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Copper-Catalyzed Sulfenylation of Boronic Acids with Sulfonyl Hydrazides

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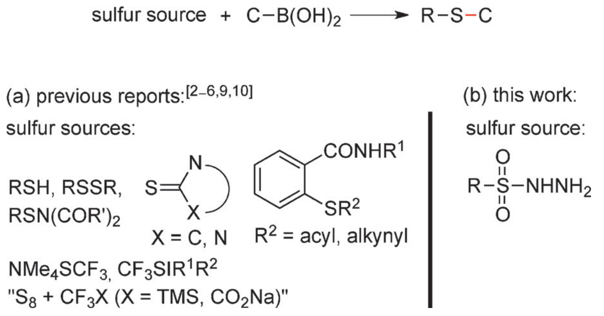
Abstract: An unprecedented sulfenylation reaction of carbon-boron bonds has been developed using sulfonyl hydrazides as sulfenyl sources. A range of sulfonyl hydrazides underwent tetrakis(acetonitrile)copper(I) tetrafluoroborate [$Cu(CH_3CN)_4BF_4$]/2,2′-bipyridine-catalyzed sulfenylation with boronic acids under air to give structurally diverse thioethers in moderate to good yields. Preliminary mechanistic studies show that sulfonyl hydrazides are subjected to decomposition into thiosulfonates and disulfides followed by formation of carbon-sulfur bonds with boronic acids.

Keywords: boronic acids; catalysis; copper; sulfonyl hydrazides; thioethers

Boronic acids have been widely employed in the transition metal-catalyzed cross-coupling reactions for the formation of carbon-carbon bonds, but seldom for the formation of carbon-heteroatom bonds, particularly carbon-sulfur bonds.[1] Nevertheless, inexpensive copper salts have been disclosed to be capable of mediating or catalyzing the carbon-sulfur bond-forming reactions between boronic acids and sulfenylating agents such as thiols,[2] disulfides,[3] *N*-thioimides,[4] thioamides,[5] and 2-thiobenzamides[6] under various conditions [Scheme 1 (a)]. These reactions provide direct access to versatile thioethers despite the fact that such sulfenylating agents are foul-smelling, volatile, and/or inconvenient to prepare and handle. Potassium thiocyanate[7] and potassium ethyl xanthogenate[8] can also undergo copper-catalyzed coupling with boronic acids to yield useful building blocks for a subsequent synthesis of thioethers. Recently, the carbon-sulfur bond-forming reactions of boronic acids have been extended to the synthesis of trifluoromethyl thioethers using either CF_3S-containing reagents[4b,9] or a combination of S_8 and CF_3-containing reagents.[10] It is noteworthy that all of these methods involve the use of low-valent sulfur to form carbon-sulfur bonds with boronic acids yielding thioethers. In this context, it would be highly desirable, yet challenging, to introduce high-valent sulfur compounds to the sulfenylation of boronic acids because they, in general, are more readily accessible and easier to handle than common sulfenylating agents.

Recently we reported the use of monosubstituted sulfonyl hydrazides (RSO_2NHNH_2) as sulfenyl sources in the synthesis of indole thioethers.[11] Later on, they were disclosed by Singh,[12] Jiang,[13] Xiang, Yuan,[14] Kumaraswamy,[15] Zhao, Lu,[16] Yan, Huang,[17] and us[18] to undergo sulfenylation with carbon-carbon multiple bonds, carbon-hydrogen bonds, carbon-halogen bonds, and phosphorus-hydrogen bonds under various conditions. When compared with commonly used sulfenylating agents such as thiols, disulfides, sulfenyl halides, sulfenamides, and sulfenate esters, sulfonyl hydrazides are readily accessible solids, free of unpleasant odor, and compatible with moisture. In continuation of exploring the synthetic utilities of substituted hydrazines,[11,18,19] we embarked on the application of sulfonyl hydrazides to



