Letter

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Development of Versatile Sulfone Electrophiles for Suzuki-Miyaura Cross-Coupling Reactions

Masakazu Nambo*[1], Eric C. Keske[2], Jason P. G. Rygus[2], Jacky C.-H. Yim[1], and Cathleen M. Crudden*[1,2]

[1]Institute of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Chikusa, Nagoya, Japan; [2]Queen's University, Department of Chemistry, Chernoff Hall, Kingston, Ontario, Canada

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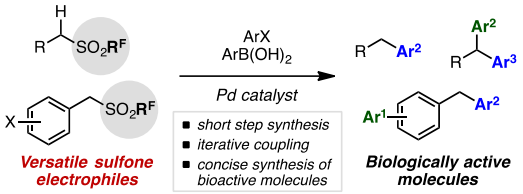
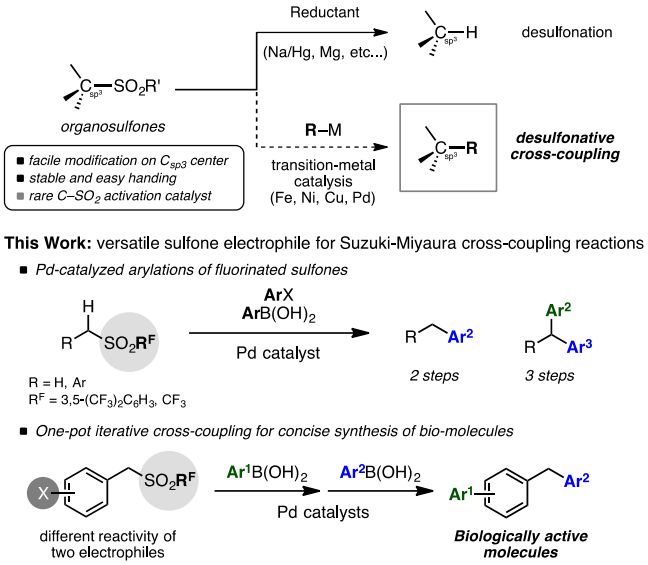
ABSTRACT: The development of fluorinated sulfone derivatives as versatile electrophiles for Suzuki-Miyaura cross coupling reactions is described. Introducing electron withdrawing groups on the aryl ring of the sulfone facilitates the Pd-catalyzed activation of C–SO_2 bonds. Cross coupling reactions with fluorinated sulfone electrophiles are reported leading to a variety of multiply arylated products in good yields. The reactivity of this unusual electrophile is benchmarked vs. common electrophiles and its use in iterative cross-couplings for concise synthesis of biologically active molecules is described.



Directing groups capable of influencing local reactivity are essential in modern organic synthesis.[1] In order to be truly useful, directing groups need to be readily removed or transformed, a feat that is often the weakest point in a synthetic method. The sulfone is an interesting functional group that permits the rapid functionalization of adjacent positions via deprotonation/alkylation, arylation or conjugate addition reactions.[2] However, after these reactions, removal of the sulfonyl group using Na amalgam or other highly reducing conditions is virtually the only choice (Figure 1).[3] Therefore the development of methods to introduce functional groups in place of the sulfone will provide tremendous opportunities for facile access to complex molecules.[2a, 4] Recently, our group reported preliminary studies on the use of the sulfone as an electrophile in cross-coupling reactions directed towards the modular synthesis of triarylmethanes.[5]

Despite the significance of this desulfonative coupling approach,[4d] the reaction required high reaction temperatures and was only effective with highly activated doubly benzylic sulfones. These two limitations are likely caused by the inherently low reactivity of the C–SO_2 bond. In particular, the lack of reactivity outside the benzhydryl substrate class does not bode well for the use of the sulfone as a general electrophile in cross-coupling chemistry. Herein we describe fluorinated sulfone electrophiles that can be employed in cross coupling of a variety of substrates (Figure 1). These rationally designed sulfones participate in iterative couplings with high selectivity, enabling the efficient synthesis of multiply-arylated alkanes[6] at temperatures as low as 40 °C. The versatile sulfone electrophile can be employed side-by-side with traditional electrophiles, providing alternative avenues for iterative couplings.[7] Unlike benzylic halides, benzylic sulfones have low toxicity, are easily handled, and can be carried through multiple transformations.

