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COMMUNICATION

## Reactions of allyl alcohols and boronic acids with trifluoromethanesulfonyl hypervalent iodonium ylide under copper-catalysis

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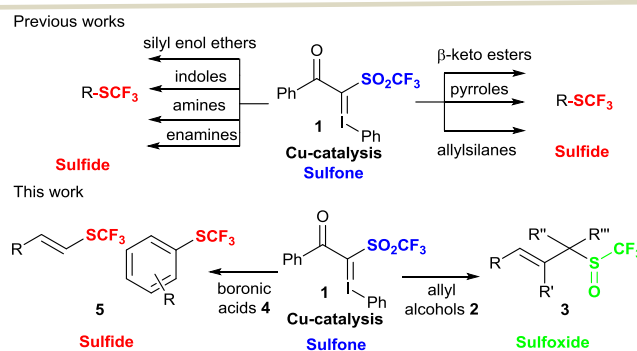
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**Trifluoromethylsulfinyl and trifluoromethylthio groups are both important substituents for pharmaceuticals, agrochemicals and functional materials. We herein report the trifluoromethylthiolation of allyl alcohols 2 with trifluoromethanesulfonyl hypervalent iodonium ylide 1 under copper catalysis to provide trifluoromethylsulfinyl compounds 3. Trifluoromethylthiolation of boronic acids 4 with 1 furnished trifluoromethylthio compounds 5.**

In recent decades, there has been tremendous interest in organofluorine compounds due to their great achievements as pharmaceuticals, agrochemicals and functional materials.<sup>1</sup> The vast majority of successful works reported in this area have dealt with fluorinated and trifluoromethylated compounds, and a huge number of effective methods have been developed for the synthesis of these fluorinated molecules.<sup>2</sup> Our group has also contributed to this area by developing shelf-stable reagents for fluorination<sup>3</sup> and trifluoromethylation reactions.<sup>4</sup> In 2013, we reported a novel reagent, trifluoromethanesulfonyl hypervalent iodonium ylide 1, for the electrophilic trifluoromethylthiolation reaction.<sup>5</sup> Trifluoromethylthio (SCF<sub>3</sub>) compounds are becoming rather attractive after fluorinated and trifluoromethylated compounds in the same research fields, since the introduction of SCF<sub>3</sub> entities into the target compounds greatly changes or improves the lipophilicity of parent molecules<sup>6</sup> without altering the original framework much; and this effect is higher than that by the trifluoromethyl substitution. In contrast to trifluoromethyl compounds, SCF<sub>3</sub> compounds can be further elaborated to exhibit more suitable lipophilic profiles by the stepwise oxidation into corresponding sulfoxides (S(O)CF<sub>3</sub>) and sulfones (SO<sub>2</sub>CF<sub>3</sub>, triflones). In this context, the synthesis of SCF<sub>3</sub> compounds has received great attention.<sup>7</sup> In particular, the development of electrophilic trifluoromethylthiolation reagents<sup>8</sup> is going to be prevalent in the next several years, because it should be a key to realizing late-stage

functionalization in preparing potential candidates in a class of medicinal significance. The trifluoromethanesulfonyl hypervalent iodonium ylide 1 we developed is useful for the trifluoromethylthiolation of enamines, indoles, β-keto esters,<sup>5</sup> pyrroles,<sup>9</sup> arylamines,<sup>10</sup> allylsilanes and silyl enol ethers.<sup>11</sup> Reagent 1 is very stable, and crucial for the fact that the trifluoromethylthiolation by 1 is the *in-situ* activation of 1 under copper catalysis to a carbene intermediate. Our interest in the utility of 1 prompted us to investigate the reactions of other substrates, allyl alcohols 2 and boronic acids 4. We demonstrate herein that the reaction of allyl alcohols 2 with 1 under copper catalysis can furnish allylic trifluoromethyl sulfoxides<sup>12</sup> 3, instead of trifluoromethylthio compounds in good yields *via* a [2,3]-sigmatropic rearrangement.<sup>13</sup> The reaction of boronic acids<sup>14</sup> 4 with 1 under the same copper catalysis provided cross coupling trifluoromethylthio compounds 5 in moderate yields (Scheme 1).



