OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 937−940

pubs.acs.org/OrgLett

Transition-Metal-Free Desulfinative Cross-Coupling of Heteroaryl Sulfinates with Grignard Reagents

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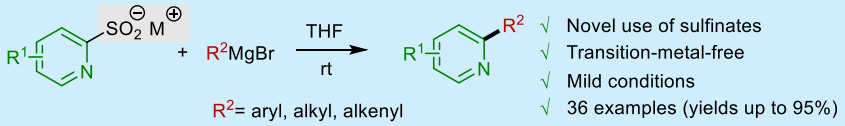
Supporting Information



ABSTRACT: A mild cross-coupling reaction of heteroaryl sulfinates with Grignard reagents has been developed under transition-metal-free conditions. This study provides an example of the SO_2^{2-} as a leaving group in an aromatic system and an effective methodology for the construction of C−C bond.

Sulfur-containing organic molecules not only act as bioactive entities and functional materials but also serve as useful building blocks and reagents in organic synthesis.[1] For organic chemists, it is also an extremely useful functional group for further manipulations. The traditional desulfitative cross-couplings of sulfinates,[2] sulfonyl chlorides,[3] or sulfonyl hydrazides[4] in the presence of transition metals provide an efficient protocol for the synthesis of heterobiaryl products (Figure 1a). However, transition-metal catalysts are expensive, and high temperatures are needed with this approach.[5] Furthermore, the sulfur atom can strongly bind to the transition metal, poisoning the catalyst and leading to deactivation.[6] Therefore, a mild, scalable, and transition-metal-free desulfinative cross-coupling is highly desirable. Recently, Wang and coworkers reported a cross-coupling reaction between aryl and heteroaryl thiols and arylzinc reagents to access the bi(hetero)-aryl products.[7] This pioneering report aroused our interest into conducting desulfinative cross-coupling reactions with other sulfur-containing compounds.

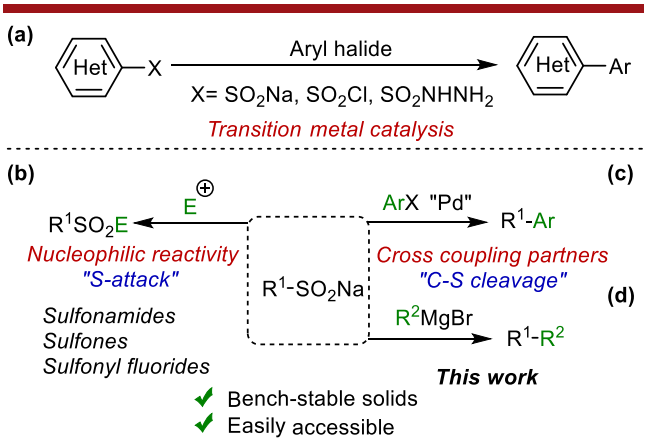


Figure 1. Traditional desulfitative cross-couplings and the applications of sulfinate.

Sulfinates are easy to prepare and are bench-stable, non-volatile solids. These superior chemical properties have permitted their widespread use in the pharmaceutical and chemical industry.[8] Sulfinates are generally used as nucleophiles to react with different electrophiles to form sulfonamides, sulfones, and sulfonyl fluorides (Figure 1b).[9,10] Sulfinates also can be used as coupling partners in Pd-catalyzed cross-coupling reactions (Figure 1c).[2] It is known that heterobiaryl skeletons are important structural motifs in various biological active compounds, including marketed medicines and herbicides (Figure 2).[11] Taking inspiration from the versatility of sulfinates, we aimed our attention at the use of heteroaryl sulfinates and Grignard reagents for the synthesis of heterobiaryl products by a desulfinative coupling reaction (Figure 1d).

