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Arylative Desulfonation of Diarylmethyl Phenyl Sulfone with Arenes Catalyzed by Scandium Triflate

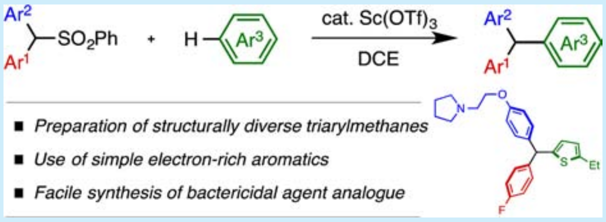
Masakazu Nambo,*[,†] Zachary T. Ariki,[‡] Daniel Canseco-Gonzalez,[†] D. Dawson Beattie,[‡] and Cathleen M. Crudden*[,†,‡]

[†]Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, 464-8601 Nagoya, Japan

[‡]Department of Chemistry, Queen's University, Chernoff Hall, Kingston, Ontario K7L 3N6, Canada

Ⓢ *Supporting Information*

ABSTRACT: A scandium-triflate-catalyzed arylative desulfonation of diarylmethyl phenyl sulfones with arenes and heteroarenes was established. A variety of both sulfone and arene substrates were reacted to afford symmetric and nonsymmetric triarylmethanes in good yields. Further transformations of the resulting triarylmethanes and application to the concise synthesis of a bactericidal agent analogue were also demonstrated.



The triarylmethane motif is a privileged structure[1] that is found in compounds with high biological activity[2] and is a key substructure in fluorescent organic materials[3] and probes.[4] To prepare triarylmethanes, a variety of chemical transformations including Friedel−Crafts reactions,[5] dehydroxylations of triarylmethanol derivatives,[6] and transition-metal-catalyzed cross-coupling reactions have been developed.[7] Recently, we described a highly modular synthesis of triarylmethanes via a Pd-catalyzed sequential arylation of methyl phenyl sulfone (Scheme 1).[8] The key step in the sequence is a unique C−SO$_2$R bond activation, which is used to install the final aryl group via a Pd-catalyzed coupling with arylboronic acids.

As an alternative strategy, we examined the use of mild Lewis acid catalysts to couple sulfones with simple, nonfunctionalized arenes. Although there have been two previous reports describing the arylation of sulfones,[9] substrate limitations in these reports are significant. Herein, we describe a method for the synthesis of a wide range of triarylmethanes from diarylmethyl phenyl sulfones without the need for precious metals or specific electronic requirements on the coupling partners. This method is illustrated in the preparation of a derivative of an antimycobacterial compound.

Scheme 1. Synthesis of Triarymethanes and Derivatives via Pd-Catalyzed Sequential Arylation and Transformation

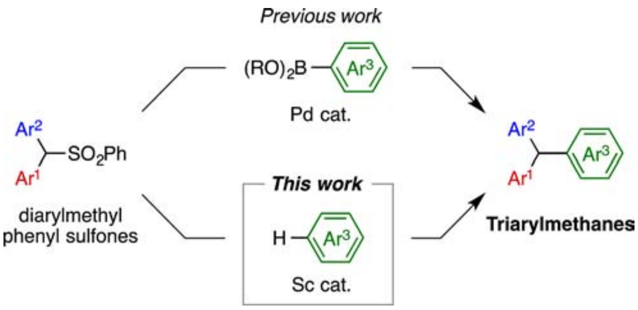
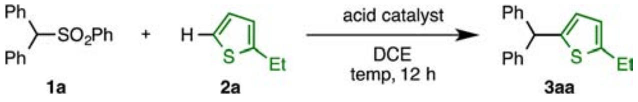


