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Modified Conditions for Copper-Catalyzed *ipso*-Thiolation of **Arylboronic Acid Esters with Thiosulfonates**

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An efficient ipso-thiolation of arylboronic acid esters with thiosulfonates has been achieved under mild and odorless conditions using a copper catalyst. The use of TMEDA and cesium fluoride as the ligand and base, facilitated respectively, dramatically the desired transformation. The method exhibited a broad substrate scope, which allowed for the expeditious synthesis of diverse aryl sulfides from easily available starting materials.

9 Aromatic sulfur compounds have broad applications in chemistry,^{1,2} 10 fields, such as medicinal various agrochemistry,³ and materials science.⁴ Although many 11 synthetic methods have been developed, the preparation of 12 13 aromatic sulfur compounds by conventional methods is still 14 limited.

15 In this context, to render a variety of aryl sulfides 16 easily available, our group has recently developed the 17 copper-catalyzed and rhodium-catalyzed ipso-thiolation methods of arylboronic acids with thiosulfonates.^{5,6} These 18 reactions are advantages because of the readily available 19 20 starting materials and broad substrate scope, and mild and 21 odorless conditions. However, we found that these methods 22 often provided insufficient results, particularly with the use 23 of arylboronic acid pinacol esters. For example, the deborylthiolation of arylboronic acid pinacol esters 1a-1d 24 25 with S-p-tolyl p-toluenethiosulfonate (2a) under the copper-26 catalyzed (Figure 1, conditions A or B, blue or orange bars, 27 respectively) or rhodium-catalyzed conditions (conditions C, 28 gray bars) generally afforded the corresponding sulfides 3a-29 3d in low to moderate yields. These results indicated that 30 methods demonstrate for our limitations the 31 deborylthiolation of arylboronic acid esters, which are 32 relatively less reactive than the corresponding arylboronic 33 acids because of the increased steric bulk of the boryl group 34 and σ -donation from the α -carbons to the oxygens resulting in decrease of the Lewis acidity of the boron center.⁷ 35 Considering the recent advances in the methods for the 36 37 synthesis of arylboronic acid esters by transition-metal-38 catalyzed borylation reactions, including the palladiumcatalyzed borylation of aryl halides¹⁰ and iridium-catalyzed 39 C-H borylation of arenes,¹¹ it is crucial to achieve an 40 efficient ipso-thiolation of arylboronic acid esters. Herein, 41 42 we report modified conditions for the efficient copper-43 catalyzed ipso-thiolation of a wide range of arylboronic acid 44 esters.

45 After the extensive rescreening of conditions carried 46 out for the copper-catalyzed reaction between 47 phenylboronic pinacol ester (1c) and thiosulfonate 2a (Figure 1, conditions B), the addition of a ligand using a 48



49 50 Figure 1. ipso-Thiolation of arylboronic acid pinacol esters under the reported conditions. Conditions A: PhBpin (1.5 equiv), CuSO₄ (5 mol %), NaHCO3 (2.0 equiv), MeOH, rt, 24 h. Conditions B: PhBpin 53 (1.5 equiv), CuSO₄ (5 mol %), K₂CO₃ (2.0 equiv), MeOH, 50 °C, 24 h. Conditions C: PhBpin (2.0 equiv), [Rh(OH)(cod)]₂ (2.5 mol %), K₃PO₄ (2.0 equiv), MeOH, 50 °C, 24 h. Yields were determined by HPLC. 56