In our initial studies, the reaction of sodium 5-(trifluoromethyl)pyridine-2-sulfinate (**1a**) with phenylmagnesium bromide **2a** was chosen as the model reaction for optimization of the reaction conditions. First, the amount of the Grignard reagent was screened (Table 1, entries 1−4), and the results showed that 1.5 equiv of phenylmagnesium bromide was optimal to furnish **3aa** in 93% yield (Table 1, entry 2). Several other solvents, including ethyl ether, toluene, 1,4-dioxane, and DME, were employed to replace THF in this reaction, while no improvement in yields were observed (Table 1, entries 5−8). In addition, Na^+ was found to be the optimal metal cation partner of the sulfinate in the reaction (Table 1,

Received: December 7, 2018
Published: January 24, 2019

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DOI: 10.1021/acs.orglett.8b03918
Org. Lett. 2019, 21, 937−940

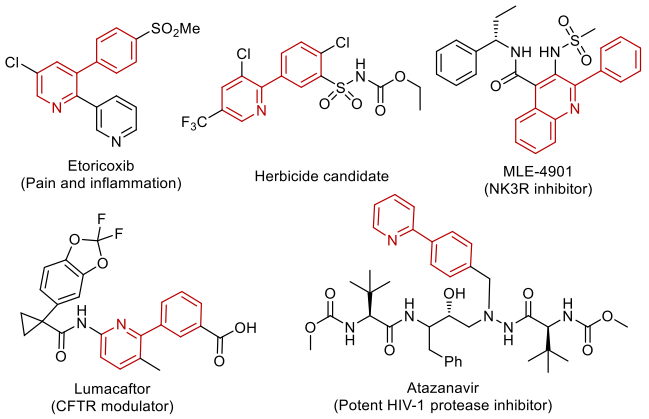
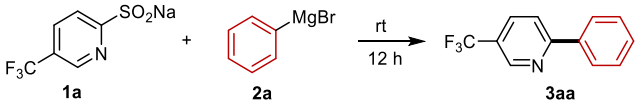


Figure 2. Examples of medicinally relevant heterobiaryl-containing molecules.

Table 1. Reaction Optimization[a]



entry	solvent	2a (equiv)	yield[b] (%)
1[c]	THF	1.0	54
2	**THF**	**1.5**	**93**
3	THF	2.0	84
4	THF	3.0	86
5	ethyl ether	1.5	83
6	toluene	1.5	84
7	1,4-dioxane	1.5	82
8	DME	1.5	43
9[c]	THF	1.5	68
10[d]	THF	1.5	73

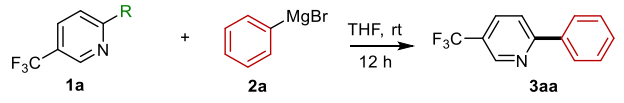
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (2.0 M in THF), solvent (1 mL), rt, 12 h. [b]Yields were determined by ^{19}F NMR using $PhOCF_3$ as an internal standard. [c]Potassium sulfinate was used. [d]Lithium sulfinate was used.

entries 9 and 10). The best result was obtained with a combination of 1.0 equiv of sulfinate and 1.5 equiv of Grignard reagent in THF at room temperature to furnish **3aa** in 93% yield (Table 1, entry 2).

In order to understand the reactivity profile of the sulfinate in this type of reaction, a solution of either the heteroaryl sulfinate (Het-SO_2Na), heteroaryl sulfonate (Het-SO_3Na),[3] heteroaryl methyl sulfide (Het-SCH_3),[12] heteroaryl methyl sulfone (Het-SO_2CH_3),[12] or heteroaryl thiol (Het-SH)[7] in THF was reacted with PhMgBr (1.5 equiv) at room temperature (Table 2). The reaction mixtures were allowed to stir at room temperature for 12 h, and the crude product mixtures were analyzed by ^{19}F NMR to determine the conversion to the product **3aa**. The results in Table 2 confirmed that the heteroaryl sulfinate showed much higher reactivity than the heteroaryl thiol and the heteroaryl methyl sulfide under standard conditions, with activity on par with the heteroaryl sulfonate and the heteroaryl methyl sulfone.

