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Divergent Synthesis of Quinolones through Radical C–H Functionalization/Cyclization

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Abstract: Divergent synthesis is an effective, yet challenging method to selectively access different molecules from a single starting material. Herein, we demonstrate a divergent and controllable synthesis of quinolones by sulfonyl chloride-controlled, copper-catalyzed, site-selective radical C–H functionalization/cyclization of quinoline scaffolds. Our catalytic system can tolerate a wide range of functional groups and provide both 2-thioquinolone and 4-quinolone derivatives in moderate to good yields. Control experiments and density functional theory calculations indicate a single-electron transfer mechanism, and the steric hindrance of sulfonyl chlorides and their electronic effect are decisive for reaction selectivity. This transformation provides not only a novel example of divergent radical C–H functionalization controlled by small organic molecules, but also an efficient way to rapidly derivatize medicinally important scaffolds and ultimately facilitate late-stage drug modification.

Introduction

In recent years, the development of high-efficiency, versatile synthetic methods for biologically relevant molecules has received considerable attention.[1] In this regard, divergent synthesis is one of the most sought-after yet challenging strategies to selectively access different molecular scaffolds using the same starting materials.[2] For instance, Glorius et al. in 2022 demonstrated a visible light-based energy-transfer strategy for the divergent synthesis of 2D/3D rings via intermolecular cascade dearomative [2+2] cycloaddition/rearrangement reactions of quinolines with alkenes (**Figure 1a**).[2a] On the other hand, direct C–H functionalization is considered the most convenient and intriguing method for organic synthesis because of its excellent atom and step economy.[3] Therefore, the merger of C–H functionalization and divergent synthesis will enable a rapid synthesis of a wide variety of structurally diverse organic molecules for biological evaluation and provide new insight into catalytic reaction mechanisms, which has received great attentions in synthetic community.[4] For example, Yu and coworkers disclosed a ligand-controlled divergent dehydrogenative reaction of carboxylic acids via C–H activation (**Figure 1b**).[5] This strategy relies on ligands with different bite angles that enable tandem vinyl C–H activation and alkynyl bromide coupling or prevent vinyl C–H activation of unsaturated acids, which are typically more reactive. By using ligand-controlled strategy, the same group successively developed many site-selective C-H functionalization reactions for divergent synthesis of valuable molecules.[6] In addition, Shi's group also demonstrated a general method for divergent C–H borylation of arenes controlled by the chelation effect (**Figure 1c**).[7] The density functional theory (DFT) calculations showed that BBr_3 in the reaction acted as both a reagent and a catalyst. Despite significant advances, these transformations mostly rely on noble-metal catalysts with ligands, which are not cost-effective. Furthermore, they commonly proceed via a non-radical mechanism in which the organic molecules coordinate with metal catalysts to change the reactivity and structure of the metal. In contrast, divergent synthesis by a radical C-H functionalization reaction remains rare probably due to the high reactivity of radical intermediates.[8]

Quinolones are an important class of nitrogen-containing heterocycles among the most widely used antimicrobial agents globally and have proven to be the most crucial pharmacophores in modern drug development (**Figure 1d**).[9] Classical methods for quinolone synthesis, such as the Niementowski reaction and Knoevenagel condensation, are commonly based on cyclocondensation under harsh reaction conditions.[10] Another alternative approach is biocatalytic condensation and cyclization (**Figure 1e**).[11] In recent years, new synthetic methods have been well established through transition metal-catalyzed functionalization/cyclization using alkynes, anilines, and arylhalides as building blocks (**Figure 1f**).[12]

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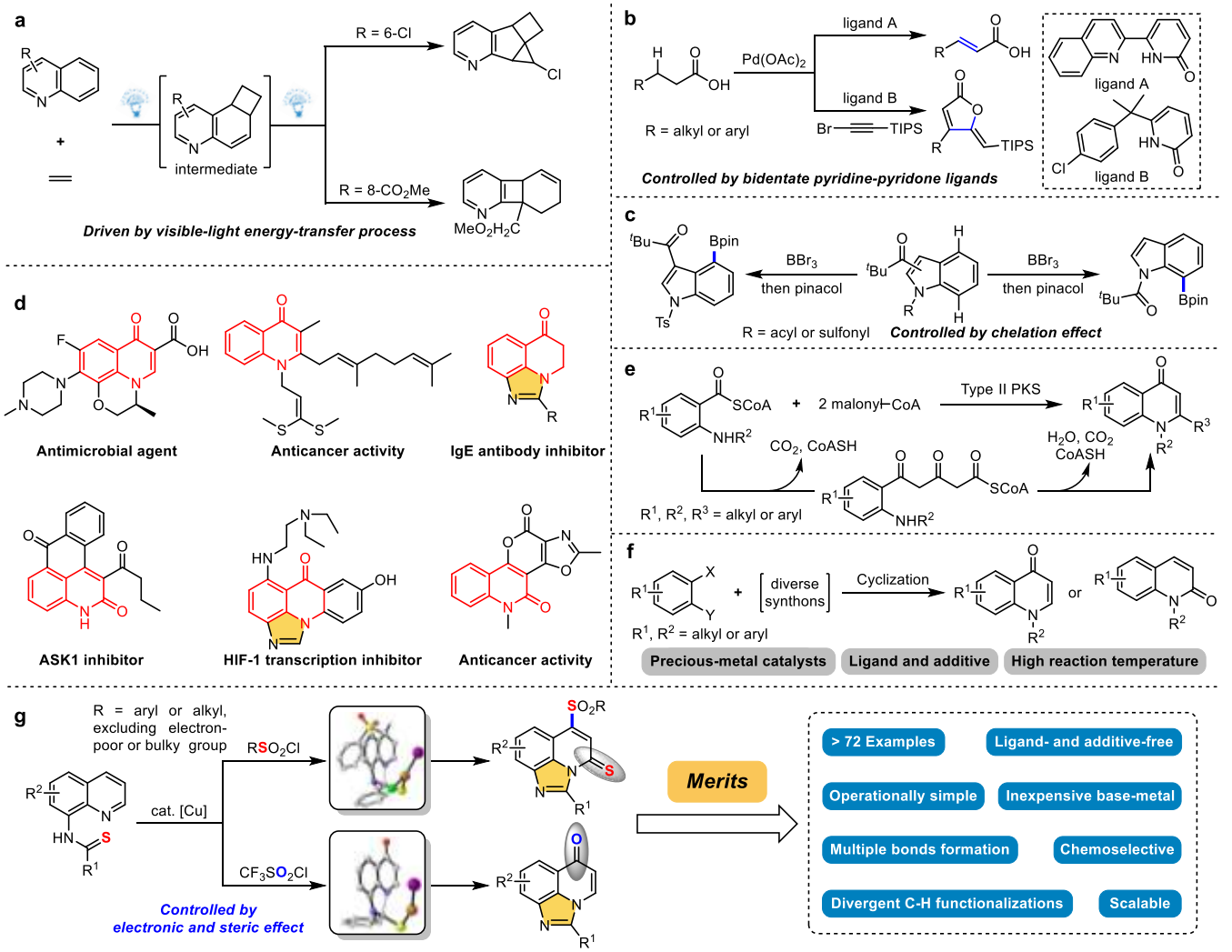