Table 1. Optimization of Arylative Desulfonation of Diphenylmethyl Phenyl Sulfone 1a with 2-Ethylthiophene 2a[a]



entry	acid catalyst (mol %)	temp (°C)	GC yield (%)[b]
1	FeCl$_3$·6H$_2$O (10)	80	8
2	Mg(OTf)$_2$ (10)	80	<1
3	Zn(OTf)$_2$ (10)	80	<1
4	AgOTf (10)	80	28
5	Cu(OTf)$_2$ (10)	80	36
6	In(OTf)$_3$ (10)	80	49
7	Sc(OTf)$_3$ (10)	80	83 (79)[d]
8	Sc(OTf)$_3$ (10)	60	16
9	Sc(OTf)$_3$ (10)	120	59
10[c]	Sc(OTf)$_3$ (10)	80	53
11	Sc(OTf)$_3$ (5)	80	15
12	TfOH (10)	80	38

[a]Conditions: **1a** (1 equiv), **2a** (3 equiv), acid catalyst, solvent (0.25 M), 12 h. [b]GC yield was determined using dodecane as an internal standard. [c]2 equiv of **2a** was used. [d]Isolated yield.

We began by screening various Lewis acid catalysts for the arylative desulfonation of diphenylmethyl phenyl sulfone **1a**, using 2-ethylthiophene **2a** as the arylation partner (Table 1). Transition metal catalysts, such as FeCl$_3$·6H$_2$O, which were reported by Kim in a related transformation,[9b] gave the desired product **3aa** in only 8% yield using 10% catalyst (entry 1). To find more effective catalysts, we focused on triflate salts. Although

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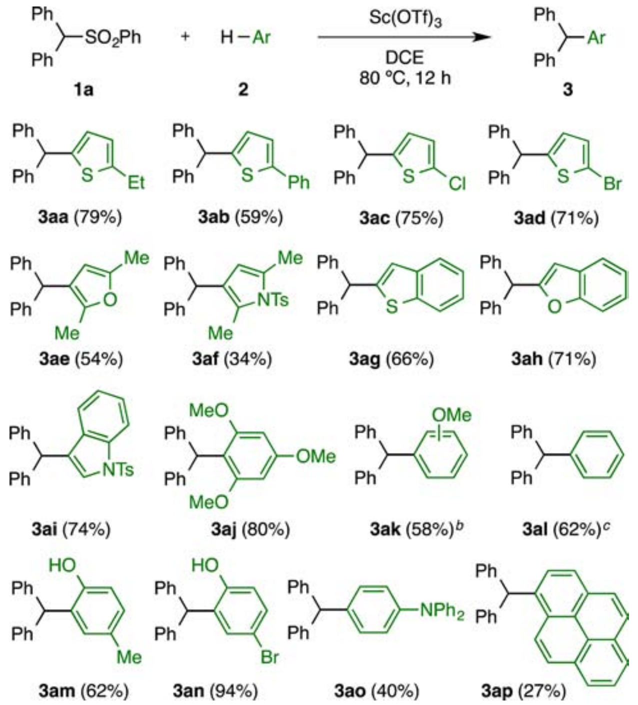
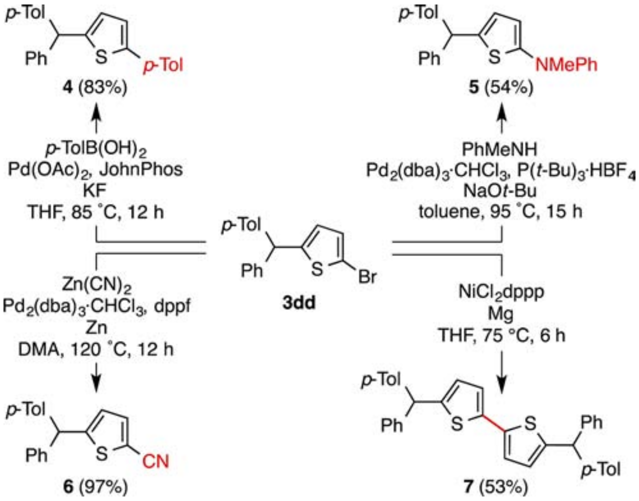
Chart 1. Scope of Arylative Desulfonation of 1a with Electron-Rich Heteroarenes and Arenes[a]



[a]Conditions: **1a** (1 equiv), **2** (3 equiv), Sc(OTf)$_3$ (10 mol %), DCE (0.25 M), 80 °C, 12 h. [b]Yield was *p*-isomer; *p*-isomer/*o*-isomer = 10:1 (determined by ^{1}H NMR). [c]Reaction was conducted in benzene at 100 °C.

