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Copper-Catalyzed Regioselective C−H Sulfonylation of 8-Aminoquinolines

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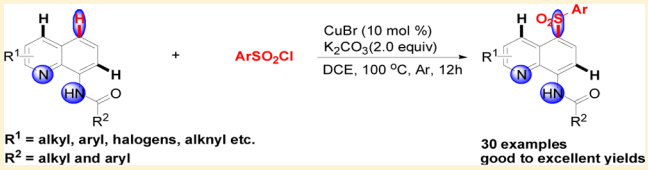
Supporting Information

ABSTRACT: Copper(I)-catalyzed 5-sulfonation of quinolines via bidentate-chelation assistance has been developed. The reaction is compatible with a wide range of quinoline substrates and arylsulfonyl chlorides. Experimental and theoretical (DFT) investigation implicated that a single-electron-transfer process is involved in this sulfonylation transformation.

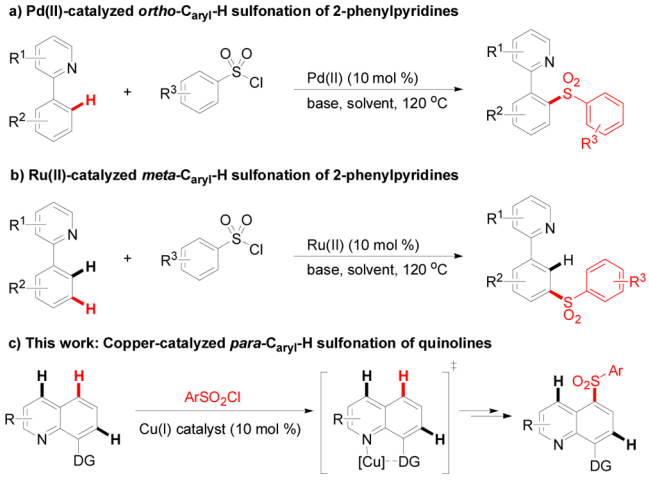


INTRODUCTION

Transition metal-catalyzed site-selective functionalization of unactive C−H bonds is emerging as an attractive methodology for the rapid construction of complex organic molecules.[1] In the past decades, σ-chelation-assisted cyclometalation strategy has been well established for achieving *ortho*-selective C−H functionalization.[2] Recent progress in transition metal-catalyzed *meta*-selective aryl C−H functionalization has also been accomplished. In this regards, Yu, Ackermann, and Dong et al. successively developed efficient *meta*-aryl C−H activation strategies to regioselectively construct C−C bonds employing a concealed directing group (DG),[3] *ortho*-metalation-triggered ArS_E,[4] a coordinating U-shaped template,[5] and others.[6] However, transition metal-catalyzed carbon-heteroatom bond forming-reactions through *para*-selective aryl C−H functionalization which is farther away from the directing group, remains highly sought.[7]

Aryl sulfones are commonly encountered in natural products, biologically active molecules, and material chemistry.[8] For example, sulfonyl-substituted quinoline derivatives belong to a kind of potent 5-HT_6 receptor antagonist for the treatment of CNs disorders.[9] Traditional cross-couplings of arylhalides,[10] arylboronic acids,[11] arylstannanes[12] arylzinc reagents,[13] etc. with sulfonyl partners are widely used to prepare arylsulfone compounds. Although regioselectivity in these cross-coupling reactions is not an issue, the tedious prior chemical transformations are required to obtain the prefunctionalized aryl partners. Therefore, much recent effort has been switched to the direct transition metal-catalyzed sulfonation of aryl C−H bonds. In this context, Dong reported Pd(II)-catalyzed *ortho*-selective aryl C−H bond activation/cross-coupling with arylsulfonyl chlorides to produce sulfones employing monodentate 2-pyridyl group as directing groups (Scheme 1a).[14] Interestingly, Frost further found changing the metal catalyst from Pd(II) to Ru(II) in the sulfonation of 2-phenylpyridines

Scheme 1. Ligand-Directed Regioselective Sulfonation of Arenes



led to the formation of *meta*-substituted products, in which Ru−C_{aryl} σ-bond played an important role in controlling the *meta*-selectivity (Scheme 1b).[4a] The above-mentioned remarkable switch in regioselectivity implies that bidentate-chelation-assisted cyclometalation could also possibly induce an unusual remote C_{aryl}-H bond functionalization via novel mechanistic pathways. In this communication, we described a direct approach for copper-catalyzed 5-sulfonation of quinolines based on the unique *para*-directed features of bidentate-chelation assistance (Scheme 1c).[15]