Figure 1. Typical synthetic methods involving divergent synthesis. **a**, Divergent synthesis of 2D/3D rings via intermolecular cascade dearomative [2+2] cycloaddition/rearrangement reactions of quinolines with alkenes**. b**, Ligand-controlled divergent C-H dehydrogenative reaction of carboxylic acids. **c**, Divergent C–H borylation of arenes controlled by the chelation effect. **d**, Selected bioactive molecules containing a quinolone scaffold: ASK: apoptosis signal-regulating kinase, HIF: hypoxia inducible factor, Ig: immunoglobulin. **e**, Biocatalyzed cyclization of polysubstituted benzenes for the synthesis of quinolone derivatives. **f**, Thermal cyclization of polysubstituted benzenes for the synthesis of quinolone derivatives. **g**, Sulfonyl chloride-controlled divergent radical C-H functionalization/cyclization of quinolines for the synthesis of quinolone derivatives.

However, the requirements for noble metal catalysts, complex ligands and additives raise production costs. In addition, some protocols require high gas pressure, which makes them troublesome for industrial application.[13]

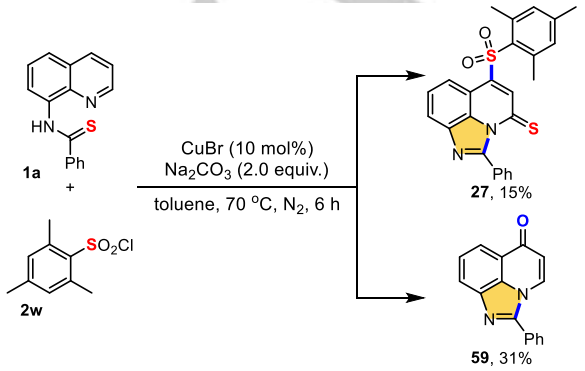
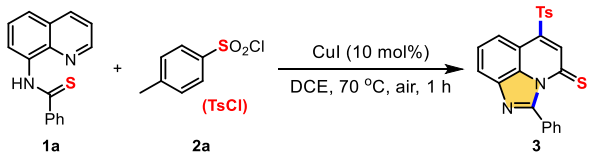


Figure 2. Discovery of divergent C-H functionalization of quinolines.

Table 1. Evaluation of reaction conditions for the synthesis of 2-thioquinolone.[a]



Entry	Variation from given conditions	Yield (%
1	none	89
2	no CuI	0
3	room temperature	0
4	2.0 equiv. of Na_2CO_3 were added	87
5	DCE was replaced by toluene	66
6	1.0 equiv. of **2a** was used	43
7	reaction time 0.5 h	57
8	under N_2 atmosphere	90

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv.), CuI (10 mol%), DCE (2.0 mL), 70 °C, air, 1 h, isolated yields. Note: DCE = 1,2-dichloroethane.

