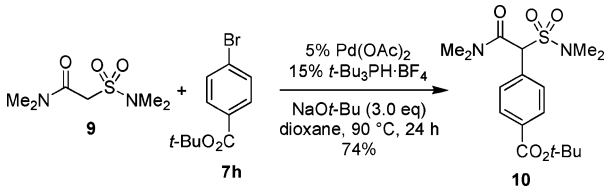
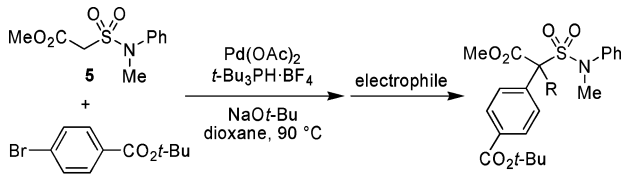
(15) Middleton, D. S.; Stobie, A. 1,2,3,4-Tetrahydro-1-naphthalenamine Compounds Useful in Therapy. (Pfizer Ltd.). WO 00/51972, 2000; *Chem. Abstr.* **2000**, *133*, 222454 .
(16) Zeevaart, J. G.; Parkinson, C. J.; de Koning, C. B. *Tetrahedron Lett.* **2005**, *46*, 1597.

SCHEME 2. Arylation of Amide-Activated Sulfonamide



SCHEME 3. One-Pot Arylation with Electrophilic Quench



electrophile	product	yield
NCS	**11a** (R = Cl)	72%
MeI	**11b** (R = Me)	66%
allyl bromide	**11c** (R = allyl)	75%

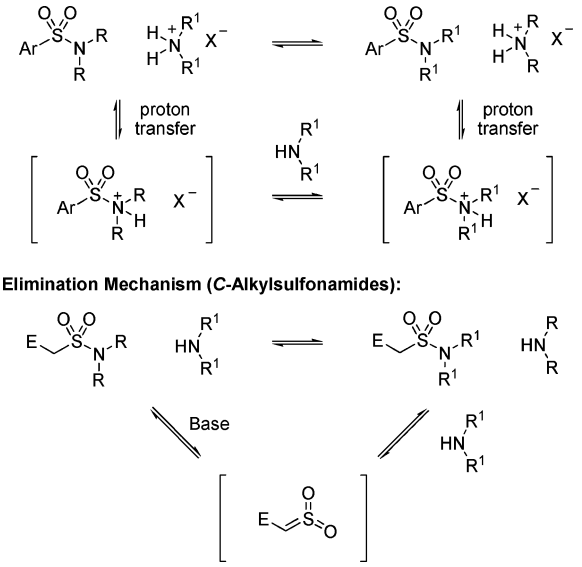
of those aryl halides to partition toward homocoupling and hydrodehalogenation reaction pathways. For aryl bromides bearing electron-withdrawing groups, reaction with **5** was generally complete within 1 h and consistently afforded arylated products **8a**−**h** in good to excellent yields (Table 2, entries 1−8, 70−85%). Importantly, the arylation conditions were tolerant of various functionalities including nitriles, esters, and ketones. Furthermore, couplings of chloro-substituted aryl bromides (**7c**−**d**) were highly halogen-selective, exclusively providing chlorophenylated products **8c**−**d** in good yield (entries 3−4, 70−72%).

The scope of the arylation reaction extended beyond electron-poor aryl bromides to include electron-rich, sterically demanding, and heterocyclic aryl halides. For example, 2-bromotoluene was a viable substrate for this transformation (entry 9, 39% yield), although it required an extended reaction time and an elevated reaction temperature (18 h, 120 °C). As demonstrated by entry 10, ortho-disubstituted aryl bromides were challenging substrates providing low conversion (entry 10, 7% yield). Electron-rich aryl bromides were also tolerated, as exemplified by reactions with 4-bromo- and 3-bromoanisole (entries 11 and 12, PCy_3 ligand, 53% and 45% yields, respectively). Heteroaryl halides, such as 2-chloropyridine, were also effectively coupled with sulfonamide **5** to provide pyridylsulfonamide **8m** in 53% yield (entry 13).

While the arylation reactions described in Table 2 employed the versatile acetate-derived sulfonamide **5**, other activated sulfonamides can be arylated under similar conditions (Scheme 2). For example, dimethylamide-containing sulfonamide **9** underwent a smooth cross-coupling reaction with bromide **7h** to afford arylated sulfonamide **10** in 74% yield, albeit with an extended reaction time (cf. entry 8, 77% yield, 15 min).

The formation of quaternary carbon centers is an important goal in synthetic chemistry. A one-pot, two-step process trapping the arylated products in situ with various electrophiles to form fully substituted carbon atoms would significantly extend the utility of this methodology.[12] To that end, sulfonamide **5** was coupled with *tert*-butyl 4-bromobenzoate (**7h**) under the optimized cross-coupling conditions in Table 2. After consumption of sulfonamide **5**, the desired electrophile was added to the reaction mixture (Scheme 3). *N*-Chlorosuccinimide (NCS), methyl iodide, and allyl bromide each functioned efficiently as electrophiles, providing the desired products **11a**−**c** in good to excellent yields (66−75% over two steps). This one-pot process allows for a rapid increase in molecular complexity and affords useful products containing a diversely functionalized quaternary carbon.