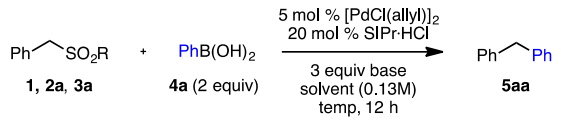
Figure 1. Transition metal-catalyzed desulfonative cross-coupling for the synthesis of multiply arylated methanes.



We began our studies with benzyl phenyl sulfone **1a**, a simple substrate that gives very low yields with simple phenyl sulfones as the coupling partners. Even at temperatures up to 150 °C yields were unacceptably low (Table 1, entries 1, 2). We

hypothesized that the introduction of electron-withdrawing groups on the sulfone would increase its eletrophilicity and facilitate metal-catalyzed C–SO_2 bond activation by stabilizing the sulfinic acid anion equivalent generated during C–SO_2 bond activation. Indeed, sulfones bearing electron-deficient substituents such as *p*-fluorophenyl, pyridyl, and *p*-trifluoromethylphenyl groups gave the desired product in significantly higher yield (Table 1, entries 3-5, 7). Although the pentafluorophenyl group was not effective (entry 8), 3,5-bis(trifluoromethyl)phenyl sulfone **2a** showed high reactivity (entries 9-11). A simple trifluoromethyl group as in triflone **3a** also proved highly successful, giving the desired product in 91% yield (entry 12).

Table 1. Investigation of substituent effect for desulfonative arylation and optimization of reaction conditions.

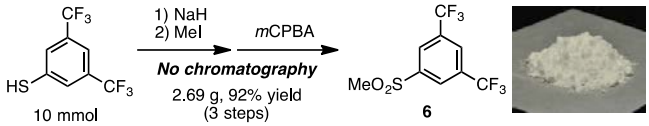


entry	R	base	solvent	temp (°C)	yield (%)[a]
1	Ph (**1a**)	NaOH	dioxane:H_2O[b]	120	27%
2	Ph (**1a**)	NaOH	dioxane:H_2O[b]	150	32%
3	4-FC_6H_4 (**1b**)	NaOH	dioxane:H_2O[b]	120	40%
4	2-pyridryl (**1c**)	NaOH	dioxane:H_2O[b]	120	48%
5	4-pyridyl (**1d**)	NaOH	dioxane:H_2O[b]	120	68%
6	4-$NO_2C_6H_4$ (**1e**)	NaOH	dioxane:H_2O[b]	120	<1%
7	4-$CF_3C_6H_4$ (**1f**)	NaOH	dioxane:H_2O[b]	120	51%
8	C_6F_5 (**1g**)	NaOH	dioxane:H_2O[b]	120	10%
9	3,5-$(CF_3)_2C_6H_3$ (**2a**)	NaOH	dioxane:H_2O[b]	120	86%
10[c]	3,5-$(CF_3)_2C_6H_3$ (**2a**)	K_3PO_4	EtOH	120	93%
11[d]	3,5-$(CF_3)_2C_6H_3$ (**2a**)	K_3PO_4	EtOH	120	94%
12[e]	CF_3 (**3a**)	Cs_2CO_3	toluene	100	91%

[a] Yield was determined by GC using dodecane as a internal standard. [b] dioxane:H_2O = 5:3. [c] 2.5 mol% $[PdCl(allyl)]_2$ and 10 mol % SIPr·HCl were used as catalyst, concentration was 0.25 M. [d] 5 mol % [PdCl(SIPr)(allyl)] and 5 mol % SIPr·HCl was used. [e] 5 mol % [PdCl(SIPr)(allyl)] and 1.5 equiv base were used.

