Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 2901

Received 21st January 2021,
Accepted 4th March 2021

DOI: 10.1039/d1ob00106j

rsc.li/obc

Copper-catalyzed *ortho*-selective direct sulfenylation of *N*-aryl-7-azaindoles with disulfides†

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A copper-catalyzed direct C–H chalcogenation of *N*-aryl-azaindoles with disulfides is described. This transformation was performed using Earth abundant $Cu(OAc)_2$ as a catalyst, benzoic acid as an additive, air as a terminal oxidant, and readily available diaryl and dialkyldisulfides (or diselenide) as chalcogenation reagents. High functional group tolerance and excellent regioselectivity are demonstrated by the efficient preparation of a wide range of *ortho*-sulfenylation-7-azaindoles.

Introduction

The 7-azaindole motif is an important scaffold in numerous natural products and pharmaceuticals.[1] Moreover, the diversification of 7-azaindole has attracted much attention in organic chemistry. Various modifications of 7-azaindoles reported in literature studies focused on transition metal catalyzed C–C bond formation.[2] Only a few examples of direct C–O,[3] C–Cl,[4] and C–N[5] bond formations at the *ortho*- and para-positions of the *N*-aryl ring of azaindole have been reported. However, the more challenging C–S and C–Se bond formations remain scarce because of the strong coordination of metal catalysts to the sulfur reagents and the highly reactive C-3 position of azaindole. Deb's group reported a rhodium-catalyzed selective *ortho*-C–H bond sulfenylation of *N*-aryl-7-azaindoles with disulfides.[6] Moreover, they realized the *ortho*-selective chalcogenation of *N*-aryl-7-azaindoles with a 7-azaindole auxiliary. However, this method needs the use of precious rhodium and silver salt as a co-catalyst and additive.

The C–S bond is of utmost importance in organic synthesis and is receiving tremendous attention.[7] Various methods have been developed over the past decades for the formation of C–S bonds, such as cross-coupling reaction with thiol, but they always needed the use of pre-functionalized starting materials or harsh reaction conditions and special substrates.[8] From the view point of atom economy, direct C–H activation/functionalization is one of the most efficient methods for the modification of the 7-azaindole scaffold.[2–5] Copper salts, **3d** transition-metal complexes, are abundant and inexpensive with low toxicity. Recently, considerable efforts have been focused on C–H functionalization by copper complexes,[9] whereas copper-catalyzed C–S[10] and C–Se bond-forming reactions remain scarce. The pioneering work by Yu's group involves copper-mediated direct sulfenylation of inactivated aryl C–H bonds with the assistance of a 2-pyridine bidentate directing group (Scheme 1a).[10a] In 2012, Daugulis and co-workers reported an elegant copper-catalyzed direct trifluoromethylsulfenylation of (hetero)aryl C–H bonds assisted by *N,N*-bidentate auxiliaries (Scheme 1b).[10b] Ackermann *et al.* recently reported a copper-catalyzed C–H sulfenylation of indolines and indoles (Scheme 1c),[10c] and Shi's group reported copper-mediated thiolation of inactivated heteroaryl C–H bonds (Scheme 1d).[10d] However, the direct C–H/C–S bond formation still suffered from narrow substrate scope and low catalytic efficiency. As part of our ongoing research on direct C–S bond formation[11] by base metal catalysts, our group also reported copper-catalyzed C–H sulfenylation of 1-naphthylamines (Scheme 1e)[12a] and nickel-catalyzed C–H sulfenylation of benzoyl hydrazides with disulfides.[12b] Herein, we wish to disclose the aerobic copper-catalyzed *ortho*-selective sulfenylation of 7-azaindole for the preparation of 1-(2-(phenylthio)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (Scheme 1f), which is an important structural motif present in bioactive molecules with anticancer and antibacterial properties.

