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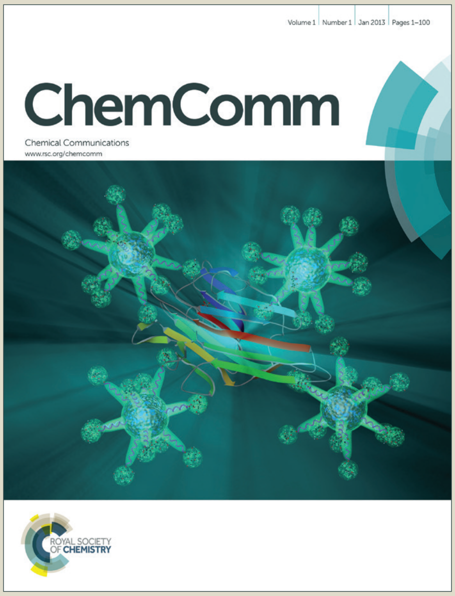

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CO_2-Promoted Oxidative Cross-Coupling Reaction for C-S Bond Formation *via* Masked Strategy in an Odourless Way

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Cu-catalyzed direct oxidative cross-coupling between boronic acids and masked sulfides delivering thioethers was described, in which the SO_3^-, as a mask, has shown a distinctive effect on oxidative cross-coupling condition. Disulfide could be suppressed efficiently *via* masked strategy under CO_2 atmosphere. A broad scope of aromatics and scalable processes indicates its practicality, which could be further applied to drug late-stage modification and unsymmetrical dibenzothiophenes (DBTs) synthesis.

Transition-metal-catalyzed oxidative cross-coupling[1] between boronic acids and heteroatom nucleophiles has been well known as the Chan–Lam reaction[2] and emerged as a powerful protocol for the construction of carbon-nitrogen bonds[3] or carbon-oxygen bonds,[4] due to a variety of readily available boronic acids and their derivatives.[5] However, direct cross-coupling between metallic nucleophile and sulfide has been less studied,[6] despite its importance in the pharmaceutical industry,[7] material science,[8] and food chemistry[9] in the race toward organosulfur compounds synthesis. There are three main reasons for this: a) strong coordination of the lone pair electrons on sulfur to the transition metal; b) preferential oxidization to disulfide when thiol meets oxidant; and c) unpleasant smell during the experimental process. Several couplings have been tried to construct carbon-sulfur bonds through boronic acids mainly in virtue of stoichiometric metal, special ligand, or by formation from disulfide or mercaptan with unpleasant smell.[10] Our group has focused on introducing a designed mask to naked sulfur, which should possess certain properties including electron effect, steric hindrance and resonance stabilization (Fig. 1). Based on our odourless sulfur atom transfer (SAT) findings[11] and inspired by the first single crystal X-ray diffraction analysis[12] of the structure **I** (Bunte salts[13]), we envisioned that SO_3^- should be the right candidate for the mask because of its unique properties: a) an electron withdrawing group preventing the strong coordination to metal; b) a sustained bulky group preventing homo-coupling; and c) a conjugated group tuning the electron effect on sulfur. In this manuscript, we will describe an odourless oxidative cross-coupling reaction through the concept of combination of mask-effect and enabling atmosphere (Scheme 1).

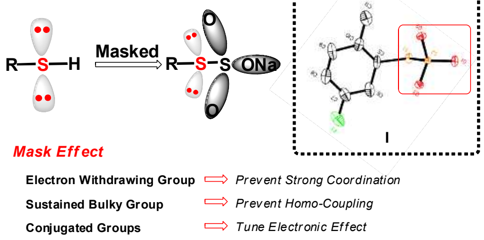
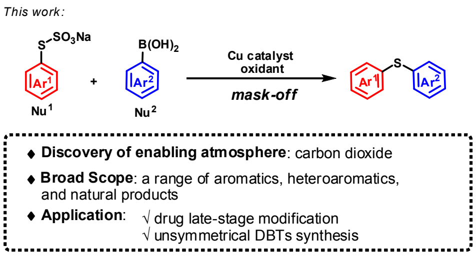


Figure 1. Masked sulfide



Scheme 1. Oxidative sulfurating cross-coupling reaction

We commenced our study with sodium *S*-*p*-tolyl sulfothioate **1a**[14] and phenylboronic acid **2a** under standard conditions, (see ESI) which afforded desired product **3a** in 85% yield with less than 2% of disulfide **4a** under 80 °C (Fig. 2). However, when 4-methylbenzenethiol served as a sulfur source, it tended to oxidize to **4a** in 49% yield. Both copper trifluoromethanesulfonate and 1,10-phenanthroline are necessary in this system, which indicated the reaction is not capable of undergoing un-catalyzed nucleophilic substitution. The consumption of trifluoromethanesulfonic acid was

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addressed depending on different reactant. During the course of condition optimization, the unique effect of carbon dioxide was detected, which could give better conversion and yield compared to inert gas (N_2), reducing gas (CO, H_2) or oxidizing gas (O_2).