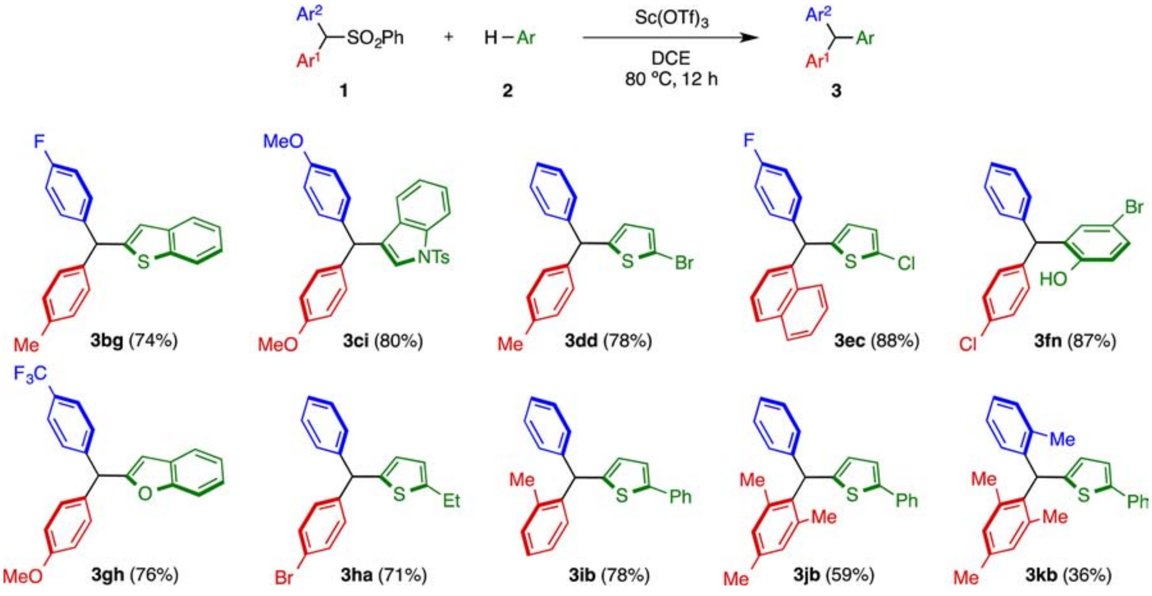
Scheme 2. Derivatization of 3dd



Mg(OTf)$_2$ and Zn(OTf)$_2$ showed poor reactivity (entries 2 and 3), AgOTf, Cu(OTf)$_2$, and In(OTf)$_3$ afforded the desired product in moderate yields (entries 4–6), and Sc(OTf)$_3$ emerged as the best catalyst (entry 7).[10] When the reaction was performed by varying the reaction temperature or using 2 equiv of **2a**, the yield was not improved (compare entries 7 and 10). TfOH, which could be generated from Sc(OTf)$_3$ with trace amounts of water, showed a lower yield, suggesting that this reaction is accelerated by the scandium cation (entry 12).