Results and discussion

Our investigation was initiated with *N*-aryl-7-azaindole (**1a**) and diphenyl disulfide (**2a**) as model substrates for the

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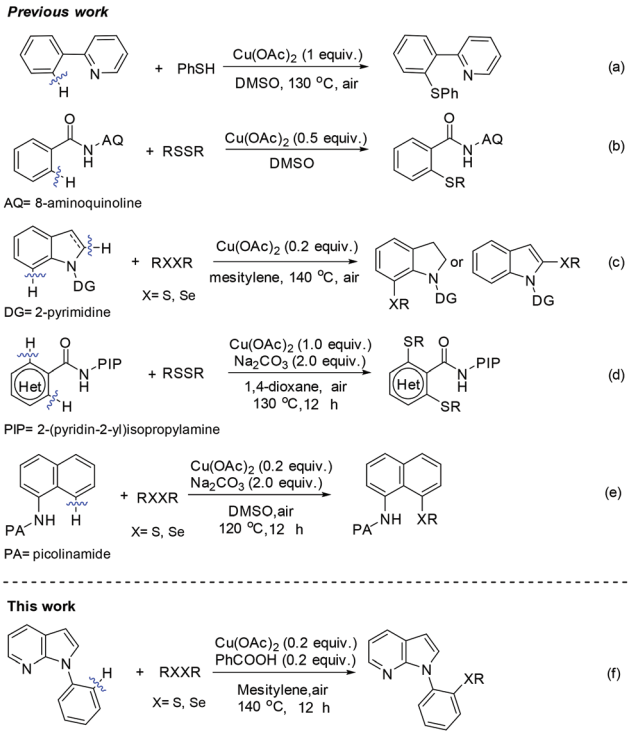
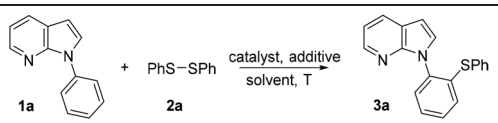
†Electronic supplementary information (ESI) available: Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra. See DOI: 10.1039/d1ob00106j



Scheme 1 $Cu(OAc)_2$catalyzed direct C–S bond formation with different directing groups.

Table 1 Optimization of the reaction conditions[a]



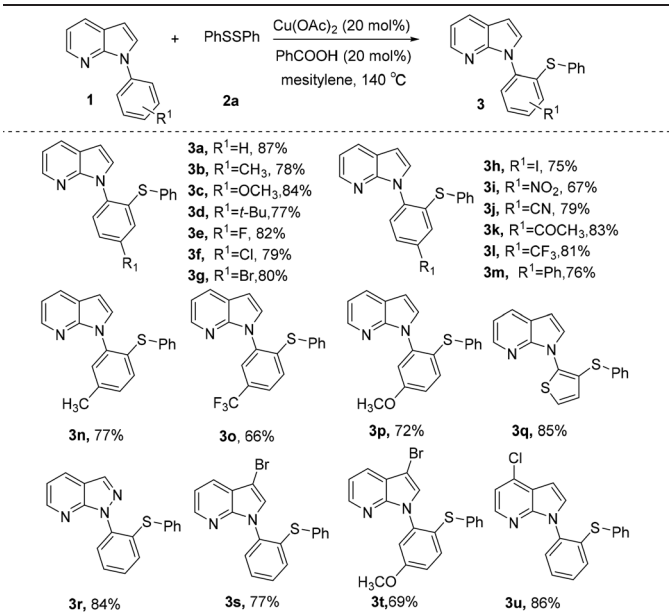
Entry	Catalyst (mol%)	Additive (2.0 equiv.)	Solvent	T (°C)	Yield[b] (%)
1	CuCl (20)	—	DCE	120	5
2	$CuCl_2$(20)	—	DCE	120	13
3	$CuBr_2$(20)	—	DCE	120	34
4	$Cu(OAc)_2$(20)	—	DCE	120	50
5	$Cu(OAc)_2$(20)	—	Toluene	120	55
6	$Cu(OAc)_2$(20)	—	DMSO	120	37
7	$Cu(OAc)_2$(20)	—	Chlorobenzene	120	38
8	$Cu(OAc)_2$(20)	—	Fluorobenzene	120	24
9	$Cu(OAc)_2$(20)	—	*para*-Xylene	120	52
10	$Cu(OAc)_2$(20)	—	Mesitylene	120	57
11	$Cu(OAc)_2$(20)	$NaHCO_3$	Mesitylene	120	23
12	$Cu(OAc)_2$(20)	$KHCO_3$	Mesitylene	120	33
13	$Cu(OAc)_2$(20)	K_2HPO_4	Mesitylene	120	24
14	$Cu(OAc)_2$ (20)	PhCOOH	Mesitylene	120	70
15	$Cu(OAc)_2$(20)	Piv-OH	Mesitylene	120	57
16	$Cu(OAc)_2$(20)	AcOH	Mesitylene	120	44
17[c]	$Cu(OAc)_2$ (20)	PhCOOH	Mesitylene	120	77
18[d]	**$Cu(OAc)_2$(20)**	**PhCOOH**	**Mesitylene**	**140**	**87**
19[e]	—	PhCOOH	Mesitylene	140	—