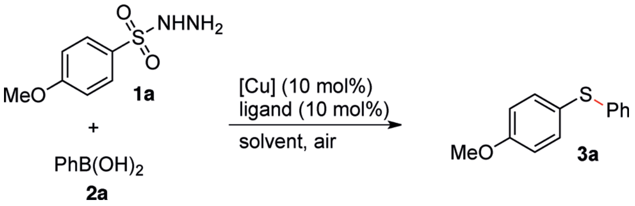
Scheme 1. Transformation of boronic acids into thioethers.

the sulfenylation of carbon-boron bonds to expand the scope of thioether synthesis [Scheme 1 (b)]. Herein we report an efficient sulfenylation reaction of boronic acids with sulfonyl hydrazides, which tolerates air and moisture, exhibits broad substrate scope, and releases water and molecular nitrogen as environmentally benign by-products.

Inspired by the fact that copper salts are effective in mediating or catalyzing the carbon-sulfur bond-forming reactions of boronic acids,[2–10] we employed a number of readily accessible copper salts (10 mol%) and *N*,*N*-ligands to catalyze the model reaction of sulfonyl hydrazide **1a** with boronic acid **2a**, which was found to proceed in 1,2-dichloroethane under air in a sealed tube at 120 °C (Table 1, entries 1–15). In general, the catalytic activity of copper(I) salts was significantly enhanced by aromatic *N*,*N*-ligands. To our delight, the use of $Cu(CH_3CN)_4BF_4$ in combination with 2,2′-bipyridine (bpy) led to the formation of thioether **3a** in 81% yield (Table 1, entry 6). It is noteworthy that a comparable yield was obtained from the reaction catalyzed by $Cu(OTf)_2$ albeit the use of a few other copper(II) salts, such as $CuCl_2{\cdot}2\,H_2O$, $CuSO_4{\cdot}5\,H_2O$, and $Cu(OAc)_2{\cdot}H_2O$, gave poor yields (Table 1, entries 7–10).[20] Much lower yields were obtained when replacing 1,2-dichloroethane with some other common solvents or when decreasing the temperature to 90 °C (Table 1, entries 16–23). Moreover, the air was proven to be essential by the control experiment performed under nitrogen, which gave thioether **3a** in only 45% yield (Table 1, entry 24). However, performing the reaction under oxygen also led to a much lower yield (57%) probably because a higher concentration of molecular oxygen could accelerate the oxidative homo-coupling of the boronic acid[1] as well as the decomposition of the sulfonyl hydrazide into a sulfonic acid through the intermediacy of a sulfinic acid (Table 1, entry 25).[21]

In the presence of 10 mol% $Cu(CH_3CN)_4BF_4$ and 10 mol% 2,2′-bipyridine, a range of arylsulfonyl hydrazides smoothly underwent sulfenylation with boronic acids under air to give structurally diverse thioethers in moderate to good yields (Table 2). Both electron-withdrawing and electron-donating groups were successfully introduced into the aromatic rings of the products by employing either the arylsulfonyl hydrazides or the arylboronic acids bearing such groups. Moreover, the reaction tolerated aryl groups bearing *ortho*-substituents and functional groups such as alkoxy, halo, nitro, and nitrile groups. While the reaction with an alkylsulfonyl hydrazide, such as octylsulfonyl hydrazide (**1k**), gave a complex mixture of products (Table 2, entry 11), the reaction worked well with both aryl- and alkylboronic acids, and consequently, a range of diaryl thioethers and alkyl aryl thioethers were obtained in moderate to good yields (Table 2, entries 12–25).

