Letter

Phthalimide-Carried Disulfur Transfer to Synthesize Unsymmetrical Disulfanes via Copper Catalysis

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Phthalimide-Carried Disulfur Transfer to Synthesize Unsymmetrical Disulfanes via Copper Catalysis

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ABSTRACT: A versatile Cu-catalyzed cross-coupling reaction to various unsymmetrical disulfanes has been presented, from phthalimide-carried disulfur transfer reagents and commercially available boronic acids under mild and practical conditions. The method features the unprecedented use of phthalimide-carried disulfurating reagents (Harpp reagent) in cross-coupling chemistry, and is highlighted by the broad substrate scopes, even applicable for the transfer of aryl-disulfur moieties (ArSS-). Notably, the robustness of this methodology is shown by the late-stage modification of bioactive scaffolds of coumarin, estrone and captopril.

KEYWORDS: phthalimide-carried disulfur transfer, unsymmetrical disulfanes, cross-coupling, Harpp reagent analogs, modification

Disulfide bond (S-S) as a critically important structural bridge, plays vital and multiple roles in oxidative folding, stability, and biological functions of peptides and proteins in living entities,[1] as well as maintaining the cellular redox balance in cell survival.[2] In pharmaceuticals, disulfide bond is an ubiquitous subunit and has profound effect on its pharmacological activities.[3] Meanwhile, disulfide bond is also utilized as a self-immolative linker unit in monoclonal antibodies (mAbs) – drug conjugates for tumor-targeting drug delivery.[4] Additionally, some specific chemicals containing disulfide bonds are able to release a biologically important cellular signaling molecule - hydrogen sulfide (H_2S) to mediate a series of physiological and pathological processes.[5] In addition to the aforementioned significance in life science, disulfide bond is abundant and important in food chemistry,[6] functional materials,[7] natural products,[8] and bioactive molecules[9] (Figure 1). All of these attributes of disulfide bond make the incorporation of it into organic frameworks receive significant attention in chemistry and related domains. According to the literatures, there are two

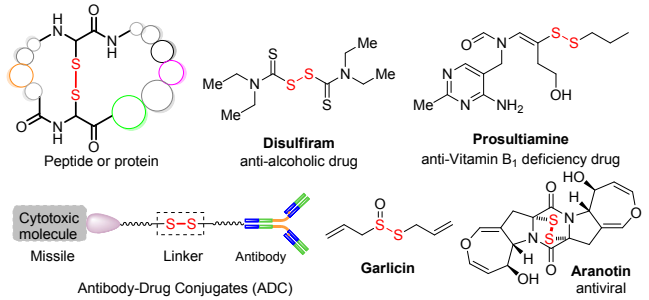
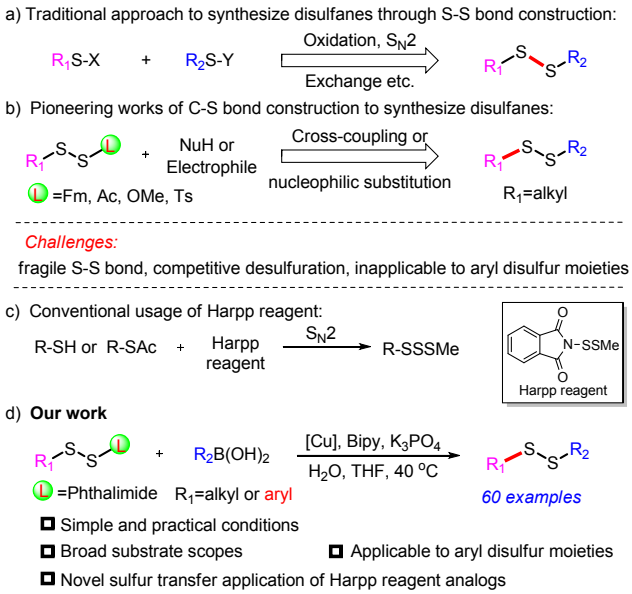


Figure 1. Representative and widespread S-S bond.