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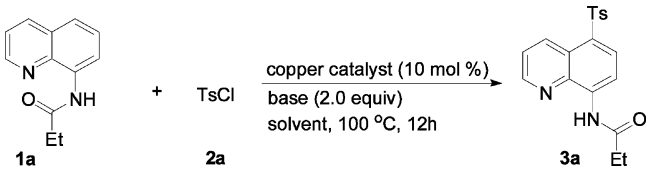
RESULTS AND DISCUSSION

In the first experiment demonstrating the feasibility of chelation-induced 5-sulfonation of quinolines, we began to explore the effect of various copper catalysts on the cross-coupling of 8-propionamido quinoline (**1a**) with *p*-toluenesulfonyl chloride (**2a**) in the presence of Na_2CO_3 (2.0 equiv) in CH_3CN under air condition at 100 °C for 12 h (Table 1, entries 1−7). As desired, all the investigated copper salts such as $CuCl_2$, $Cu(OAc)_2$, CuCl, etc. showed less to good catalytic activity for the sulfonation of quinoline **1a** at the 5-position, and CuBr proved to be the optimal catalyst which could bring us 35% yield of 8-propionamido-5-(4-tosyl)-quinoline (**3a**) (compare entries 1−6 with 7). Subsequently, we continued to evaluate various bases and solvents for further improving the sulfonation conversion of **1a**. Among them, employing K_2CO_3 as a base could significantly increase yield of **3a** from 35% to 49% (compare entries 7−11 with 12). Moreover, a slightly improvement of the reaction (74% yield of **3a**) was also achieved by employing 1,2-dichloroethane (DCE) as solvent (entries 12−18 vs 19). It should be noted that decreasing or increasing the reaction temperature could not further improve the reaction yield (entries 20−21 vs 19). Finally, considering that oxygen possibly deactivates the Cu(I) catalysts by oxidizing Cu(I) to Cu(II), we performed the transformation in Ar atmosphere and obtained the best yield of **3a** (79% yield, entries 19 and 23 vs 22). However, this reaction could not occur in the absence of copper catalysts or K_2CO_3 (entries 24 and 25).

Table 1. Optimization of the Cu(I)-Catalyzed Regioselective Sulfonation of Quinolines[a]

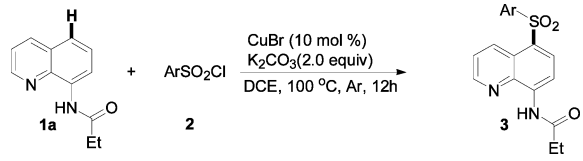


entry	copper catalyst	base	solvent	yield (%)[b]
1	$CuBr_2$	Na_2CO_3	CH_3CN	9
2	$CuCl_2$	Na_2CO_3	CH_3CN	11
3	$Cu(OAc)_2$	Na_2CO_3	CH_3CN	15
4	CuCN	Na_2CO_3	CH_3CN	19
5	CuCl	Na_2CO_3	CH_3CN	27
6	CuI	Na_2CO_3	CH_3CN	25
7	CuBr	Na_2CO_3	CH_3CN	35
8	CuBr	NaOAc	CH_3CN	27
9	CuBr	$NaHCO_3$	CH_3CN	20
10	CuBr	Cs_2CO_3	CH_3CN	30
11	CuBr	Li_2CO_3	CH_3CN	5
12	CuBr	K_2CO_3	CH_3CN	49
13	CuBr	K_2CO_3	toluene	trace
14	CuBr	K_2CO_3	ethyl acetate	62
15	CuBr	K_2CO_3	DMSO	0
16	CuBr	K_2CO_3	DMF	0
17	CuBr	K_2CO_3	1, 4-dioxane	0
18	CuBr	K_2CO_3	THF	67
19	CuBr	K_2CO_3	DCE	74
20	CuBr	K_2CO_3	DCE	56[c]
21	CuBr	K_2CO_3	DCE	71[d]
22	CuBr	K_2CO_3	DCE	79[e]
23	CuBr	K_2CO_3	DCE	28[f]
24	–	K_2CO_3	DCE	0[e]
25	CuBr	–	DCE	0[e]

[a]Unless otherwise noted, all the reactions were carried out using quinoline **1a** (0.10 mmol) with *p*-toluene sulfonyl chrolide **2a** (0.15 mmol) in solvent (1.0 mL) under air atmosphere at 100 °C for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield. [c]The reaction temperature is 80 °C. [d]The reaction temperature is 120 °C. [e]Under Ar atmosphere. [f]Under oxygen atmosphere.

