Organic LETTERS

Letter

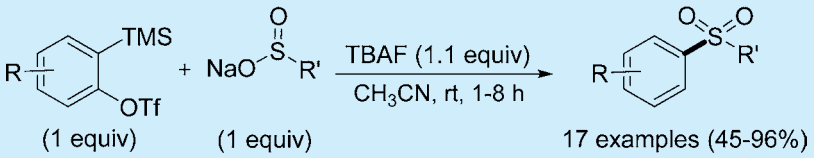
pubs.acs.org/OrgLett

Transition-Metal-Free C–S Bond Formation: A Facile Access to Aryl Sulfones from Sodium Sulfinates via Arynes

Virat G. Pandya and Santosh B. Mhaske*

CSIR-National Chemical Laboratory, Division of Organic Chemistry, Pune 411 008, India

Supporting Information



ABSTRACT: Sulfones have been attractive targets for synthetic organic chemists owing to their immense applications in medicinal, material, and synthetic chemistry. In this context, an efficient transition-metal-free process has been demonstrated, wherein a broad range of alkyl/aryl/heteroaryl sodium sulfinates react with varyingly substituted aryne precursors (*o*-silyl aryl triflates) under mild reaction conditions to afford structurally diverse sulfones in good to excellent yields.

Sulfones are ubiquitous in pharmaceuticals,[1] agrochemicals,[2] and advanced organic materials.[3] They are versatile intermediates in organic synthesis[4] and used in well-known organic transformations such as the Ramberg–Backlund reaction[5] and the Julia olefination.[6] Particularly, aryl sulfones are vital building blocks in organic[4] and medicinal chemistry.[7] They are commonly found in various drugs and possess a wide range of biological properties (Figure 1).[1,7,8]

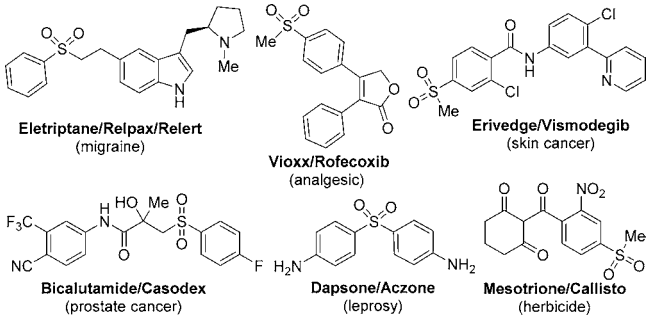


Figure 1. Drugs and pesticide containing aryl sulfone motif.

Development of efficient processes for the synthesis of sulfone derivatives has been a subject of enduring interest due to their compelling synthetic utility and substantial biological as well as material applications. The latest advancements authenticate the significance of this research area (Figure 2).[9−12] The methods by Jiang,[9] Mascitti and Toste,[10a] and Willis[11a] require a transition-metal catalyst, whereas the methods by Manolikakes,[12a,b] Kumar,[12c] and Willis[11c] are transition-metal-free. In addition to these recent advances numerous procedures for the synthesis of sulfones have been reported, which comprise the oxidation of sulfides and sulfoxides, sulfonylation of arenes, reaction between organomagnesium and organolithium compounds with sulfonate

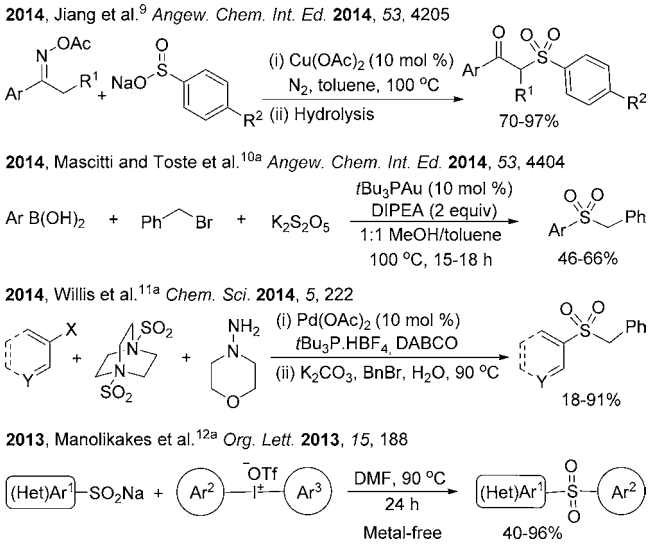


Figure 2. Latest advances in the field of sulfone synthesis.

esters, oxidative coupling of aryl boronic acids with aryl sulfonyl chlorides or other Pd- and Cu-catalyzed coupling reactions, and transition-metal-free synthesis from sodium sulfinates.[13] However, to the best of our knowledge the highly electrophilic aryne species has never been utilized to date for the synthesis of aryl sulfones.

