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Copper-Mediated Remote C−H Bond Chalcogenation of Quinolines on the C5 Position

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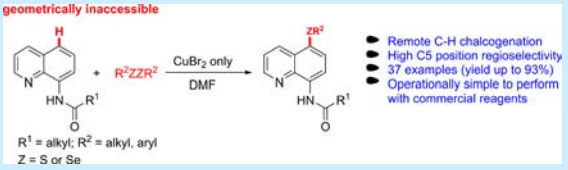
Supporting Information

ABSTRACT: An efficient and convenient method is developed for the remote C−H bond chalcogenation of 8-aminoquinoline scaffolds on the C5 position that is geometrically inaccessible. The protocol makes use of inexpensive $CuBr_2$ as mediator and shows good tolerance toward numerous disulfides/diselenides and aliphatic amides, giving the corresponding products in good to excellent yield.



Quinolines are skeletons common in natural products and bioactive molecules (Figure 1).[1] They can be used as

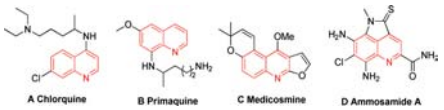


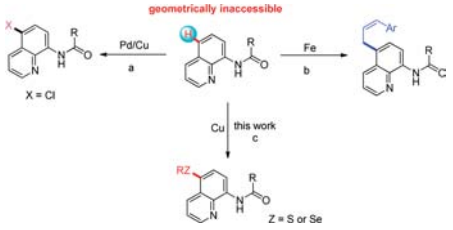
Figure 1. Representative biologically active compounds.

bidentate directing groups or as ligands participating in various kinds of organic reactions.[2] It should be noted that quinolines are also used as fluorescent probes to detect Zn^{2+} and Fe^{3+}[3] and are even utilized for fluorescence imaging in living cells.[4]

Although highly efficient traditional classic methods,[5] such as metal-catalyzed coupling cyclization and acid-catalyzed cycloaddition of appropriate anilines as precursors with carbonyl compounds or alkynes, have been reported,[6] the modification of quinolines, especially those with readily accessible quinoline frameworks, on the C5 position has rarely been reported.[7] Because of the electron effect of quinolines, it is difficult to control the regioselectivity. Examples of the modification of quinoline scaffolds are mainly on the C2,[8] C3,[9] C4,[10] and C8[11] positions that are easily accessible. As for the C5 position that is geometrically inaccessible, it was not until very recently that its chlorination was first reported by Stahl et al.,[7a] followed by Xie and Zhang et al.[7b] (Scheme 1a). Furthermore, Zeng and coworkers[7c] described the regiodivergent C−H allylation of quinolines on the C5 position that was enabled by 8-amino and catalyzed by iron via remote C−H activation (Scheme 1b).[12] However, as for the remote C−H chalcogenation of quinolines on C5 position, there was no disclosed example.[7e,f]

Aryl chalcogenide skeletons are also ubiquitous in biologically active natural products, and they are common in areas of pharmaceuticals and material science.[13] Given the importance of quinolines and chalcogenides, it is of great interest to combine the two into a single entity. In this context,

Scheme 1. Direct Modification of Geometrically Inaccessible C5 Position of Quinolines



it is desirable and challenging to develop methods that are efficient for the synthesis of quinolines aryl chalcogenoethers on the C5 position from readily available and simple substrates, preferably using transition metals as catalysts. Generally, the coupling of RZH (Z = S or Se, hereinafter) or RZZR with halides catalyzed by a transition metal enables C−Z bond formation.[14] The addition reaction of Z−Z or Z−H bonds with alkynes or alkenes is another method.[15] The method of C−H bond chalcogenation employing a C−H bond as a transformable functional group allows the shortening of reaction pathways, thus leading to efficient production of the desired substances.[16] Another important feature of C−H bond chalcogenation is the ability to achieve unique regioselectivity that is often unattainable by employing classical methods such as Friedel−Crafts chemistry.[17] As part of our continuing efforts on the search for C−Z coupling,[7f,18] we studied the thiolation of inactive methyl C(sp^3)−H bonds of aliphatic amides with disulfide over transition-metal catalysts.[18b] During the investigation, we observed copper(II)-mediated remote C−H bond chalcogenation that selectively builds up the 5-arylthio/alkythio to form quinolines thioethers/selenoethers (Scheme 1c). To

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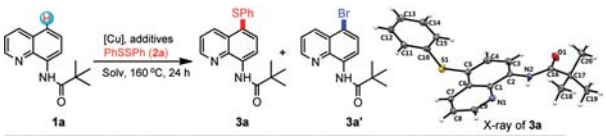
the best of our knowledge, such a result has never been reported before.