Then, the reaction scope and limitations of sulfinates **1** were surveyed, and the results are summarized in Scheme 1. In general, the electronic effect influences the yields of this reaction obviously. Pyridine sulfinates with electron-withdrawing substituents (**1a**, **1b**, **1c**, **1d**) react with the Grignard reagent **2a** smoothly to afford the desired products (**3aa**, **3ba**, **3ca**, and **3da**) in good to excellent yields (74−87%), whereas for substrates

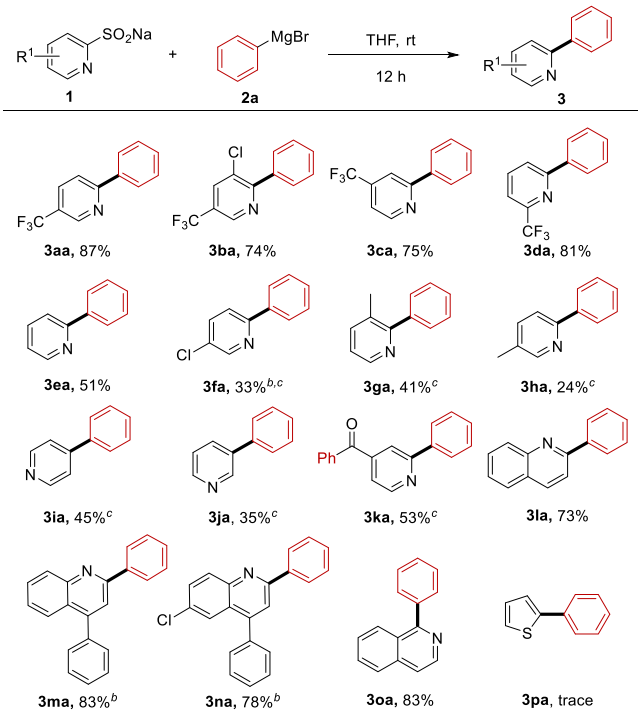
Table 2. Survey of Various S-Containing Electrophiles[a]



entry	R	yield[b] (%)
1	**SO_2Na**	**93**
2	SO_3Na	85
3	SO_2Me	89
4	SMe	0
5	SH	0

[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), PhMgBr (2 M in THF, 0.75 mmol, 1.5 equiv), THF (2 mL), 12 h. [b]Yields were determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.

Scheme 1. Investigation of the Scope of Pyridine Sulfinates[a]



[a]Reaction conditions: sulfinates (1.0 mmol, 1.0 equiv), PhMgBr (1.5 mmol, 1.5 equiv), THF (3 mL), 12 h. Isolated yields. [b]Sulfinates (0.5 mmol, 1.0 equiv), PhMgBr (0.75 mmol, 1.5 equiv), THF (2 mL), 12 h. [c]PhMgBr (3.0 equiv).

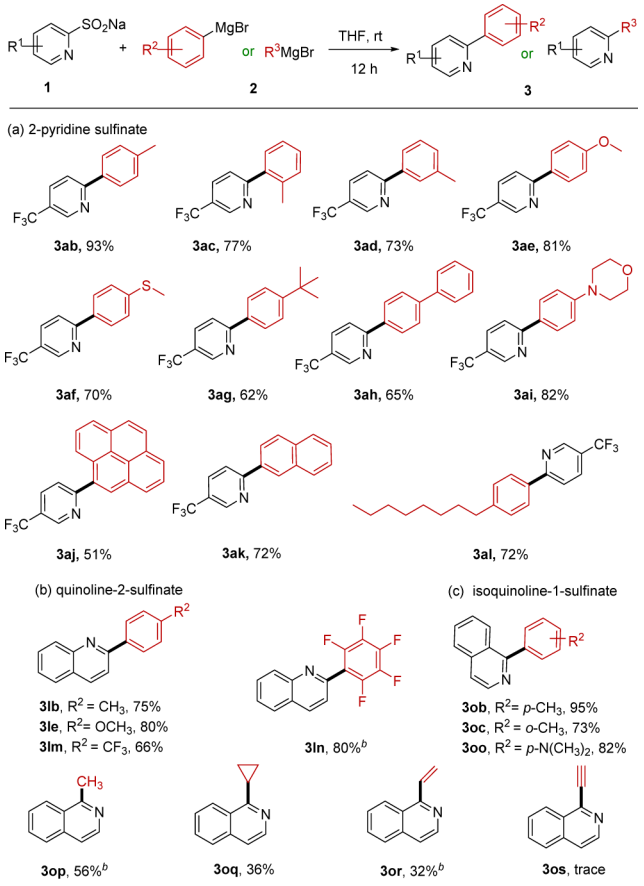
without electron-withdrawing groups (**1e**, **1f**, **1g**, and **1h**), the respective products (**3ea**−**ha**) were isolated in low to moderate yields (24−51%). Sodium pyridine-4-sulfinate **1i** and sodium pyridine-3-sulfinate **1j** afforded **3ia** and **3ja**, respectively, which indicates that the 2-azaaryl group is not necessary for this transformation. Note that when 1.5 equiv of PhMgBr was used, only a small amount of 2-phenylisonicotinonitrile was detected by GC−MS. When we increased the equivalents of Grignard reagent, the product of the ketone **3ka** was obtained in a yield of 56%, indicating the higher reactivity of cyano group than the sulfinate group toward nucleophilic attack. Other heteroaromatic sulfinates, including sodium quinoline-2-sulfinate **1l**−**n** and sodium isoquinoline-1-sulfinate **1o**, were also suitable substrates for this transformation and gave the respective products **3la**−**oa** in good to excellent yields (73−83%). However, the electron-rich heteroaryl sulfinate, sodium thiophene-2-sulfinate **1p**, only provided trace of **3pa**, indicating