Table 1. Optimization of reaction conditions.[a]

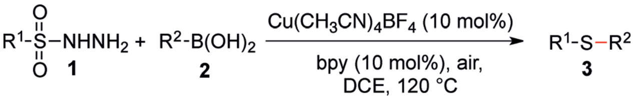


Entry	[Cu]	Ligand	Solvent	Yield [%][b]
1	CuCl	bpy	DCE	62
2	CuBr	bpy	DCE	46
3	CuI	bpy	DCE	49
4	$Cu(CH_3CN)_4ClO_4$	bpy	DCE	50
5	$Cu(CH_3CN)_4PF_6$	bpy	DCE	60
6	$Cu(CH_3CN)_4BF_4$	bpy	DCE	81
7	$CuCl_2{\cdot}2\,H_2O$	bpy	DCE	28
8	$CuSO_4{\cdot}5\,H_2O$	bpy	DCE	13
9	$Cu(OAc)_2{\cdot}H_2O$	bpy	DCE	trace
10	$Cu(OTf)_2$	bpy	DCE	80
11	$Cu(CH_3CN)_4BF_4$	none	DCE	60
12	none	bpy	DCE	0
13	$Cu(CH_3CN)_4BF_4$	1,10-phen·H_2O	DCE	66
14	$Cu(CH_3CN)_4BF_4$	TMEDA	DCE	9
15	$Cu(CH_3CN)_4BF_4$	$(CH_2NH_2)_2$	DCE	23
16	$Cu(CH_3CN)_4BF_4$	bpy	toluene	61
17	$Cu(CH_3CN)_4BF_4$	bpy	dioxane	41
18	$Cu(CH_3CN)_4BF_4$	bpy	CH_3CN	54
19	$Cu(CH_3CN)_4BF_4$	bpy	CH_3NO_2	60
20	$Cu(CH_3CN)_4BF_4$	bpy	DMSO	trace
21	$Cu(CH_3CN)_4BF_4$	bpy	DMF	trace
22	$Cu(CH_3CN)_4BF_4$	bpy	ethanol	33
23[c]	$Cu(CH_3CN)_4BF_4$	bpy	DCE	10
24[d]	$Cu(CH_3CN)_4BF_4$	bpy	DCE	45
25[e]	$Cu(CH_3CN)_4BF_4$	bpy	DCE	57

[a] *Reaction conditions:* sulfonyl hydrazide **1a** (0.20 mmol), boronic acid **2a** (0.40 mmol), [Cu] (10 mol%), ligand (10 mol%), solvent (0.30 mL), under air in a sealed tube at 120 °C (oil bath) for 15 h.
[b] Isolated yield.
[c] The reaction was performed at 90 °C (oil bath).
[d] The reaction was performed under nitrogen.
[e] The reaction was performed under oxygen.

Treatment of *N*′-substituted sulfonyl hydrazide **4a** with boronic acid **2b** under the standard reaction conditions gave thioether **3k** in only 16% yield (Scheme 2). This result suggests that the $NHNH_2$ group is essential for the sulfonyl hydrazide to serve as an effective sulfenylating agent in the coupling reaction. Moreover, we successfully trapped certain electrophilic sulfur species generated from sulfonyl hydrazides during the reaction. As demonstrated by the results shown in Scheme 3, addition of indole (**5a**) to the reaction mixture of sulfonyl hydrazide **1c** and boronic acid **2b** led to the formation of thioether **3k** in 21% yield as well as thioether **6a** in 26% yield.

Table 2. Sulfenylation of boronic acids with sulfonyl hydrazides.[a]