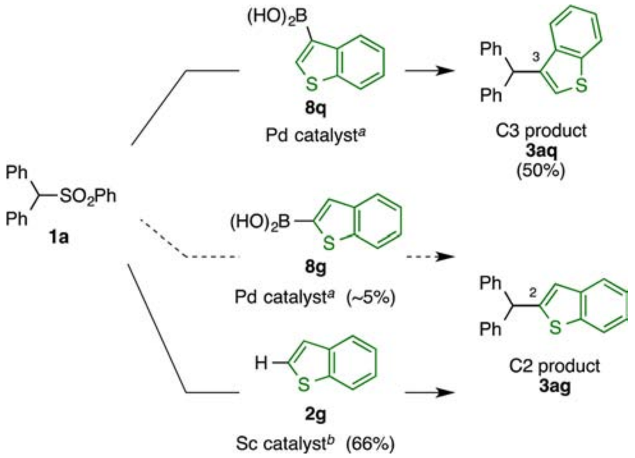
With optimized conditions in hand, we examined the scope of the arylative desulfonation of diphenylmethyl phenyl sulfone with various heteroarenes and arenes (Chart 1). 2-Substituted thiophenes such as 2-phenyl-, 2-chloro-, and 2-bromothiophene selectively reacted at the 5 position to give the corresponding products in good yields. When nonsubstituted thiophene was used, a mixture of mono- and dibenzhydrylated products was formed (see Supporting Information). Triarylmethanes bearing 2,5-dimethylated-3-furyl and 1-tosyl-3-pyrrolyl groups were obtained in moderate yield. Benzo[*b*]thiophene and 2,3-benzofuran reacted smoothly at the 2 position, while *N*-tosylindole reacted at the 3 position. Electron-rich benzenes were also reactive. For example, the reaction with 1,3,5-trimethoxybenzene afforded product in good yield, and the reaction of anisole gave products as a 10:1 mixture of *p*- and *o*-

Chart 2. Synthesis of Nonsymmetric Triarylmethanes[a]



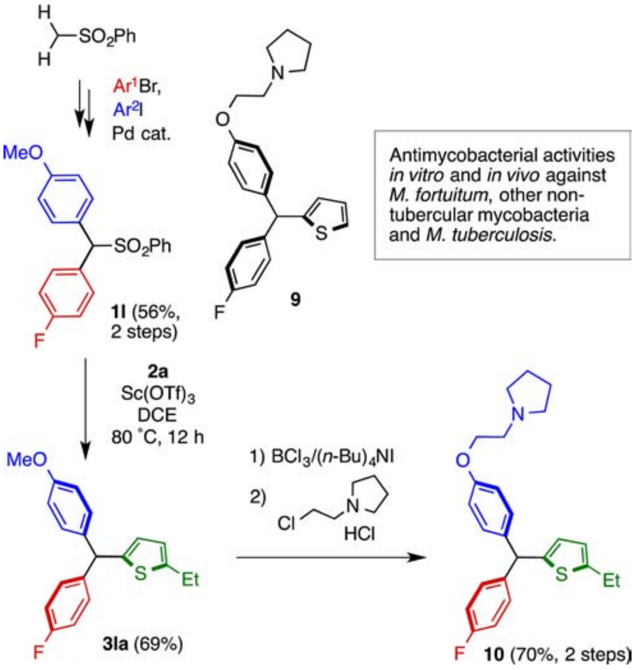
[a]Conditions: **1** (1 equiv), **2** (3 equiv), Sc(OTf)$_3$ (10 mol %), DCE (0.25 M), 80 °C, 12 h.

Scheme 3. Pd- and Sc-Catalyzed Selective Synthesis of Regioisomers



^{a}Condition: **8q** or **8g** (2 equiv), 5 mol % of [PdCl(allyl)]$_2$, 10 mol % of SIPr·HCl, 3 equiv of NaOH, dioxane/H$_2$O = 5:3, 150 °C, 12 h. ^{b}Condition: **2g** (3 equiv), 10 mol % of Sc(OTf)$_3$, DCE, 80 °C, 12 h.

Scheme 4. Synthesis of Bactericidal Agent Analogue 10



regioisomers. Triphenylmethane **3al** was obtained when benzene was used as a solvent. *p*-Substituted phenols proved to be useful substrates, yielding the corresponding triarylmethanes bearing unprotected *o*-hydroxy groups in good yields. Interestingly, triarylamine and pyrene, which are widely used for organic electronic materials, could be installed, albeit with lower efficiency.