**Scheme 1** Utilization of trifluoromethanesulfonyl hypervalent iodonium ylide 1.

## Results and Discussion

We first examined the reaction of 1-phenyl-2-propen-1-ol (2a) with 1 as a model substrate to optimize the reaction conditions by a [2,3]-sigmatropic rearrangement to provide S(O)CF<sub>3</sub>-product 3a instead of regular SCF<sub>3</sub>-products. The reaction was initially

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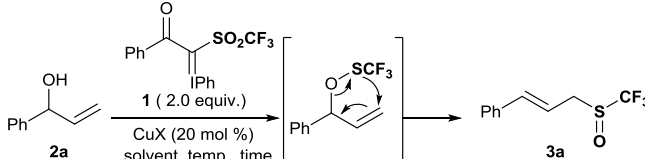
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examined under similar conditions for the trifluoromethylthiolation of allylsilanes and silyl enol ethers in our previous work<sup>11</sup> (Table 1, runs 1-2). The desired S(O)CF<sub>3</sub>-product **3a** was obtained in 67% yield. A longer reaction time gave **3a** in higher yield (72%, Table 1, run 2). When it comes to screening solvents, amide solvents (NMP, DMF) gave **3a** in comparatively favorable yields (43-58%, runs 3-4), but a halogenated solvent (CH<sub>2</sub>Cl<sub>2</sub>), an ether solvent (THF), an ester solvent (AcOEt) and other polar solvents (MeCN, DMSO, EtOH) were not suitable for this transformation (runs 5-10). We next optimized the copper catalysts (runs 11-16). The use of Cu (II) species was found to be better than Cu (I) species (CuCl vs CuCl<sub>2</sub>, CuOAc vs Cu(OAc)<sub>2</sub>), but no improvement was observed. A higher reaction temperature did not improve the yield of **3a** (run 17). The reaction did not proceed in the absence of CuF<sub>2</sub> (run 18).

**Table 1** Optimization of transformation of 1-phenyl-2-propen-1-ol (**2a**) into **3a**.<sup>a</sup>

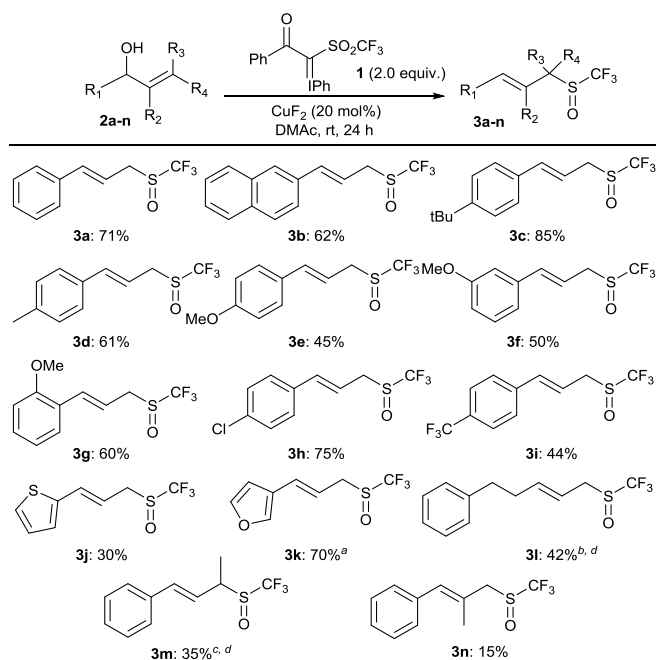


run	CuX	solvent	temp (°C)	time (h)	yield (%) <sup>b</sup>
1	CuF <sub>2</sub>	DMAc	rt	10	67
2	CuF <sub>2</sub>	DMAc	rt	24	72
3	CuF <sub>2</sub>	NMP	rt	24	58
4	CuF <sub>2</sub>	DMF	rt	24	43
5	CuF <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	24	trace
6	CuF <sub>2</sub>	THF	rt	24	0
7	CuF <sub>2</sub>	MeCN	rt	24	23
8	CuF <sub>2</sub>	DMSO	rt	24	0
9	CuF <sub>2</sub>	EtOH	rt	24	0
10	CuF <sub>2</sub>	AcOEt	rt	24	trace
11	CuCl	DMAc	rt	24	0
12	CuCl <sub>2</sub>	DMAc	rt	24	6
13	CuBr <sub>2</sub>	DMAc	rt	24	36
14	CuOAc	DMAc	rt	24	12
15	Cu(OAc) <sub>2</sub>	DMAc	rt	24	50
16	Cu(OTf) <sub>2</sub>	DMAc	rt	24	13
17	CuF <sub>2</sub>	DMAc	50	24	54
18	-	DMAc	rt	24	0

<sup>a</sup> The reactions were carried out with **2a** (0.25 mmol), **1** (0.50 mmol) and CuX (0.05 mmol) in each solvent (1.25 ml). <sup>b</sup> <sup>19</sup>F NMR yields with PhF (0.75 mmol) as an internal standard.

