A Mild and Base-Free Synthesis of Unsymmetrical Diaryl Sulfones from Arylboronic Acids and Arylsulfonyl Hydrazides

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Abstract: A mild and efficient synthesis of diaryl sulfones from arylboronic acids and arylsulfonyl hydrazides is described. Promoted by cupric acetate and in the absence of additional ligand and base, the cross-coupling reaction could afford a series of unsymmetrical diaryl sulfones in moderate to good yields at room temperature under neutral and ambient conditions.

Key words: diaryl sulfone, arylboronic acid, arylsulfonyl hydrazide, cross-coupling reaction, copper

Diaryl sulfones are attractive synthetic targets due to their promising biological properties such as antifungal, antibacterial, or antitumor activities. For example, some of them have been proven to be potent inhibitors of HIV-1 reverse transcriptase and consequently been identified as an important class of compounds which can address the toxicity and resistance problems of nucleoside inhibitors.[1] Moreover, diaryl sulfones are exceptionally versatile building blocks in organic synthetic chemistry.

Traditional approaches to the synthesis of diaryl sulfones mainly include the oxidation of corresponding sulfides[2] and the sulfonylation of suitable arenes in the presence of strong acids,[3] which generally suffer from narrow substrate scope, mixture of isomeric products or sometimes drastic reaction conditions. Recently, palladium- or copper-catalyzed coupling reactions between aryl halides or arylboronic acids and arylsulfinic acid salts or arylsulfonyl chlorides have been developed as a milder alternative.[4] Nevertheless, the high cost of palladium catalyst limits the practical application and some sulfenylating agents are sensitive to air and moisture. In addition, the high reaction temperature and inorganic or organic base were often necessary in these previously reported systems. Hence, improved methods, especially under mild and neutral conditions, for the preparation of aryl sulfones are still highly desirable from a synthetic practicality viewpoint.

In recent years, the readily accessible arylsulfonyl hydrazides have attracted considerable attention in organic synthesis as sulfonyl sources,[5] arylating reagents,[6] and very recently as aryl thiol surrogates.[7] On the other hand, arylboronic acids have been widely used as precursors in various cross-coupling reactions due to the easy availability and the compatibility with numerous functional groups. However, to the best of our knowledge, the C–S bond formation from arylboronic acids and arylsulfonyl hydrazides has not been explored so far. Herein, we wish to report a mild and efficient procedure to build diaryl sulfones promoted by cupric acetate under ligand- and base-free conditions.

Initially, the reaction was carried out between *p*-toluenesulfonyl hydrazide and phenylboronic acid, using 20 mol% of $Cu(OAc)_2·H_2O$ as catalyst in THF under air at 60 °C. However, only small amount of the desired cross-coupling product was found and at the same time, substantial amount of biphenyl resulted from consumption of phenylboronic acid and trace amount of di-*p*-tolyl sulfone derived from the undesired homocoupling of *p*-toluenesulfonyl hydrazide were determined by GC–MS (Table 1, entry 1). To our delight, after several attempts on the amount of $Cu(OAc)_2·H_2O$, we found that stoichiometric quantity of $Cu(OAc)_2·H_2O$ (1.5 equiv) as reaction promoter was necessary and effective and the target product was obtained in 65% yield (Table 1, entry 2). And the product yield did not increase by using more than 1.5 equivalents $Cu(OAc)_2·H_2O$, whereas it resulted in low yield of the corresponding product when less than 1.5 equivalents were adopted. When a control experiment was proceeded in the absence of $Cu(OAc)_2·H_2O$, it resulted in almost quantitative recovery of the substrate. Comparison of different copper sources indicated that $Cu(OAc)_2·H_2O$ was superior to the other copper(II) sources such as $Cu(NO_3)_2·5H_2O$, $CuSO_4·5H_2O$, $CuCl_2·2H_2O$, $CuBr_2·2H_2O$, and CuO. Indeed, only modest yield was obtained when they were tested as reaction promotor (Table 1, entries 3–7). In addition, it was obvious that copper(I) source was also inferior to $Cu(OAc)_2·H_2O$ under the same conditions (Table 1, entries 8–10). Then the effect of solvents was investigated, and it was observed that the desired product was almost not isolated in toluene and only about 20% of yield were obtained in PEG-400 or ethylene glycol. And 62% of yield were obtained when MeCN was used as a solvent (Table 1, entries 11–14). Although the reaction was also effective with polar aprotic solvents such as DMSO, DMF, and NMP, the best result was obtained when EtOH was used as a solvent (Table 1, entries 15–18). Generally, the presence of base was found to be necessary or crucial for the synthesis of aryl sulfones in previous reports, however, addition of bases such as Cs_2CO_3, K_2CO_3, K_3PO_4, and Et_3N did not improve the yield in this work (Table 1, entries 19–22). Further studies to investigate the optimal