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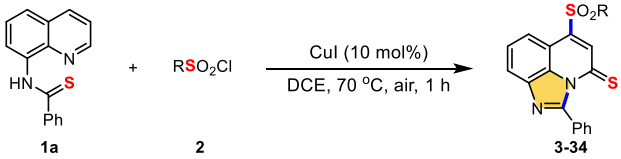
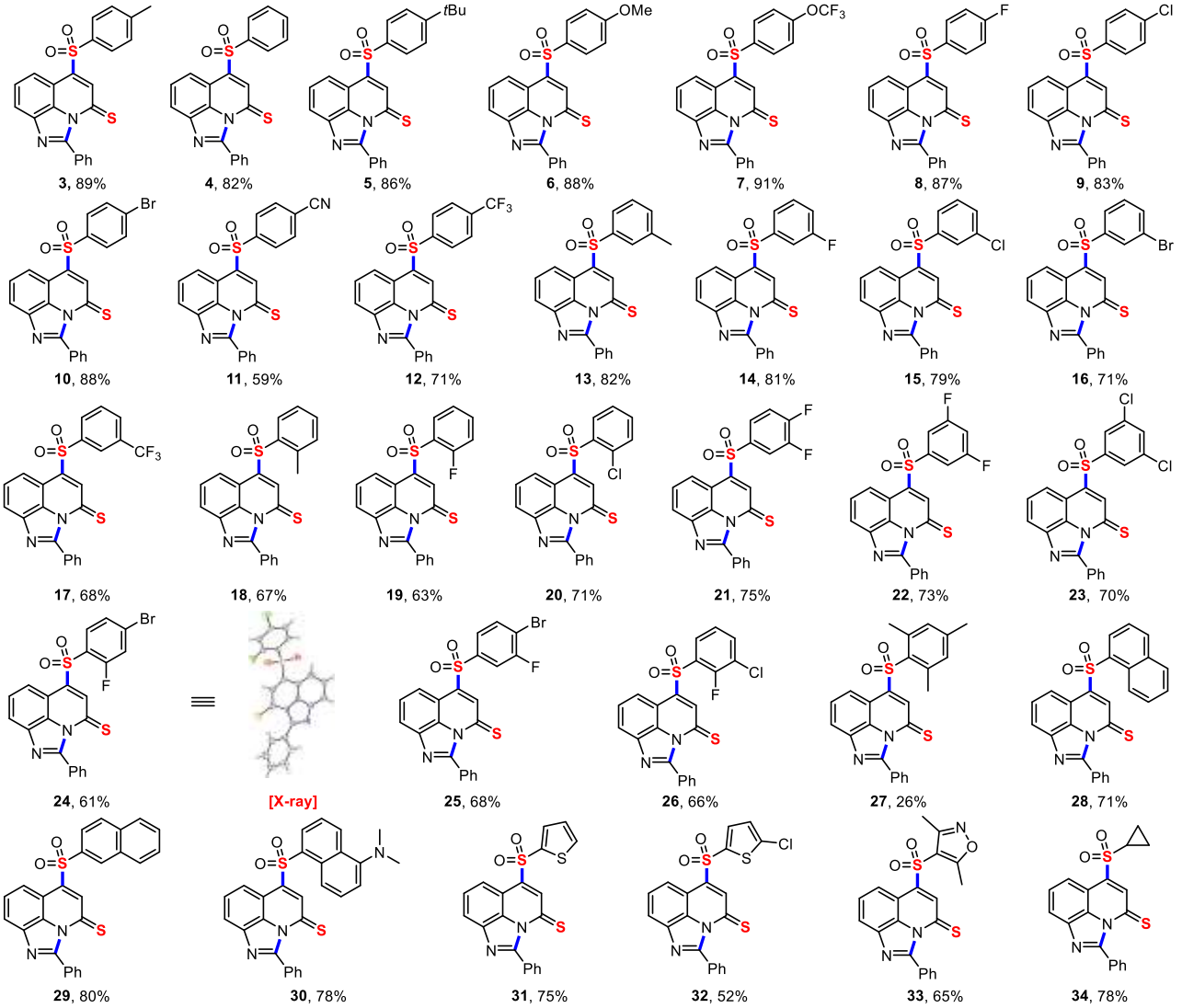
Table 2. Substrate scope of sulfonyl chlorides for the synthesis of 2-thioquinolone.[a]





[a] Reaction conditions: **1a** (0.2 mmol), **2** (2.0 equiv.), CuI (10 mol%), DCE (2.0 mL), 70 °C, air, 1 h, isolated yields.

Quinolines represent a readily available and accessible heterocyclic core and are widely used as building blocks for the synthesis of pharmaceuticals and fine chemicals.[14] From the viewpoint of both synthetic method development and its potential contribution to drug discovery, including quinolines as starting materials to selectively construct quinolone skeletons can be considered an intriguing approach toward chemical synthesis, in accordance with diversity-oriented synthesis and skeletal diversity. However, quinolones can be divided into 2- and 4-quinolones according to the different position of the carbonyl group. The introduction of (thio)carbonyl groups into the quinoline core is still a challenge in site-selective C–H functionalization due to the presence of sterically or electronically similar C–H bonds.[15]

Copper catalysts are available in a wide range of accessible oxidation states (Cu^0, Cu^I, Cu^{II}, and Cu^{III}) that allow the promotion of redox transformations in multiple pathways, which makes them useful for catalyzing reactions that are difficult to initiate.[16] Here, we report sulfonyl chloride-controlled, copper-catalyzed divergent radical C–H functionalization/cyclization of quinolines toward diverse quinolone derivatives (**Figure 1g**). Through the control of sulfonyl chlorides, selectively divergent synthesis of 2-thioquinolone and 4-quinolone derivatives can be achieved in moderate-to-good yields, thereby enabling a straightforward and controllable synthesis of quinolone derivatives. The key to the success of divergent radical C–H functionalization/cyclization is the control of sulfonyl radicals. Computational studies have shown that