To adapt the copper-catalyzed sulfonation conditions to more complex substrates, we investigated the scope of the current procedure by testing various sulfonyl chlorides in the reaction with 8-propionamido quinoline (**1a**). As shown in Table 2, the reactivity of arylsulfonyl chlorides (**2**) was partly dependent on the electronic and structural properties of substituted aryl groups. *Para*, *meta*, or *ortho* substitution of aryl rings with electron-donating group (Me and MeO) or electron-withdrawing halogen substituents did not significantly affect the sulfonation conversion and produced good to excellent yield of **3a**-**3h** (Table 2, entries 1−8, 62−83% yields). In contrast, the strong electron-withdrawing nitro or trifluomethyl group containing sulfonyl chlorides (**2i** and **2j**) afforded moderate yield of the arylsulfones **3i** and **3j** (Table 2, entries 9−10, 52−54% yields).

Table 2. Substrate Scope[a]



entry	quinoline (**1a**)	sulfonyl chloride (**2**)	product (**3**), yield[b]
1	**1a**	**2a:** Ar = 4-Me-Ph	**3a:** Ar = 4-Me-Ph, 79%
2	**1a**	**2b:** Ar = Ph	**3b:** Ar = Ph, 81%
3	**1a**	**2c:** Ar = 3-Me-Ph	**3c:** Ar = 3-Me-Ph, 68%
4	**1a**	**2d:** Ar = 2-Me-Ph	**3d:** Ar = 2-Me-Ph, 62%
5	**1a**	**2e:** Ar = 4-MeO-Ph	**3e:** Ar = 4-MeO-Ph, 83%
6	**1a**	**2f:** Ar = 4-Cl-Ph	**3f:** Ar = 4-Cl-Ph, 72%
7	**1a**	**2g:** Ar = 4-Br-Ph	**3g:** Ar = 4-Br-Ph, 77%
8	**1a**	**2h:** Ar = 2-Naphthyl	**3h:**Ar= 2-Naphthyl, 75%
9	**1a**	**2i:** Ar = 4-CF_3−Ph	**3i:** Ar = 4-CF_3−Ph, 54%
10	**1a**	**2j:** Ar = 4-NO_2−Ph	**3j:** Ar = 4-NO_2−Ph, 52%

[a]All the reactions were carried out using quinolines **1** (0.10 mmol) with sulfonyl chrolides **2** (0.15 mmol) in DCE (1.0 mL) under Ar atmosphere at 100 °C for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield.

Subsequently, the scope of the procedure with regard to various quinoline coupling partners was further evaluated with *p*-toluenesulfonyl chloride (**2a**) as the sulfonating reagent (Tables 3 and 4). Overall, the reaction tolerated a broad range of substituted quinolines to provide the corresponding 5-arylsulfonyl quinolines with good conversions. Remarkably, the reaction worked well for aliphatic amido or arylamido-substituted quinolines under our standard conditions and produced the corresponding sulfonation products in 66−80% yields, regardless of whether sterically hindered alkyl groups, electron-deficient or electron-rich phenyl groups were introduced into the amido moieties (Table 3, entries 1−10; Table 4, entries 1−2). It is worth noting that alkylamino-substituted quinolines are also suitable substrates for this transformation and provided around 80% yield of the sulfonation product **3v**