DOI: 10.1021/acs.orglett.8b03918
Org. Lett. 2019, 21, 937−940

the electron-rich heteroaryl sulfinates were not suitable for this reaction.

The scope of Grignard reagents was also evaluated (Scheme 2). Grignard reagents bearing either electron-donating groups or

Scheme 2. Investigation of the Scope of Grignard Reagents[a]

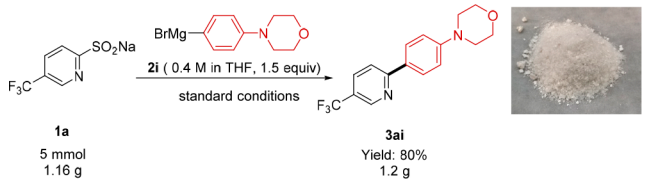


[a]Reaction conditions: sulfinates (1.0 mmol, 1.0 equiv), Grignard reagents (1.5 mmol, 1.5 equiv), THF (3 mL), 12 h. Isolated yields. [b]Sulfinates (0.5 mmol, 1.0 equiv), Grignard reagents (0.75 mmol, 1.5 equiv), THF (2 mL), 12 h.

electron-withdrawing groups on the aromatic ring were well tolerated in the reaction and provided the coupling products **3ab**−**al**, **3lb**, **3le**, **3 lm**, **3ob**, **3oc**, and **3oo** in 62−95% yields. The much lower product yield **3ac** comparing with that of **3ab** (77% vs 93%) indicated the obvious effect of steric hindrance on yields in this reaction. Reaction of 4-pyrenylmagnesium bromide **2j**, 2-naphthylmagnesium bromide **2k**, and (4-octylphenyl)magnesium bromide **2l** with **1a** proceeded smoothly and gave **3aj**, **3ak** and **3al** in a yield of 51%, 72%, and 72%, respectively. Interestingly, perfluorophenyl magnesium bromide **2n** was also a suitable substrate for this reaction and afforded the product **3ln** in 80% yield. In addition, methylmagnesium bromide **2p**, cyclopropylmagnesium bromide **2q**, and vinylmagnesium bromide **2r** react with pyridine sulfinate **1a** to give the corresponding products **3op**, **3oq**, and **3or** in moderate yields (32−56%), while ethynylmagnesium bromide **2s** only gave a trace amount of coupling product.

