Synthetic Methods

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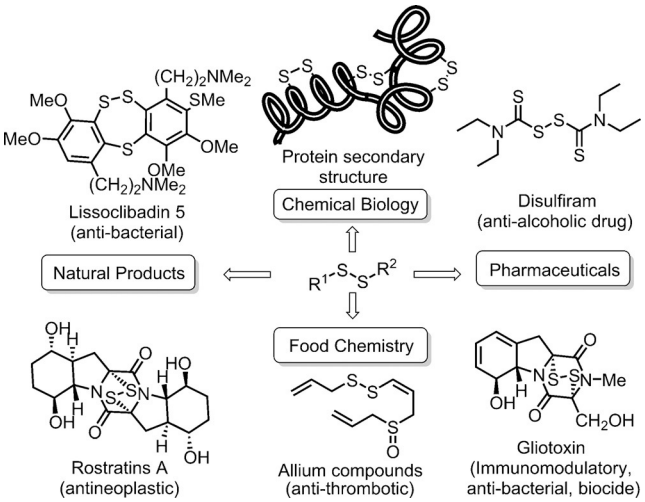
New Design of a Disulfurating Reagent: Facile and Straightforward Pathway to Unsymmetrical Disulfanes by Copper-Catalyzed Oxidative Cross-Coupling

*Xiao Xiao, Minghao Feng, and Xuefeng Jiang**

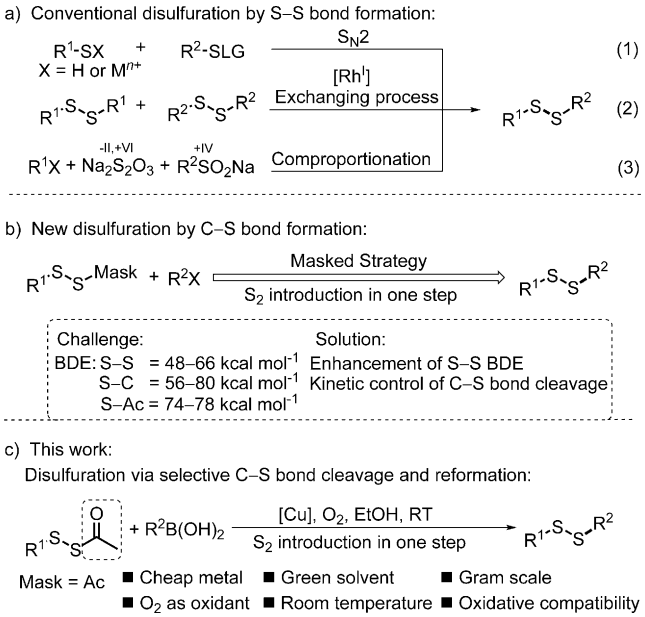
Abstract: *A novel reagent, which introduces two sulfur atoms in one step, was designed and used for the construction of diverse disulfanes by copper-catalyzed oxidative cross-coupling under mild reaction conditions. By applying this stable and readily prepared reagent, late-stage modification of pharmaceuticals and natural products can be achieved straightforward. The scaled-up experiments further indicated the practicality of this protocol. The pH value of the system plays a key role in achieving highly selective cleavage of the C–S bond instead of a S–S bond in the transformation.*

Disulfane, which exists extensively in nature,[1] presents a broad range of applications in chemical biology,[2] pharmaceutical industry,[3] and food chemistry[4] (Scheme 1). This vital motif plays a critical role in the formation of secondary and tertiary structures of proteins, and leads to a great impact on life code.[2] Recently, abundant natural products containing S–S bonds have been demonstrated to possess various activities, such as anti-bacterial (Lissoclibdin 5)[1a] and anti-Polio virus (epidithiodiketopiperazines, ETPs).[1d,e–f] The disulfane moiety is also indispensable for pharmaceuticals, which are used in treatment of thrombi[3a] and alcohol addiction.[3d] The sulfur–sulfur framework is a collective structure in allium compounds, which serve a unique role in food chemistry.[4] Accordingly, synthetic methods for disulfane have been pursued for decades.[5–9]

Although effective methods for symmetrical disulfane synthesis were established, unsymmetrical disulfane construction still remains a great challenge. Conventionally, S_N2 replacement is a typical method for disulfane construction with prefunctionalization of two different thiols [Scheme 2a, Eq. (1)].[6] Oxidative cross-coupling between two different thiols is an alternative pathway in which homocoupling byproducts are unavoidable.[7] A significant achievement is an exchange protocol between two distinct symmetrical disulfanes with the assistance of a rhodium(I) catalyst as reported by the group of Yamaguchi [Scheme 2a, Eq. (2)].[8] Our group disclosed a strategy for the construction of unsymmetrical disulfanes by a comproportionation process between two different valent inorganic sulfur salts[9] [Sche-



Scheme 1. Representative significant disulfanes.