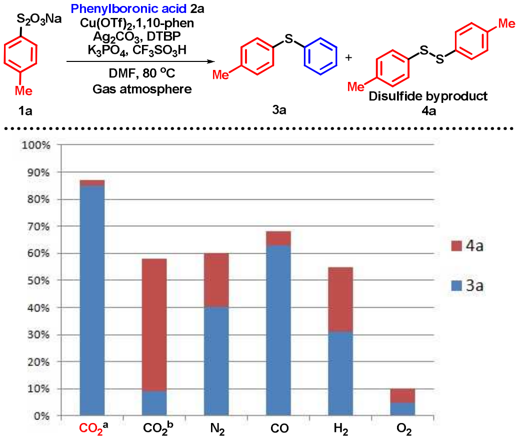
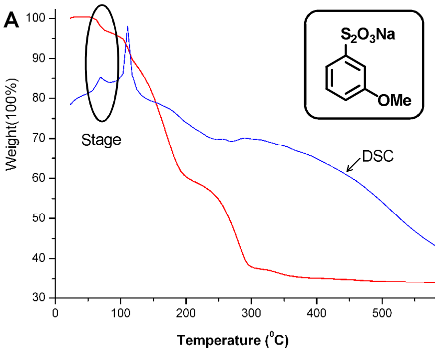


Figure 2. Dramatic atmosphere effect in oxidative sulfurating cross-coupling reaction

[a]Sodium *S*-*p*-tolyl sulfothioate served as sulfur source. [b]4-methylbenzenethiol served as sulfur source.

The interaction between organic thiosulfate salt and carbon dioxide was preliminarily investigated. Carbon dioxide was bubbled into sodium *S*-3-methoxyphenyl sulfothioate in methanol at ambient temperature for 1 h, affording CO_2-bubbled thiosulfate salt. There is no sharp difference between bubbled and unbubbled organic thiosulfate salt in the ^1H NMR signal, which meant that a chemical change has not taken place. Two kinds of thiosulfate salts were investigated through ^{13}C NMR spectroscopy as well, which showed that one more peak (at about 126.3 ppm) was detected when using CO_2-bubbled (see ESI). Followed by thermogravimetric analysis (TGA) in the temperature range of 30-800 °C under a flow of nitrogen, the TG curve of CO_2-bubbled thiosulfate salt displayed one more stage, which showed a rapid initial weight loss of 2.0 wt % before the release of water molecules in the temperature range of 90–100 °C (Fig. 3A). N_2, O_2, H_2, or CO was bubbled into organic thiosulfate salt, which has not shown similar stage (Fig. 3B). These evidences implied that CO_2 could partially prevent the formation of disulfide in the form of physical absorption but not in a chemical way.



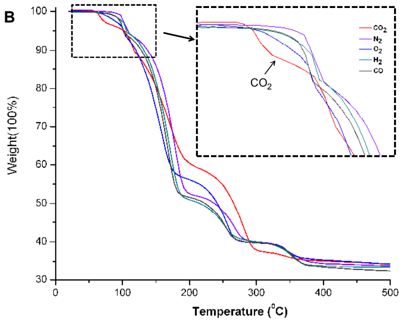
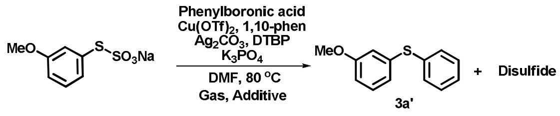


Figure 3. TGA curves for sodium *S*-3-methoxyphenyl sulfothioate (A) DSC-TG spectra of CO_2-bubbled organic thiosulfate salt (B) DSC-TG spectra of organic thiosulfate salt bubbled by different gases.

Control experiments showed that the desired product **3a'** could be obtained in a yield of 63% by CO_2-bubbled thiosulfate salt (Table 1, entry 1), which was similar to unbubbled salt under the CO_2 condition (Table 1, entry 2). However, unbubbled thiosulfate salt under a N_2 atmosphere only achieved 37% yield, in which more disulfide has been produced in the yield of 27% (Table 1, entry 3). Alternatively, additives, which could generate CO_2 in situ, were subjected to the reaction under a N_2 atmosphere, inhibiting disulfide in different levels (Table 1, entries 4-6). These current observations from the physical absorption phenomenon and control experiments demonstrated that the enabling atmosphere played the role of stabilization and slow oxidation of the revealed thiolate to disulfide, perhaps by the formation of carbonate, bicarbonate, or carbonic acid.