To further demonstrate the practicability and effectiveness of this methodology, gram-scale syntheses were tested (Scheme 3). When 5 mmol of sodium 5-(trifluoromethyl)pyridine-2-sulfinate **1a** was reacted with 7.5 mmol of 4-morpholinophenyl

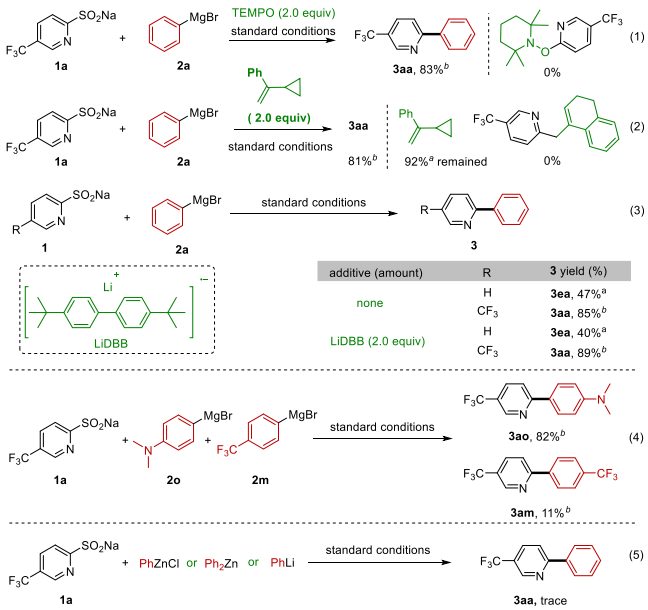
Scheme 3. Preparative-Scale Synthesis of 3ai



magnesium bromide **2i**, the corresponding product **3ai** can be obtained with a satisfactory yield of 80%, demonstrating a great potential in pharmaceutical synthesis.

We then turned our attention to the mechanistic features of this reaction. First, when 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was introduced to the reaction mixture under standard conditions, the reaction could give the cross-coupling product **3aa** in 83% yield. No TEMPO-trapped intermediate was observed (Scheme 4, eq 1). Second, the radical

Scheme 4. Preliminary Mechanistic Study



[a]Isolated yields. [b]Yields were determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.

clock reaction using (1-cyclopropylvinyl)benzene as the radical-trapping reagent gave no radical trapping product but a direct coupling product **3aa** in 81% yield, and 92% (1-cyclopropylvinyl)benzene was recovered (Scheme 4, eq 2). Third, single electron-donor lithium di-*tert*-butylbiphenyl (LiDBB) was reported to accelerate the coupling reaction of Grignard reagent with aryl halides;[13] however, in the presence of LiDBB, the yield of product **3aa** remains unaffected in the present coupling reaction (Scheme 4, eq 3). These experimental facts could exclude a single-electron-transfer mechanism. When *p*-Me_2N-PhMgBr **2o** and *p*-CF_3-PhMgBr **2m** in a 1:1 molar ratio were employed to react with the sulfinate **1a**, a mixture of **3ao** and **3am** was obtained in an 8:1 ratio (Scheme 4, eq 4); this product distribution is consistent with the nucleophilic activity of the Grignard reagents. This result indicated that a nucleophilic aromatic substitution pathway may be involved in the reaction mechanism.[14] However, when PhMgBr was replaced with PhZnCl, PhZnPh, or PhLi, the reaction to form

DOI: 10.1021/acs.orglett.8b03918
Org. Lett. 2019, 21, 937−940

3aa was fully inhibited (Scheme 4, eq 5), suggesting that an interaction between Mg^{2+} and the sulfinate may activate the C–S bond (see the SI).

In conclusion, we have developed a transition-metal-free[15] cross-coupling reaction of heteroaryl sulfinates with Grignard reagents that provides an efficient method to synthesize heterobiaryls under mild conditions. In this reaction, the heteroaryl sulfinates were employed as electrophilic substrates in a nucleophilic substitution reaction, and we anticipate this will expand the future use of heteroaryl sulfinates in organic chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03918.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (2015CB931900), the National Natural Science Foundation of China (21672187, 21632009, 21421002, 21472221), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), Shanghai Science and Technology program (16QA1404600), and ZJNSF (LZ17H300002).

■ REFERENCES

(1) (a) Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; Wiley: New York, 1996. (b) Ruano, J. L. G.; de la Plata, B. C. In *Organosulfur Chemistry I*; Page, P. C. B., Ed.; Springer: Heidelberg, 1999; p 1. (c) Furukawa, N.; Sato, S. In *Organosulfur Chemistry II*; Page, P. C. B., Ed.; Springer: Heidelberg, 1999; p 89. (d) Rayner, C. M. *Advances in Sulfur Chemistry*; JAI Press: Greenwich, 2000; Vol. 2.