Scheme 2. Strategies for disulfane construction.

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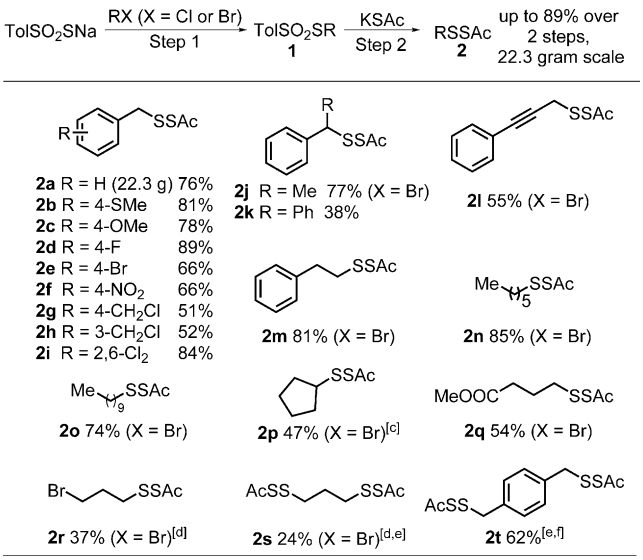
me 2a, Eq. (3)]. Nevertheless, introduction of inorganic sulfur to organic molecules restricts the region of application in organic synthesis. This aspect motivated us to pursue a more efficient and practical reaction for direct construction of "disulfur", as it could offer a convenient protocol for late-stage modification of natural products and pharmaceuticals.

Hydrodisulfide (RSSH), a key intermediate in the cell-killing action of anticancer natural products leinamycin and varacin,[10a–d] may serve as an ideal disulfane reagent. However, RSSH is a short half-life time intermediate because of its high sensitivity and activity.[10d,f–h] Based on our previous study,[11] sulfide with a mask displayed unique properties in sulfur-transfer reactions. This finding inspired us to design a mask for RSSH to afford a new type of reagent. Paradoxically, a thermodynamic effect, which favors S–S bond (BDE = 48–66 kcal mol^{-1})[12] cleavage over S–C bond (BDE = 56–80 kcal mol^{-1}) cleavage, is the challenge for the design of a reagent to deliver disulfanes.[13] Acetyl (S–Ac BDE = 74–78 kcal mol^{-1}), a readily dissociated electron-withdrawing group, could serve as a preeminent mask for disulfane. The C–S bond-cleavage rate will be determined through kinetic control and the electron-withdrawing effect of the acetyl will also increase the thermodynamic stability of the S–S bond by restraining strong coordination from sulfur to transition metal simultaneously. With this concept, a set of odourless and air-stable reagents were systemically established.[10e]

The designed reagents were smoothly achieved in two steps. The *S*-alkyl 4-methylbenzenesulfonothioate **1** was conveniently obtained through combination of sodium 4-methylbenzenesulfonothioate and alkyl halides (Scheme 3). A

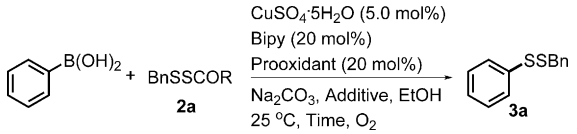


Scheme 3. Construction of disulfane reagents.[a,b] [a] Step 1: RX (6 mmol, 1.2 equiv), $TolSO_2SNa$ (5 mmol, 1 equiv), and TBAI (0.25 mmol, 5 mol%) were added to CH_3CN (20 mL) stirring at 50°C for 12 hours. Step 2: $TolSO_2SR$ (3 mmol, 1 equiv), and KSAc (3.9 mmol, 1.3 equiv) were added to DCM (20 mL) stirring at RT for 5 hours. [b] Yield of isolated products. [c] DMF at 80°C instead of CH_3CN at 50°C in Step 1. [d] RX (0.8 equiv) was added in Step 1. [e] KSAc (2.4 equiv) was added in Step 2. [f] RX (3 mmol, 1 equiv) and $TolSO_2SNa$ (9 mmol, 3 equiv) were added in Step 1.

replacement of **1** with thioacetate afforded the reagent **2**. Successfully, reagents bearing both electron-donating and electron-withdrawing groups on aromatic rings were both well established (**2a–i**). Secondary benzyl derivatives were achieved as well (**2j**, **k**). Reagents containing a propargyl group (**2l**), aliphatic chains (**2m–r**) and even a bromo-substituted alkyl group (**2r**) were generated in this manner efficiently. Furthermore, bisfunctionalized reagents were acquired in this way (**2s**, **t**).