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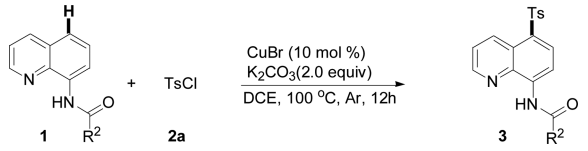
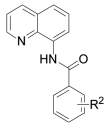
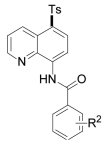
Table 3. Substrate Scope[a]



entry	quinoline (1)	sulfonyl chloride (2a)	product (3), yield [b]
1	**1b**, R^2 = Me	**2a**	**3k**, R^2 = Me, 71%
2	**1c**, R^2 = *n*Pr	**2a**	**3l**, R^2 = *n*Pr, 66%
3	**1d**, R^2 = *i*Pr	**2a**	**3m**, R^2 = *i*Pr, 68%
4	**1e**, R^2 = *s*Bu	**2a**	**3n**, R^2 = *s*Bu, 71%
5	**1f**, R^2 = *t*Bu	**2a**	**3o**, R^2 = *t*Bu, 68%
6	**1g**, R^2 = $ClCH_2$	**2a**	**3p**, R^2 = $ClCH_2$, 70%
		TsCl	
	1	**2a**	**3**
7	**1h**: R^2 = 4-H	**2a**	**3q**: R^2 = 4-H, 70%
8	**1i**: R^2 = 4-MeO	**2a**	**3r**: R^2 = 4-MeO, 80%
9	**1j**: R^2 = 4-Br	**2a**	**3s**: R^2 = 4-Br, 76%
10	**1k**: R^2 = 4-NO_2	**2a**	**3t**: R^2 = 4-NO_2, 75%

[a]All of the reactions were carried out using quinolines **1** (0.10 mmol) with sulfonyl chrolides **2** (0.15 mmol) in DCE (1.0 mL) under Ar atmosphere at 100 °C for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield.

and **3w**, but for the phenylamino-substituted quinoline **1l**, no reaction took place and starting material was recovered (Table 4, entry 1). Importantly, it still revealed that the reaction efficiency was maintained irrespective of the type of substitutes and substituted position in quinoline rings (Table 4). For examples, 2-methyl, 2-chloro, 2-phenyl, 4-methoxyl, 6-chloro, or 6-methyl-substituted quinoline substrates all allowed for this sulfonation and afforded the desired 5-arylsulfonyl quinolines in good yields (Table 4, entries 2−4, 70−77% yields). In addition, this reaction protocol could still smoothly convert 2-thienylsulfonyl chloride (**2k**) and 2-alknyl-substituted quinoline (**1u**) to the corresponding 5-(2-thienylsulfonyl)- quinoline **33c** and 2-alknyl-5-arylsulfonyl quinoline **33d** in good yields, respectively (Table 4, entries 4−5), but alkylsulfonyl chlorides were not allowed for this transformation.[16] Finally, the structure of the product **3b** was already unambiguously assigned by its single crystal X-ray analysis (see the SI for more details), and this compound (**3b**) could be further hydrolyzed to provide free (N−H) 8-amino-5-phenylsulfonyl-quinoline **3b-1** in 93% yield.

We then conducted several controlled reactions to further investigate the primary mechanism of the present transformation. The sulfonation of *N*-naphthalen-1-yl-propionamide (**1v**) and *N*-methyl-*N*-quinolin-8-yl-propionamide (**1w**) with *p*-toluenesulfonyl chloride (**2a**) was performed under our standard conditions, respectively, and no sulfonation products were monitored by the ^1H NMR and GC-MS methods (Scheme 2a,b). These results obviously implied the quinoline nitrogen and amide nitrogen played a key role in the chelation-directed sulfonation process. Moreover, 8-amidoquinoline (**1x**) which bears two methyl group in the 5 and 6 positions was not allowed for this reaction (Scheme 2c). Subsequently, using radical scavenger reagent TEMPO (2.0 equiv), the desired sulfonation reaction was completely suppressed, and also no sulfonation product **3a** was formed; the starting material **1a** was recovered in almost 100% yield (Scheme 2d). On the other hand, when the radical trapper 1,1-diphenylethylene **4a** was subjected to the standard reaction system, the 5-sulfonation of quinoline **1a** was suppressed to some degree, and the main product was the 1-(2,2-diphenyl-ethenesulfonyl)-4-methyl-benzene (**33h**, 72% yield, Scheme 2e). In addition, independent reactions of **1a** and *d*-**1a** exhibited nearly identical time courses (Figure S11), and no KIE was observed for this reaction (Scheme 2f, KIE ≈ 1). On the basis of these results, we may conclude that a free-radical-mediated process was most likely involved in our reaction system.