Entry	1	R^1	2	R^2	3	Yield [%][b]
1	**1a**	4-$MeOC_6H_4$	**2a**	Ph	**3a**	81
2	**1b**	Ph	**2a**	Ph	**3b**	70
3	**1c**	4-MeC_6H_4	**2a**	Ph	**3c**	78
4	**1d**	4-$Me_3CC_6H_4$	**2a**	Ph	**3d**	69
5	**1e**	4-ClC_6H_4	**2a**	Ph	**3e**	60
6	**1f**	4-IC_6H_4	**2b**	4-$MeOC_6H_4$	**3f**	58
7	**1g**	4-$O_2NC_6H_4$	**2a**	Ph	**3g**	37
8	**1h**	2,4,6-$Me_3C_6H_2$	**2a**	Ph	**3h**	63
9	**1i**	1-naphthyl	**2a**	Ph	**3i**	51
10	**1j**	2-naphthyl	**2a**	Ph	**3j**	51
11	**1k**	$Me(CH_2)_7$	**2a**	Ph	–	complex
12	**1c**	4-MeC_6H_4	**2b**	4-$MeOC_6H_4$	**3k**	66
13	**1a**	4-$MeOC_6H_4$	**2c**	4-MeC_6H_4	**3k**	70
14	**1a**	4-$MeOC_6H_4$	**2d**	4-PhC_6H_4	**3l**	59
15	**1a**	4-$MeOC_6H_4$	**2e**	4-FC_6H_4	**3m**	64
16	**1a**	4-$MeOC_6H_4$	**2f**	4-ClC_6H_4	**3n**	76
17	**1a**	4-$MeOC_6H_4$	**2g**	4-NCC_6H_4	**3o**	54
18	**1a**	4-$MeOC_6H_4$	**2h**	4-$O_2NC_6H_4$	**3p**	73
19	**1a**	4-$MeOC_6H_4$	**2i**	3,5-$(F_3C)_2C_6H_3$	**3q**	53
20	**1a**	4-$MeOC_6H_4$	**2j**	2-MeC_6H_4	**3r**	43
21	**1a**	4-$MeOC_6H_4$	**2k**	2-naphthyl	**3s**	69
22	**1a**	4-$MeOC_6H_4$	**2l**	Me	**3t**	68
23	**1a**	4-$MeOC_6H_4$	**2m**	Me_2CH	**3u**	88
24	**1a**	4-$MeOC_6H_4$	**2n**	$Me(CH_2)_4$	**3v**	48
25	**1a**	4-$MeOC_6H_4$	**2o**	cyclohexyl	**3w**	79

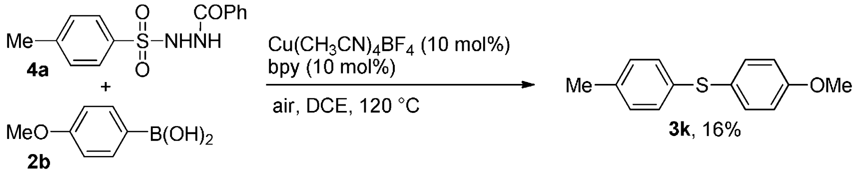
[a] *Reaction conditions:* sulfonyl hydrazide **1** (0.20 mmol), boronic acid **2** (0.40 mmol), $Cu(CH_3CN)_4BF_4$ (10 mol%), bpy (10 mol%), 1,2-dichloroethane (0.30 mL), under air in a sealed tube at 120 °C (oil bath) for 15 h.

[b] Isolated yield.

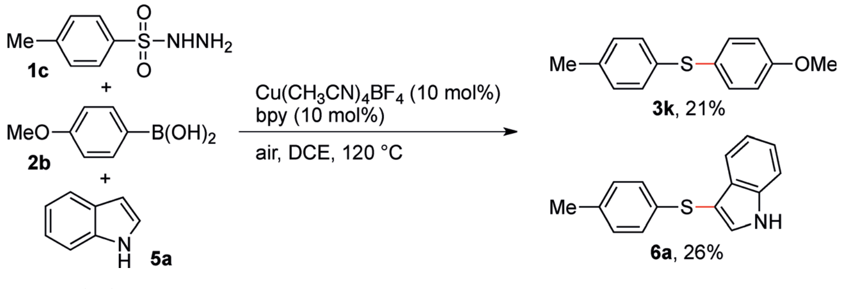
To gain more insights into the reaction mechanism, we monitored the reaction mixture of sulfonyl hydrazide **1c** and boronic acid **2b** by ^1H NMR spectroscopic analysis and found that sulfonyl hydrazide **1c** decomposed completely at an early stage (1 h) to give a 64:36 mixture of thiosulfonate **7a** and disulfide **8a**, both of which were gradually converted to thioether **3k** (Scheme 4). In contrast, in the absence of 10 mol% $Cu(CH_3CN)_4BF_4$ only 17% of sulfonyl hydrazide **1c** decomposed in the same amount of time (1 h) to give a 76:24 mixture of thiosulfonate **7a** and disulfide **8a**. These results clearly demonstrated that $Cu(CH_3CN)_4BF_4$ could catalyze the aerobic decomposition of sulfonyl hydrazides into thiosulfonates and disulfides.