Once the reagent library was established, we commenced the investigation with oxidative cross-couplings between the reagent **2a** and the commercial available phenylboronic acid (Table 1). Firstly, the desired product benzyl-

Table 1: Optimization of the reaction.[a,b]

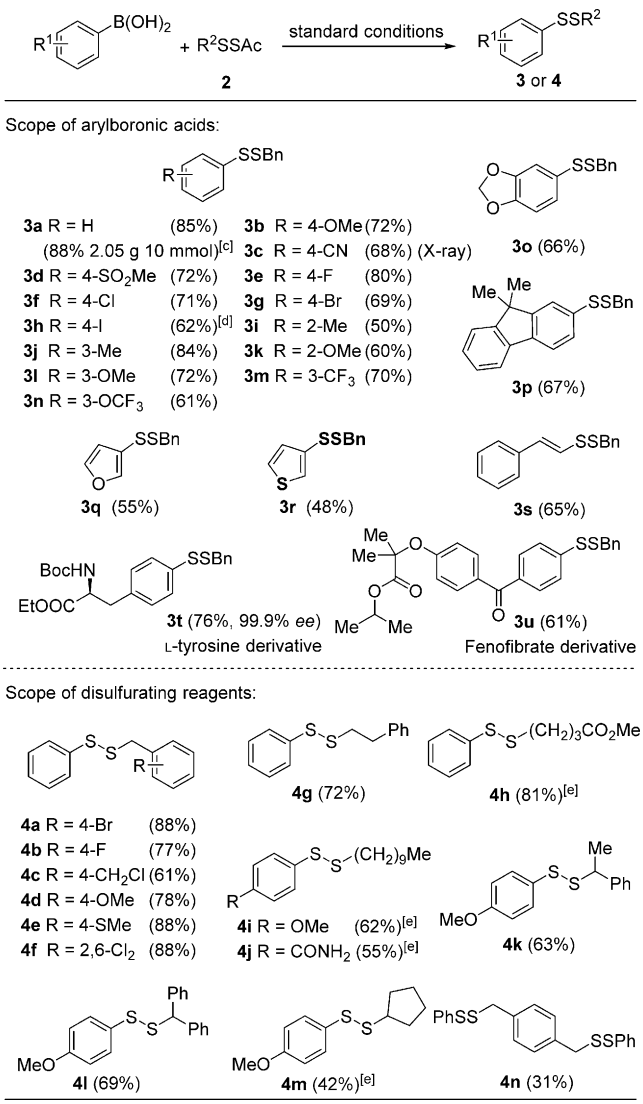


Entry	R	Prooxidant	Additive (equiv)	*t* [h]	Yield [%]
1[c]	Me	–	–	12	n.d.
2	Me	–	–	12	60
3[d]	Me	–	–	4	n.d.
4	Me	MnO_2	–	4	65
5	Me	$Fe(ClO_4)_3{\cdot}H_2O$	–	12	65
6	Me	$Fe(OTf)_3$	–	12	84
7	Me	$FeSO_4{\cdot}7H_2O$	–	12	70
8	Me	$FeSO_4{\cdot}7H_2O$	LiOTf (0.4)	12	85
9	Et/*i*Pr/*t*Bu/Ph	$FeSO_4{\cdot}7H_2O$	LiOTf (0.4)	12	42/12/2/24
10[e]	–	$FeSO_4{\cdot}7H_2O$	LiOTf (0.4)	12	12

[a] Phenylboronic acid (0.28 mmol, 1.4 equiv), **2** (0.2 mmol, 1 equiv), $CuSO_4{\cdot}5H_2O$ (0.01 mmol, 5 mol%), bipy (0.04 mmol, 20 mol%), prooxidant (0.04 mmol, 20 mol%), additive (0.08 mmol, 40 mol%) and Na_2CO_3 (0.2 mmol, 1 equiv) were added to EtOH (2 mL) stirring at RT for 12 hours under O_2 atmosphere. [b] Yield of isolated product. [c] Air atmosphere instead of O_2 atmosphere. [d] Without Na_2CO_3. [e] BnSSH instead of BnSSAc.

