



Nucleophilic disulfurating reagents for unsymmetrical disulfides construction via copper-catalyzed oxidative cross coupling



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ABSTRACT

Novel disulfuration was established via cross coupling between nucleophilic disulfurating reagent and arylsilane introducing two sulfur atoms in one step. This methodology was applied to synthesize various unsymmetrical disulfides under mild conditions via copper-catalyzed oxidative Hiyama-type cross coupling, providing a new pathway for disulfide synthesis. In addition, pH value of system displayed a key role in alcoholysis process.

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1. Introduction

Disulfide extensively exists in numerous significant molecules with biological and pharmaceutical activity (Scheme 1).¹ Therefore, development of highly efficient synthetic methods to access sulfur-sulfur bond has been intensively pursued by synthetic community.^{2,3} Symmetrical disulfide can be facilely synthesized via oxidation of thiol,^{2a} while efficient examples have been scarcely reported for the unsymmetrical disulfide synthesis.^{2b,3} Continuous with our concept of sulfur atom transfer study,⁴ a strategy of constructing unsymmetrical disulfides with two different valent inorganic sulfur source via a comproportionation process had been reported.^{5a} On the basis of masked strategy, a new type of nucleophilic disulfurating reagent had been designed and synthesized, which was utilized to construct unsymmetrical disulfide with arylboronic acid under mild copper-catalyzed oxidative cross-coupling conditions through a highly selective C–S bond cleavage and reformation (Scheme 2a).^{5b}

In our previous Suzuki-type cross-coupling, prooxidant of

molysite/manganese dioxide have to be utilized, and pH value of the system regulated by sodium carbonate plays a key role in the disulfuration. Compared to organoboron reagents and other metal reagents employed in cross coupling processes, silicon-based nucleophiles possess the characteristic of neutrality, easy handling, high chemical stability, low toxicity, and relatively low cost.^{6,7} In this manuscript, we report a novel and facile methodology for Hiyama-type cross-coupling of disulfurating reagent with oxygen as sole oxidant under mild conditions.

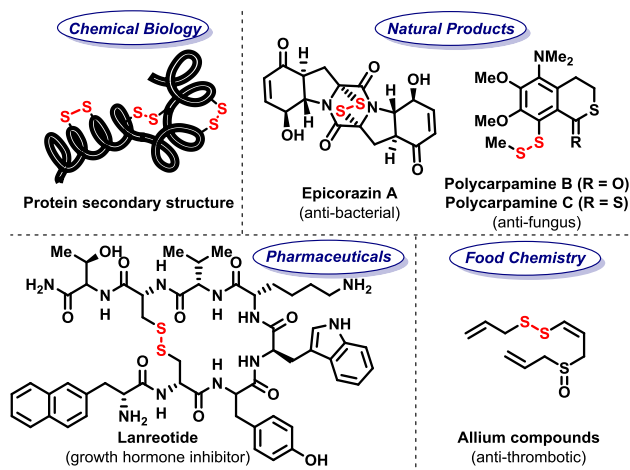
2. Result and discussion

We commenced our study with trimethoxy(phenyl)silane **1a** and BnSSAc **2a** as the disulfur coupling partner in the presence of copper sulfate pentahydrate (10 mol %) and 2,2'-bipyridine (12 mol %) in MeOH at room temperature. When one equivalent of TBAF as the activator of inert C–Si bond was added, the desired unsymmetrical disulfide **4a** was obtained in 12% yield (Table 1, entry 1). Ligand screening shown that 4,4'-dimethoxy-2,2'-bipyridine was the best ligand in this disulfuration (Table 1, entries 1–3). Further investigation revealed the yields were improved when phenolic derivatives were utilized as additive (Table 1, entries 4–7).⁸ However, decreasing the amount of fluoride source did not affected the yield of desired product **4a** (Table 1, entry 8). A better result was achieved when TsOH·H₂O (0.3 equiv.) as pH value conditioner was

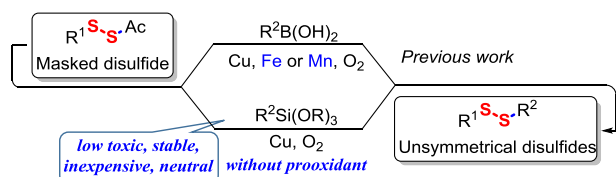
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Scheme 1. Representative significant disulfides.



Scheme 2. Strategies for disulfide construction.