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reaction temperature appeared that almost the same result was obtained even at room temperature. Moreover, the reaction was cleaner at room temperature than at 60 °C, which is consistent with the observation for the reaction of boronic acids with sulfinic acid salts reported by Evans.[8] Indeed, the homocoupling of *p*-toluenesulfonyl hydrazide was advantageous at higher temperature. And the change from air to oxygen did not affect the conversion, which might improve its operational simplicity. Therefore, 1.5 equivalents of $Cu(OAc)_2 \cdot H_2O$ in EtOH at room temperature under air for six hours was chosen as the optimal conditions for the synthesis of diphenyl sulfone from *p*-toluenesulfonyl hydrazide and phenylboronic acid.

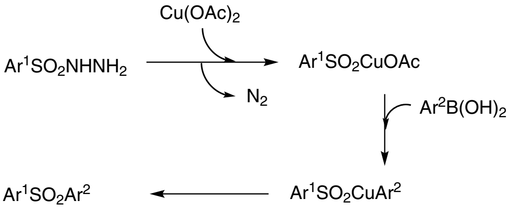
Table 1 Optimization of Reaction Conditions[a]

Entry	Catalyst	Solvent	Yield (%)[b]
1[c]	$Cu(OAc)_2 \cdot H_2O$	THF	15
2	$Cu(OAc)_2 \cdot H_2O$	THF	65
3	$Cu(NO_3)_2 \cdot 5H_2O$	THF	38
4	$CuSO_4 \cdot 5H_2O$	THF	15
5	$CuCl_2 \cdot 2H_2O$	THF	20
6	$CuBr_2 \cdot 2H_2O$	THF	23
7	CuO	THF	18
8	CuI	THF	35
9	CuBr	THF	30
10	CuCl	THF	28
11	$Cu(OAc)_2 \cdot H_2O$	toluene	<5
12	$Cu(OAc)_2 \cdot H_2O$	PEG-400	20
13	$Cu(OAc)_2 \cdot H_2O$	ethylene glycol	22
14	$Cu(OAc)_2 \cdot H_2O$	MeCN	62
15	$Cu(OAc)_2 \cdot H_2O$	EtOH	78
16	$Cu(OAc)_2 \cdot H_2O$	DMF	70
17	$Cu(OAc)_2 \cdot H_2O$	DMSO	68
18	$Cu(OAc)_2 \cdot H_2O$	NMP	57
19[d]	$Cu(OAc)_2 \cdot H_2O$	EtOH	76
20[e]	$Cu(OAc)_2 \cdot H_2O$	EtOH	74
21[f]	$Cu(OAc)_2 \cdot H_2O$	EtOH	70
22[g]	$Cu(OAc)_2 \cdot H_2O$	EtOH	62

[a] Reaction conditions: phenylboronic acid (1.2 mmol), *p*-toluenesulfonyl hydrazide (1.0 mmol), catalyst (1.5 mmol), solvent (2.0 mL), r.t., 6 h, in air.
[b] Isolated yield.
[c] $Cu(OAc)_2 \cdot H_2O$ (0.2 mmol).
[d] Cs_2CO_3.
[e] K_2CO_3.
[f] K_3PO_4.
[g] Et_3N.

The substrate scope was found to be very general for the cross-coupling reaction under the optimized reaction conditions, and a range of diaryl sulfones was prepared in moderate to good yields as listed in Table 2. It is noteworthy that either an electron-donating or an electron-withdrawing group such as methyl, methoxy, fluoro, chloro, bromo, acetyl, nitro, and trifluoromethyl was introduced into the diaryl sulfones without any problem by employing arylboronic acid bearing such a group on the aromatic ring at *para* or *meta* position (Table 2, entries 1–15). In general, the expected product yields were higher with arylboronic acids bearing electron-donating substituents whereas the use of arylboronic acids containing electron-withdrawing substituents led to the products in modest isolated yields. Unfortunately, the same group at *ortho* position afforded a poor yield with the reaction mixture probably due to the steric effect. Of particular interesting, under the reaction conditions, bromo and chloro substituents on the arylboronic acid moiety did not participate in the coupling reaction, which could allow for further functionalization on the aromatic ring (Table 2, entries 6, 7, and 10).