In line with previous studies that thiosulfonates and disulfides could serve as sulfenylating agents in the presence of copper(I) salt catalysts,[3a,b,13] either thiosulfonate **7a** or disulfide **8a** was found to undergo $Cu(CH_3CN)_4BF_4$/2,2′-bipyridine-catalyzed sulfenylation with boronic acid **2b** under the standard reaction conditions to give thioether **3k** (Scheme 5) albeit in a lower yield relative to the corresponding reaction with sulfonyl hydrazide **1c** (Table 2, entry 12). As detected by thin layer chromatography, a small amount of disulfide **8a** was generated during the reaction of thiosulfonate **7a** with boronic acid **2b**.

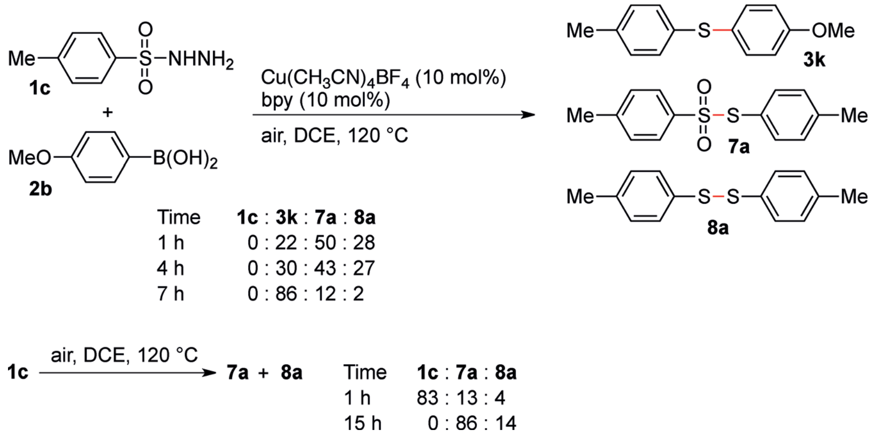
According to the above experimental results and previous relevant studies,[3b,11,13,21] we propose the following reaction pathways for the copper-catalyzed sulfenylation of boronic acids with sulfonyl hydrazides (Scheme 6). At an early stage, sulfonyl hydrazide **1** is subjected to redox decomposition, initiated by copper(I)-catalyzed aerobic oxidation, to give thiosulfonate **7** and disulfide **8** through the intermediacy of sulfonyl diazene **9** and sulfinic acid **10**.[11,21] Then, oxidative addition of either thiosulfonate **7** or disulfide **8** to the copper(I) catalyst leads to the formation of copper(III) species **11**,[22] which undergoes transmetalla-



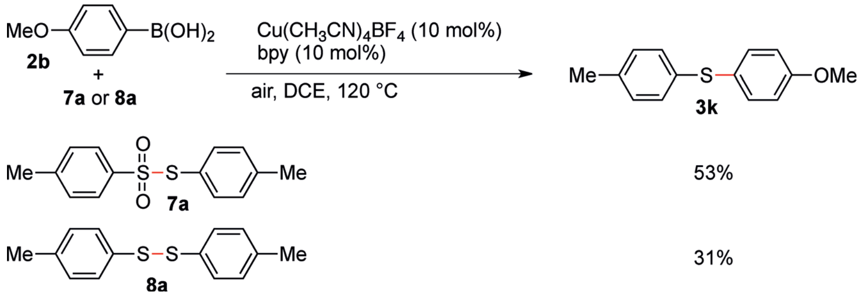
Scheme 2. Reaction with sulfonyl hydrazide **4a**.