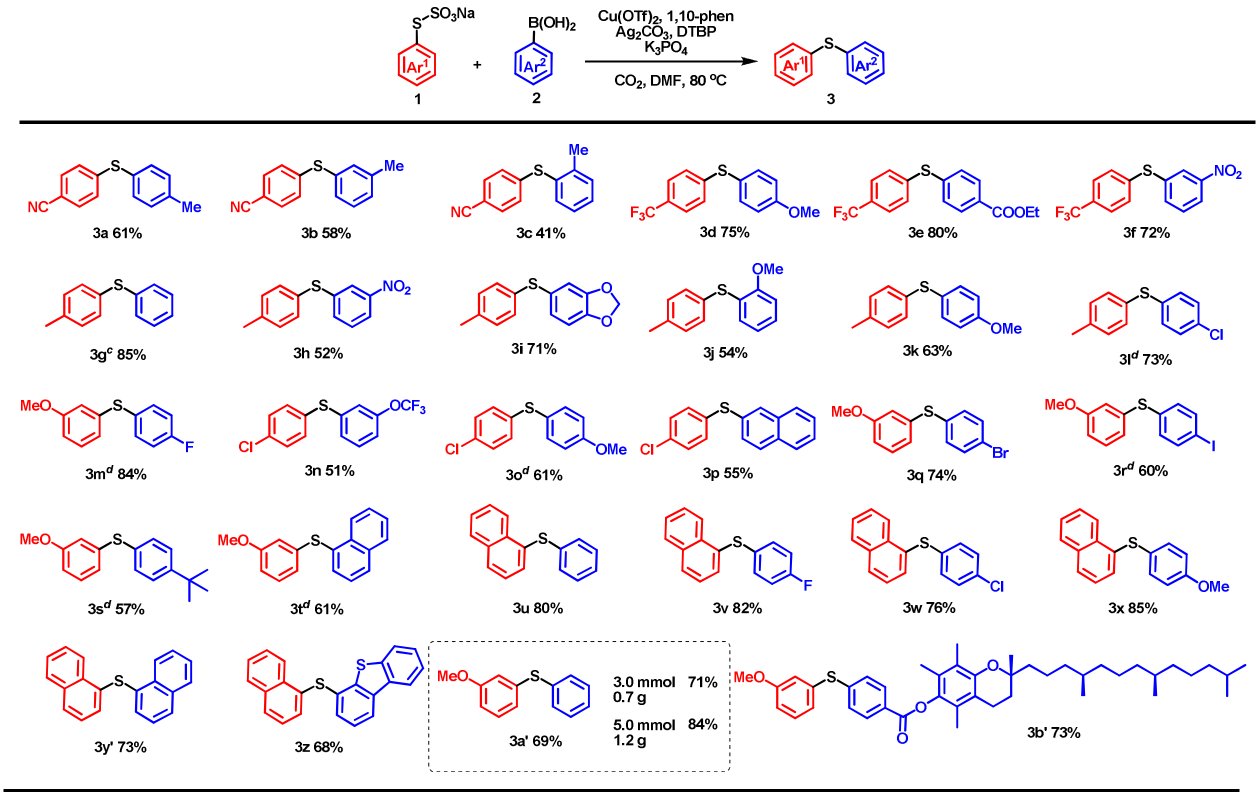
Table 1. Control Experiments



entry	thiosulfate	gas	additive	3a'	disulfide
1	CO_2-bubbled	N_2	/	63%	<2%
2	unbubbled	CO_2	/	69%	<2%
3	unbubbled	N_2	/	37%	27%
4	unbubbled	N_2	K_2CO_3	33%	<2%
5	unbubbled	N_2	Na_2CO_3	46%	<2%
6	unbubbled	N_2	$NaHCO_3$	55%	<2%

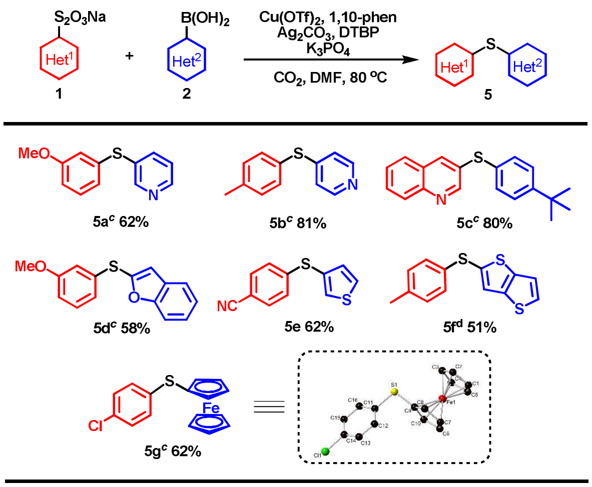
The scope of this catalytic sulfuration was investigated in Table 2. Generally, a variety of arylboronic acids, bearing both electron-withdrawing and -donating groups at the para-, meta-, or ortho-positions afford moderate to excellent yields (**3a**-**3l**). All halogen substituted substrates proceed smoothly, such as F (**3m**), Cl (**3n**-**3p**), Br (**3q**), and even I (**3r**), which was rarely benign in traditional cross-coupling. On the other hand, diversity of organic thiosulfate salts were also examined, which indicated that the electronic effect from sulfur sources did not affect the efficiency of the transformations either. The reaction was further extended to scalable processes, in which sodium *S*-3-methoxyphenyl sulfothioate (1.2 g) could be efficiently converted to **3a'** in 84% yield with even reduced loading of catalyst (see ESI). Remarkably, the boronic acids embedded in the tocopherol framework could provide thioether-substituted