Arynes have been successfully used for the development of several useful synthetic methodologies[14] and total synthesis of natural products.[15] There are several methods available for aryne generation,[15a,16,17] but the Kobayashi's protocol[16] using *o*-silyl aryl triflate and a fluoride source provides an excellent opportunity to demonstrate the application of arynes in various

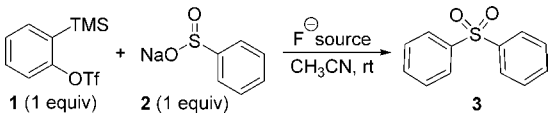
Received: June 27, 2014
Published: July 8, 2014

dx.doi.org/10.1021/ol5018646 | *Org. Lett.* 2014, 16, 3836–3839

useful synthetic methodologies. In continuation of our interest in the development and application of aryne methodologies,[18] we envisaged that the high reactivity of arynes could be explored to access synthetically useful and biologically important sulfone derivatives. In this context, we report herein a facile access to various aryl sulfones via arynes.

The protocol was first optimized using *o*-silyl aryl triflate **1** and sodium benzenesulfonate **2** (Table 1). Three different

Table 1. Optimization Studies[a]



1 (1 equiv) 2 (1 equiv) 3

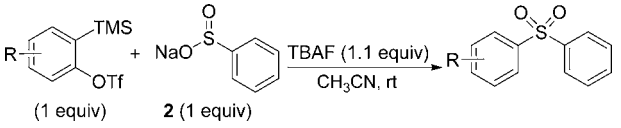
entry	F⁻ source (equiv)	additive[b]	time	yield
1	CsF (5.5)	–	6.0 h	86%
2	CsF (2.5)	A	6.0 h	88%
3	CsF (2.0)	A	7.0 h	82%
4	CsF (1.5)	A	7.0 h	56%
5	KF (2.0)	A	6.0 h	67%
6	TBAF (2.5)	–	1.5 h	95%
7	TBAF (1.5)	–	2.5 h	94%
8	**TBAF (1.1)**	–	**3.0 h**	**94%**
9	TBAF (1.0)	–	5.0 h	72%

[a]All the reactions were performed on 25 mg scale of *o*-silyl aryl triflate **1**. [b]A = 18-crown-6-ether (5 mol %).

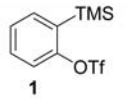
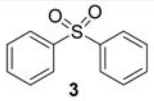
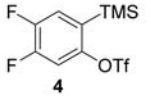
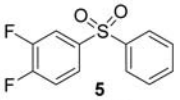
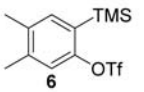
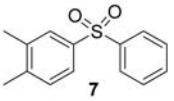
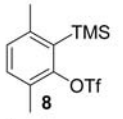
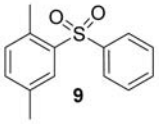
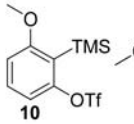
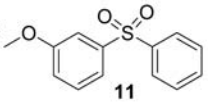
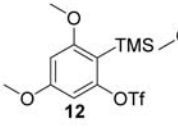
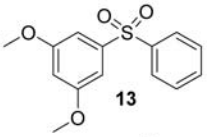
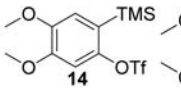
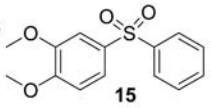
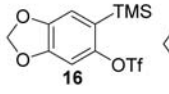
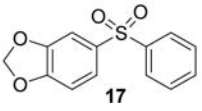
commonly used fluoride sources were screened under various conditions. Though CsF alone provided diaryl sulfone **3** in good yield (entry 1), it was required in large excess. Use of phase transfer catalyst 18-crown-6-ether reduced the required amount of CsF to 2 equiv maintaining almost the same yield. A further decrease in the amount of CsF reduced the yield drastically. The combination of KF (2 equiv) and 18-crown-6-ether provided sulfone **3** in a lower yield than that obtained under similar conditions using CsF. Use of TBAF as a fluoride source however proved to be fruitful and the final conditions were optimized, wherein the treatment of *o*-silyl aryl triflate **1** (1 equiv) and sodium sulfinate **2** (1 equiv) with TBAF (1.1 equiv) at room temperature furnished the desired sulfone **3** in excellent yield (entry 8). We believe that the high yields and faster reaction could be due to the effect of TBAF acting as a phase transfer catalyst in addition to being an efficient fluoride source.