Initially, *N*-(quinolin-8-yl)pivalamide (**1a**) and diphenyl disulfide (**2a**) were selected as substrates for the optimization of reaction conditions (Scheme 2). When the reaction was

Scheme 2. Optimization of Reaction Conditions[a]



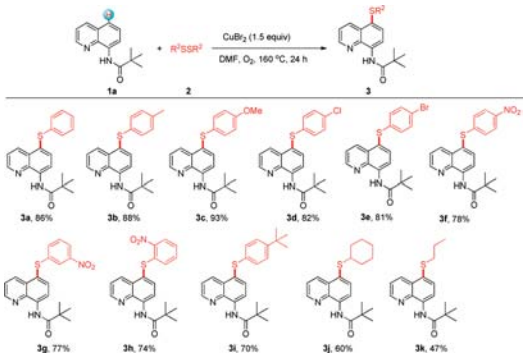
entry	[Cu] (equiv)	solv (1 mL)	temp (°C)	yield (%) (3a/3a')[b]
1	$CuBr_2$ (0.1)	DMF	160	10
2	$CuCl_2$ (0.1)	DMF	160	7
3	CuO (0.1)	DMF	160	NR
4	$Cu(OTf)_2$ (0.1)	DMF	160	NR
5	CuI (0.1)	DMF	160	8
6	Cu powder (0.1)	DMF	160	NR
7	$CuBr_2$ (2)	DMF	160	90/8
8[c]	$CuBr_2$ (0.1)	DMF	160	17
9[d]	$CuBr_2$ (0.1)	DMF	160	10
10[e]	$CuBr_2$ (0.1)	DMF	160	28
11	***$CuBr_2$ (1.5)***	***DMF***	***160***	***89(86)/5***
12	$CuBr_2$ (1.5)	NMP	160	78/10
13	$CuBr_2$ (1.5)	toluene	160	NR
14	$CuBr_2$ (1.5)	dioxane	160	22/15
15	$CuBr_2$ (1.5)	*p*-xylene	160	15
16	$CuBr_2$ (1.5)	DMF	140	50/18
17	$CuBr_2$ (1.5)	DMF	120	22/40
18[f]	$CuBr_2$ (1.5)	DMF	160	75/7

[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.36 mmol), copper salt, solvent (1.0 mL), O_2 atmosphere; [b]GC yield, using *n*-tridecane as internal standard; the number in parentheses is isolated yield. [c]2 equiv of $AgNO_3$ was added. [d]2 equiv of $K_2S_2O_8$ was added. [e]2 equiv of $PhI(OAc)_2$ was added. [f]Under N_2.

carried out at 160 °C for 24 h in the presence of a catalytic amount of $CuBr_2$ (0.1 equiv) under O_2 atmosphere using DMF as solvent, *N*-(5-(phenylthio)quinolin-8-yl)pivalamide **3a**, which was a result of quinoline thiolation at the C5 position, was generated in 10% yield as the only product (entry 1). The use of $CuCl_2$ and CuI showed similar reactivity, while CuO, $Cu(OTf)_2$, and copper powder were found to be less effective (entries 2−6). When the amount of $CuBr_2$ was 2 equiv, there was 8% yield of the byproduct *N*-(5-bromoquinolin-8-yl)-pivalamide **3a′** (entry 7). The structure of thiolated product *N*-(5-(phenylthio)quinolin-8-yl)pivalamide **3a** was confirmed by single-crystal X-ray analysis (see the structure in Scheme 2).[19] It was found that 1.5 equiv of $CuBr_2$ is the best choice for avoiding the byproduct (entries 7−11 and Table S1, Supporting Information). When the reaction was conducted with basic and acid additives (see Tables S2 and S3, SI), there was a decline of reactivity. The results are different from that reported on acid-promoted thiolation reactions catalyzed by nickel catalysts.[20] Further screening showed that DMF is the most suitable solvent for the reaction (entries 12−15). It was observed that the lowering of reaction temperature from 160 to 120 °C results in an increase of byproduct *N*-(5-bromoquinolin-8-yl)pivalamide **3a′** (entries 16 and 17, up to 40%). The presence of N_2 enabled a somewhat lower yield relative to aerobic reaction conditions (entry 18) implies the oxygen may be benefit for the reaction.[7a]

