Copper-Mediated Regioselective C–H Sulfenylation and Selenation of Phenols with Phenanthroline Bidentate Auxiliary

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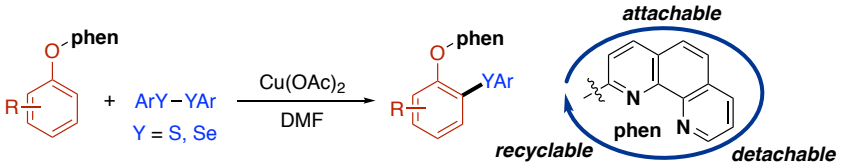
Supporting Information Placeholder



ABSTRACT: A copper-mediated, phenanthroline-directed highly *ortho*-selective C–H sulfenylation of phenols with diaryl disulfides proceeds to form the corresponding unsymmetrical diaryl sulfides in good yield. The key to success is the introduction of a phenanthroline directing group of the bidentate-chelating nature, which is easily attachable, detachable, and even recyclable. Moreover, the same strategy is applicable to the C–H selenation, giving the diaryl selenides with high efficiency and regioselectivity.

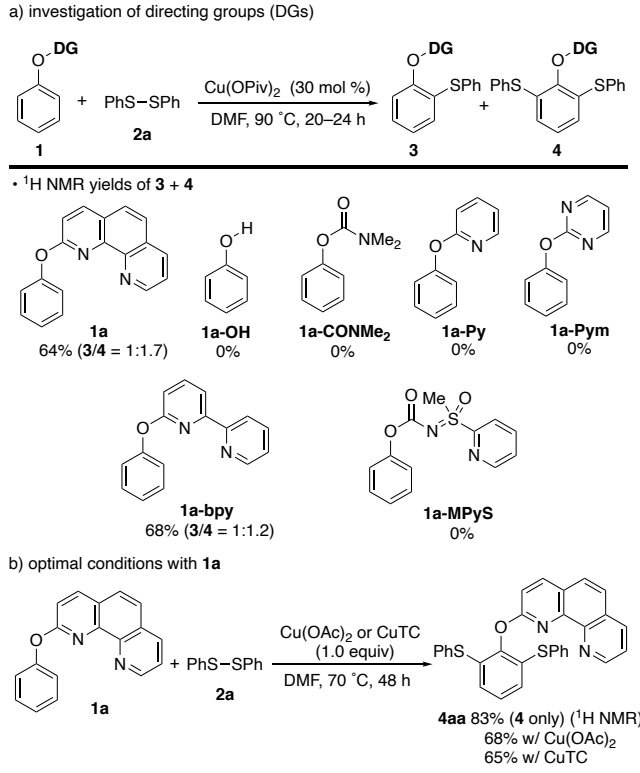
Diaryl sulfide is an important class of compounds in organic chemistry because it is frequently occurring in biologically active compounds and natural products.[1] In particular, the phenol moiety-containing diaryl sulfides are pivotal structural motifs in the treatment of cancer, HIV, and heart disease.[2] Accordingly, considerable attention has been focusing on their concise and selective synthesis. The most convergent approach is the metal-mediated aryl–S cross-coupling reactions of aryl halides with SH thiols or their derivatives.[3] However, the preparation of the starting halogenated aromatic compounds is often tedious and problematic. The classical aromatic electrophilic sulfenylation-type reaction of phenols is more straightforward and attractive from the viewpoint of atom efficiency, but the regioselectivity is controlled by the innate electronic nature of the phenol ring; a mixture of *ortho*- and *para*-regioisomers is generally obtained.[4] Thus the development of new protocols for the regioselective direct sulfenylation of phenol derivatives is strongly desired.

On the contrary, the metal-promoted C–H activation chemistry has greatly progressed in recent decades and now provides potentially more effective synthetic methodologies than the conventional cross-coupling reactions relying on the organic halides.[5] In this context, the aromatic C–H sulfenylation reactions have also been developed by using Pd,[6] Rh,[7] and Cu[8] catalysts. However, the viable substrates are limited to electron-rich (hetero)arenes, phenylpyridines, and benzamides; the regioselective C–H sulfenylation of phenols still remains largely elusive. Herein we report a Cu-mediated highly *ortho*-selective C–H sulfenylation of phenols with diaryl disulfides by using a phenanthroline-type bidentate auxiliary.[9] The chelating nature of phenanthroline uniquely promotes the reaction to form the targeted diaryl sulfides with the phenol moiety. Additionally, the phenanthroline auxiliary is readily accessible and easily attachable, detachable, and recyclable. Moreover, the Cu/phenanthroline system is also applied to the C–H selenation reaction with diaryl diselenides.[10] We note that during the course of this research project, the related Co-mediated, carbonyl-directed C–H sulfenylation of phenols with thiols was reported, but the reaction includes a radical species, and in some cases, the regioselectivity is thus complementary to the present work (vide infra).[11]