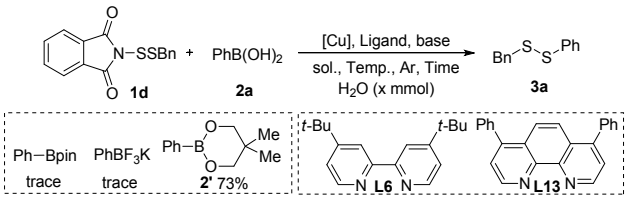
Scheme 1. Preparation of disulfanes.

strategies to access unsymmetrical disulfanes: initiated from S-S bond construction[10] and C-S bond construction[11-13] respectively (Scheme 1). Conventional methodologies in the former strategy, including oxidation, S_N2 replacement, and exchange pathways etc.,[10] suffer from some longstanding restraints like undesirable homocoupling byproducts. C-S Bond formation as an emerged strategy to deliver unsymmetrical disulfanes has brought the disulfane chemistry into a new sight, and several pioneering works like cross-coupling or nucleophilic substitution of

nucleophilic or electrophilic disulfur reagents (RSS-L) have been disclosed by Xian[11], Jiang[12] and Xu[13] (Scheme 1b). Despite significant progress, these reports share identical challenges like competitive desulfuration and unable to transfer ArSS- moieties onto aryls to deliver diaryl disulfanes, and this may be due to the hyperconjugation of ArSS- weakens the S-S bond. In this context, a versatile and robust disulfur reagent or new catalytic process has to be explored for resolving these key problems.

Since firstly synthesized by David N. Harpp, Harpp reagent was mainly employed as electrophile to react with thiols or RSAc in natural product synthesis to afford trisulfides[14] (Scheme 1c). Although several decades have passed by, new application of this kind of reagent has been rarely explored. Inspired by the aforementioned pioneering works and challenges, we envisioned Harpp reagent may serve as a desired disulfur transfer reagent for the weak coordination between oxygen in the phthalimide and copper could induce the selective oxidation insertion of copper into N-S bond. After extensive studies, we herein disclose a new usage of Harpp reagent analogs in Cu-catalyzed Chan-Lam

Table 1. Optimization of reaction[a]



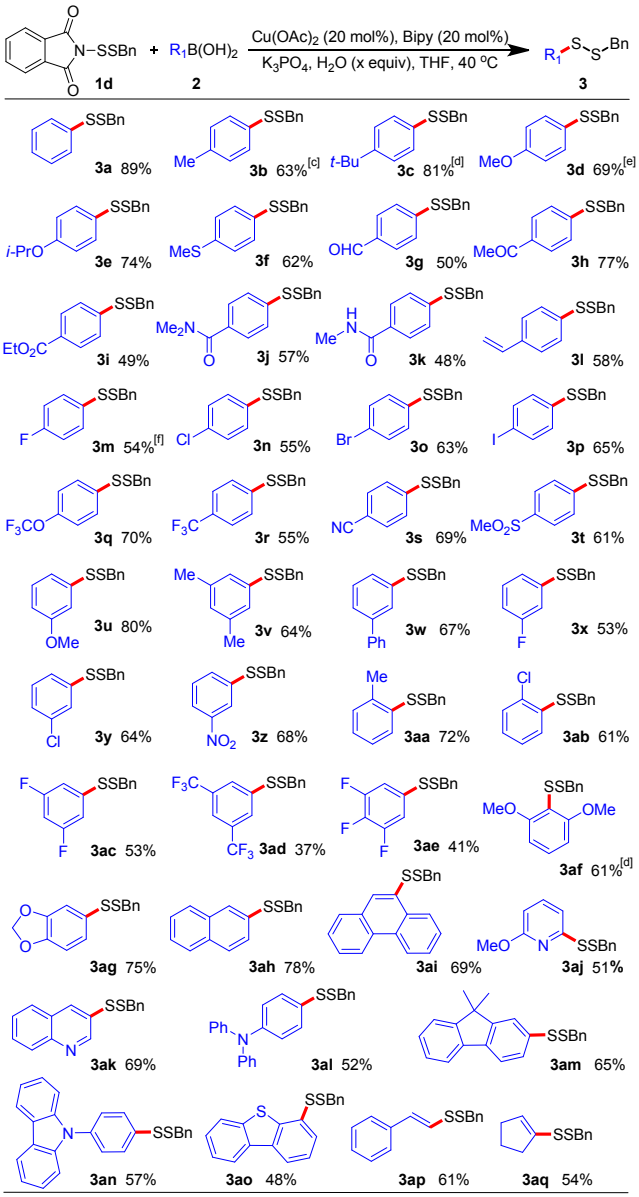
Entry	[Cu]	Ligand	Base	Sol.	yield/%[b]
1	$Cu(OAc)_2$	Bipy	NaOAc	CH_3CN	49
2	$CuBr_2$	Bipy	NaOAc	CH_3CN	27
3	CuI	Bipy	NaOAc	CH_3CN	33
4	$Cu(OAc)_2$	Bipy	K_2CO_3	CH_3CN	37
5	$Cu(OAc)_2$	Bipy	K_3PO_4	CH_3CN	54
6	$Cu(OAc)_2$	Bipy	K_3PO_4	THF	67
7	$Cu(OAc)_2$	L6	K_3PO_4	THF	69
8	$Cu(OAc)_2$	L13	K_3PO_4	THF	61
9[c]	$Cu(OAc)_2$	Bipy	K_3PO_4	THF	89
10[d]	$Cu(OAc)_2$	Bipy	K_3PO_4	THF	81
11[e]	$Cu(OAc)_2$	Bipy	K_3PO_4	THF	58
12	-	Bipy	K_3PO_4	THF	N.R.
13	$Cu(OAc)_2$	-	K_3PO_4	THF	N.R.
14	$Cu(OAc)_2$	Bipy	-	THF	N.R.
15	$Cu(OAc)_2$	Bipy	K_3PO_4	THF	81[f]/76[g]
16[h]	$Cu(OAc)_2$	Bipy	K_3PO_4	THF	21