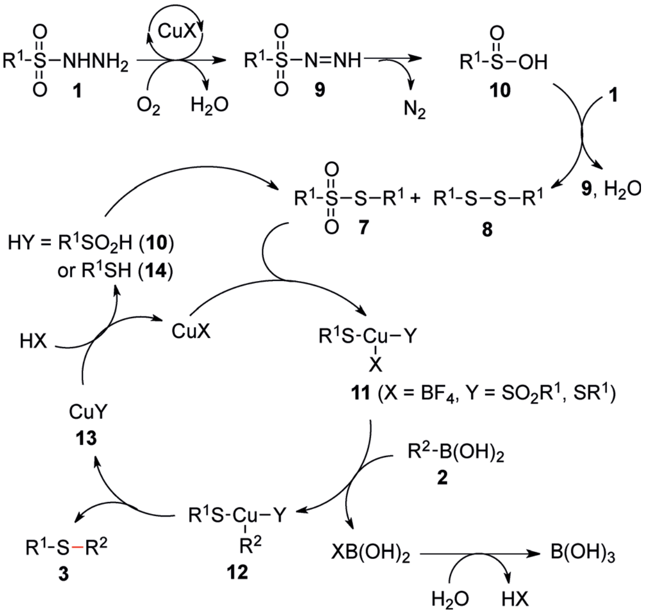
Scheme 3. Addition of indole (**5a**) to the reaction mixture.



Scheme 4. ^{1}H NMR spectroscopic analysis of the reaction mixture.



Scheme 5. Reaction of boronic acid **2b** with thiosulfonate **7a** or disulfide **8a**.



Scheme 6. Proposed reaction pathways.

tion with boronic acid **2** to give copper(III) species **12**. Reductive elimination of copper(III) species **12** gives thioether **3** as well as copper(I) species **13**.[3b] Anion exchange of copper(I) species **13** releases sulfinic acid **10** or thiol **14** and regenerates the copper(I) catalyst to continue the catalytic cycle. As reported previously, simple heating permits the disproportionation of sulfinic acid **10** to thiosulfonate **7** and disulfide **8**.[21] On the other hand, thiol **14** is oxidized by air to regenerate disulfide **8**.[2c] Such transformations between different valent sulfur species might be accelerated by the copper catalyst, and importantly, they significantly contribute to the formation of the desired thioethers in good yields.

In summary, we have successfully applied sulfonyl hydrazides to the sulfenylation of carbon-boron bonds to expand the scope of thioether synthesis. In the presence of 10 mol% $Cu(CH_3CN)_4BF_4$ and 10 mol% 2,2′-bipyridine, a range of sulfonyl hydrazides underwent sulfenylation with boronic acids under air to give structurally diverse thioethers in moderate to good yields. Preliminary mechanistic studies show that sulfonyl hydrazides are subjected to decomposition into thiosulfonates and disulfides followed by formation of carbon-sulfur bonds.[23]

Experimental Section

General Procedure for the Sulfenylation of Boronic Acids with Sulfonyl Hydrazides

A mixture of sulfonyl hydrazide **1** (0.20 mmol), boronic acid **2** (0.40 mmol), $Cu(CH_3CN)_4BF_4$ (6.3 mg, 10 mol%), and

2,2′-bipyridine (3.2 mg, 10 mol%) in 1,2-dichloroethane (0.30 mL) was heated under air in a sealed tube at 120 °C (oil bath) for 15 h. The mixture was cooled to room temperature and purified by silica gel chromatography (ethyl acetate/petroleum ether, 0:1 ~ 1:4) to give thioether **3**.

Acknowledgements

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