With the optimized reaction conditions in hand, we investigated the substrate scope with respect to disulfides (Scheme 3). Diaryl disulfides with an electron-donating or

Scheme 3. Investigation of Disulfide Scope[a]

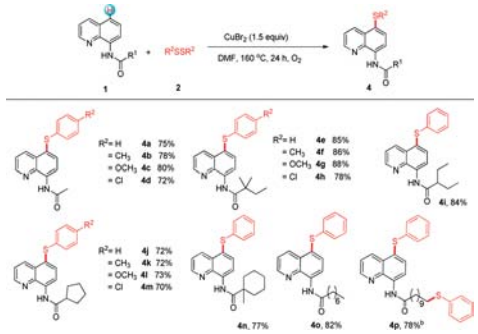


[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.36 mmol), $CuBr_2$ (0.45 mmol), DMF (1 mL), isolated yield.

electron-withdrawing group at the *p*-position of the phenyl ring performed as well in good to excellent yields under the optimized (standard) conditions (**3a−i**). The reaction showed good tolerance toward a wide range of functional groups such as methyl, methoxy, halogen, and nitro groups attached to diaryl disulfides. Notably, the diphenyl disulfides with nitro at the *o*-, *m*-, or *p*-position gave the corresponding products in similar yield, which is different from the thiolation of quinones[21] and carbazoles.[18a] Similar to substituted diaryl disulfides, dialkyl disulfides such as dicyclohexyl disulfide and dipropyl disulfide proceeded smoothly to yield the desired products in moderate yields (**3j** and **3k**).

As depicted in Scheme 4, we explored the reactions of disulfides with several kinds of 8-aminoquinoline derivatives.

Scheme 4. Investigation of Aliphatic Amide Scope[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.36 mmol), $CuBr_2$ (0.45 mmol), DMF (1 mL), isolated yield. [b]2.5 equiv of PhSSPh was used.

Replacement of *tert*-butyl with other alkyl groups results in the desired products in good to excellent yield (**4a−p**). It is noted that cycloalkanes such as those with a cyclopentyl or cyclohexyl group proceeded well (**4j−m,n**). For those with long-chain alkyl groups, the thiolation reaction goes smoothly as well (**4o** and **4p**). Interestingly, when there is a bromide attached to the alkyl chain, there is one-pot generation of double-thiolation product (**4p**). In other words, the strategy offers a way to achieve double thiolation of quinoline derivatives by remote C−H thiolation and simple cross-coupling reaction.

Encouraged by the viability of the protocol for direct C−S bond formation on quinolines, we applied the system to diaryl diselenides with an aliphatic amide, and the desired C−Se cross-coupling compounds **5a−g** were obtained in good yields

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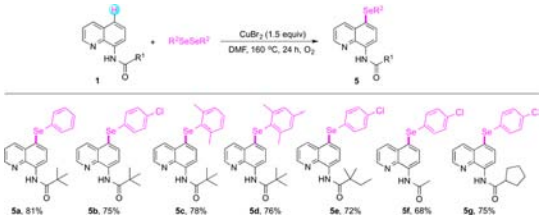
(Scheme 5). However, when ditellurides were used under the standard conditions, the desired products could only be obtained in very low efficiency.

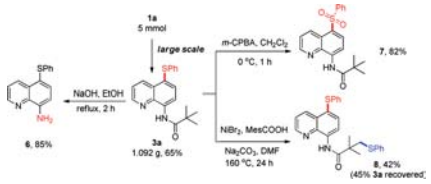
Scheme 5. Investigation of Diselenide Scope[a]



[a]Reaction conditions: **1** (0.3 mmol), diaryl diselenides (0.36 mmol), $CuBr_2$ (0.45 mmol), DMF (1 mL), isolated yield.