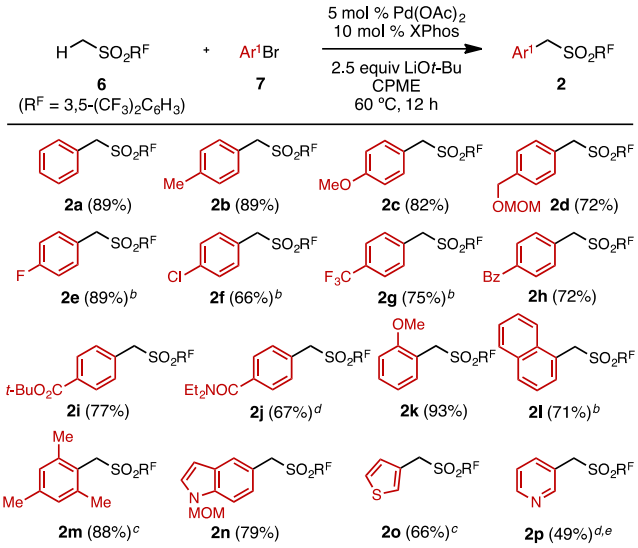
Fluorinated sulfone electrophiles can be readily prepared from ,methyl aryl sulfone **6**, which is itself an air stable solidthat is easily prepared from simple starting materials on a multi-gram scale without chromatographic purification (Scheme 1).[8] Starting from compound **6**, a variety of benzyla ted sulfones **2** can be prepared in good yields, without any double arylation (Table 2).[9] The reaction was compatible with important functional groups including ketone, ester, and amide groups. Bulky aryl groups such as 2-methoxyphenyl, 1-naphthyl, and mesityl groups were installed efficiently, and heteroaryl bromides afforded arylation products in good yields.

Scheme 1. Gram-scale synthesis of **6**.



The use of these more highly functional fluorinated sulfones in the Suzuki-Miyaura coupling reaction was then examined (Table 3). Bis(trifluoromethyl)aryl sulfones **2** and triflones **3** were reacted with various arylboronic acids to give the desired coupling products in good to excellent yields. Heteroarylboronic acids were less reactive, but at 5% catalyst loading, yields of 62-90% were routinely obtained. Electron-rich (**5cb**) and electron-deficient functional groups were tolerated in both partners (**5gc**). Esters (**5ia**), phenols (**5jn**), heteroaromatics (**5ko, 5os** and **5pt**), primary amides (**5os**) and π-extended groups (**6lp**) all gave the desired products in good yields. Bulky mesityl groups presented little problem (**5mq**), even in both partners, although in this case, reduced yields were observed (**5mr**).

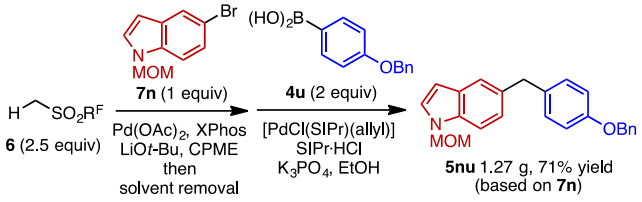
Table 2. Pd-catalyzed α-arylation of sulfone template **1** with bromoarenes **7**.



[a] Reaction condition: **6** (2.5 equiv), bromoarene **7** (1.0 equiv), $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), LiO*t*-Bu (2.5 equiv), CPME (0.2 M), 60 °C, 12 h. Isolated yield was given in parenthese. [b] 70 °C. [c] 80 °C. [d] 110 °C. [e] 10 mol % $Pd(OAc)_2$ and 20 mol % XPhos were used.