(2) (a) Taniguchi, N. *Synlett* **2013**, *24*, 2571–2574. (b) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 4437–4442. (c) Markovic, T.; Rocke, B. N.; Blakemore, D. C.; Mascitti, V.; Willis, M. C. *Org. Lett.* **2017**, *19*, 6033–6035. (d) Ortgies, D. H.; Hassanpour, A.; Chen, F.; Woo, S.; Forgione, P. *Eur. J. Org. Chem.* **2016**, *2016*, 408–425. (e) Sévigny, S.; Forgione, P. *Chem. - Eur. J.* **2013**, *19*, 2256–2260. (f) Zhao, F.; Tan, Q.; Xiao, F.; Zhang, S.; Deng, G.-J. *Org. Lett.* **2013**, *15*, 1520–1523. (g) Chen, J.; Li, J.; Su, W. *Molecules* **2014**, *19*, 6439–6449. (h) Liu, S.; Chen, J.; Zhang, R.; Zhao, F.; Deng, G.-J. *Asian J. Org. Chem.* **2014**, *3*, 1150–1153. (i) Liu, J.; Zhou, X.; Rao, H.; Xiao, F.; Li, C.-J.; Deng, G.-J. *Chem. - Eur. J.* **2011**, *17*, 7996–7999. (j) Skillinghaug, B.; Sköld, C.; Rydfjord, J.; Svensson, F.; Behrends, M.; Sävmarker, J.; Sjöberg, P. J. R.; Larhed, M. *J. Org. Chem.* **2014**, *79*, 12018–12032. (k) Cheng, K.; Hu, S.; Zhao, B.; Zhang, X.-M.; Qi, C. *J. Org. Chem.* **2013**, *78*, 5022–5025. (l) Zhou, C.; Liu, Q.; Li, Y.; Zhang, R.; Fu, X.; Duan, C. *J. Org. Chem.* **2012**, *77*, 10468–10472.

(3) (a) Beladhria, A.; Yuan, K.; Ben Ammar, H.; Soulé, J.-F.; Ben Salem, R.; Doucet, H. *Synthesis* **2014**, *46*, 2515–2523. (b) Jin, R.; Yuan, K.; Chatelain, E.; Soulé, J.-F.; Doucet, H. *Adv. Synth. Catal.* **2014**, *356*, 3831–3841. (c) Zhang, W.; Liu, F.; Zhao, B. *Appl. Organomet. Chem.* **2015**, *29*, 524–527. (d) Yuan, K.; Sang, R.; Soulé, J.-F.; Doucet, H. *Catal. Sci. Technol.* **2015**, *5*, 2904–2912. (e) Loukotova, L.; Yuan, K.; Doucet, H. *ChemCatChem* **2014**, *6*, 1303–1309. (f) Hfaiedh, F.; Yuan, K.; Ben Ammar, H.; Ben Hassine, B.; Soulé, J.-F.; Doucet, H. *ChemSusChem* **2015**, *8*, 1794–1804. (g) Rao Volla, C. M.; Vogel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1305–1307.

(4) (a) Yu, X.; Li, X.; Wan, B. *Org. Biomol. Chem.* **2012**, *10*, 7479–7482. (b) Chen, W.; Chen, H.; Xiao, F.; Deng, G.-J. *Org. Biomol. Chem.* **2013**, *11*, 4295–4298. (c) Miao, H.; Wang, F.; Zhou, S.; Zhang, G.; Li, Y. *Org. Biomol. Chem.* **2015**, *13*, 4647–4651. (d) Zhong, S.; Sun, C.; Dou, S.; Liu, W. *RSC Adv.* **2015**, *5*, 27029–27033. (e) Huang, L.; Qi, J.; Wu, X.; Wu, W.; Jiang, H. *Chem. - Eur. J.* **2013**, *19*, 15462–15466. (f) Yuen, O. Y.; So, C. M.; Wong, W. T.; Kwong, F. Y. *Synlett* **2012**, *23*, 2714–2718. (g) Liu, B.; Li, J.; Song, F.; You, J. *Chem. - Eur. J.* **2012**, *18*, 10830–10833. (h) Yang, F.-L.; Ma, X.-T.; Tian, S.-K. *Chem. - Eur. J.* **2012**, *18*, 1582–1585.