With the optimized reaction conditions in our hand (Table 1, run 2), we next investigated the substrate scope of allyl alcohols (Scheme 2). Applying the reaction of **2** having naphthyl or alkyl substituted phenyl groups, the desired trifluoromethyl sulfinyl products **3b-d** were obtained in good to high yields (61-85%, Scheme 2). The electron-donating group (OMe) could be applied without a high steric effect in the reaction (**3e-g**). Phenyl allyl alcohols substituted with electron-withdrawing groups (Cl, CF<sub>3</sub>) gave the desired products **3h-i** in modest to high yield (44-75%). Additionally, hetero aromatic allyl alcohols **3j-k** were also relevant in this transformation, providing the corresponding trifluoromethyl sulfinates without any functionalization of the heteroaryl moieties. It is interesting to note that even when alkyl and branched allyl

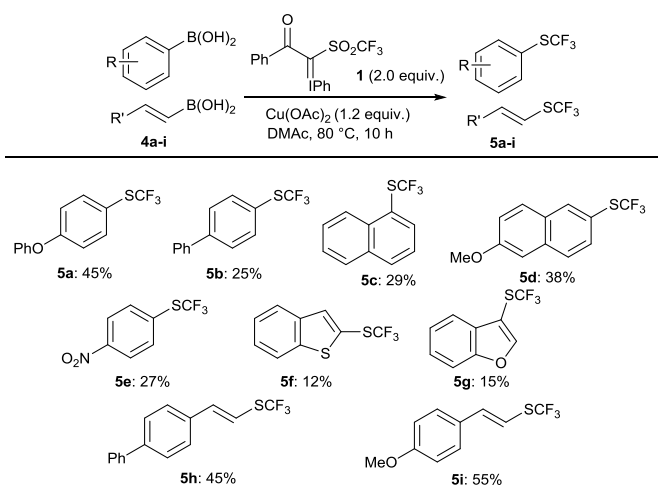
alcohols **2l-n** were applied, the reaction proceeded to give the sulfinates, although in moderate yields (15-42%).



**Scheme 2** Transformation of allyl alcohols **2a-n** into **3a-n** (isolation yields, reaction conditions: **2** (0.25 mmol), **1** (0.50 mmol) and CuF<sub>2</sub> (0.05 mmol) in DMAc (1.25 ml), rt, 24 h under N<sub>2</sub>).

<sup>a</sup> The reaction time was 5 h. <sup>b</sup> E/Z = 22/3. <sup>c</sup> d.r. = 3/2. <sup>d</sup> The reaction time was 2 h.

We next attempted the cross coupling trifluoromethylthiolation reaction of boronic acids **4** with **1**. 4-Phenoxy-phenyl boronic acid (**4a**) was first examined in the reaction with **1** under the same conditions as in scheme 2, i.e., with a catalytic amount of CuF<sub>2</sub> in DMAc. The reaction did not proceed at rt, but 13% of the desired SCF<sub>3</sub> cross coupling product **5a** was obtained at 80 °C using a higher amount of CuF<sub>2</sub> (1.2 equiv.) (runs 1-2, Table 1S, ESI). When Cu(OAc)<sub>2</sub> (1.2 equiv.) was used, the yield of **5a** improved to 47% (run 7, Table 1S, ESI). The substrate scope was next examined for the trifluoromethylthiolation reaction of aryl- and vinylboronic acids (Scheme 3). Although the yields were moderate, various boronic acids were applicable in the cross coupling reaction. Simple arylboronic acid **4b-c** were converted into the desired trifluoromethylthiolated products **5b-c** in modest yields (25-29%). The electron-donating and -withdrawing substituted arylboronic acids **4d-e** were also transformed into **5d-e** in 27-38% yield. Furthermore, hetero arylboronic acid **4f-g** were applied to the trifluoromethylthiolation reaction, although the yield of **5f-g** was low (12-15%). Both arylboronic acids and vinylboronic acids **4h-i** also could be transformed into the F<sub>3</sub>CS-products **5h-i** in good yields (45-55%).



**Scheme 3** Trifluoromethylthiolation of boronic acids **4a-i** (isolation yields, reaction conditions: **4** (0.25 mmol), **1** (0.50 mmol) and Cu(OAc)<sub>2</sub> (0.30 mmol) in DMAc (1.25 ml), 80 °C, 10 h under N<sub>2</sub>).