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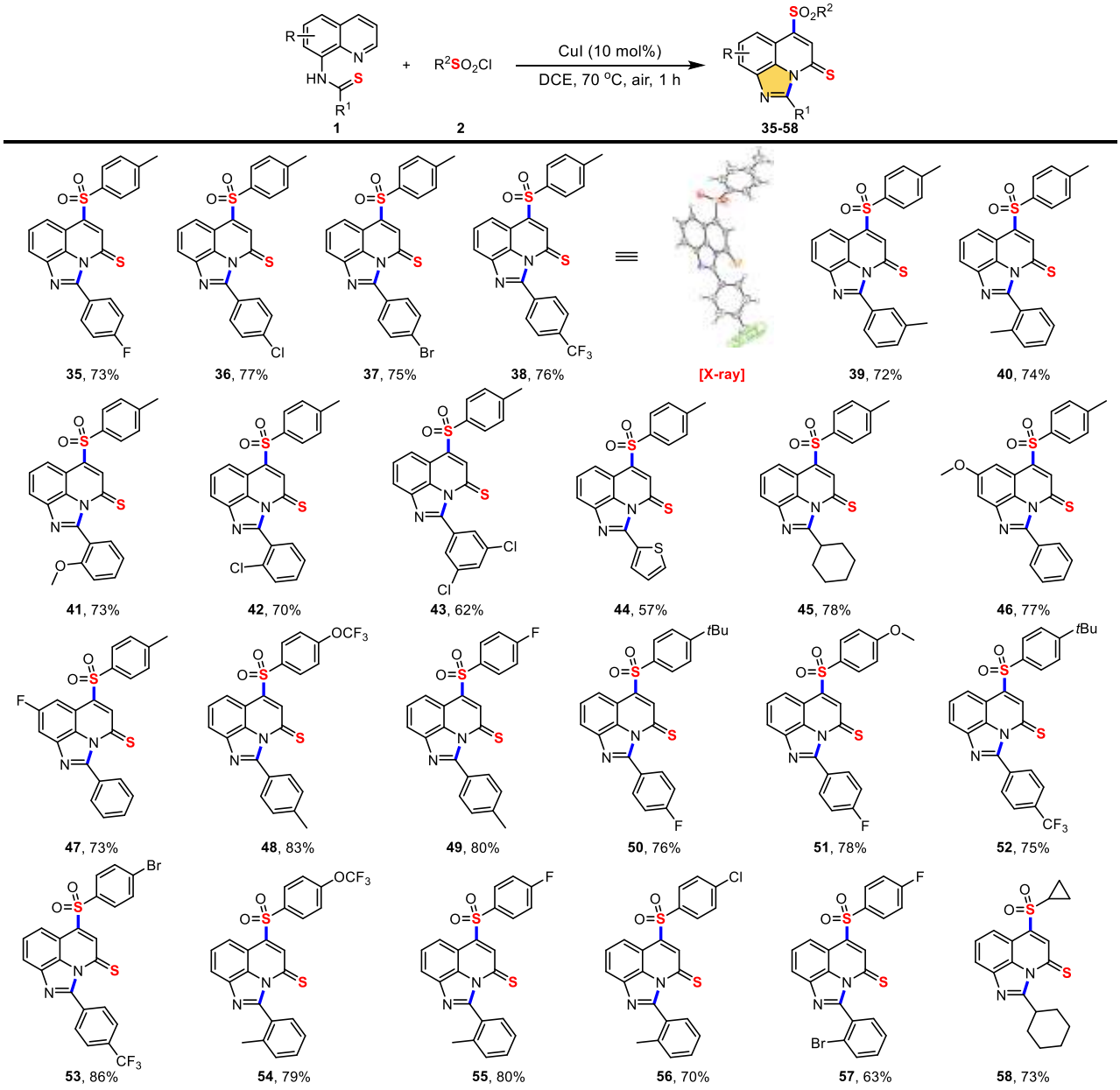
sulfonyl radicals directly attack the quinoline skeleton to initiate the reaction for the synthesis of 2-thioquinolone. In accordance with our experimental results, sulfonyl chlorides with bulky or electron-deficient groups readily form disulfones (RSO_2SO_2R) that provide access to 4-quinolones.

Results and Discussion

Discovery of sulfonyl chloride-controlled site-selective C–H functionalization/cyclization of quinolines and method optimization for the synthesis of 2-thioquinolone. Our research began with an interesting result observed in the reaction between quinoline thioamide **1a** and 2,4,6-trimethylbenzenesulfonyl chloride **2w**. When the transformation was performed in the presence of a copper catalyst, both 2-thioquinolone **27** and 4-quinolone **59** were obtained (**Figure 2**). These observations revealed that a divergent synthesis strategy might be involved. Inspired by these results, we started to evaluate the C–H sulfonylation/cyclization of quinoline thioamides by investigating the transition-metal catalysts, additives, solvents, reaction time, and temperature. (**Table 1 and Tables S1-S5**). A 2-thioquinolone derivative **3** was obtained in 89% yield by performing the C-H sulfonylation/cyclization of quinoline thioamide **1a** (0.2 mmol) with tosyl chloride **2a** (2.0 equiv.), CuI (10 mol%), and 1,2-dichloroethane (DCE) (2.0 mL) at 70°C for 1 h (**Table 1**, entry 1). In general, the catalytic performance of Cu(I) salts was much better than that of Cu(II) salts (**Table S1**, entries 1-7). Other transition-metal catalysts, such as $Pd(OAc)_2$, $FeCl_3$, $CoCl_2$, and NiI_2, failed to promote the transformation (**Table S1**, entries 8-11). No target product

Table 3. Substrate scope of quinoline thioamides for the synthesis of 2-thioquinolone.[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv.), CuI (10 mol%), DCE (2.0 mL), 70 °C, air, 1 h, isolated yields.

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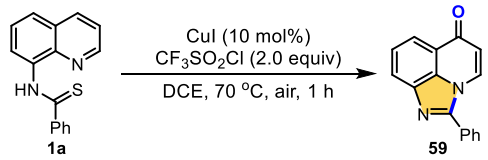
Table 4. Evaluation of reaction conditions for the synthesis of 4-quinolone.[a]



Entry	Variation from given conditions	Yield (%
1	none	87
2	no CuI	0
3	no CF_3SO_2Cl	0
4	1.0 equiv. of CF_3SO_2Cl were used	55
5	CF_3SO_2Cl was replaced with DTBP	0
6	room temperature	0
7	reaction time 0.5 h	67
8	under N_2 atmosphere	86

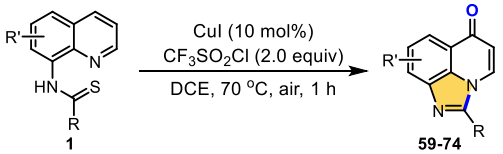
[a] Reaction conditions: **1a** (0.2 mmol), CF_3SO_2Cl (2.0 equiv.), CuI (10 mol%), DCE (2.0 mL), 70 °C, air, 1 h, isolated yields. Note: DTBP = di-*t*-butyl peroxide.