[a]Reaction conditions: **1d** (0.20 mmol, 1.0 equiv), **2a** (0.40 mmol, 2.0 equiv), [Cu] (0.04 mmol, 0.2 equiv), ligand (0.04 mmol, 0.2 equiv), base (0.40 mmol, 2.0 equiv) and THF (2 mL) at 40 °C for 10 h under argon atmosphere. [b]Isolated yields. [c]H_2O: 1.5 equiv. [d]0.28 mmol (1.4 equiv) of **2a** and K_3PO_4 was added. [e]0.20 mmol (1.0 equiv) of **2a** and K_3PO_4 was added. [f]TEMPO (0.30 mmol, 1.5 equiv) was added. [g]BHT (0.30 mmol, 1.5 equiv) was added. [h] Air instead of Ar.

type coupling to furnish categories of structurally diversified disulfanes (Scheme 1d).

We commenced our studies by choosing 2-(benzylsulfinothioyl)isoindoline-1,3-dione (**1d**) as the model disulfur reagent to react with phenylboronic acid (**2a**) in the presence of 20 mol % $Cu(OAc)_2$, 20 mol % 2, 2'-bipyridine (Bipy), and 2 equivalents of NaOAc under argon (Ar) atmosphere at 40 °C for 10 h, and the desired product **3a** was obtained in 49% yield (Table 1, entry 1). Next, a series of copper catalysts were examined but no enhancement on the yield was observed (entries 2 - 3; Table S1). Given the significance of base in transmetalation process,[15] a range of strong and weak bases were screened and K_3PO_4 was found

Table 2. Substrate scopes of boronic acids[a], [b]



[a]Standard conditions: **1d** (0.20 mmol, 1.0 equiv), **2** (0.40 mmol, 2.0 equiv), $Cu(OAc)_2$ (0.04 mmol, 0.2 equiv), Bipy (0.04 mmol,

0.2 equiv), H_2O (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv) and THF (2 mL) , 40 °C, 10 h, Ar. [b]Isolated yields. [c]H_2O: 3.0 equiv. [d]H_2O: 2.0 equiv. [e]H_2O: 1.0 equiv. [f]H_2O: 2.5 equiv.