## Conclusions

We have succeeded in the synthesis of both trifluoromethylsulfinyl and trifluoromethylthio compounds using trifluoromethanesulfonyl hypervalent iodonium ylide **1** under copper catalysis. The reaction of various allyl alcohols **2** with **1** in the presence of a catalytic amount of CuF<sub>2</sub> furnished trifluoromethylsulfinyl compounds instead of trifluoromethylthio compounds *via* a [2,3]-sigmatropic rearrangement. On the other hand, trifluoromethylthiolation of boronic acids **4** with **1** under similar reaction conditions using Cu(OAc)<sub>2</sub> provided trifluoromethylthio compounds in moderate yields *via* a cross coupling reaction. Although the same reactions providing **3** and **5** have been reported using “other trifluoromethylthiolation reagents” under different conditions, these “trifluoromethylthiolation reagents” themselves should be prepared in advance by “trifluoromethylthiolation or related trifluoromethylation”. On the other hand, our reagent **1** can be prepared from ubiquitous CF<sub>3</sub>SO<sub>2</sub> compounds such as CF<sub>3</sub>SO<sub>2</sub>Na, without using any trifluoromethylthiolation reagent. These results show the further expansion of the scope and utility of reagent **1** for trifluoromethylthiolations. A separate study will focus on this aspect of the chemistry of **1** as well as further applications to accommodate a broader range of reactions.

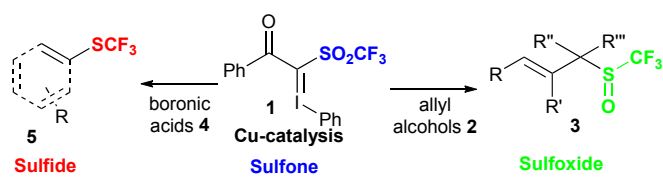
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## References

- (a) P. Jeschke, *ChemBioChem*, 2004, **5**, 570; (b) H. –J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *ChemBioChem*, 2004, **5**, 637; (c) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (d) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (e) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359.
- (a) G. K. S. Prakash and A. K. Yudin, *Chem. Rev.*, 1997, **97**, 757; (b) P. T. Nyffeler, S. G. Durón, M. D. Burkart, S. P. Vincent and C. –H. Wong, *Angew. Chem. Int. Ed.*, 2005, **44**, 192; (c) M. Schlosser, *Angew. Chem. Int. Ed.*, 2006, **45**, 5432; (d) N. Shibata, T. Ishimaru, S. Nakamura and T. Toru, *J. Fluorine Chem.* 2007, **128**, 469; (e) J. Nie, H. –C. Guo, D. Cahard and J. –M. Ma, *Chem. Rev.*, 2011, **111**, 455; (f) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214; (g) L. Chu and F. –L. Qing, *Acc. Chem. Res.*, 2014, **47**, 1513; (h) A. J. Cresswell, S. G. Davies, P. M. Roberts and J. E. Thomson, *Chem. Rev.*, 2015, **115**, 566; (i) M. G. Campbell and T. Ritter, *Chem. Rev.*, 2015, **115**, 612; (j) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (k) Y. –Y. Huang, X. Yang, Z. Chen, F. Verpoort and N. Shibata, *Chem. Eur. J.*, 2015, **21**, 8664; (l) R. Smits, C. D. Cadicamo, K. Burgger and B. Kocsch, *Chem. Soc. Rev.*, 2008, **37**, 1727; (m) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475.
- (a) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem. Int. Ed.*, 2008, **47**, 4157; (b) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem. Int. Ed.*, 2008, **47**, 8051; (c) T. Furukawa, J. Kawazoe, W. Zhang, T. Nishimine, E. Tokunaga, T. Matsumoto, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.*, 2011, **50**, 9684.
- (a) S. Noritake, N. Shibata, S. Nakamura, T. Toru and M. Shiro, *Eur. J. Org. Chem.*, 2008, 3465; (b) A. Matsnev, S. Noritake, Y. Nomura, E. Tokunaga, S. Nakamura and N. Shibata, *Angew. Chem. Int. Ed.*, 2010, **49**, 572; (c) S. Arimori and N. Shibata, *Org. Lett.*, 2015, **17**, 1632.
- Y. –D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782.
- T. Le, V. C. Epa, F. R. Burden and D. A. Winkler, *Chem. Rev.*, 2012, **112**, 2889.
- (a) A. Tlili and T. Billard, *Angew. Chem. Int. Ed.*, 2013, **52**, 6818; (b) X. –H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (c) X. Yang, T. Wu, R. J. Phipps, F. D and Toste, *Chem. Rev.*, 2015, **115**, 826; (d) J. –B. Liu, X. –H. Xu, Z. –H. Chen and F. –L. Qing, *Angew. Chem. Int. Ed.*, 2015, **54**, 897; (e) A. Ferry, T. Billard, B. R. Langlois and E. Baqué, *Angew. Chem. Int. Ed.*, 2009, **48**, 8551; (f) F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.*, 2012, **51**, 10382; (g) F. Hu, S. Dianhu, L. Lu and Q. Shen, *Angew. Chem. Int. Ed.*, 2014, **53**, 6105; (h) T. Yang and L. Lu, Q. Shen, *Chem. Commun.*, 2015, **51**, 5479; (i) X. Shao, T. Liu, L. Lu and Q. Shen, *Org. Lett.*, 2014, **16**, 4738; (j) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K. –W. Huang, *Angew. Chem. Int. Ed.*, 2013, **52**, 1548; (k) S. –Q. Zhu, X. –H. Xu and F. –L. Qing, *Eur. J. Org. Chem.*, 2014, 4453; (l) Y. H, X. He, H. Li, Z. Weng, *Eur. J. Org. Chem.*, 2014, 7324; (m) D. J. Adams, A. Goddard, J. H. Clark and D. J. Macquarrie, *Chem. Commun.*, 2000, 987; (n) C. –P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183; (o) C. Chen, L. Chu and F. –L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 12454. (p) L. Dieu, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; (q) S. –G. Li and S. Z. Zard, *Org. Lett.*, 2013, **15**, 5898. (r) Y. Huang, X. He, X. Lin, M. Rong and Z. Weng, *Org. Lett.*, 2014, **16**, 3284; (s) C. Xu and Q. Shen., *Org. Lett.*, 2014, **16**, 2064; (t) F. Yin and X. –S. Wang, *Org. Lett.*, 2014, **16**, 1128; (u) W. Wu, X. Zhang, F. Liang and S. Cao, *Org. Biomol. Chem.*, DOI: 10.1039/c5ob00960j; (v) R. Honeker, J. B. Ernst and F. Glorius, *Chem. Eur. J.* 2015, **21**, 8047; (w) Y. Huang, J. Ding, C. Wu, H. Zheng and Z. Weng, *J. Org. Chem.*, 2015, **80**, 2912; (x) O. G. Mancheño and C. Bolm, *Org. Lett.*, 2006, **8**,