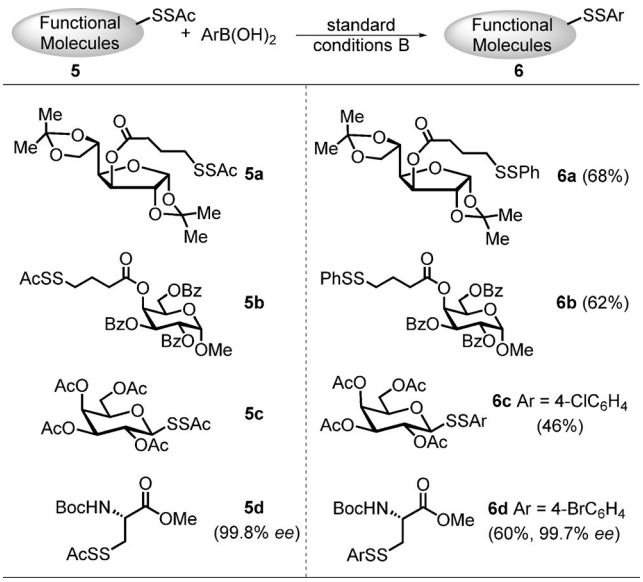
(phenyl)disulfane (**3a**) was not found when only copper sulfate pentahydrate was used as a catalyst under an open air atmosphere (entry 1). Dramatically, by altering the atmosphere from air to oxygen, **3a** was isolated in a yield of 60% (entry 2). It is worth noting that a base was essential for this reaction for both transmetalation and alcoholysis (entry 3), and sodium carbonate was demonstrated to be the most suitable (for details see the Supporting Information). Addition of manganese dioxide as a prooxidant improved the yield slightly (entry 4).[14] Iron(III) trifluoromethanesulfonate was proven to be the most efficient prooxidant, and was in accord with the principle of standard electrode potentials (entries 5–7).[14b] Further study showed that iron(III) trifluoromethanesulfonate could be replaced by a combination of ferrous sulfate heptahydrate and lithium triflate, which is more convenient to handle and store (entry 8). It is noteworthy that the reagent masked with the acetyl group was the most efficient disulfur source (entries 8–10).

Based on the optimized reaction conditions, the oxidative cross-coupling was comprehensively investigated. Diverse



Scheme 4. The reaction scope.[a,b] [a] Standard reaction conditions A: $ArB(OH)_2$ (0.28 mmol, 1.4 equiv), **2** (0.2 mmol, 1 equiv), $CuSO_4{\cdot}5H_2O$ (0.01 mmol, 5 mol%), bipy (0.04 mmol, 20 mol%), $FeSO_4{\cdot}7H_2O$ (0.04 mmol, 20 mol%), LiOTf (0.08 mmol, 40 mol%) and Na_2CO_3 (0.2 mmol, 1 equiv) were added to EtOH (2 mL) at RT for 12 hours under O_2 atmosphere. [b] Yield of isolated product. [c] 48 hours. [d] Na_2CO_3 (0.1 mmol, 0.5 equiv) was used. [e] Standard reaction conditions B: 4,4′-diMebipy (0.04 mmol, 20 mol%), MnO_2 (0.04 mmol, 20 mol%) and Na_2CO_3 (0.1 mmol, 0.5 equiv) were added to EtOH (3 mL) at 15 °C for 4 hours under O_2 atmosphere.

arylboronic acids bearing electron-withdrawing and electron-donating functional groups at the *ortho*-, *meta*-, and *para*-positions afforded the desired unsymmetrical disulfanes in moderate to excellent yields (Scheme 4; **3a**–**o**). The structure of **3c** was further confirmed through X-ray analysis.[15] Notably, halogen-substituted arylbronic acids, especially iodo-substituted arylbronic acids, proceed smoothly in the transformation, which do not react in traditional cross-coupling reactions (**3e**, **h**). Sterically hindered (2-methylphenyl)boronic acid was successfully used to afford the corresponding disulfane (**3i**). Arylboronic acids with a fused-ring (**3p**), heterocycles (**3q**, **r**), and olefin (**3s**) performed efficiently. Furthermore, this transformation was smoothly applied to the late-stage modification of a pharmaceutical and natural product (**3t**, **u**), thus providing a potential method for drug discovery. A gram-scale operation was performed on 10 mmol of **2a**, thus affording benzyl(phenyl)disulfane in good yield (88%, 2.05 grams under conditions A; **3a**). The scope with respect to the reagent was further studied. Both benzyl and alkyl groups with various substituents were reacted efficiently under the standard reaction conditions with moderate to excellent yields (**4a**–**i**). An array of secondary disulfane reagents were well tolerated (**4k**–**m**). Bis-substituted reagents could be coupled with two molecules of an arylbronic acid (**4n**). Modification of sugars and amino acids was also achieved (Scheme 5; **6a**–**d**).