Table 1. Optimization of the reaction conditions						
			u source (5 mo and, Base (2.0 e	I %) equiv)		
		Bpin Bpin	Solvent		s , <i>p</i> -Tol	
	1c (1.5 equiv) 2a		30 0, 24 li	3c		
	Entry	Cu source/ Ligand (mol %)	Base	Solvent	Yield /% ^a	
	1	CuSO ₄ /–	K_3PO_4	MeOH	trace	
	2	CuSO ₄ /–	KOAc	MeOH	14	
	3	CuSO ₄ /–	KF	MeOH	65	
	4	CuSO ₄ /–	CsF	MeOH	74	
	5	CuSO ₄ /–	RbF	MeOH	48	
	6	CuSO ₄ /PPh ₃ (12)	CsF	MeOH	9	
	7	CuSO ₄ /Xantphos (6)	CsF	MeOH	12	
	8	$CuSO_4/acac$ (6)	CsF	MeOH	63	
	9	CuSO ₄ /bpy (6)	CsF	MeOH	63	
	10	CuSO ₄ /1,10-phen (6)	CsF	MeOH	53	
	11	CuSO ₄ /TMEDA (6)	CsF	MeOH	81 ^b	
	12	CuI/TMEDA (6)	CsF	MeOH	55	
	13	$Cu(OAc)_2 \cdot H_2O/TMEDA$ (6)	CsF	MeOH	60	
	14	CuSO ₄ /TMEDA (6)	CsF	DMF	trace	
	15	CuSO ₄ /TMEDA (6)	CsF	1,4-dioxane	trace	

59 ^aYields were determined by HPLC analysis, unless otherwise noted. 60 ^bIsolated yield.

1 fluoride salt as the base considerably improved the yield of 2 the desired sulfide 3c (Table 1). Instead of weak bases, such as K₂CO₃, K₃PO₄, and KOAc, the use of alkali metal 3 4 fluorides, particularly cesium fluoride, dramatically 5 facilitated the reaction (Table 1, Entries 1-5). The addition 6 catalytic amount of N,N,N',N'of а 7 tetramethylethylenediamine (TMEDA) as the ligand further 8 improved the yield of 3c (Entry 11). In contrast, the addition 9 of other ligands, such as phosphines, acetylacetonate, and 10 pyridines, decreased the yield of **3c** (Entries 6–10). Notably, for the reaction conducted under the conditions shown in 11 Entry 11, the formation of di(4-tolyl) disulfide as the side 12 13 product, which exhibits polarity similar to that of the desired 14 diaryl sulfide making purification difficult, was not detected.¹² Changing the copper source from CuSO₄ to CuI 15 16 or Cu(OAc)₂·H₂O decreased the yield of 3c (Entries 12 and 17 13). In addition, the use of other solvents, such as DMF and 18 dioxane, instead of methanol were completely unsuccessful 19 (Entries 14 and 15).

20 The optimized conditions (Table 1, Entry 11) were 21 applicable to the *ipso*-thiolation of a wide range of aryl- and 22 alkenylboronic acid pinacol esters 1 as exemplified by the 23 reaction with thiosulfonate 2a affording sulfides 3a-3j 24 (Figure 2). Various diaryl sulfides **3a-3h** were successfully 25 obtained in high yields from the corresponding arylboronic 26 acid pinacol esters 1. In particular, arylboronic acid pinacol 27 esters 1 bearing an electron-donating group, including 28 methoxy, dimethylamino, and an unprotected hydroxyl 29 group, underwent thiolated under the optimized conditions. 30 This result is in stark contrast to those observed for 31 reactions carried out under previously reported copper-32 catalyzed conditions shown in Figure 1, wherein the 33 reaction of electron-rich arylboronic acid pinacol esters 34 afforded the desired sulfides only in low yields. Moreover, 35 the method was also applicable to the deborylthiolation of 36 heteroaryl- and alkenylboronic acid esters to afford products 37 such as 3-thienyl and (E)-styryl sulfides 3i and 3j, 38 deborylthiolation respectively. Unfortunately, of 39 alkylboronic acid esters, including *n*-butyl- and allylboronic 40 acid pinacol ester, did not proceed.