- 2349; (y) G. Yin, I. Kalvet and F. Schoenebeck, *Angew. Chem. Int. Ed.*, 2015, **54**, 6809; (z) H. Wu, Z. Xiao, J. Wu, Y. Guo, J. –C. Xiao, C. Liu and Q. –Y. Chen, *Angew. Chem. Int. Ed.*, 2015, **54**, 4070.
- 8 (a) S. Munavalli, D. K. Rohrbaugh, D. L. Rossman, F. J. Berg, G. W. Wagnern and H. D. Durst, *Synth. Commun.*, 2000, **30**, 2847; (b) A. Ferry, T. Billard, B. Langlois and E. Bacqué, *J. Org. Chem.* 2008, **73**, 9362; (c) C. Xu, B. Ma and Q. Shen, *Angew. Chem. Int. Ed.*, 2014, **53**, 9316.
- 9 Z. Huang, Y. –D. Yang, E. Tokunaga and N. Shibata, *Org. Lett.*, 2015, **17**, 1094.
- 10 Z. Huang, Y. –D. Yang, E. Tokunaga and N. Shibata, *Asian J. Org. Chem.*, 2015, **4**, 525.
- 11 S. Arimori, M. Takada and N. Shibata, *Org. Lett.*, 2015, **17**, 1063.
- 12 During our investigation of this work, we noticed that Cahard also was examining the same reaction of allyl alcohols but using different reagents under different conditions; M. Maeno, N. Shibata and D. Cahard, *Org. Lett.*, 2015, **17**, 1990.
- 13 J. Holoch and W. Sundermeyer. *Chem. Ber.*, 1986, **119**, 269.
- 14 (a) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem. Int. Ed.*, 2014, **53**, 1650; (b) X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem. Int. Ed.*, 2013, **52**, 3457; (c) X. Shao, C. Xu, L. Lu and Q. Shen, *J. Org. Chem.*, 2015, **80**, 3012; (d) C. Chen, Y. Xie, L. Chu, R. –W. Wang, X. Zhang and F. –L. Qing, *Angew. Chem. Int. Ed.*, 2012, **51**, 2492.



Trifluoromethylsulfinyl **3** and trifluoromethylthio **5** compounds are independently obtained by the sulfone-type reagent **1** under Cu catalysis.