Taking these controlled experimental results into account, and in combination with the DFT calculations based on the regioselective sulfonation of quinoline **1a** with TsCl **2a** (for the detailed DFT calculations, see the SI), we proposed a plausible reaction mechanism for this novel transformation (Scheme 3). Starting from a Cu(I)-quinoline complex **A**, there may exist two pathways to generate the radical intermediate **D** via the intermolecular single electron transfer (SET) and the intramolecular SET. The intermolecular SET from **A** to TsCl produces a Cu(II) intermediate **B** and an arylsulfonyl radical, while the intramolecular SET within **A** forms a Cu(II) anion radical **C**. This anion radical **C** is clearly demonstrated by DFT, in which the d^9 Cu(II) center bears spin density of 0.77, and the heterocyclic anion radical residues 1.23 spin density (Figure 1). This intramolecular SET process is uphill by 14.6 kcal/mol. Instead, the intermolecular SET to arylsulfonyl radical[17] is more preferred (downhill by 26.4 kcal/mol). The subsequent radical addition of Ts● to **B** leads to a Cu(II) radical species **D**. DFT calculation revealed a spin density of 0.85 for the d^9 Cu(II) center and 1.05 for the heterocyclic radical, respectively (Figure 1). Then the deprotonation of **D** generates a Cu(II) anion radical **E**, which is further downhill by 21.4 kcal/mol. Both as Cu(II) anion radicals, species **E** has similar spin density distribution to **C** (Figure 1), however, species **E** is more stable than **C** along the reaction pathway, which should be attributed to the stabilization of anion by the arylsulfonyl group. Then an SET process transfer one electron from heterocyclic anion to Cu(II) center, yielding the Cu(I) species **F**, and finally the catalytic cycle will be regenerated by the release of product **3a**.

With an understanding of the reaction mechanism, we further studied the regioselectivity of sulfonylation. The radical addition of sulfonyl radical to quinoline occurs at **B** → **D**. The resonance structures of **B** are depicted at Figure 2, from which we can see that the 5 and 7 positions are more favored for radical addition. NBO charge also suggests that the 5 (−0.211) and 7 (−0.229) positions are more negative than the 6 position. Actually, a 6-sulfonyl substituted species was not able to locate during optimization, which automatically collapses to **B** and radical Ts● (Figure S12). The optimized 5- and 7-side radical addition transition states are shown in Figure 2. The 5-sulfonylation transition state **TS-*p*** is more stable than the 7-sulfonylation transition state **TS-*o***, indicating the *para* regioselectivity in the sulfonylation of quinolones.

In summary, we have reported a highly regioselective copper(I)-catalyzed 5-sulfonation of 8-amino quinoline derivatives via bidentate-chelation assistance. This method provides a useful tool for the rapid construction of 5-arylsulfonyl substituted quinolines. Moreover, we have also presented a detailed mechanism for this transformation based on DFT

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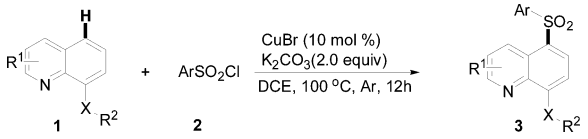
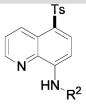
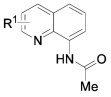
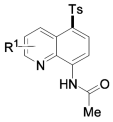
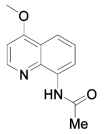
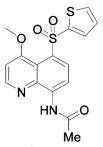
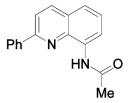
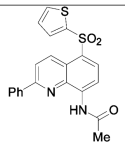
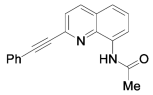
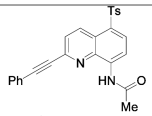
Table 4. Substrate Scope[a]