Next, we applied this reaction to the synthesis of non-symmetric triarylmethanes using diarylmethyl phenyl sulfones as the starting materials. Representative results are shown in Chart 2. Electronically and structurally diverse triarylmethanes could be prepared in moderate to excellent yields. Substituents on the aryl group in sulfone substrates were not confined to electron-donating groups, with groups such as *p*-methyl, -fluoro, -chloro, and -bromo being well-tolerated. Even a sulfone bearing an electron-withdrawing *p*-trifluoromethyl group reacted smoothly when paired with a methoxy group on another aryl ring. Remarkably, sulfones bearing bulky aryl groups such as *o*-tolyl and mesityl groups also reacted in good yield. A decrease in reactivity was observed relative to unhindered substrates, but these substrates illustrate the high utility of this reaction for the synthesis of diverse, even sterically hindered, triarylmethanes.

Another significant advantage of the Sc-catalyzed method is that haloarenes can be employed in either partner without reaction at the halide. These substrates would lead to complex mixtures in Pd-catalyzed routes, and their inclusion in the triarylmethane products provides valuable opportunities for iterative coupling. Compounds **3dd**, **3ec**, **3fn**, and **3ha** are all capable of undergoing a second metal-catalyzed coupling reaction. To illustrate this concept, **3dd** was subjected to Pd-catalyzed Suzuki−Miyaura arylation with *p*-tolylboronic acid, yielding **4**. Buchwald−Hartwig amination with *N*-methylaniline was successful, yielding **5**, and cyanation with Zn(CN)$_2$ yielded **6** (Scheme 2). In addition, a unique 2,2′-bithiophene-bridged triarylmethane **7** was obtained by NiCl$_2$(dppp)-catalyzed dimerization of **3dd** in the presence of stoichiometric magnesium.

An added feature of the Sc-catalyzed method is that it can also provide access to compounds inaccessible using our previously developed Pd-catalyzed method.[8] For example, while the reaction of **1a** with benzo[*b*]thiophene-3-boronic acid **8q** afforded C3 product **3aq** in 50% yield, coupling with isomeric boronic acid **8g** gives less than 5% yield, most likely due to rapid protodeborylation of **8g**. However, as described in Scheme 3, the Sc-catalyzed reaction of **1a** with **2g** selectively affords **3ag** in 66% yield, illustrating the power of this complementary approach to the concise synthesis of triarylmethanes.

Finally, we illustrated the utility of this approach in the synthesis of a bactericidal agent analogue. The Srivastava group discovered that triarylmethanes such as **9** bearing a 2-thienyl group showed antimycobacterial activity in vitro and in vivo against *M. tuberculosis*, *M. fortuitum*, and other nontubercular mycobacteria.[11] Thus, modification of **9** focusing on the thiophene ring would be an attractive method to investigate structure−activity relationships and find more potent analogues. As shown in Scheme 4, (*p*-fluorophenyl)(*p*-methoxyphenyl)-methyl phenyl sulfone **1l** can be prepared from methyl phenyl sulfone through two stepwise Pd-catalyzed C−H arylations. Subsequent reaction with thiophene **2a** gave triarylmethane **3la** in 69% yield. Demethylation with BCl$_3$/(*n*-Bu)$_4$NI followed by alkylation afforded **10** in 51% yield over the two steps. Based on this simple procedure, a wide variety of biologically active triarylmethanes should be accessible.

In conclusion, we have established a general and easily accomplished Sc-catalyzed arylative desulfonation of diarylmethyl phenyl sulfones employing a variety of heteroarenes and arenes. This method can provide a wide variety of triarylmethanes, including those that are inaccessible by Pd-catalyzed reactions alone or which require sensitive aryl boronic acids. Several applications of this reaction were demonstrated by further transformations using transition metal catalysts and the synthesis of an antitubercular agent analogue. Further investigation of other transformations based on catalytic C−SO$_2$ bond activation and syntheses of biologically active triarylmethanes is currently underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00744.

Experimental procedures and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: mnambo@itbm.nagoya-u.ac.jp.
*E-mail: cruddenc@chem.queensu.ca.

Notes

The authors declare no competing financial interest.

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