The generality and scope of the developed protocol to obtain diaryl sulfones was demonstrated by varying *o*-silyl aryl triflates (Table 2). The synthesis of diaryl sulfone **3** worked equally well on a large scale (entry 1). Triflate **4** having two fluorine substituents also provided the corresponding sulfone **5** in good yield (entry 2). The substrates with two alkyl substituents *meta* (triflate **6**) and *ortho* (triflate **8**) to the reaction center furnished corresponding sulfones **7** and **9** respectively, but it is interesting to note that the presence of both methyl substituents away from the reaction center (entry 3) enables easy attack of a nucleophile, thus providing an excellent yield in a shorter reaction time. However, in the case of triflate **8** the steric hindrance probably increases the reaction time and reduces the yield. In the case of unsymmetrically substituted silyl triflate **10**, excellent regioselectivity was observed to obtain only the *meta* substituted diaryl sulfone **11**. Highly electron-rich silyl triflates **12**, **14**, and **16** furnished the desired sulfones **13**, **15**, and **17** respectively in good to excellent yields.

Table 2. Preparation of Sulfones from Various Silyl Triflates[a]



(1 equiv) **2** (1 equiv)

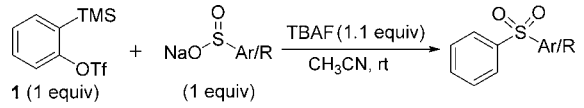
entry	silyl triflate	product	time	yield
1[b]	 **1**	 **3**	3 h	95%
2	 **4**	 **5**	6 h	76%
3	 **6**	 **7**	4 h	92%
4	 **8**	 **9**	8 h	55%
5	 **10**	 **11**	4 h	64%
6	 **12**	 **13**	4 h	86%
7	 **14**	 **15**	3 h	60%
8	 **16**	 **17**	6 h	96%

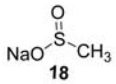
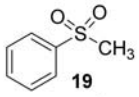
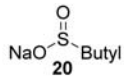
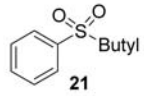
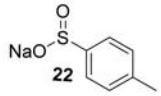
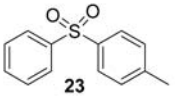
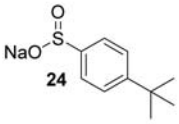
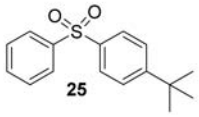
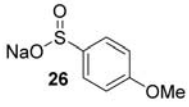
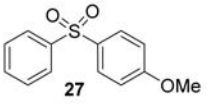
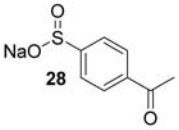
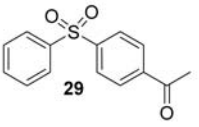
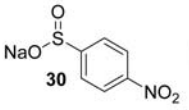
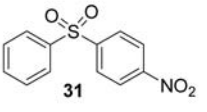
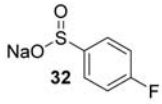
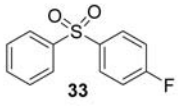
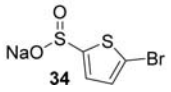
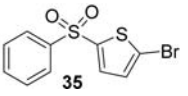
[a]All the reactions were performed on 50 mg scale of *o*-silyl aryl triflates. [b]This reaction was also performed on 500 mg scale of *o*-silyl aryl triflate **1**.