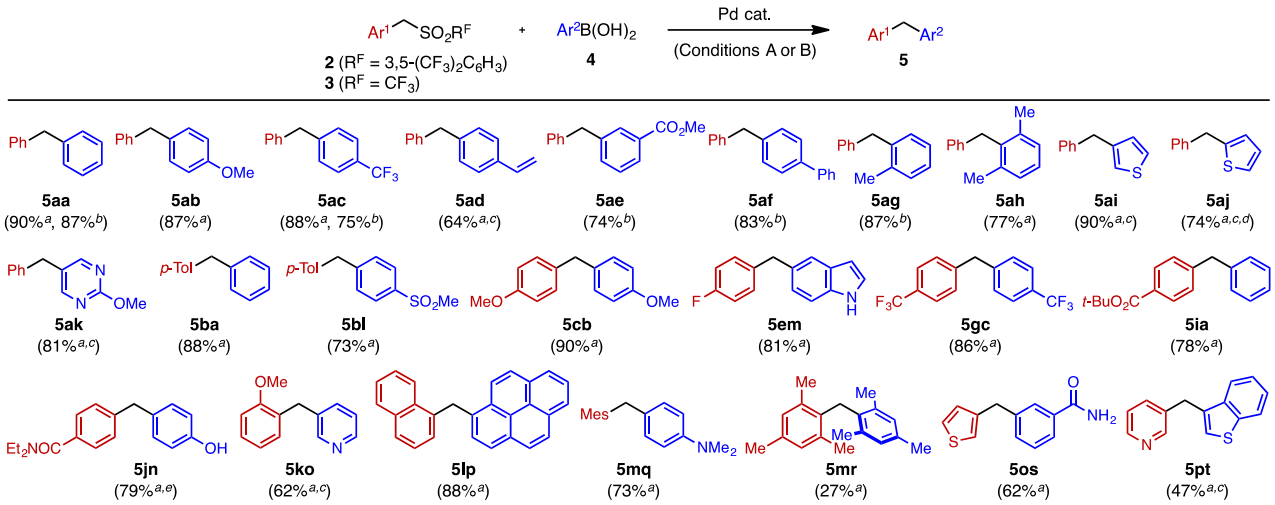
Having demonstrated that fluorinated sulfones serve as competent electrophiles in Suzuki-Miyaura cross couplings, we then sought to determine whether the arylation and coupling sequence could be accomplished in one-pot. In the event, *N*- MOM-5-bromoindole **7n** and *p*-benzyloxyphenyl-boronic acid **4u** were sequentially reacted with **6** in the presence of Pd catalysts to afford the desired product **5nu** in 71% yield, in one-pot, on gram scale (Scheme 2).

Scheme 2. One-pot gram-scale synthesis of unsymmetric diarylmethane **5nu** (R^F = 3,5-$(CF_3)_2C_6H_3$).



Fluorinated sulfones **2** can also be used in the synthesis of triarylmethanes under extremely mild conditions. Thus arylation of naphthyl derivative **2l** with iodobenzene can be affect-

Table 3. Pd-catalyzed desulfonative arylation of mono-arylated sulfones **2** and **3** with arylboronic acids **4**.

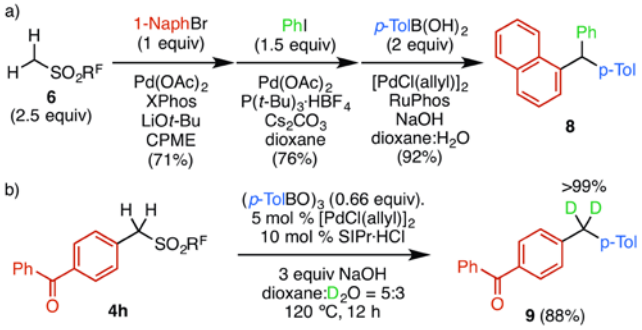


[a] Reaction conditions A: **2** (1 equiv), arylboronic acid **4** (2 equiv), $[PdCl(allyl)]_2$ (2.5 mol %), SIPr·HCl (10 mol %), K_3PO_4 (3 equiv), EtOH (0.2 M), 120 °C, 12 h. Isolated yield was given in parenthese. [b] Reaction conditions B: **3** (1 equiv), arylboronic acid **4** (1.5 equiv), [PdCl(allyl)(SIPr)] (5 mol %), Cs_2CO_3 (1.5 equiv), toluene (0.13 M), 100 °C, 18 h. Isolated yield was given in parenthese. [c] 5 mol % $[PdCl(allyl)]_2$ and 20 mol % SIPr·HCl were used. [d] ArB(pin) was used instead of $ArB(OH)_2$. [e] *p*-$TBSOC_6H_4B(OH)_2$ was used. TBS was removed by TBAF before purification.