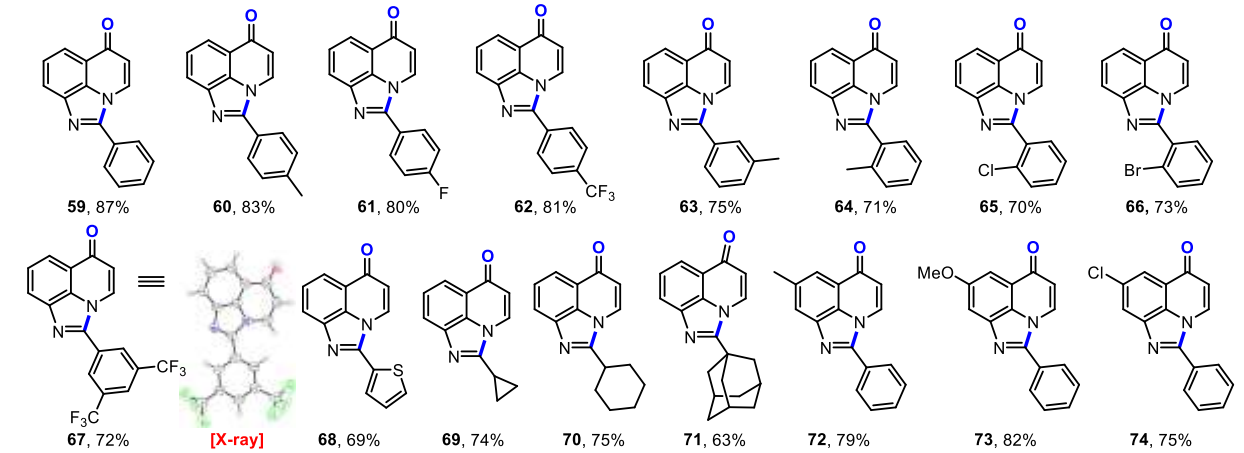
was generated in the absence of CuI or at room temperature (**Table 1**, entries 2 and 3). An 87% yield of the 2-thioquinolone derivative **3** was isolated when 2.0 equivalents of Na_2CO_3 were added as an additive (**Table 1**, entry 4). The yield decreased to 66% when the solvent was changed to toluene (**Table 1**, entry 5). Reducing the amount of tosyl chloride (**2a**) and the reaction time markedly decreased the yield (**Table 1**, entries 6 and 7). Notably, the reaction also proceeded well under nitrogen atmosphere, revealing that O_2 was not required in the C–H sulfonylation/cyclization reaction (**Table 1**, entry 8).

Substrate scope for the synthesis of 2-thioquinolone. With optimized reaction conditions in hand (**Table 1**, entry 1), we then examined the substrate scope of sulfonyl chlorides for copper-catalyzed C–H sulfonylation/cyclization (**Table 2**). This protocol is generally applicable to various sulfonyl chlorides, giving a wide range of 2-thioquinolone derivatives **3–33** in 26–91% yield. Benzenesulfonyl chlorides bearing various electron-donating groups, such as methyl, *t*-butyl, methoxy, and trifluoromethoxy groups, were well tolerated under standard conditions and gave the corresponding products **3–7** in excellent yields. Halogenated benzenesulfonyl chlorides, which could be further functionalized, were also suitable for the reaction and gave target products **8-10** in 83–88% yield. The 2-thioquinolone derivatives **11** and **12** were isolated in lower yields (59% and 71%, respectively), probably due to the fact that the strong electron-withdrawing effect of sulfonyl chloride was not advantageous for the synthesis of 2-thioquinolone. The *meta*- and *ortho*-substituted benzenesulfonyl chlorides reacted with quinoline thioamide **1a** to afford the corresponding products **13–20** in slightly low yields, implying that the reaction performance is sensitive to the steric effect of substrates. The reactions also tolerate polysubstituted benzenesulfonyl chlorides and other sulfonyl chlorides with aromatic moieties, such as naphthalene, thiophene, and isoxazole, giving the corresponding 2-thioquinolone derivatives **21–33** in 26–80% yield. It should be noted that this process also tolerates non-aromatic sulfonyl chlorides such as cyclopropanesulfonyl chloride to yield the corresponding product **34** in 78% yield.

We next explored the substrate scope of quinoline thioamides for this copper-catalyzed C–H sulfonylation/cyclization (**Table 3**). Notably, the transformation exhibited excellent compatibility with different functional groups. A variety of quinoline thioamides bearing electron-withdrawing and electron-donating groups on the phenyl moieties were readily reacted with sulfonyl chlorides, yielding 2-thioquinolone derivatives **35–43** in 62-77% yield. It is also possible to

Table 5. Substrate scope of quinoline thioamides for the synthesis of 4-quinolone.[a]





[a] Reaction conditions: **1** (0.2 mmol), CF_3SO_2Cl (2.0 equiv.), CuI (10 mol%), DCE (2.0 mL), 70 °C, air, 1 h, isolated yields.