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), additive (0.2 mmol), and solvent (1 mL) under air for 12 h. [b] Isolated yield. [c] Using 20 mol% PhCOOH. [d] Using 20 mol% PhCOOH and stirring at 140 °C. [e] Without $Cu(OAc)_2$.

optimization of the reaction conditions (Table 1). We are delighted that the *ortho*-C–H bond sulfenylation on the aryl ring took place and gave the corresponding product **3a** in 50% isolated yield in the presence of $Cu(OAc)_2$ (20 mol%) in DCE (1 mL) under air atmosphere at 120 °C (Table 1, entry 1). Inspired by this result, we then evaluated different metal catalysts such as $Pd(OAc)_2$, $Co(OAc)_2$, and $Ni(OAc)_2$, and found them less efficient than $Cu(OAc)_2$ in this transformation (entries 1–4, see the ESI Table S1†). We surprisingly found that mesitylene was the most effective solvent in this coupling reaction, providing the desired product **3a** in 57% yield (entry 10), whereas other solvents such as toluene, DMSO, chlorobenzene, fluorobenzene, and *para*-xylene were less effective (entries 5–10). Different additives were examined subsequently (entries 11–16), and switching the additive to PhCOOH improved the yield to 70% (entry 14). Further investigations on the amounts of additives and the reaction temperatures were conducted (entries 17 and 18), and 20 mol% PhCOOH and 140 °C were found optimal for the highest yield of 87% (entry 19). In addition, control experiments showed that the reaction did not take place in the absence of copper salts.

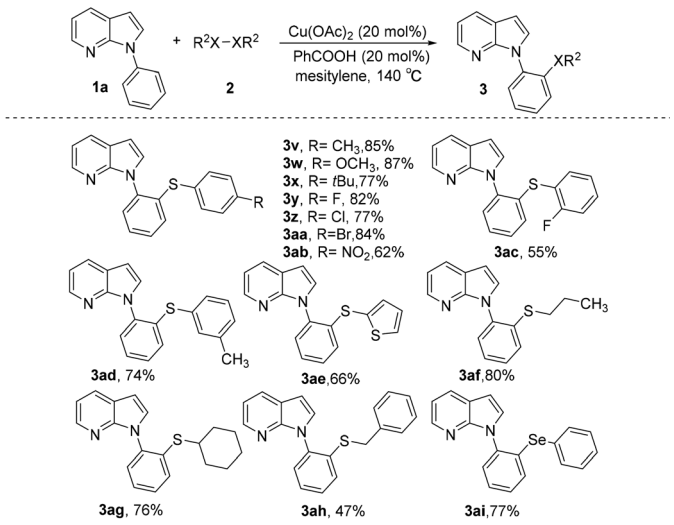
With the optimized reaction conditions in hand (Table 1, entry 18), the substrate scope and limitations were evaluated and the results are shown in Tables 2 and 3. A broad range of *N*-aryl-7-azaindoles with electron-donating groups such as methyl (–Me), methoxy (–OMe), and *tert*-butyl (–*t*Bu) groups, and electron-withdrawing groups such as halides (–F, –Cl, –Br and –I), nitro ($-NO_2$), cyanide (–CN), acetyl (–COMe), and trifluoromethyl ($-CF_3$) groups at the *para*-position of the

Table 2 Substrate scope of *N*-aryl-7-azaindoles[a,b]



[a] Reaction conditions: **1** (0.2 mmol), $(PhS)_2$ (0.3 mmol), $Cu(OAc)_2$ (20 mol%), and PhCOOH (20 mol%) in mesitylene (2 mL) at 140 °C under air for 12 h. [b] Isolated yield.