To demonstrate the synthetic utility of the new method, the reaction was carried out on a 5 mmol gram scale, and the desired product was obtained in 65% yield (Scheme 6). The

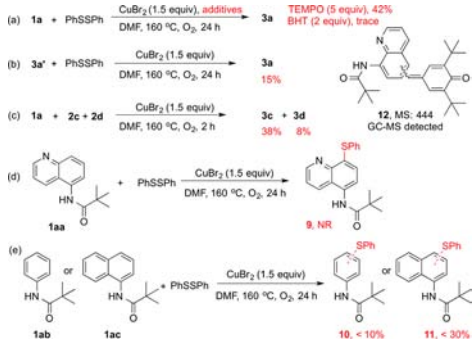
Scheme 6. Gram Scale and Synthesis Applications



amide bond can be easily broken in 85% yield without damaging the thioether **3a** to obtain **6**.[18b] The thioether **3a** can be oxidized to afford sulfone **7** in 82% yield or further converted to disulfide **8** in moderate yield according to the report of Zhang et al.[22] and that of ours,[18b] respectively.

To shed light on the possible pathway of this thiolation reaction, we performed a number of preliminary experiments as depicted in Scheme 7. It was found that the addition of

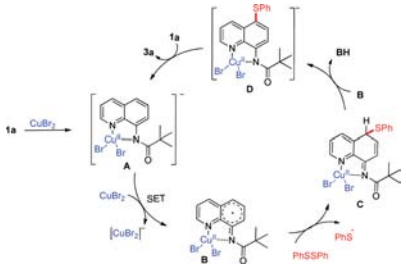
Scheme 7. Control Experiments



TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) inhibits the reaction, and the yield is sharply decreased to 42% or trace (Scheme 7a), suggesting the involvement of a single electron transfer (SET) pathway in this reaction. Moreover, adduct **12** of the quinoline radical with BHT was detected by GC–MS.[23] An experiment using the byproduct *N*-(5-bromoquinolin-8-yl)pivalamide **3a′** to react with PhSSPh resulted in **3a** in 15% yield (Scheme 7b), which excluded the possibility that the brominated product was a possible intermediate.[7] This indicates that the thiolation is not a cascade reaction after brominated but rather one that is direct C–H remote thiolation in nature. Furthermore, an intermolecular competition experiment between **2c** and **2d** was conducted (Scheme 7c), and it was observed that the electron-rich disulfide shows a higher reaction rate (**3c**, 38%; **3d**, 8%). We found that the thiolation does not go with **1aa** to yield **9** at all and goes rather ineffectively to **1ab** and **1ac**, obtaining **10** and **11** with low yield and regioselectivity, respectively (Scheme 7d), implying that there is the generation of an essential copper-center intermediate in the reaction and the nitrogen atom in the quinoline motif is essential for improving the regioselectivity.

Based on the above results and those reported in the literature,[7,16m] we propose a possible pathway for thiolation that takes place on the C5 position of quinolines (Scheme 8).

Scheme 8. Possible Pathway



Coordination of the amide **1a** to the Cu center forms an anionic complex **A**.[7a,b] Subsequently, the intermolecular SET between the electron-rich imidoquinoline moieties and the highly oxidative Cu(II) center occurs, giving the radical complexes **B** with $CuBr_2$ being reduced to $CuBr_2^-$. Then, the transfer of the PhS group to **B** occurs, producing the imino–Cu(II) complex **C**. Next, the deprotonation of **C** provides the thiolated imidate–Cu(II) complex **D**. The ligand exchange of **D** with the starting material **1a** affords the C5-thiolated product **3a** and regenerates the amidate–Cu(II) anionic complex **A** for the next catalytic cycle. Further investigation is being conducted to provide evidence for the proposed mechanism.

In summary, we developed an efficient and convenient method for C5-chalcogenation of 8-aminoquinoline scaffolds making use of inexpensive $CuBr_2$. It is possible that the chalcogention reaction involves a step of remote C–H activation. The reaction system shows tolerance toward numerous diaryl/dialkyl disulfides and aliphatic amides, giving the corresponding products in good to excellent yield. This protocol can be easily extended to diaryl diselenides in good yield.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02511.

Detailed experimental procedures, characterization data, spectra copies of the ^1H, ^{13}C NMR (PDF)
X-ray data of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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