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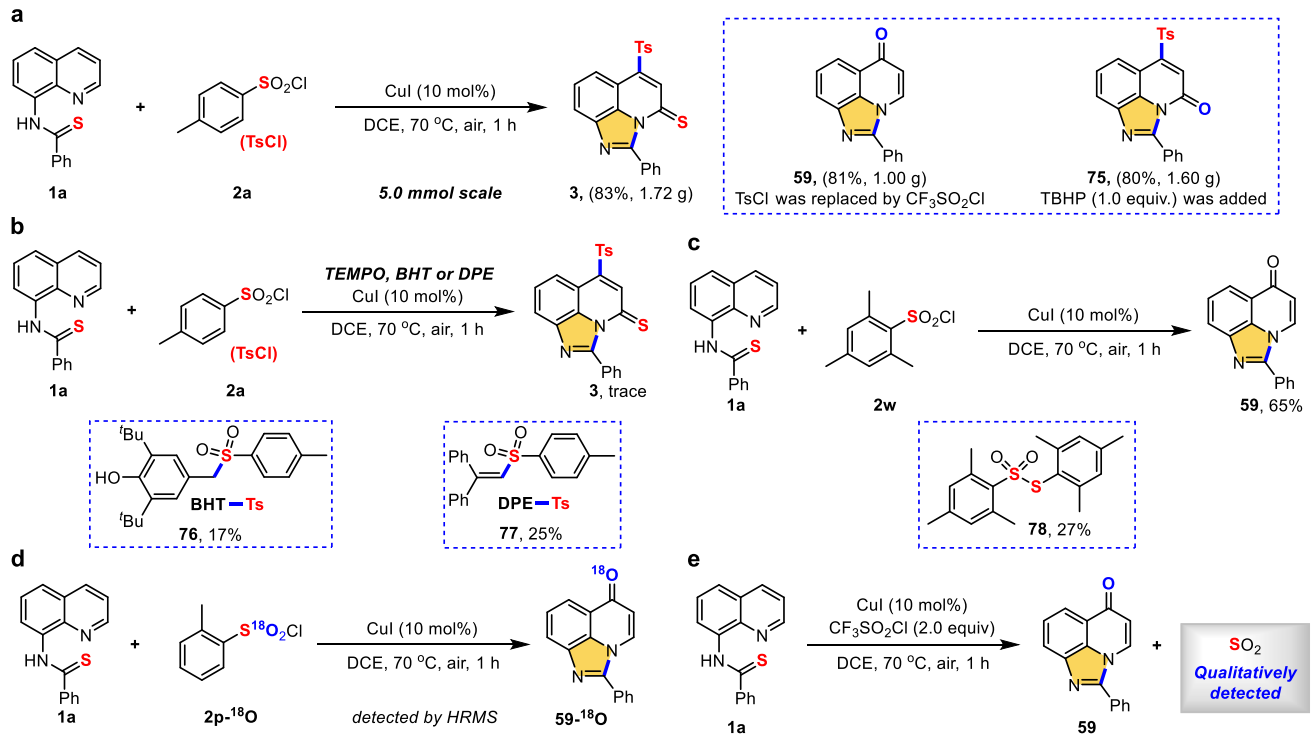

Figure 3. Scale-up studies and experiments for mechanistic insights. **a**, Synthesis of 2-thioquinolone, 4-quinolone and 2-quinolone performed in a 5 mmol scale, respectively. **b**, Radical inhibition and capture experiments. **c**, Detection of intermediate **78**. **d**, ^{18}O-labeling experiments. **e**, Qualitative detection of SO_2 in the synthesis of 4-quinolone.

replace the phenyl moiety of quinoline thioamides with heterocyclyl and alkyl groups, affording the corresponding products **44** and **45** in acceptable yields. Importantly, quinoline thioamides bearing an electron-donating group (methoxy-) and electron-withdrawing group (fluoro-) on the quinoline skeleton were good candidates to afford 2-thioquinolone derivatives **46** and **47** in satisfactory yields. Moreover, transformations between various substituted quinoline thioamides and sulfonyl chlorides can also proceed, giving the corresponding products (**48-58**) in 63-83% yield. Of note, the molecular structures of 2-thioquinolones **24** and **38** were further confirmed by X-ray crystallographic analysis.[17]

Optimization of method for the synthesis of 4-quinolone. It was found that when reaction conditions for the synthesis of 2-thioquinolone were optimized, no 4-quinolone was formed. However, when the substrate scope of sulfonyl chlorides was evaluated, a small amount of 4-quinolone **59** was obtained in the presence of electron-deficient or bulky sulfonyl chlorides as the substrates (**Figure S1**). Based on the above results, we assumed that the divergent radical C-H functionalization reactions were controlled by sulfonyl chlorides and that steric hindrance and electronic effect of sulfonyl chlorides played an important role in this process. Therefore, other bulky sulfonyl chlorides (2,4,6-trichlorobenzenesulfonyl or 2,6-dichlorobenzenesulfonyl chloride) and electron-deficient sulfonyl chlorides (pentafluorobenzenesulfonyl or trifluoromethanesulfonyl chloride) were evaluated for the synthesis of 4-quinolone (**Scheme S1**). To our delight, 4-quinolone **59** was obtained in 87% yield by employing trifluoromethanesulfonyl chloride as an oxidant (**Table 4**, entry 1). Further optimization of reaction conditions revealed that the copper catalyst and trifluoromethanesulfonyl chloride were crucial for the reaction (**Table 4**, entries 2 and 3). Reducing the amount of trifluoromethanesulfonyl chloride decreased the product yield (**Table 4**, entry 4). Changing the oxidant to di-*t*-butyl peroxide (DTBP), performing the reaction at room temperature, or reducing the reaction time to 0.5 hour resulted in lower yield of product **59** (**Table 4**, entries 5-7). It should be noted that 4-quinolone **59** could also be isolated in 86% yield when the C–H oxygenation/cyclization reaction was conducted under N_2 atmosphere (**Table 4**, entry 8). This result rules out the possibility that oxygen acted as an oxidant in this reaction.