ed using only Cs_2CO_3 as base, and the resulting diarylmethyl sulfone undergoes desulfonative coupling in excellent yield at only 40 °C (Scheme 3a). This demonstrates the higher activity of the C–SO_2 bond in fluorinated systems compared to simple phenyl derivatives, which require 120 °C to undergo desulfonative coupling.[5]

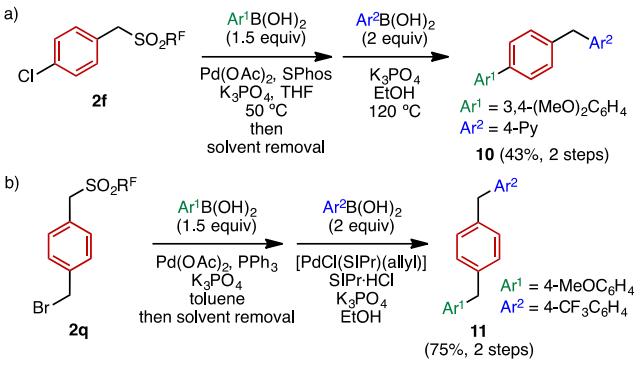
Sulfones are known to acidify α-protons, which can also be used to introduce isotopic labels prior to desulfonative coupling. For example, when the reaction of **2h** with *p*-tolylboroxine was carried out in mixture of dioxane and D_2O, coupling product **9** was obtained along with complete incorporation of deuterium at the benzylic position (Scheme 3b). Alternative methods for the preparation of deuterated diarylmethanes require reaction of diarylketones with expensive metal deuterides[10a] or H_2/D_2O in the presence of metal catalysts[10b] and would not be compatible with the ketone functionality present in **9** (Scheme 3b).

Scheme 3. Sequential α-functionalization and Pd-catalyzed desulfonative arylations (R^F = 3,5-$(CF_3)_2C_6H_3$).



To test the ability of the sulfone to participate in iterative coupling reactions in substrates containing multiple electrophiles, we prepared derivatives of **2** bearing aryl chlorides, and benzylic bromides (Scheme 4). In all cases, the halides underwent coupling when treated with simple triaryl or trialkylphosphine-modified Pd catalysts, while sulfones were unreactive under these conditions, requiring NHC–based catalysts for C–SO_2 bond activation. An important exception to this is the use of bulky electron-rich phosphines such as SPhos, which are able to promote the coupling of both halides and sulfones (Supporting information). Since the latter requires higher temperatures, we are able to effect the sequential one-pot introduction of two different aryl groups *using the same charge of Pd and same ligand*. Thus compound **10** could be produced by reaction of *p*-chlorobenzyl sulfone **2f** with two different boronic acids through merely a solvent switch and increase in temperature (Scheme 4a). Product **10** is one step away from a selective CYP17 inhibitor, under study for the treatment of prostate cancer.[11] Dibenzylic substrate **2q** was reacted sequentially and in the same pot with *p*-anisylboronic acid **4b** and *p*-trifluoromethylphenyl-boronic acid **4c** to give unsymmetric 1,4-(diarylmethyl)benzene **11** in 75% yield (Scheme 4b).

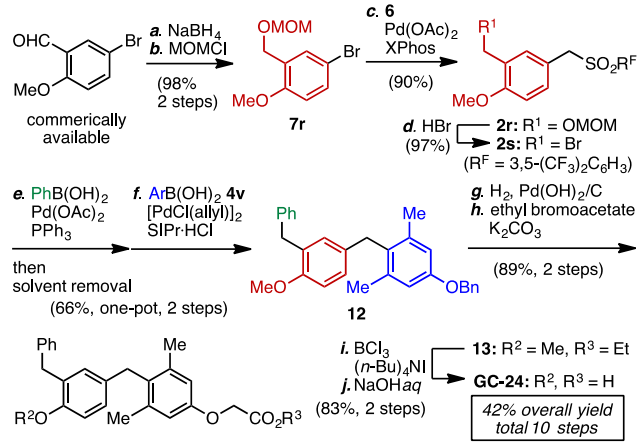
Scheme 4. Application to one-pot iterative cross-coupling reactions (R^F = 3,5-$(CF_3)_2C_6H_3$).