The scope of the protocol was also established by varying sodium sulfinates (Table 3). All the sodium sulfinates were prepared easily by using literature procedures.[12a] Methyl sodium sulfinate **18** furnished the alkyl-aryl sulfone **19** in good yield. We could obtain sulfone **21** in only 45% yield from butyl sodium sulfinate **20** using TBAF, but a very good yield was observed with CsF. The reason behind this observation is obscure. The alkyl substituted aryl sodium sulfinates **22** and **24** reacted smoothly to furnish diaryl sulfones **23** and **25** respectively in good yields. The sodium sulfinate **26** having an electron-donating group requires much less reaction time as compared to the sodium sulfinate **28** and **30** having electron-withdrawing groups to give corresponding sulfones **27**, **29**, and **31** respectively. Fluorine substituted sodium sulfinate **32** provides diaryl sulfone **33** in very good yield. Similar to the alkyl/aryl sodium sulfinates the heteroaryl sodium sulfinate **34** also worked well to furnish aryl-heteroaryl sulfone **35** having a labile bromine substituent, thus indicating the mildness of the developed protocol (entry 9, Table 3).

dx.doi.org/10.1021/ol5018646 | *Org. Lett.* 2014, 16, 3836−3839

Table 3. Preparation of Sulfones from Various Sulfinates[a]



entry	NaO–S(=O)–Ar/R	product	time	yield
1			4 h	75%
2			8 h 3 h	45%[b] 86%[c]
3			3 h	68%
4			4 h	85%
5			1 h	61%
6			4 h	54%
7			3 h	74%
8			3 h	86%
9			3 h	73%

[a]All the reactions were performed on 50 mg scale of *o*-silyl aryl triflate **1**. [b]TBAF (6 equiv). [c]CsF (4 equiv), 18-crown-6-ether.

In conclusion, we have demonstrated an efficient, transition-metal-free approach for the synthesis of aryl sulfones starting from easily accessible alkyl/aryl sodium sulfinates and *o*-silyl aryl triflates. The developed protocol is mild and robust and avoids the use of excess reagents or additives. It is capable of delivering a diverse array of sulfones such as diaryl sulfones, aryl-alkyl sulfones, and aryl-heteroaryl sulfones. It could also be extended to the double functionalization of arynes. Application of this C–S bond forming methodology for the synthesis of complex bioactive sulfone hetereocycles and existing drugs is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and copies of NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sb.mhaske@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

V.G.P. thanks UGC-New Delhi for the research fellowship. S.B.M. gratefully acknowledges generous financial support from DST, CSIR-ORIGIN, CSIR-OSDD New Delhi as well as CSIR-NCL (start-up grant).

■ REFERENCES

(1) (a) Harrak, Y.; Casula, G.; Basset, J.; Rosell, G.; Plescia, S.; Raffa, D.; Cusimano, M. G.; Pouplana, R.; Pujol, M. D. *J. Med. Chem.* **2010**, *53*, 6560. (b) Brot, E. C. A.; Keefe, D. K. J.; Haney, B. P.; Metcalfe, N.; Palmer, G. J.; Isbester, P. K. (CeNeRx BioPharma Inc.) US2008009542 (A1), 2008. (c) Schnellhammer, P. F. *Expert Opin. Pharmacother.* **2002**, *3*, 1313. (d) Zhu, Y. I.; Stiller, M. J. *J. Am. Acad. Dermatol.* **2001**, *45*, 420. (e) Tfelt-Hansen, P.; De Vries, P.; Saxena, P. R. *Drugs* **2000**, *60*, 1259 and references cited therein.

(2) (a) Xu, W.-M.; Han, F.-F.; He, M.; Hu, D.-Y.; He, J.; Yang, S.; Song, B.-A. *J. Agric. Food Chem.* **2012**, *60*, 1036. (b) Boger, P. *J. Pestic. Sci.* **2003**, *28*, 324. (c) Mitchell, G.; Bartlett, D. W.; Fraser, T. E. M.; Hawkes, T. R.; Holt, D. C.; Townson, J. K.; Wichert, R. A. *Pest Manage. Sci.* **2001**, *57*, 120.

(3) "Polysulfones": El-Hibri, M. J.; Weinberg, S. A. *Encyclopedia of Polymer Science and Technology*; Wiley: New York, 2002.

(4) (a) Yang, H.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2008**, *130*, 9238. (b) Crowley, P. J.; Fawcett, J.; Kariuki, B. M.; Moralee, A. C.; Percy, J. M.; Salafia, V. *Org. Lett.* **2002**, *4*, 4125. (c) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (d) Patai, S., Rappoport, Z., Stirling, C. J. M., Eds. *The Chemistry of Sulfones and Sulfoxides*; Wiley: New York, 1988.