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45 Various thiosulfonates 2 were also applied to the 46 modified method as demonstrated in the deborylthiolation of 47 phenylboronic acid pinacol ester (1c) (Figure 3). S-Aryl 48 thiosulfonates bearing an electron-donating or electron-49 withdrawing substituent, including an unprotected amino, 50 carbamate, and amide group, on the aryl moiety successfully 51 furnished diaryl sulfides 3k-3q, demonstrating the excellent 52 functional-group tolerance of the method. Moreover, S-53 heteroaryl and S-alkyl thiosulfonates also participated in the 54 reaction, affording 3-thienyl and phenethyl sulfides 3r and 55 3s, respectively. 56







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Figure 4. Comparison of the reactivity of various boronates with thiosulfonate 2a under respective conditions. Conditions A: boronate (1.5 equiv), $CuSO_4$ (5 mol %), $NaHCO_3$ (2.0 equiv), MeOH, rt, 24 h. Conditions D: boronate (1.5 equiv), $CuSO_4$ (5 mol %), TMEDA (6 mol %), CsF (2.0 equiv), MeOH, 50 °C, 24 h. "Yield when the reaction was conducted under conditions D without CsF is shown in brackets.

The modified conditions established herein were effective for the *ipso*-thiolation of other phenylboronic acid alkanediol esters (Figure 4, conditions D, orange bars), e.g., trimethylene, neopentyl, and hexylene glycol esters **5**–**7**, affording the desired sulfide **3c** in high yields. This result is in stark contrast to that observed from the reactions carried

out under the previously reported conditions (conditions A, 1 blue bars), where the result considerably depended on the 2 boronates used.^{7,13} The decrease in the yield of 3c was 3 observed with the increase in the steric bulk around the 4 boron moiety. These contrasting results indicated that the 5 new catalytic system using copper(II) sulfate and TMEDA 6 7 with cesium fluoride as the Lewis base significantly 8 facilitates deborylthiolation compared to the previous 9 system, probably via the acceleration of transmetalation. 10 Moreover, phenylcyclic-triolborate potassium salt 8 was deborylthiolated under the new conditions, whereas 11 potassium phenyltrifluoroborate (9) afforded 3c in poor 12 13 yields under both conditions.

14 As various arylboronic esters can be easily prepared 15 from simple starting materials by the transition-metalcatalyzed borylative transformation of C–X,¹⁰ C–H,¹¹ C–F,¹⁴ 16 C-S,¹⁵ and C-COSR¹⁶ bonds, performing the *ipso*-thiolation 17 just after borylation facilitated the two-step synthesis aryl 18 sulfides. For example, formal C-H thiolation was 19 accomplished by the iridium-catalyzed C-H borylation¹¹ of 20 1,2-dimethoxybenzene $(10)^{17}$ followed by deborylthiolation, 21 22 affording desired sulfide 3t in high yield (Scheme 1). In this 23 case, the use of the modified conditions was crucial to 24 efficiently achieve ipso-borylation as the previous conditions afforded 3t only in low yield. Notably, in 25 addition, the transformation of 10 to 3t was achieved with 26 27 the same efficiency even when the sequential reaction was 28 conducted in a same pot without purifying intermediate 1k. 29 This procedure demonstrated promise as a rapid route to 30 synthesize aryl sulfides from boron-free substrates. 31



32 Scheme 1. Formal C–H thiolation of 1,2-dimethoxybenzene (10).
34 "Yield of 3t when the reaction was carried out under the previous copper-catalyzed conditions (Conditions A: CuSO₄ (5 mol %), NaHCO₃
36 (2.0 equiv), MeOH, rt, 24 h) in brackets.

38 In summary, the efficient ipso-thiolation of arylboronic 39 acid esters with thiosulfonates using modified copper-40 catalyzed conditions was reported. The use of cesium 41 fluoride and catalytic amount of TMEDA as the base and 42 ligand, respectively, dramatically facilitated the desired 43 transformation, affording diverse aryl sulfides from easily 44 available starting materials. In addition, the formal C-H 45 thiolation of a simple arene was achieved via the iridiumcatalyzed C-H borylation followed by ipso-thiolation. This 46 47 sequential reaction was conducted in the same pot, 48 considerably expanding the range of synthesizable sulfides 49 in an expeditious manner.

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62 References and Notes

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