Finally, the utility of this sequential desulfonative cross coupling was demonstrated by the concise synthesis of the

synthetic thyroid hormone receptor β-selective analog, GC-24 as a potential agent for the treatment of obesity and arteriosclerosis (Scheme 5).[12] The Pd-catalyzed α-arylation of **6** with functionalized bromoarene **7r** gave the corresponding arylmethyl sulfone **2r**, which was smoothly converted into bromomethyl benzylsulfone **2s** by the use of HBr in AcOH, without any effect on the sulfonyl group. The sequential one-pot cross-coupling of **2s** with phenylboronic acid **4a** and 4-benzyloxy-2,6-dimethylphenylboronic acid **4v** was then carried out to give 1,3-diarylmethylbenzene **12** in 66% yield. Removal of the benzyl group followed by alkylation provided ester **13**. Demethylation and basic hydrolysis furnished GC-24. Overall, the synthesis of GC-24 was accomplished in 10 steps from commercially available materials in 42% yield. The high modularity and easy accessibility of our method provides enormous opportunities for the rapid discovery of potent thyroid hormone mimics.

Scheme 5. Short step synthesis of GC-24.



[a] Reaction conditions: (a) $NaBH_4$, MeOH, 0 °C-rt, (b) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt. (c) **6**, $Pd(OAc)_2$, XPhos, Li*Ot*-Bu, CPME, 70 °C. (d) HBr, AcOH, rt. (e) $PhB(OH)_2$, $Pd(OAc)_2$, PPh_3, K_3PO_4, toluene, 80 °C. (f) 4-benzyloxy-2,6-dimethylphenylboronic acid **4v**, $[PdCl(allyl)]_2$, SIPr·HCl, K_3PO_4, EtOH, 120 °C. (g) H_2 (1 atm), $Pd(OH)_2$/C, THF/MeOH, rt. (h) ethyl bromoacetate, K_2CO_3, acetone, reflux. (i) BCl_3, (*n*-Bu)$_4$NI,CH_2Cl_2, -78 °C-0 °C. (j) NaOH, MeOH/H_2O, rt.

In conclusion, we have demonstrated that fluorinated sulfone derivatives are effective electrophiles for Pd-catalyzed Suzuki-Miyaura reactions leading to the modular and selective synthesis of multiply-arylated methanes. Structurally diverse arylmethanes have many potential applications for organic materials and pharmaceuticals, and can be obtained in a facile and modular manner using our method. Most importantly, we have established a new electrophile capable of activation through transition-metal catalysts and compatible with diverse functionality. Mechanistic investigations, theoretical calculation and the development of other unique C–SO_2 bond transformations are currently underway in our laboratory.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website

Experimental details and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

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

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

SIPr·HCl, 1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride; *m*CPBA, *m*-Chloroperbenzoic acid; XPhos, 2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl; CPME, Cyclopentyl methyl ether; Bz, Benzoyl; MOM, Methoxymethyl; RuPhos, 2-Dicyclohexylphosphino-2',6'-diisopropoxy-1,1'-biphenyl; SPhos, 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl.

REFERENCES

(1) Reviews: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1993**, *93*, 1307–1370. (b) Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450–2494. (c) Wang, C.; Huang, Y. *Synlett*, **2013**, 24, 145-149. (d) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.*, **2014**, *43*, 6906–6919.

(2) (a) Trost, B. M.; Schmuff, N. R.; Miller, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 5979–5981. (b) Costa, A.; Nájera, C.; Sansano, J. M. *Synlett*, **2001**, *12*, 1881–1884. (c) Zheng, B.; Jia, T.; Walsh, P. J. *Org. Lett.* **2013**, *15*, 1690–1693.

(3) Review: (a) Alonso, D. A.; Nájera, C. *Desulfonylation Reactions. Organic Reactions.* **2009**, *72*, *2*, 367–656. Recent application, see: (b) Zhao, Y.; Ni, C.; Jiang, F.; Gao, B.; Shen, X.; Hu, J. *ACS catal.* **2013**, *3*, 631–634. (c) Su, Y.-M.; Hou, Y.; Yin, F.; Xu, Y.-M.; Li, Y.; Zheng, X.; Wang, Z.-S. *Org. Lett.* **2014**, *16*, 2958–2961. (d) Gui, J.; Zhou, Q.; Pan, C.-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853–4856.