Substrate scope for the synthesis of 4-quinolone. The optimized conditions (**Table 4**, entry 1) were then applied to investigate the substrate scope of copper-catalyzed C–H oxygenation/cyclization. As demonstrated in **Table 5**, the transformation of quinoline thioamides, possessing both electron-donating and electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-positions of the phenyl moieties, led to corresponding 4-quinolones **59-67** in 70-87% yields. The molecular structure of 4-quinolone **67** was confirmed by X-ray crystallographic analysis.[18] Meanwhile, the quinoline thioamides bearing both heterocyclyl and alkyl groups were suitable to afford target products (**68**–**71**) in moderate-to-good yields. Additionally, the quinoline thioamides with various substituted quinoline skeletons

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were studied, and the reaction proceeded well to give desired products (**72**–**74**) in 75–82% yield.

Scale-up studies of the developed methods. The reactions were amenable to scale to gram-scale to demonstrate the practical synthetic utility (**Figure 3a**). 2-Thioquinolone **3** and 4-quinolone **59** were successfully obtained in 83% and 81% yields, respectively, under the standard reaction conditions. It is important to note that gram-scale 2-quinolone **75** could also be obtained in good yield by a simple one-pot protocol.

Mechanistic investigations. We next performed a series of control experiments to study the reaction mechanism. First, the copper-catalyzed C–H sulfonylation/cyclization reaction was completely suppressed when radical inhibitors, such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), butylated hydroxytoluene (BHT) or 1,1-diphenylethylene (DPE) were introduced (**Figure 3b**). Furthermore, the formation of adducts **76** and **77** indicates the formation of sulfonyl radicals, as confirmed by electron spin resonance (ESR) spectroscopy (**Figure S2**). These results suggest that a radical pathway is responsible for the transformation. Copper(II) signal was also detected by ESR in the copper-catalyzed C–H sulfonylation/cyclization, indicating the involvement of single-electron transfer (**Figure S2**). In the reaction between quinoline thioamide **1a** and 2,4,6-trimethylbenzenesulfonyl chloride **2w**, we also observed a 27% yield of byproduct thiosulfonate **78**, with the exception of 4-quinolone **59** (**Figure 3c**). An ^{18}O-labeling experiment was performed using ^{18}O-labeled 2-methylbenzene sulfonyl chloride **2p**–^{18}**O** as the oxidant. The successful detection of ^{18}O-labeled 4-quinolone **59**–^{18}**O** confirmed that the oxygen atom of 4-quinolone originated from the sulfonyl chloride in this reaction (**Figure 3d**).

To further investigate the feasibility of the two mechanistic pathways, we then conducted a computational analysis of the copper-catalyzed C–H functionalization/cyclization reactions (**Figure 4 and Figure S6**). First, Cu^{I}I interacts with sulfonyl chloride via a single-electron-transfer (SET) process to give a sulfonyl radical **A** ($PhSO_2\cdot$) with the realease of Cu^{II}ICl, which then coordinates with substrate **1** to produce a stabilized copper complex **B**.[19] Subsequently, the sulfonyl radical **A** attacks the C4 position of the quinoline ring and overcomes an energy barrier of 15.1 kcal/mol to generate an intermediate **C**. Subsequent attack of nitrogen on the electrophilic carbon of thiocarbonyl group via **TSde** leads to an imidazole ring, with an energy barrier of 26.9 kcal/mol. This is the rate-determining step. Compared to other modes involving a different catalyst and coordination site, Cu^{II} provides significant stabilization through coordination with the S atom (**Figure S7-8**). The imidazole ring **E** generates along with the elongated C=S bond, promoting the desulfuration to form the radical anion via **TSef**.[20] A stepwise mechanism in which Cu^{II} abstracts the S atom. Subsequent attack of the radical anion at the C2 position via **TSfg** generates an intermediate **G**. In contrast, a concerted mechanism via a four-membered ring transition state with high energy barrier (**Figure S9**, **TSef-4r**). A spin density plot shows the radical transfer from the S atom to the C3 position of quinoline (**Figure S10**). **G** then coordinates with Cu^{II} to generate **H**, which then undergoes three steps of dehydrogenation. The hydrogen at the C2-position of quinoline is plucked by the Cu^{II} catalyst, leading to a stable intermediate **I**. Subsequent deprotonation of NH to form intermediate **J** is thermodynamically uphill. The last hydrogen at the C4 position of quinoline is abstracted by a sulfonyl radical to generate the product, along with a Cu^{II}/Cu^{I} redox process.