Table 2. Substrate Scope[a, b]



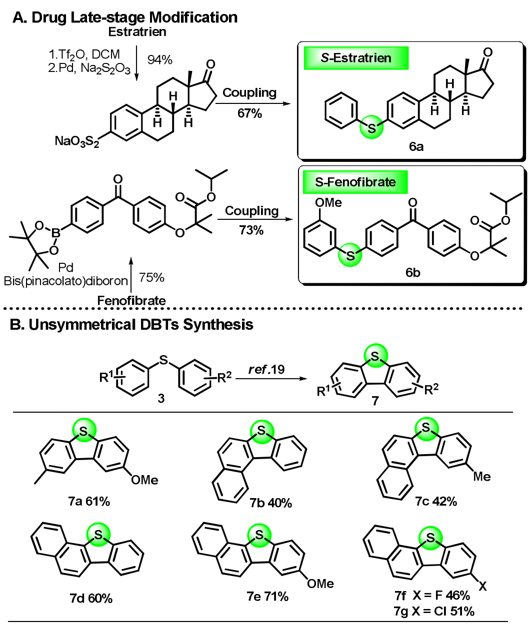
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), Cu(OTf)$_2$ (20 mol%), 1, 10-phen (40 mol%), Ag$_2$CO$_3$ (0.12 mmol), K$_3$PO$_4$ (0.14 mmol), DTBP (0.1 mmol), and DMF (2.0 mL); 80 °C; 7 h. [b] Isolated yields. [c] 0.03 mmol of CF$_3$SO$_3$H was added. [d] 0.05 mmol of CF$_3$SO$_3$H was added.

Table 3. Sulfuration of Heteroarenes.[a, b]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Cu(OTf)$_2$ (20 mol%), 1, 10-phen (40 mol%), Ag$_2$CO$_3$ (0.12 mmol), K$_3$PO$_4$ (0.14 mmol), DTBP (0.1 mmol), and DMF (2.0 mL); 80 °C; 7 h. [b] Isolated yield. [c] Cu(OTf)$_2$ (20 mol%) was replaced by CuCl$_2$. [d] Cu(OTf)$_2$ (0.1 mmol), 1, 10-phen (0.1 mmol).

Table 4. Application in Parmaceutical and Material



tocopherol **3b’** in 73% yield, which has shown potential value in complex molecule modification.

Heteroaromatics are always crucial and challenge in drug discovery,[15] whose coupling was also demonstrated in Table 3. Compounds containing nitrogen (**5a**, **5b**, and **5c**), oxygen (**5d**), and sulfur (**5e** and **5f**) atoms all performed well. Ferrocene-containing product **5g**[16] could be achieved in moderate yield, which provides the opportunity for developing new sulfur-containing ferrocene ligands.

This method could be readily applied to drug late-stage diversification (Table 4A).[17] Estratrien, a kind of female hormone drug, could be easily transformed to the corresponding organic thiosulfate salt in 94% yield, to afford sulfur-modified estratrien **6a** followed by oxidative sulfurating cross-coupling. Sulfur-decorated Fenofibrat **6b** could derive from its boronic acid ester efficiently through a similar transformation. This method offers great potential for the generation of drug analogue libraries. From another aspect, this method could be carried out to establish unsymmetrical dibenzothiophenes (DBTs), which consititute a core framework in certain kinds of organic compounds including pharmaceuticals, photoactive compounds, dyes, liquid crystals, and conducting polymers (Table 4B).[8,18] For example, benzo[*d*]naphtho[1,2-*b*]thiophene which was substituted by OMe, F, or Cl could be obtained untrammeled through this protocol followed by oxidative dehydrogenative cyclization.[19]

In conclusion, relying on the versatile effect of SO_3^- and CO_2, sulfur could be compatible with oxidizing condition in an odourless way. A dramatic masked strategy and an interesting CO_2 accelerated phenomenon were uncovered, which have been studied by TGA. The extensive adaptability of this sulfuration present in both reactants renders this reaction highly efficient and practical for the synthesis of medicinally important and materially unobtainable units using readily available boronic acids. Further explorations for more synthetic applications are ongoing in our laboratory.

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