(4) For chemical transformations of C–SO_2 bond, see: (a) Julia, M.; Righini, A.; Verpeaux, J.-N. *Tetrahedron Lett.* **1979**, *26*, 2393–2396. (b) Kasatkin, A. N.; Kulak, A. N.; Tolstikov, G. A.; Lomakina, S. I. *Izv. Akad. Nauk SSSR Ser. Khim.* **1988**, 2159–2166. (c) Moure, A. L.; Arrayás, R. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2012**, *134*, 7219–7222. (d) Denmark, S. E.; Cresswell, A. J. *J. Org. Chem.* **2013**, *78*, 12593–12628. (e) Bhanuchandra, M.; Murakami, K.; Vasu, D.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 10234–10238. (f) Nambo, M.; Ariki, Z. T.; Canseco-Gonzalez, D.; Beattie, D. D.; Crudden, C. M. *Org. Lett.* **2016**, *18*, 2339–2342.

(5) Nambo, M.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 742–746.

(6) For recent advances for the synthesis of multiply-arylated methanes by transition-metal catalysis, see: (a) Tellis, J. C.; Primer, D. N.; Molander, G. A. *Science*, **2014**, *345*, 433–436. (b) Mondal, S.; Panda,

G. *RSC Adv*. **2014**, *4*, 28317–28358. (c) Nambo, M.; Crudden, C. M. *ACS Catal.* **2015**, *5*, 4734–4742. (d) Zhou, Q.; Cobb, K. M.; Tan, T.; Watson, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 12057–12060.

(7) For recent example of iterative cross-coupling reactions, see: a) Woerly, E. M.; Roy, J.; Burke, M. D. *Nat. Chem.* **2014**, *6*, 484–491; b) Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386–390; c) Li, J.; Ballmer, S. G.; Gillis, E. P.; Fujii, S.; Schmidt, M. J.; Palazzolo, A. M. E.; Lehmann, J. W.; Morehouse, G. F.; Burke, M. D. *Science*, **2015**, *347*, 1221–1226; d) Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717–1726; e) Muto, K.; Yamaguchi, J.; Musaev, D. G.; Itami, K. *Nat. Commun.* **2015**, *6*, 7508; f) Seath, C. P.; Fyfe, J. W. B.; Molloy, J. J.; Watson, A. J. B. *Angew. Chem. Int. Ed.* **2015**, *54*, 9976–9979. g) Yamashita, Y.; Tellis, J. C.; Molander, G. A. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 12026–12029. h) Crudden, C. M.; Ziebenhaus, C.; Rygus, J. P. G.; Ghozati, K.; Unsworth, P. J.; Nambo, M.; Voth, S.; Hutchinson, M.; Laberge, V. S.; Maekawa, Y.; Imao, D. *Nat. Commun.* **2016**, *7*, 11065.

(8) The synthesis of **6** has been first reported by Nájera group for the direct Julia–Kocienski Olefination: Alonso, D. A.; Fuensanta, M.; Nájera, C.; Varea, M. *J. Org. Chem.* **2005**, *70*, 6406–6416.

(9) We attempted to synthesize methyl triflone for α-arylation, but it is difficult to isolate it as pure product.

(10) (a) Ofosu-Asante, K.; Stock, L. M. *J. Org. Chem.* **1990**, *55*, 3409-3410. (b) Sajiki, H.; Hattori, K.; Aoki, F.; Yasunaga, K.; Hirota, K. *Synlett*, **2002**, 7, 1149–1151.

(11) Hu, Q.; Jagusch, C.; Hille, U. E.; Haupenthal, J.; Hartmann, R. W. *J. Med. Chem.* **2010**, *53*, 5749–5758.

(12) Borngraeber, S.; Budny, M.-J.; Chiellini, G.; Cunha-Lima, S. T.; Togashi, M.; Webb, P.; Baxter, J. D.; Scanlan, T. S.; Fletterick, R. J. *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 15358–15363.