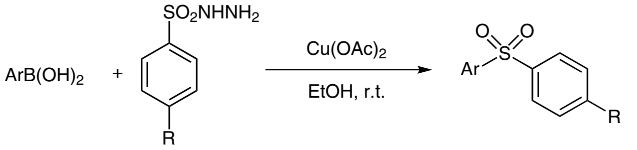
The scope of arylsulfonyl hydrazide was subsequently examined in the coupling reaction with phenylboronic acid under the optimized reaction conditions. It was shown that a variety of arylsulfonyl hydrazides could react smoothly in this reaction, thus afforded the desired products in moderate to good yields, no matter if bearing electron-donating or electron-withdrawing functional groups (Table 2, entries 16–21). Similarly, the reaction of bromo- and chloro-substituted sulfonyl hydrazides exhibited excellent chemoselectivity, that is, only the sulfonyl hydrazide group occurred and the bromo and chloro groups were well tolerated. According to our experimental results and proposed mechanism reported in the literatures,[4f,6c] a probable and simple reaction pathway for the cross-coupling of arylsulfonyl hydrazides and arylboronic acids to prepare diaryl sulfones is given in Scheme 1.



Scheme 1 Plausible reaction pathway for the cross-coupling

In summary, we have developed an efficient and convenient route to a variety of diaryl sulfones from readily available arylsulfonyl hydrazides and arylboronic acids, promoted by cupric acetate in the absence of additional ligand and base. The reaction conditions are mild and neutral and avoid the use of excess reagents or additives.

Table 2 Synthesis of Diaryl Sulfones from Various Arylboronic Acids and Arylsulfonyl Hydrazides[a,9]



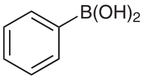
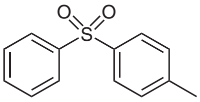
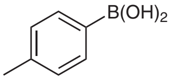
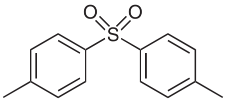
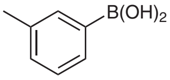
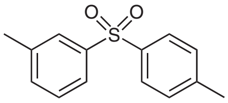
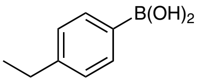
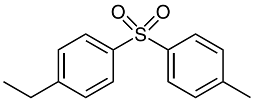
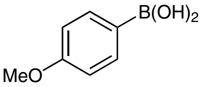
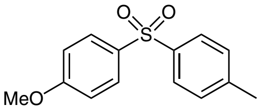
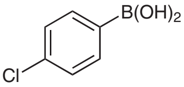
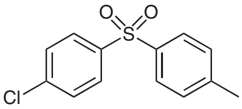
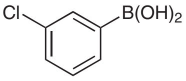
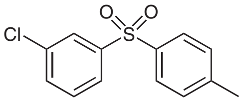
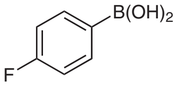
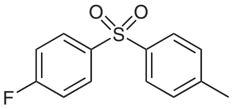
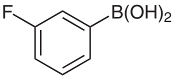
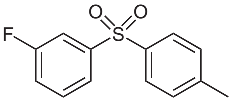
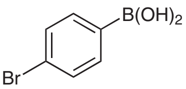
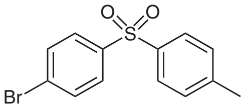
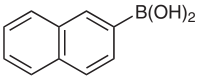
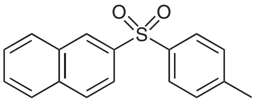
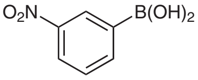
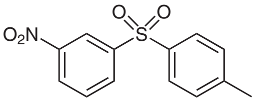
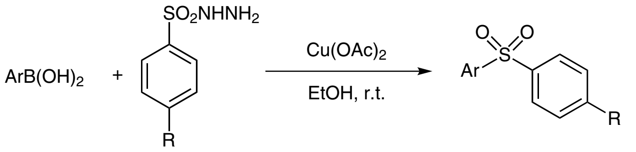
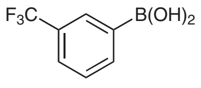
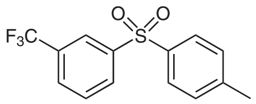
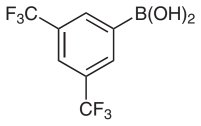
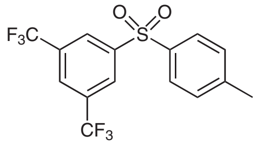
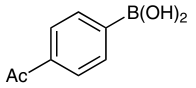
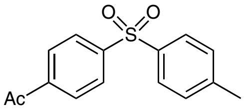
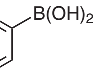
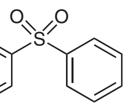
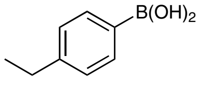
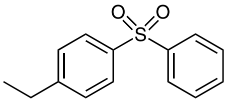
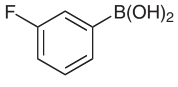
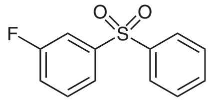
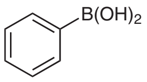
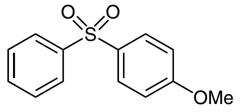
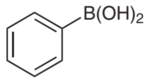
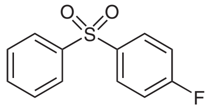
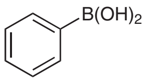
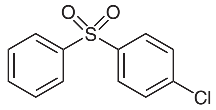
Entry	Arylboronic acid	R	Sulfone product	Yield (%)[b]
1		Me		78
2		Me		80
3		Me		76
4		Me		82
5		Me		86
6		Me		79
7		Me		75
8		Me		68
9		Me		60
10		Me		70
11		Me		65
12		Me		50