(5) Rattanangkool, E.; Sukwattanasinitt, M.; Wacharasindhu, S. *J. Org. Chem.* **2017**, *82*, 13256–13262.

(6) Murray, S. G.; Hartley, F. R. *Chem. Rev.* **1981**, *81*, 365–414.

(7) Yang, B.; Wang, Z.-X. *Org. Lett.* **2017**, *19*, 6220–6223.

(8) Li, Y.; Yang, W.; Cheng, G.; Yang, D. *J. Org. Chem.* **2016**, *81*, 4744–4750.

(9) (a) Martin, C.; Sandrinelli, F.; Perrio, C.; Perrio, S.; Lasne, M. C. *J. Org. Chem.* **2006**, *71*, 210–214. (b) Shavnya, A.; Coffey, S. B.; Hesp, K. D.; Ross, S. C.; Tsai, A. S. *Org. Lett.* **2016**, *18*, 5848–5851. (c) Yang, K.; Ke, M.; Lin, Y.; Song, Q. *Green Chem.* **2015**, *17*, 1395–1399.

(10) (a) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 1233–1237. (b) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2014**, *53*, 9430–9448.

(11) (a) Riendeau, D.; Percival, M. D.; Brideau, C.; Charleson, S.; Dube, D.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Gordon, R.; Greig, G.; Guay, J.; Mancini, J.; Ouellet, M.; Wong, E.; Xu, L.; Boyce, S.; Visco, D.; Girard, Y.; Prasit, P.; Zamboni, R.; Rodger, I. W.; Gresser, M.; Ford-Hutchinson, A. W.; Young, R. N.; Chan, C.-C. *Br. J. Pharmacol.* **2001**, *296*, 558–566. (b) Xie, Y.; Chi, H.-W.; Guan, A.-Y.; Liu, C.-L.; Ma, H.-J.; Cui, D.-L. *Bioorg. Med. Chem.* **2016**, *24*, 428–434. (c) Burt, T. D.; Agan, B. K.; Marconi, V. C.; He, W.; Kulkarni, H.; Mold, J. E.; Cavrois, M.; Huang, Y.; Mahley, R. W.; Dolan, M. J.; McCune, J. M.; Ahuja, S. K. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 8718–8723. (d) Li, Y.; Zhou, D.; Ferguson, S. S.; Dorff, P.; Simpson, T. R.; Grimm, S. W. *Xenobiotica* **2010**, *40*, 721–729. (e) Croom, K. F.; Dhillon, S.; Keam, S. J. *Drugs* **2009**, *69*, 1107–1140.

(12) (a) Someya, C. I.; Weidauer, M.; Enthaler, S. *Catal. Lett.* **2013**, *143*, 424–431. (b) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590–9599.

(13) (a) Shirakawa, E.; Hayashi, Y.; Itoh, K.; Watabe, R.; Uchiyama, N.; Konagaya, W.; Masui, S.; Hayashi, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 218–221. (b) Uchiyama, N.; Shirakawa, E.; Hayashi, T. *Chem. Commun.* **2013**, *49*, 364–366. (c) Hill, R. R.; Rychnovsky, S. D. *J. Org. Chem.* **2016**, *81*, 10707–10714.

(14) (a) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273–412. (b) Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261–2280.

(15) ICP-OES analysis of the reaction mixture showed that there was less than 1 ppm (within the detection limit) of Co, Ni, Cu, and Pd and 26 ppm of Fe. To rule out the effect of Fe, the reaction was conducted in the presence of $FeCl_3$ (5 mol %) to give 20% yield of **3aa** accompanied by biphenyl as a major product (see the SI). This fact shows that Fe drastically lowered the yield of **3aa**, so it is unlikely that the trace amount of Fe is involved in the coupling reaction between heteroaryl sulfinates and Grignard reagents.

DOI: 10.1021/acs.orglett.8b03918
Org. Lett. 2019, 21, 937–940