On the basis of the previous success of the Cu-catalyzed C–H amination with the phenanthroline-type auxiliary,[9a] our studies commenced with the phenol derivative **1a** and diphenyl disulfide (**2a**) as model substrates. In an early experiment, the treatment of **1a** with **2a** (4.0 equiv) in the presence of $Cu(OPiv)_2$ (30 mol%) in heated DMF (90 ˚C) formed a 1:1.7 mixture of mono- (**3aa**) and disulfenylated (**4aa**) products in 64% combined yield (Scheme 1a). Notably, only the *ortho* C–H bobds were selectively sulfenylated, and any *para* C–H sulfenylated products were not detected at all. Additionally, the structure of **4aa** was unambiguously confirmed by X-ray analysis (CCDC 1989583). Under these conditions, other directing groups were also tested: The parent phenol (**1a-OH**) and its carbamate (**1a-CONMe$_2$**) resulted in decomposition and no reaction, respectively. The pyridyl- (**1a-Py**) and pyrimidyl- (**1a-Pym**) substituted substrates, which are effective for some noble transition-metal-catalyzed C–H activation,[12] also underwent no conversion. On the contrary, the bipyridyl-type system **1a-bpy** showed comparable reactivity (**3**/**4** 1:1.2, 68% combined yield). As a different type of bidentate auxiliary, we also tried the reaction of a pyridylsulfoximine derivative (**1a-MPyS**).[13] However, no sul-

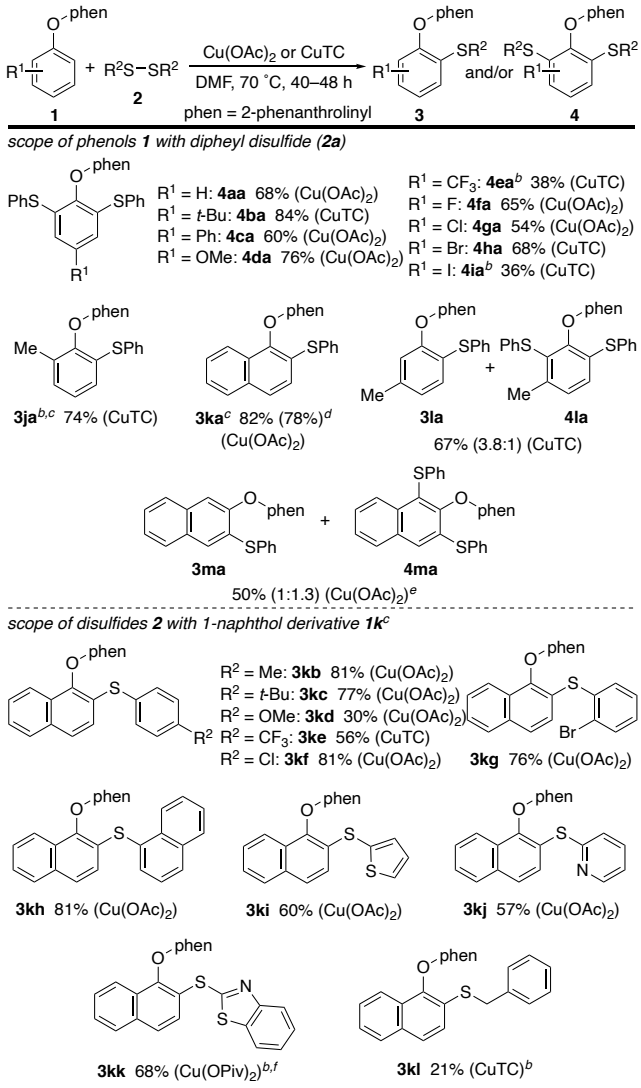
fenylated products were observed. Apparently, the bidentate chelating nature of the auxiliary as well as its sp^2-hybridization-based high planarity played pivotal roles in this reaction. Given the more ready availability of the phenanthroline auxiliary (easily prepared on a decagram scale from commercial phenanthroline),[9] further optimizations were performed with **1a**. Extensive investigations of Cu salts, solvents, and the reaction temperature finally revealed that the reaction proceeded more efficiently and selectively at 70 ˚C with a $Cu(OAc)_2$ or CuTC (TC = 2-thiophenecarboxylate) promotor to deliver the corresponding disulfenylated product **4aa** in >80% ^{1}H NMR yield (68 and 66% yields after purification, respectively; Scheme 1b).[14]