Table 3 Substrate scope of disulfides 2[a,b]



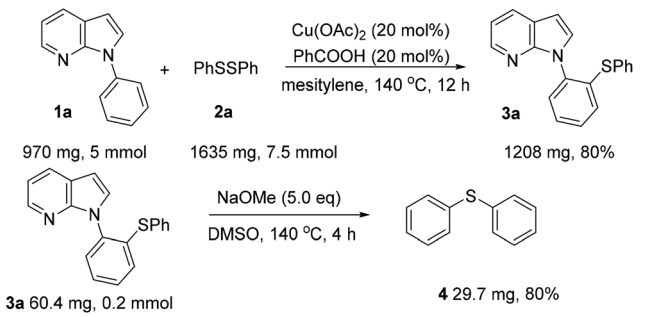
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $Cu(OAc)_2$ (20 mol%), and PhCOOH (20 mol%) in mesitylene (2 mL) at 140 °C under air for 12 h. [b] Isolated yield.

N-arylring underwent the reaction efficiently, affording the corresponding products **3b–3l** in moderate to high yields. We are also glad to find that *para*-phenyl substituted *N*-aryl-7-azaindole **1m** was tolerated in this transformation. However, substrates with *meta*-substituents offered lower yields than those with *para*-substituents (**3l** *vs.* **3o**; **3c** *vs.* **3p**; **3b** *vs.* **3n**). We assumed that steric factors clearly reduced the reaction efficiency. Heteroarenes such as thiophene underwent thioetherification reaction efficiently under optimized catalytic conditions and gave up to 85% yield of product **3q**. Finally, we also examined the thioetherification reaction of substituted 7-azaindoles under the standard reaction conditions, and 1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine **1r** was proved to be a suitable substrate, providing the corresponding product **3r** in good yield. C–Br/C–Cl bonds remained untouched at high temperature. For example, **1s**, **1t**, and **1u** were also well compatible under the standard reaction conditions, affording the products **3s**, **3t**, and **3u** in yields of 77%, 69%, and 86%, respectively, and these products could be used for further transformations.