Table 1
Optimization of disulfuration.^a

Entry	TBAF (equiv.)	Ligand (mol%)	Additive 1 (equiv.)	Additive 2 (equiv.)	Yield ^b (%)
1	1	Bipy (12)	–	–	12
2	1	4,4'-diMe-Bipy (12)	–	–	14
3	1	4,4'-diMeO-Bipy (12)	–	–	33
4	1	4,4'-diMeO-Bipy (12)	PhOH (1.0)	–	45
5	1	4,4'-diMeO-Bipy (12)	C ₆ F ₆ OH (1.0)	–	46
6	1	4,4'-diMeO-Bipy (12)	<i>p</i> -CF ₃ C ₆ H ₄ OH (1.0)	–	37
7	1	4,4'-diMeO-Bipy (12)	<i>p</i> -FC ₆ H ₄ OH (1.0)	–	48
8	0.5	4,4'-diMeO-Bipy (12)	<i>p</i> -FC ₆ H ₄ OH (1.0)	–	47
9	0.5	4,4'-diMeO-Bipy (12)	<i>p</i> -FC ₆ H ₄ OH (1.0)	TsOH·H ₂ O (0.3)	57
10	0.5	4,4'-diMeO-Bipy (20)	<i>p</i> -FC ₆ H ₄ OH (1.0)	TsOH·H ₂ O (0.3)	92
11	0.5	4,4'-diMeO-Bipy (20)	PhOH (1.0)	TsOH·H ₂ O (0.3)	92 (85) ^c
12	0.5	4,4'-diMeO-Bipy (20)	PhOH (0.5)	TsOH·H ₂ O (0.3)	92 (84) ^c

^a Trimethoxy(phenyl)silane (0.6 mmol, 3 equiv.), **2a** (0.2 mmol, 1 equiv.), CuSO₄·5H₂O (0.02 mmol, 10 mol%), 4,4'-dimethoxy-2,2'-bipyridine (0.04 mmol, 20 mol%), TBAF (0.1 mmol, 0.5 equiv.), PhOH (0.1 mmol, 0.5 equiv.) and TsOH·H₂O (0.06 mmol, 0.3 equiv.) were added to MeOH (2 mL) stirring at r.t. for 10 h under O₂ atmosphere.

^b Yield was determined by ¹H NMR of the crude reaction mixture using an internal standard.

^c Isolated yield.

employed in the reaction (Table 1, entry 9). The optimized conditions were obtained by enhancing the loading of ligand to afford 92% yield of benzyl(phenyl)disulfane (Table 1, entry 10). Finally, we were pleased to observe that cross-coupling was also efficient with phenol as additive (Table 1, entries 11 and 12).

With this preliminary result in hand, the scope of these copper-catalyzed Hiyama-type coupling reactions of silane reagents was investigated under the optimized conditions, and the results are shown in Scheme 3. A spectrum of functional groups furnished on silane substrates, bearing electron-withdrawing and electron-

donating functional groups are compatible with the cross-coupling conditions (Scheme 3; **3a–h**). Arylsilane with amide containing active hydrogen was successfully used to afford the corresponding disulfane (Scheme 3; **3d**). Notably, the halogen-substituted arylsilane, proceed favourably in the transformation, which was arduously compatible in traditional cross-coupling reactions (Scheme 3; **3e, f**). Thiophenylsilane leads to formation of the desired product in more modest yield as well (Scheme 3; **3i**). Significantly, vinylsilane performed efficiently in this transformation (Scheme 3; **3j**). The scope with respect to the disulfurating reagents was further studied. For most cases, the reaction of disulfurating reagent was found to tolerate both benzyl and alkyl groups with various substituents in moderate to excellent yields (Scheme 3; **4a–i**). For example, reaction of trimethoxy(phenyl)silane **1a** and disulfurating reagents **2b** or **2c** gave rise to the corresponding products **4b** or **4c** in 85% or 89 yields (Scheme 3; **4b, c**), respectively. Disulfurating reagents with halide groups were also found to be suitable substrates for coupling with trimethoxy(phenyl)silane **1a** (Scheme 3; **4d–h**), and the desired products were generated in moderate to high yields. Propargyl substituted reagent was also tolerant in this transformation (Scheme 3; **4l**). Secondary disulfurating reagents were well compatible in this cross-coupling (Scheme 3; **4m, n**). A host of disulfide reagents with heterocycles, indolyl and benzofuranyl, were suitable partners in this process and the desired products were isolated in good yields (Scheme 3; **4o–q**). When 6 mmol of **2a** was carried out in the reaction, the unsymmetrical disulfide **4a** was afforded in 61% yield.

A plausible mechanism for the Hiyama-type cross-coupling re-

action of disulfurating reagents with arylsilanes is shown in Scheme 4.^{6,9} Disulfur anion **5**¹⁰ was tardily released in-situ through alcoholysis of disulfane reagent **2** under the appropriate pH value conditions. Ligand-exchange of Cu(II) **6** with intermediate **5** proceeded to complex **7**. The complex **8** was generated via transmetalation with arylsilane. The resulting aryl Cu(II) **8** specie was further oxidized through single electron transfer process under the assistance of another Cu(II) **6** to afford aryl Cu(III) **10** intermediate and Cu(I) **9**.^{9a–c} Product **3** was subsequently formed through reductive elimination, releasing Cu(I) **9** simultaneously.^{9d} Rapid

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