Scheme 1. Representative Optimization Studies for Cu-Mediated Regioselective C–H Sulfenylation of Phenols 1 with Diphenyl Disulfide (2a)



With the conditions in Scheme 1b, we next examined the scope of the reaction (Scheme 2): The more abundant $Cu(OAc)_2$ was generally used, but in some cases, CuTC showed a better performance. In addition to the simple **1a**, several electron-rich phenols **1b**–**d** containing *t*-Bu, Ph, and MeO groups at the *para* position were readily coupled to **2a** to form the corresponding C–H sulfenylated products **4ba**–**da** in good yields. On the contrary, the electron-deficient CF_3-substituted substrate showed moderate reactivity (**4ea**). Particularly notable is the halogen compatibility: The sulfenylation occurred at the *ortho*-C–H bonds over the C–halogen bonds to deliver the unsymmetrical diaryl sulfides **4fa**–**ia**, the remaining halogens of which can be useful synthetic handles for further manipulations by the transition-metal-catalyzed cross-coupling technology. Even in the cases of moderate yields of disulfenylated products, the monosulfenylated products were not detected at all. The *ortho*-substituted phenols **1j** and **1k** also underwent the reaction smoothly and regioselectively even in the presence of potentially reactive *para* C–H, and the monosulfenylated products **3ja** and **3ka** were obtained as the sole regioisomers. In the case of **1l** with the *meta* substituent, the reaction proceeded preferably at the more sterically accessible position (**3la** and **4la**), which is complementary to the Co-mediated, radical-promoted C–H sulfenylation.[11,15] A similar trend was also observed in the 2-naphthol derivative (**3ma** and **4ma**). The reaction could also be performed on a preparative scale (**3ka**), thus indicating the good reproducibility of this process.[16]

Scheme 2. Cu-Mediated Regioselective C–H Sulfenylation of Phenols 1 with Disulfides 2[a]



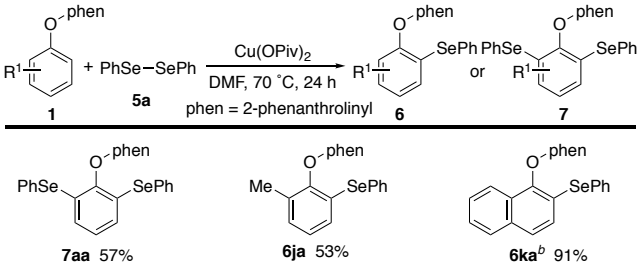
[a] Reaction conditions: $Cu(OAc)_2$ or CuTC (0.25 mmol), **1** (0.25 mmol), **2** (1.0 mmol), DMF (1.5 mL), 70 ˚C, 40–48 h, N_2. Isolated yields are shown. [b] On a 0.10 mmol scale. [c] With 2.0 equiv of **2**. [d] On a 1.0 mmol scale. [e] ^{1}H NMR yield. [f] With $Cu(OPiv)_2$ and DMF (3.0 mL).

Sterically and electronically diverse diaryl disulfides **2** were amenable to the reaction. Except for the strongly

electron-donating MeO-substituted disulfide (**3kd**), functionalized SAr moieties were successfully introduced to the phenol ring in good to high yields (**3kb**, **kc**, **ke**–**kh**). Again, the high halogen compatibility was observed (**3kf** and **3kg**). Moreover, the conceivably more challenging heteroaryl disulfides could also be employed, and the thiophene-, pyridine-, and benzothiazole-containing diaryl sulfides **3ki**–**kk** were formed in acceptable yields. On the contrary, the reaction with dialkyl disulfide provided a reduced yield (**3kl**).