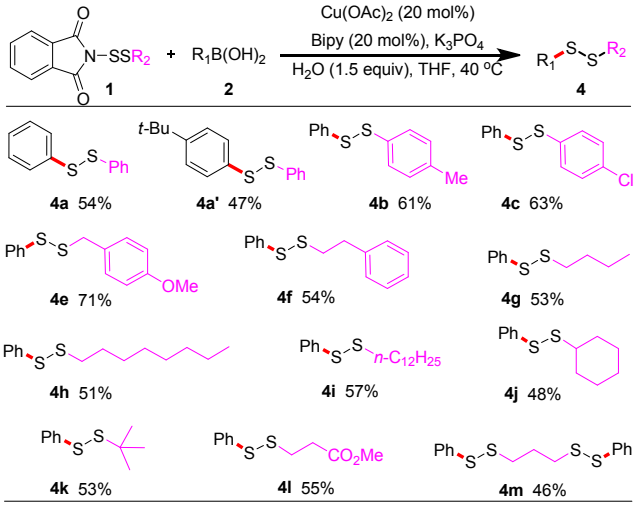
to be the optimal base providing **3a** in 54% yield (entries 4-5; Table S2). As for solvents, THF afforded the target product **3a** in 67% yield (entry 6; Table S3). When several kinds of mono-, di- and tridentate ligands were tested (entries 7 - 8; Table S4), the yield was slightly increased as di-tert-butyl bipyridine employed (entry 7). However, we still chose Bipy as the ligand to continue optimization for economic considerations. Neither elevated nor reduced temperature was beneficial for the transformation (Table S5). Since water would probably increase the solubility of bases, we screened different equivalents of water in the reaction, and the yield dramatically jumped to 89% when 1.5 equiv H_2O was added (entry 9; Table S6). Decreasing the amount of base and boronic acid decreased the yield (entries 10 - 11; Table S7). Additionally, other organoboronic reagents such as PhBpin, $PhBF_3K$, and boronic acid ester **2'** were also explored, but merely **2'** yielded the product **3a** in 73% (Table 1). Control experiments showed copper catalyst, ligand, and base were indispensable for the reaction (entries 12 - 14). Inert atmosphere was also crucial for this transformation as the yield of **3a** fell to 21% when the reaction was performed under Air instead of Ar (entry 16).

With the optimized reaction conditions in hand, we investigated the substrate scopes with respect to varieties of boronic acids. As shown in Table 2, both electron-donating and electron-withdrawing substituents at para-, meta- and ortho-positions of arylboronic acids provided the corresponding products in moderate to good yields (**3a - 3ag**, 37% - 89%). Notably, various sensitive functional groups such as -CHO, -CO-, -CO_2-, -$CONMe_2$, -CON(H)-, -vinyl, -OCF_3, -CF_3, -CN, -SO_2Me, -NO_2 etc. were all tolerant in this reaction. Di-fluoro, di-trifluoromethyl and tri-fluoro substituted highly electron-deficient aryl boronic acids also proceeded smoothly under the standard conditions (**3ac - 3ae**, 37% - 53%). On the whole, no apparent electrical effect was observed in this reaction. Sterically hindered arylboronic acids afforded the target products **3aa** and **3af** in good yields as well (**3aa**, 72%; **3af**: 61%), as well as fused aromatic rings and hetero-aromatic rings (**3ah - 3ak**, 51% - 78%). Remarkably, BnSS- motif was successfully inserted into several important organic optoelectronic material frameworks, such as triphenylamine, fluorine, carbazole, and diben-zo[b,d]thiophene (**3al - 3ao**, 48% - 65%).[16] Vinylboronic acids were applicable to afford unsymmetrical disulfanes under the standard conditions (**3ap**, 61%; **3aq**, 54%). Unfortunately, when cyclopropylboronic acid and cyclo-pentylboronic acid were used, no corresponding target products were obtained. This is presumably because their transmetalation with transition metals is more difficult than that of aryl and alkenyl boronic acids, as well as the inferior stability of alkylboronic acids.[17]

Subsequently, we further examined the compatibility of diverse disulfur transfer reagents under the standard conditions (Table 3). Gratifyingly, aryl disulfur transfer groups (R_2 = Aryl) were unprecedentedly feasible under our system even in moderate yields (**4a'**, **4a - 4c**, 47% - 63%). With respect to benzyl and primary, secondary or tertiary alkyl disulfur groups (R_2 = alkyl), this reaction also performed smoothly giving the corresponding unsymmetrical disulfanes in moderate to good yields (**4e - 4m**, 46% - 71%).