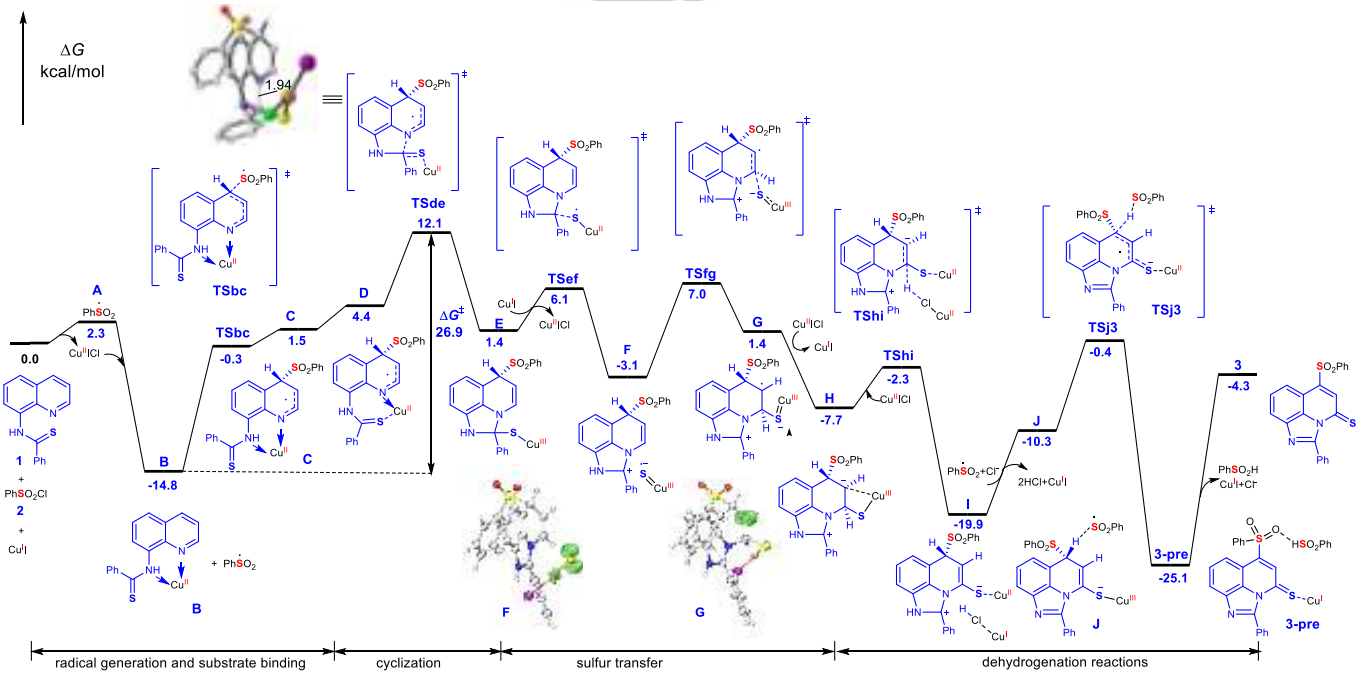

Figure 4. Computational analysis for copper-catalyzed C–H sulfonylation/cyclization (the enerngy in magenta is for CF_3SO_2Cl). (The electronic energy: ΔE (TSbc)-ΔE (C)= 0.1 kcal/mol).

When benzenesulfonyl chloride **2b** was replaced by bulky sulfonyl chloride **2w**, compound **78** was formed as a byproduct (**Figure 3c**). We assume that it is formed by the reduction of disulfone.[21] For 2,4,6-Me_3PhSO_2Cl (**2w**) and CF_3SO_2Cl, the energy barrier is high when following the same pathway as $PhSO_2Cl$ (37.3 kcal/mol and 28.5 kcal/mol, respectively , **Figure S6**). The significantly high energy barrier of the former could be due to steric hindrance of the 2,4,6-trimethylphenyl group. A new mechanism involving the formation of thiosulfonate (RSO_2SR) was proposed. The calculated thermodynamics of the reaction with CF_3SO_2Cl is 12.0 kcal/mol more favorable than $PhSO_2Cl$ (**Scheme S4**). In addition, the redox potential suggests that $CF_3SO_2SO_2CF_3$ is a stronger oxidant than $PhSO_2SO_2Ph$ (**Scheme S4**). The sulfur atom of the thioamide, which exits in the form of $HSCu^{II}$, is further oxidized to produce sulfur and SO_2 (**Scheme S4 and Figure S11**). This is consistent with the experimentally observed precipitate and the detected SO_2 (**Scheme S1 and Figure 3e**). In contrast, the reaction of $PhSO_2Cl$ is thermodynamically unfavorable because the final oxidation step is largely endogenous.

Conclusion

In summary, we have reported a sulfonyl chloride-controlled divergent radical C–H functionalization/cyclization of quinoline under copper catalysis. Using different sulfonyl chlorides, a variety of substrates can be selectively and smoothly converted to give 2-thioquinolone and 4-quinolone derivatives in moderate to good yields. Based on the control experiments and DFT calculations, a single-electron transfer mechanism is proposed. The steric effect of sulfonyl chloride and the oxidative capacity of thiosulfonate determine the selectivity. This transformation presents not only a new example of small molecule-directed divergent synthesis but also a versatile approach for the selective synthesis of quinolone derivatives.

Experimental Section

General procedure for the synthesis of 2-thioquinolone through C-H sulfonylation/cyclization. A mixture of thioamide (**1**) (0.2 mmol), sulfonyl chloride (**2**) (2.0 equiv.), CuI (10 mol%) and 1,2-dichloroethane (2.0 mL) in a 15-mL tube was stirred under air for 1 h. After completing the reaction as indicated by thin-layer chromatography (TLC), a saturated $NaHCO_3$ solution was added to the reaction mixture. The mixture was then extracted with dichloromethane, and the collected organic layer was washed with brine, and dried with $MgSO_4$. The solvent was removed in vacuo, and the obtained residue was further purified by silica gel column chromatography (200-300 mesh silica gel).

General procedure for the synthesis of 4-quinolone through C-H oxygenation/cyclization. A mixture of thioamide (**1**) (0.2 mmol), trifluoromethanesulfonyl chloride (**2z**) (2.0 equiv.), CuI (10 mol%) and 1,2-dichloroethane (2.0 mL) in a 15-mL tube was stirred under air for 1 h. After completing the reaction as indicated by thin-layer chromatography (TLC), a saturated $NaHCO_3$ solution was added to the reaction mixture. The mixture was then extracted with dichloromethane, and the collected organic layer was washed with brine, and dried with $MgSO_4$. The solvent was removed in vacuo, and the obtained residue was further purified by silica gel column chromatography (200-300 mesh silica gel).

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Conflict of interest

The authors declare no conflict of interest.

Supporting Information

Supplementary information is available from Wiley Online Library.

Keywords: divergent synthesis • copper catalysis • quinolones • radical C–H functionalization • C-S couplings

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