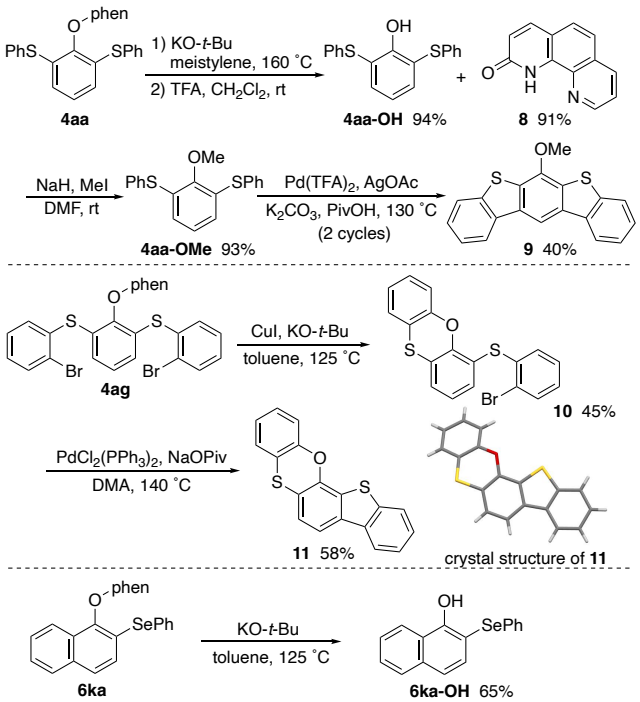
The phenanthroline-based auxiliary was also applicable to the Cu-mediated regioselective C–H selenation of phenols with diselenides (Scheme 3): Under slightly modified conditions with $Cu(OPiv)_2$, diphenyl diselenide **5a** reacted with some phenol derivatives **1** to afford the corresponding unsymmetrical diaryl selenides **7aa**, **6ja**, and **6ka** in good yields. Such diaryl selenides are also important core structures in bioactive molecules and organic photosensitizers.[17] Again, the exclusive *ortho*-selectivity was observed in all cases.

Scheme 3. Cu-Mediated Regioselective C–H Selenation of Phenols 1 with Diphenyl Diselenide (5a)[a]



[a] Reaction conditions: $Cu(OPiv)_2$ (0.10 mmol), **1** (0.10 mmol), **5a** (0.40 mmol for **1a**, 0.20 mmol for **1j** and **1k**), DMF (1.0 mL), 70 °C, 24 h, N_2. Isolated yields are shown. [b] 12 h.

Scheme 4. Derivatizations of Products



Finally, we attempted to derivatize the C–H sulfenylated products (Scheme 4). The phenanthroline directing group was readily removed from **4aa** by KO-*t*-Bu-mediated alcoholysis to form the corresponding disulfenylated free phenol **4aa-OH** in 94% yield. Upon treatment with TFA, the directing group was concurrently recovered as the 2-phenanthrolinone **8** in 91% yield, which can be recycled for the 2-chlorophenanthroline.[9] The obtained **4aa-OH** further underwent the *O*-methylation and Pd-catalyzed double intramolecular C–H/C–H coupling[18] to afford the bent-type benzobisbenzothiophene **9**. This pentacyclic system is frequently found in organic semiconductors.[19] Interestingly, the Br-containing substrate **4ag**, which was prepared from **1a** and **2g** in 42% yield, was directly transformed to the phenoxathiine **10** via successive deprotection and intramolecular C–O coupling under CuI/KO-*t*-Bu-mediated conditions. The subsequent Pd-catalyzed intramolecular C–H/C–Br coupling reaction[6b,c] successfully formed the benzothienophenoxathiine (**11**), the structure of which was determined by X-ray crystallographic analysis (CCDC 2010305). On the contrary, the removal of the directing group from the C–H selenated product **6ka** was also possible (**6ka-OH**).

In conclusion, we have developed a Cu-mediated regioselective C–H sulfenylation and selenation of phenols with diaryl disulfides and diselenides, respectively. Different from the conventional aromatic electrophilic substation reaction, the reaction exclusively occurs at the *ortho* position. The key to success is the introduction of the bidentately coordinating phenanthroline auxiliary, which is readily prepared and easily attachable, detachable, and recyclable. The obtained phenol-containing unsymmetrical diaryl sulfides and selenides are of potent interest in medicinal and pharmaceutical chemistry as well as a useful platform for the preparation of highly condensed heterocyclic molecules. The further development of related C–H activation Cu catalysis and the application of the phenanthroline auxiliary to other challenging C–H activation reactions are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.xxxx.

^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra, ORTEP drawing, detailed optimization studies (PDF)

Accession Codes

CCDC 1989583 and 2010305 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(14) Attempts to apply air or O_2 to make the reaction catalytic in Cu remained unsuccessful. See the Supporting Information for more detailed optimization studies.

(15) The control experiment of **1k** with **2a** in the presence of a radical inhibitor, TEMPO (1.0 equiv), also provided **3ka** in 75%

^{1}H NMR, thus suggesting that a radical pathway is unlikely operative under the present Cu-promoted conditions.

(16) Attempts to prepare some heterocycle-containing phenol starting materials such as 4-quinolinol remained unsuccessful: The phenanthroline moiety was introduced at the N atom but not O.

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