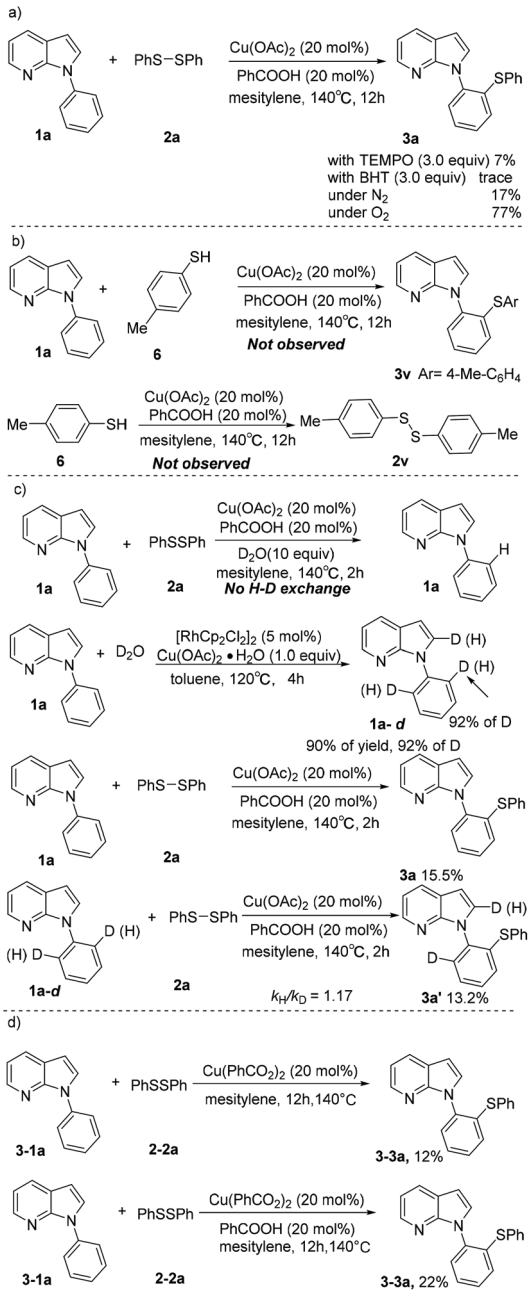
To further explore the scope of this transformation, various disulfides were examined. As shown in Table 3, diaryl disulfides bearing either electron-donating groups (–Me, –OMe, and –*t*-Bu) or electron-withdrawing groups (–F, –Cl, –Br and $–NO_2$) on the phenyl ring underwent the reaction efficiently, affording the corresponding products **3v–3aa** in moderate to high yields. Moreover, the position of the substituent had some effects on the reaction. Disulfides that bear either electron-donating groups (–Me) or electron-withdrawing groups (–F) at the *para*-position of the phenyl ring were superior to their *ortho*-substituted counterparts in isolated yields (**3v** *vs.* **3ad**; **3y** *vs.* **3ac**), showing that steric factors clearly reduced the reaction efficiency. Moreover, dithiophenedisulfides underwent chalcogenation with 7-azaindole to afford product **3ae** in 66% yield. In addition to the aromatic disulfide, less reactive dialkyldisulfides, such as dipropyldisulfide, dicyclohexyldisulfide and dibenzyldisulfide were tolerated in this transformation, affording products **3af–3ah** in good yields. Moreover, diphenyl diselenide was efficiently transformed into the desired selenylated product **3ai**, thereby demonstrating the robustness of the present copper-catalyzed C–H chalcogenation.

The synthetic utility of the copper-catalyzed sulfenylation is also demonstrated in Scheme 2. The present transformation could be smoothly scaled up to 5 mmol under the standard conditions without an apparent loss of yield (Scheme 2). We also could remove the drifted group 7-azaindolein in a traceless fashion, thereby obtaining diphenylsulfane **4** with 80% yield.[10c]

To gain insight into the reaction mechanism, a series of control experiments was carried out. Firstly, a radical capture experiment was performed (Scheme 3a). This reaction was suppressed by the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), suggesting that this reaction might go through a SET pathway. Moreover, performing the reaction under N_2 and O_2 atmospheres resulted in 17% and 77% yields, which implied that O_2 might act as an oxidant in this reaction. Furthermore, on using *p*-toluenethiol **6** instead of disulfide, the reaction did not take place, and *p*-toluenethiol **6** could not be oxidized to *p*-tolyldisulfide under standard reaction conditions. We speculated that the hemolytic cleavage of disulfides generated the sulfenyl radicals (Scheme 3b). In addition, no deuterium was incorporated into the recovered starting material, which indicated that an irreversible C–H cleavage event occurred during the reaction. We carried out an intermolecular kinetic isotope effect (KIE) of **1a** and **1a–*d*** and observed a k_H/k_D value of 1.17, which indicated that the aromatic C–H bond cleavage might not be the rate-determining step (Scheme 3c).[13] Finally, we evaluated the role of PhCOOH in this reaction. When 20 mol% $Cu(PhCO_2)_2$ was used as a catalyst in this reaction, 5% yield of product **3a** was observed in the absence of 20 mol% PhCOOH as an additive, whereas 12% yield of **3a** was obtained in the presence of 20 mol% PhCOOH. We propose that PhCOOH