Table 2 Synthesis of Diaryl Sulfones from Various Arylboronic Acids and Arylsulfonyl Hydrazides[a,9] (continued)



Entry	Arylboronic acid	R	Sulfone product	Yield (%)[b]
13		Me		52
14		Me		45
15		Me		48
16		H		73
17		H		75
18		H		57
19		OMe		83
20		F		66
21		Cl		70

[a] Reaction conditions: arylboronic acid (1.2 mmol), arylsulfonyl hydrazide (1.0 mmol), $Cu(OAc)_2$ (1.5 mmol), EtOH (2.0 mL), r.t., 6 h, in air.
[b] Isolated yield.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

(1) (a) Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. K.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. A. *J. Med. Chem.* **1993**, *36*, 1291. (b) Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; La Colla, P. *J. Med. Chem.* **1996**, *39*, 522. (c) Jones, T. R.; Webber, S. E.; Varney, M. D.; Reddy, M. R.; Lewis, K. K.; Kathardekar, V.; Mazdiyasni, H.; Deal, J.; Nguyen, D.; Welsh, K. M.; Webber, S.; Johnston, A.; Matthews, D. A.; Smith, W. W.; Janson, C. A.; Bacquet, R. J.; Howland, E. F.;

Booth, C. L. J.; Herrmann, S. M.; Ward, R. W.; White, J.; Bartlett, C. A.; Morse, C. A. *J. Med. Chem.* **1997**, *40*, 677. (d) Dinsmore, C. J.; Williams, T. M.; O'Neill, T. J.; Liu, D.; Rands, E.; Culberson, J. C.; Lobell, R. B.; Koblan, K. S.; Kohl, N. E.; Gibbs, J. B.; Oliff, A. I.; Graham, S. L.; Hartman, G. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3301. (e) Sun, Z. Y.; Botros, E.; Su, A. D.; Kim, Y.; Wang, E.; Baturay, N. Z.; Kwon, C. H. *J. Med. Chem.* **2000**, *43*, 4160. (f) Doherty, G. A.; Kamenecka, T.; McCauley, E.; Van Riper, G.; Mumford, R. A.; Tonga, S.; Hagmanna, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 729. (g) Pal, M.; Veeramaneni, V. R.; Nagabelli, M.; Kalleda, S. R.; Misra, P.; Casturib, S. R.; Yeleswarapua, K. R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1639. (h) 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. (i) 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.

(2) (a) Aldea, R.; Alper, H. *J. Org. Chem.* **1995**, *60*, 8365. (b) Reddy, T. I.; Varma, R. S. *Chem. Commun.* **1997**, *5*, 471. (c) Al-Maksoud, W.; Daniele, S.; Sorokin, A. B. *Green Chem.* **2008**, *10*, 447. (d) Rahimizadeh, M.; Rajabzadeh, G.; Khatami, S. M.; Eshghi, H.; Shiri, A. *J. Mol. Catal. A: Chem.* **2010**, *323*, 59. (e) Rostami, A.; Akradi, J. *Tetrahedron Lett.* **2010**, *51*, 3501.