(5) (a) Söderman, S. C.; Schwan, A. L. *J. Org. Chem.* **2012**, *77*, 10978. (b) Meyers, C. W.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510.

(6) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (b) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833.

(7) (a) Hartz, R. A.; Arvanitis, A. G.; Arnold, C.; Rescinito, J. P.; Hung, K. L.; Zhang, G.; Wong, H.; Langley, D. R.; Gilligan, P. J.; Trainor, G. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 934. (b) Otzen, T.; Wempe, E. G.; Kunz, B.; Bartels, R.; Lehwark-Yvetot, G.; Hänsel, W.; Schaper, K. J.; Seydel, J. K. *J. Med. Chem.* **2004**, *47*, 240 and references cited therein.

(8) (a) Rueeger, H.; Lueoend, R.; Rogel, O.; Rondeau, J.-M.; Möbitz, H.; Machauer, R.; Jacobson, L.; Staufenbiel, M.; Desrayaud, S.; Neumann, U. *J. Med. Chem.* **2012**, *55*, 3364. (b) Liu, K. K.-C.; Bailey, S.; Dinh, D. M.; Lam, H.; Li, C.; Wells, P. A.; Yin, M.-J.; Zou, A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5114. (c) Meadows, D. C.; Sanchez, T.; Neamati, N.; North, T. W.; Gervay-Hague, J. *Biorg. Med. Chem.* **2007**, *15*, 1127 and references cited therein.

(9) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 4205.

(10) (a) Johnson, M. W.; Bagley, S. W.; Mankad, N. P.; Bergman, R. G.; Mascitti, V.; Toste, F. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 4404. (b) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226.

(11) (a) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci.* **2014**, *52*, 12679. (b) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 12679. (c) Deeming, A. S.; Russell, C. J.; Hennessy, A. J.; Willis, M. C. *Org. Lett.* **2014**, *16*, 150. (d) Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* **2014**, *16*, 154.

(12) (a) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 188. (b) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 4972.

(c) Kumar, D.; Arun, V.; Pilania, M.; Chandra Shekar, K. P. *Synlett* **2013**, *24*, 831.
(13) Selected references: (a) Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G.-J. *Org. Lett.* **2014**, *16*, 50. (b) Cullen, S. C.; Shekhar, S.; Nere, N. K. *J. Org. Chem.* **2013**, *78*, 12194. (c) Liang, S.; Zhang, R.-Y.; Xi, L.-Y.; Chen, S.-Y.; Yu, X.-Q. *J. Org. Chem.* **2013**, *78*, 11874. (d) Zhou, X.; Luo, J.; Liu, J.; Peng, S.; Deng, G.-J. *Org. Lett.* **2011**, *13*, 1432. (e) Maloney, K. M.; Kuethe, J. T.; Linn, K. *Org. Lett.* **2011**, *13*, 102. (f) Bahrami, K.; Khodaei, M. M.; Arabi, M. S. *J. Org. Chem.* **2010**, *75*, 6208. (g) Gruffin, R. J.; Henderson, A.; Curtin, N. J.; Echalier, A.; Endicott, J. A.; Hardcastle, I. R.; Newell, D. R.; Noble, M. E. M.; Wang, L.-Z.; Golding, B. T. *J. Am. Chem. Soc.* **2006**, *128*, 6012. (h) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696. (i) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett.* **2007**, *9*, 3405. (j) Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Org. Lett.* **2004**, *6*, 2105. (k) Zhao, Z.; Messinger, J.; Schön, U.; Wartchow, R.; Butenschön, H. *Chem. Commun.* **2006**, 3007. (l) Charmant, J. P. H.; Dyke, A. M.; Lloyd-Jones, G. C. *Chem. Commun.* **2003**, 380 and references cited therein.
(14) (a) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (b) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140.
(15) (a) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (b) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766.
(16) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
(17) García-López, J.-A.; Greaney, M. F. *Org. Lett.* **2014**, *16*, 2338.
(18) (a) Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett.* **2013**, *15*, 2218. (b) Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett.* **2012**, *14*, 3994.

dx.doi.org/10.1021/ol5018646 | *Org. Lett.* 2014, 16, 3836−3839