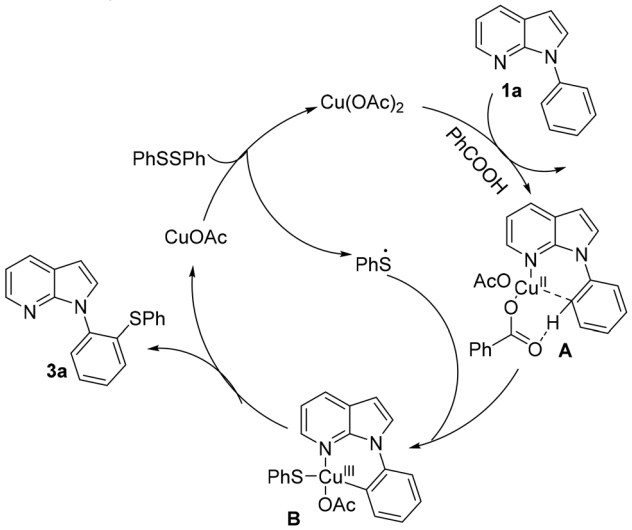
Scheme 2 Gram-scale preparation of **3a** and removal of the 7-azaindole group.



Scheme 3 Key mechanistic studies.

might act as an auxiliary ligand in the catalytic cycle (Scheme 3d).

Although the mechanism remains unclear at this moment, based on the mechanistic studies and previous reports,[14] we propose a plausible catalytic cycle for the copper-catalyzed C(sp^2)-sulfur bond formation (Scheme 4). Firstly, the coordination of 7-azaindole **1a** with copper acetate in the presence of PhCOOH produces the bicyclic Cu(II) intermediate **A**. Oxidation of intermediate **A** by a sulfenyl radical (PhS-SPh bond hemolytic cleavage) can deliver a Cu(III)-sulfur species **B**.[15] The sulfenylation product **3a** is obtained through reductive elimination together with the Cu(I) species, which is further oxidized to Cu(II) by oxygen.



Scheme 4 Proposed mechanism.

Conclusions

In summary, we developed a copper-catalyzed C(sp^2)–H sulfenylation reaction of various *N*-aryl-7-azaindoles with disulfides as sulfur sources. The reaction involved the use of the inexpensive $Cu(OAc)_2$ catalyst, removable directing groups, diaryl or dialkyldisulfide (or diselenide) reagents, and air as a terminal oxidant. The operationally simple method is characterized by ample substrate scope under aerobic reaction conditions. Mechanistic studies provide evidence for a SET-type process and indicate an operative facile C–H cleavage.

Experimental section

General information

Reagents and solvents. All starting materials, which were purchased from commercial sources, were used without further purification. Solvents for column chromatography were of technical standards. Column chromatography was performed with silica gel 200–400 mesh. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra were reported in parts per million (ppm) downfield from the internal standard Me_4Si (TMS). Chemical shifts in ^{13}C NMR spectra were reported relative to the central line of the chloroform signal (δ = 77.0 ppm). Peaks were labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). High resolution mass spectra were obtained with a Shimadzu LCMS-IT-TOF mass spectrometer. Analytical TLC was performed using EM separations with percolated silica gel 0.2 mm layer UV 254 fluo-

rescent sheets. *N*-Aryl-7-azaindole derivatives were synthesized according to literature reports.[10b,15]

General procedures for thiolation

Into an oven-dried sealed tube was added *N*-aryl-7-azaindoles **1** (0.2 mmol), disulfide **2** (0.3 mmol), $Cu(OAc)_2$ (7.2 mg, 0.04 mmol), PhCOOH (4.9 mg, 0.04 mmol) and mesitylene (2.0 mL). The mixture was stirred at 140 °C for 12 hours until the complete consumption of **1** as monitored by TLC analysis. The reaction mixture was then diluted with water and extracted with ethyl acetate. After the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure, the residue was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent (8 : 1, V/V) to afford the pure product **3**.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

This work was financially supported by the Department Education Science and Technology Research Project of Jiangxi, China (GJJ190619) and Jiangxi Science & Technology Normal University (2019BSQD016, JGZD-19-10-9).

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