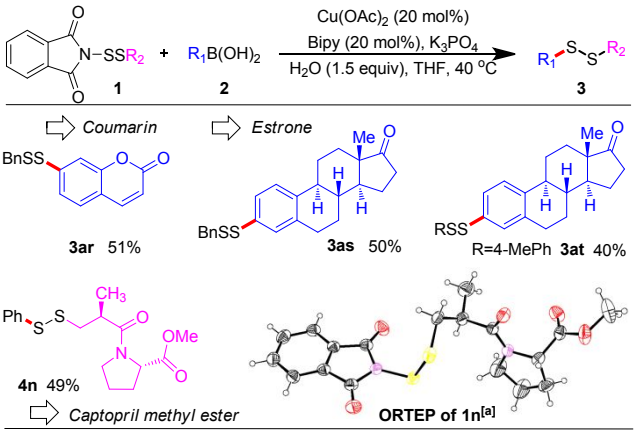
Finally, the robustness of this method was shown by the late-stage modification of the scaffolds of natural products and pharmaceuticals (Table 4). Disulfur motif BnSS- was smoothly installed at C7-position of coumarin, which is a universally bioactive scaffold in many natural products (**3ar**, 51%). Modification of estrone, a natural hormone as well as a medication, was also achieved to deliver **3as** and **3at** in moderate yields (**3as**, 50%; **3at**, 40%). Besides, captopril, a potent and competitive angiotensin-converting enzyme (ACE) inhibitor used in the treatment of hypertension, was successfully modified (**4n**, 49%) through preparation of phthalimide-carried disulfur reagent (**1n**), and the structure of **4n** was characterized by X-ray diffraction (CCDC Number:1948200).

Table 3. Substrate scopes of disulfur transfer reagents[a,b]



[a]Standard conditions: **1** (0.20 mmol, 1.0 equiv), **2** (0.40 mmol, 2.0 equiv), $Cu(OAc)_2$ (0.04 mmol, 0.2 equiv), Bipy (0.04 mmol, 0.2 equiv), H_2O (0.30 mmol, 1.5 equiv), K_3PO_4 (0.40 mmol, 2.0 equiv) and THF (2 mL) , 40 °C, 10 h, Ar. [b]Isolated yields.

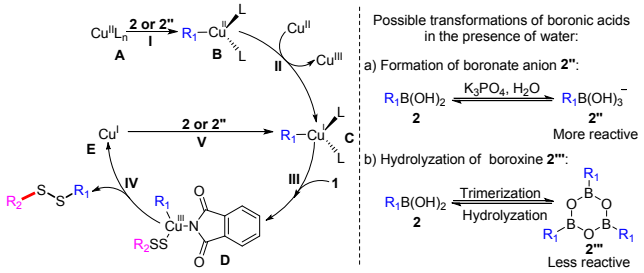
Table 4. Late-stage modification of natural product and pharmaceuticals[b]



[a]Non-hydrogen atoms are shown as 30% ellipsoids. [b]Isolated yields.

Based on the control experiments in Table 1 (entries 12 - 15) and literatures,[18] a possible mechanism was described in Scheme 2. Initially, transmetalation (**I**) of boronic acid derivatives took place. In this step, water may play a crucial role in facilitating the transmetalation in some aspects, similar to previous works.[15, 17, 19] In addition to increasing the solubility of K_3PO_4 and $Cu(OAc)_2$, [15, 19c] it was likely to favor the generation of more-reactive boronate anion **2''** in the presence of K_3PO_4,[17, 19] and also contribute to suppressing the formation of less-reactive boroxine **2'''** which was easily produced by trimerization of boronic acids.[17, 19c] Despite these hypotheses, the exact role of water remains unclear to date. Following the transmetalation, disproportionation (**II**) of Cu^{II} species **B** proceeds to give Cu^{I} intermediate **C** and CuIII.[18b, 18c] Subsequently, oxidation insertion of **C** into N-S bond takes place to form **D** (**III**).[18a, 18d] Lastly, reductive elimination of **D** releases the target product and CuI (**IV**), which go through transmetalation (**V**) to reenter the next catalytic cycle.[18]

In summary, we have disclosed an unprecedented phthalimide-carried disulfur transfer strategy to deliver categories of unsymmetrical disulfanes. The reaction was highlighted by the use of low-cost metal catalyst and excellent compatibility with diversely sensitive functional groups, especially applicable for the transfer of aryldisulfur moieties (ArSS-) onto aryls to deliver diaryl disulfanes. Meanwhile, the robust nature of the reaction was demonstrated by the late-stage modification of natural product and pharmaceuticals. The practical reaction conditions and extensive applicability of this reaction suggest it may have further applications in sulfur-containing lead compounds discovery, and related works are under progress in our lab.



Scheme 2. A possible mechanism.

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Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interests.

ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, and characterization data and spectra of compounds, CIF data for compound **1n** and other additional data. This material is available free of charge via the Internet at http://pubs.acs.org.

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