Scheme 5. Late-stage functionalization for functional molecules.[a,b] [a] Standard reaction conditions B. [b] Yield of isolated product. Bz = benzoyl, Boc = *tert*-butoxycarbonyl.

From the optimization stage, different masks displayed different efficiencies for the generation of disulfane. Alcoholysis substrates with distinct masks were conducted in [D_6]ethanol with sodium carbonate (Figure 1). The alcoholysis rate was determined by both sterics and conjugation, and was revealed by the rate curves of Me ≈ Et > Ph > *i*Pr > *t*Bu (Figure 1, Curves 1–5). It's noteworthy that alcoholysis of BnSSAc and BnSSCOEt were quite similar (Figure 1, Curves 4 and 5), while BnSSCOEt afforded **3a** in a much lower yield (42%) than BnSSAc (85%; Table 1, entry 9). Comparatively, BnSSH gave **3a** in extremely low yield (12%; Table 1, entry 10). These results indicate that the release rate of the hydrodisulfane anion is key to the transformation. The effect of the base was then examined in [D_6]ethanol (Figure 1). Cesium carbonate and potassium carbonate displayed rapid alcoholysis with BnSSAc within two hours (Figure 1, Curves 9 and 10). In contrast, BnSSAc was recovered in almost 60% after thirteen hours when weak bases (lithium carbonate, sodium bicarbonate and triethylamine) were applied. In

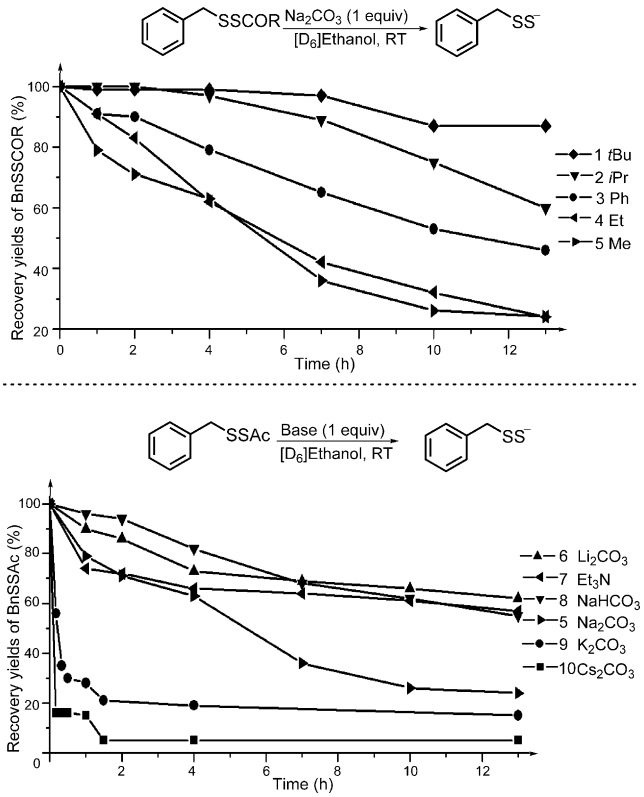


Figure 1. Mask effect and base effect on matching pace.

conclusion, the alcoholysis, based on sodium carbonate, matched the transmetalation rate perfectly (Figure 1, Curve 5).

In summary, a new type of practical and stable disulfurating reagent masked with an acetyl group has been designed and synthesized. Efficient and mild copper-catalyzed oxidative cross-coupling for unsymmetrical disulfane construction is developed by a highly selective C–S bond cleavage and reformation. Diverse disulfane reagents and arylboronic acids are compatible for unsymmetrical disulfane formation through introducing disulfur in one step. Further studies on applying the reagents to biomolecule modification are ongoing.

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[15] **3c**: $C_{14}H_{11}NS_2$, MW = 257.36, monoclinic, space group *P*21/*c*, final *R indices* [$I > 2\sigma(I)$], *R1* = 0.0350, *wR2* = 0.0845, *R indices* (all data), *R1* = 0.0479, *wR2* = 0.0919, $a = 7.7125(3)$ Å, $b = 5.9307(3)$ Å, $c = 28.7783(13)$ Å, $\alpha = 90°$, $\beta = 93.2190(10)°$, $\gamma = 90°$, $V = 1314.26(10)$ Å^3, $Z = 4$, Reflections collected/unique: 14499/2313 ($R_{(int)} = 0.0363$). CCDC 1486574 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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