SCHEME 4. Proposed Mechanisms for Sulfonamide Metathesis

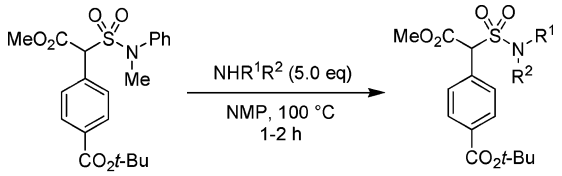


Having achieved the initial goal of developing a sulfonamide arylation reaction (Scheme 1, Step A), we next set out to perform a sulfonamide metathesis reaction (i.e., amine exchange, Scheme 1, Step B) with our coupled products **8a**−**m** to complete a two-step strategy for preparing diverse benzylic sulfonamides. While Klamann and co-workers[17] established over 50 years ago that an amine metathesis reaction was possible for *C*-arylsulfonamides and amine salts at elevated temperatures (≥200 °C), this transformation has been largely overlooked by the synthetic community and has not been previously demonstrated for simple *C*-alkylsulfonamides.[17d] In the present case, the high reaction temperatures and mildly acidic media of Klamann's conditions were unsuitable due to the propensity of compounds **8** to undergo decarboxylation and other decomposition reactions. In selecting new conditions for the sulfonamide metathesis reaction, we considered an alternative mechanistic hypothesis to Klamann's proposal[17c] that elimination of *N*-methylaniline followed by amine addition to a sulfene intermediate could provide the desired products under basic conditions (Scheme 4).

Gratifyingly, a mild and operationally simple sulfonamide metathesis procedure was developed that affords useful yields for a wide range of amine substrates (Table 3). The ease of the sulfonamide metathesis procedure readily lends itself to rapid analogue preparation and proved invaluable to our medicinal chemistry studies. As demonstrated by entries 1−4, primary amines, electron-deficient amines, and even aniline functioned efficiently as nucleophiles in this reaction (55−79% yield). Additionally, secondary amines were within the scope of this metathesis procedure including sterically demanding *N*,*N*-diisopropylamine (entries 5−7, 40−53% yield). As demonstrated in Scheme 5, a simple one-pot sulfonamide metathesis/

(17) (a) Klamann, D. *Oester. Chem.* **1953**, *54*, 299. (b) Klamann, D. *Liebigs Ann. Chem.* **1953**, *581*, 182. (c) Klamann, D.; Fabienke, E. *Chem. Ber.* **1959**, *92*, 712. (d) A survey of the CAS database (SciFinder, 2007) as well as the ISI Web of Science found a combined 19 publications citing refs 17a−c at the time of submission of this manuscript.

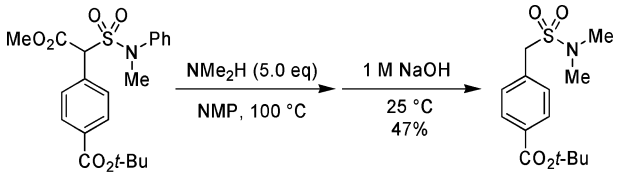
TABLE 3. Sulfonamide Metathesis Reaction



8h **12a-g**

entry	R^1	R^2	product	yield (%)
1	Ph	H	**12a**	79
2	Et	H	**12b**	55
3	CH_2CF_3	H	**12c**	58
4	CH_2CO_2Me	H	**12d**	65
5	Me	Me	**12e**	53
6	*i*-Pr	*i*-Pr	**12f**	46
7	Bn	Bn	**12g**	40

SCHEME 5. One-Pot Metathesis and Decarboxylation



8h **13**

decarboxylation procedure was developed that allows convenient access to α-unsubstituted benzylic sulfonamides via addition of NaOH to the metathesis reaction mixture after cooling to room temperature.

In summary, we have developed a convenient and efficient strategy for the synthesis of functionalized benzylic sulfonamides. Bulky monophosphine-based catalyst systems are uniquely suited to promoting the α-arylation of activated methanesulfonamides with a diverse range of aryl halides. In situ treatment of the cross-coupled products with various electrophiles afforded products containing functionalized quaternary carbon centers in a two-step, one-pot process. Additional derivatization of the products was accomplished through a novel sulfonamide metathesis procedure that provides synthetically useful benzylic sulfonamides with convenient functional handles. Future studies will investigate the mechanism and scope of the new sulfonamide metathesis procedure.