(3) (a) Graybill, B. M. *J. Org. Chem.* **1967**, *32*, 2931. (b) Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* **1984**, 323. (c) Choudary, B. M.; Chowdari, N. S.; Kantam, M. L. *J. Chem. Soc., Perkin Trans* **2000**, *1*, 2689. (d) Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, *66*, 8616. (e) Frost, C. G.; Hartley, J. P.; Whittle, A. J. *Synlett* **2001**, 830. (f) Bandgar, B. P.; Kasture, S. P. *Synth. Commun.* **2001**, *31*, 1065.

(4) (a) Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, *36*, 6239. (b) Baskin, J. M.; Wang, Z. *Org. Lett.* **2002**, *4*, 4423. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 4719. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Synlett* **2003**, 361. (e) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608. (f) Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Org. Lett.* **2004**, *13*, 2105. (g) Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 2696. (h) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Org. Lett.* **2007**, *9*, 3405. (i) Huang, F.; Batey, R. A. *Tetrahedron* **2007**, *63*, 7667. (j) Bian, M.; Xu, F.; Ma, C. *Synthesis* **2007**, 2951. (k) Reeves, D. C.; Rodriguez, S.; Heewon, L.; Haddad, N.; Krishnamurthy, D.; Senayake, C. H. *Tetrahedron Lett.* **2009**, *50*, 2870.

(5) (a) Ballini, R.; Marcantoni, E.; Petrin, M. *Tetrahedron* **1989**, *45*, 6791. (b) Kamijo, S.; Al-Masum, M.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 691. (c) Taniguchi, T.; Idota, A.; Ishibashi, H. *Org. Biomol. Chem.* **2011**, *9*, 3151. (d) Li, X.; Xu, X.; Zhou, C. *Chem. Commun.* **2012**, *48*, 12240.

(6) (a) Liu, B.; Li, J.; Song, F. J.; You, J. S. *Chem. Eur. J.* **2012**, *18*, 10830. (b) Yu, X. Z.; Li, X. W.; Wan, B. S. *Org. Biomol. Chem.* **2012**, *10*, 7479. (c) Yang, F. L.; Ma, X. T.; Tian, S. K. *Chem. Eur. J.* **2012**, *18*, 1582. (d) Yuen, O. Y.; So, C. M.; Wong, W. T.; Kwong, F. Y. *Synlett* **2012**, *23*, 2714.

(7) (a) Yang, F. L.; Tian, S. K. *Angew. Chem. Int. Ed.* **2013**, *125*, 5029. (b) Singh, N.; Singh, R.; Raghuvanshi, D. S.; Singh, K. N. *Org. Lett.* **2013**, *15*, 5874.

(8) Beaulieu, C.; Guay, D.; Wang, Z. Y.; Evans, D. A. *Tetrahedron Lett.* **2004**, *45*, 3233.

(9) **General Procedure**

Arylboronic acids (1.2 mmol), arylsulfonyl hydrazides (1.0 mmol), cupric acetate (1.5 mmol), and EtOH (2.0 mL) were taken in a 25 mL two-neck flask. The reaction mixture was stirred at r.t. for 6 h in air. The solution was evaporated under reduced pressure and H_2O (20 mL) was added, and then the mixture was extracted with EtOAc (4 10 mL). The extracts were combined and washed with brine (3 10 mL), dried over $MgSO_4$, filtered, evaporated, and purified by chromatography on silica gel to obtain the desired products with EtOAc–hexane (v/v = 1:5 to 1:10). The products were characterized by their spectral and analytical data and compared with those of the known compounds (see Supporting Information).

Typical Data for Representative Compound: *p*-Ethylphenyl *p*-Tolyl Sulfone (Table 2, Entry 4)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.81 (m, 4 H), 7.31–7.27 (m, 4 H), 2.68–2.66 (m, 2 H), 2.38 (s, 3 H), 1.22 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.0, 139.1, 139.0, 129.9, 128.7, 127.6, 28.8, 21.6, 15.1. GC–MS (EI): *m/z* = 260 [M^+]. Anal Calcd for $C_{15}H_{16}O_2S$ C: 69.20; H, 6.19. Found: C, 69.12; H, 6.15.