Experimental Section

General Procedure for Cross-Coupling with Sulfonamide 5 (Table 2). The following procedure for **8a** is representative. To a solution of sulfonamide **5** (200 mg, 0.82 mmol) in dioxane (5 mL) was added sodium *tert*-butoxide (237 mg, 2.47 mmol). After stirring for 15 min at room temperature, 4-bromobenzotrifluoride (185 mg, 0.82 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), and tri-*tert*-butylphosphonium tetrafluoroborate (35 mg, 0.12 mmol) were added. The mixture was degassed with N_2 for 20 min at room temperature. The flask was subsequently heated to 90 °C and stirred for 15 min. The pale yellow slurry was then cooled to room temperature, acidified with 0.5 N HCl, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography on silica gel (0−25% EtOAc/hexanes) afforded **8a** (234 mg, 74%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.73 (2H, d, J = 8.4 Hz), 7.63 (2H, d, J = 8.2 Hz), 7.37−7.33 (2H, m), 7.30−7.26 (3H, m), 5.16 (1H, s), 3.79 (3H, s), 3.21 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.2, 140.8, 132.8, 131.9 (q, J = 32.3 Hz), 131.1, 129.6, 127.8, 126.7, 125.8 (q, J = 3.9 Hz), 124.0 (q, J = 273.4 Hz), 70.0, 53.7, 40.3; HRMS (ESI) calcd for $C_{17}H_{16}F_3NO_4S$ $[M + H]^+$ 388.0830, found 388.0809.

General Procedure for the Sequential Cross-Croupling and Electrophilic Quench (Scheme 3). The following procedure for **11a** is representative. To a solution of sulfonamide **5** (300 mg, 1.23 mmol) in dioxane (10 mL) was added sodium *tert*-butoxide (356 mg, 3.70 mmol). After stirring for 15 min at room temperature, *tert*-butyl 4-bromobenzoate (476 mg, 1.85 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), and tri-*tert*-butylphosphonium tetrafluoroborate (45 mg, 0.19 mmol) were added. The mixture was degassed with N_2 for 20 min at room temperature. It was subsequently heated to 90 °C and stirred for 60 min. The reaction was cooled to room temperature, and *N*-chlorosuccinimide (247 mg, 1.85 mmol) in dioxane (3 mL) was added in one portion. After stirring for an additional 30 min at room temperature, the reaction was acidifed with 0.5 N HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography on silica gel (0−30% EtOAc/hexanes) afforded 404 mg (72%) of **11a** as a yellow gum. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.95 (2H, d, J = 8.6 Hz), 7.84 (2H, d, J = 8.4 Hz), 7.29−7.19 (5H, m), 3.73 (3H, s), 3.23 (3H, s), 1.58 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.1, 165.0, 142.2, 135.7, 133.7, 129.3, 129.1, 129.0, 127.7, 127.5, 88.0, 81.8, 54.6, 43.1, 28.4; HRMS (ESI) calcd for $C_{21}H_{24}ClNO_6S$ $[M + Na]^+$ 476.0911, found 476.0908.

General Procedure for Sulfonamide Metathesis (Table 3). The following procedure for **12a** is representative. To a solution of sulfonamide **8h** (100 mg, 0.238 mmol) in *N*-methyl-2-pyrrolidine (2 mL) was added aniline (111 mg, 1.19 mmol). The mixture was heated to 100 °C on a prewarmed hot plate and allowed to stir for 2 h. The reaction was cooled to room temperature. Flash chromatography on silica gel (EtOAc/hexanes) afforded **12a** (76.2 mg, 79%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.90 (2H, d), 7.47 (2H, d), 7.28 (2H, dd), 7.14 (4H, m), 5.12 (1H, s), 3.74 (3H, s), 1.55 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.8, 165.2, 136.5, 133.3, 132.5, 130.5, 130.0, 129.8, 125.9, 121.3, 81.7, 70.1, 53.8, 28.3; HRMS (ESI) calcd for $C_{20}H_{23}NO_6S$ $[M + Na]^+$ 428.1144, found 428.1125.

***tert*-Butyl 4-{[(dimethylamino)sulfonyl]methyl}benzoate (13).** To a solution of sulfonamide **8h** (100 mg, 0.238 mmol) in *N*-methyl-2-pyrrolidine (2 mL) was added 2 *M* dimethylamine in THF (0.6 mL, 1.2 mmol). The solution was heated to 100 °C in a prewarmed hot plate and allowed to stir for 1 h. The mixture was cooled to room temperature, and 1 M sodium hydroxide (1.2 mL, 1.2 mmol) was added. After 30 min, the reaction was added to aqueous sodium hydrogen carbonate (saturated) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (ethyl acetate/hexanes) afforded **13** (33.5 mg, 0.112 mmol, 47% yield) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.96 (2H, d), 7.43 (2H, d), 4.24 (2H, s), 2.70 (6H, s), 1.56 (9H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.4, 133.7, 132.5, 130.7, 130.0, 81.6, 55.9, 38.0, 28.4; HRMS (ESI) calcd for $C_{14}H_{21}NO_4S$ $[M + H]^+$ 300.1270, found 300.1303.

Acknowledgment. We thank Naim Nazef for HRMS analysis of all compounds and Rachael White for the preparation of sulfonamide **5**.

Supporting Information Available: General and detailed experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701431J