entry	quinoline (**1**)	sulfonyl chloride (**2**)	product (**3**), yield[b]
1	 **1**	TsCl **2a**	 **3**
	1l, R^2 = Ph	**2a**	**3u**, R^2 = Ph, 0%
	1m, R^2 = Bn	**2a**	**3v**, R^2 = Bn, 79%
	1n, R^2 = Me	**2a**	**3w**, R^2 = Me, 80%
2	 **1**	TsCl **2a**	 **3**
	1o, R^1 = 2-Me	**2a**	**3x**, R^1 = 2-Me, 77%
	1p, R^1 = 6-Me	**2a**	**3y**, R^1 = 6-Me, 77%
	1q, R^1 = 2-Cl	**2a**	**3z**, R^1 = 2-Cl, 75%
	1r, R^1 = 6-Cl	**2a**	**33a**, R^1 = 6-Cl, 70%
3	 **1s**	 **2k**	 **33b**, 74%
4	 **1t**	 **2k**	 **33c**, 70%
5	 **1u**	TsCl **2a**	 **33d**,73%

[a]All of the reactions were carried out using quinolines **1** (0.10 mmol) with sulfonyl chrolides **2** (0.15 mmol) in DCE (1.0 mL) under Ar atmosphere at 100 °C for 12 h in a sealed reaction tube, followed by flash chromatography on SiO_2. [b]Isolated yield.

calculations, in which a SET-based C−H sulfonation was proposed. Further applications to other heteroarene systems are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all experiments were performed under argon atmosphere. Solvents were treated with 4 Å molecular sieves or sodium and distilled prior to use. Flash chromatography was performed on silica gel (40−63 mm) by standard technique. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer (400 MHz for ^{1} H and 100 MHz for ^{13} C). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), and quartet (q). Splitting patterns that could not be interpreted or easily visualized are designated as multiple (m). Low resolution mass spectra were recorded using HPLC mass spectrometer. High resolution exact mass measurements (HR-MS) were performed on a TOF spectrometer. Infrared spectra (IR) were reported as wavelength numbers (cm^{-1}). Infrared spectra were recorded by preparing a KBr pellet containing the title compound. Crystal data were obtained by employing graphite monochromated Mo Kα radiation (λ = 1.54178 Å) at 293 (2) K and operating in the $\varphi-\omega$ scan mode. The structure was solved by direct methods SHELXS-97. Quinoline substrates including *N*-(quinolin-8-yl)propionamide (**1a**),[18] *N*-(quinolin-8-yl)acetamide (**1b**),[18] *N*-(quinolin-8-yl)butyramide (**1c**),[19] *N*-(quinolin-8-yl)-isobutyramide (**1d**),[19] 3-methyl-*N*-(quinolin-8-yl)butanamide (**1e**),[19] *N*-(quinolin-8-yl)pivalamide (**1f**),[18] 2-chloro-*N*-(quinolin-8-yl)-acetamide (**1g**),[20] *N*-(quinolin-8-yl)benzamide (**1h**),[21] 4-methoxy-*N*-(quinolin-8-yl)benzamide (**1i**),[21] 4-bromo-*N*-(quinolin-8-yl)-benzamide (**1j**),[21] 4-nitro-*N*-(quinolin-8-yl)benzamide (**1k**),[21] *N*-(2-methylquinolin-8-yl)acetamide (**1o**),[22] *N*-(6-methylquinolin-8-yl)-acetamide (**1p**),[23] *N*-(2-chloroquinolin-8-yl)acetamide (**1q**),[22] *N*-(6-chloroquinolin-8-yl)acetamide (**1r**),[22] *N*-phenylquinolin-8-amine (**1l**),[23] *N*-benzylquinolin-8-amine (**1m**),[24] *N*-methylquinolin-8-amine (**1n**),[24] *N*-(naphthalen-1-yl)propionamide (**1v**),[25] *N*-methyl-*N*-(quinolin-8-yl)propionamide (**1w**),[26] and 8-amino-5,7-dideuteroquinoline (***D*-1**),[27] were prepared using the previous reported procedure. All of the arylsulfonyl substrates are commercially available.

Procedures for the Preparation of Quinoline Substrates (1s, 1t, 1u, and 1x). *General Procedure for the Synthesis of 1s, 1t, and 1x.* To a solution of the corresponding 8-amidoquinoline[28] (0.9 mmol, 1.0 equiv) in $CHCl_3$ (2 mL) was added dropwise the solution of CH_3COCl (0.9 mmol, 1.0 equiv) in $CHCl_3$ (1.0 mL) at 0 °C, and the resulting solution was stirred for 3 h at room temperature. After the

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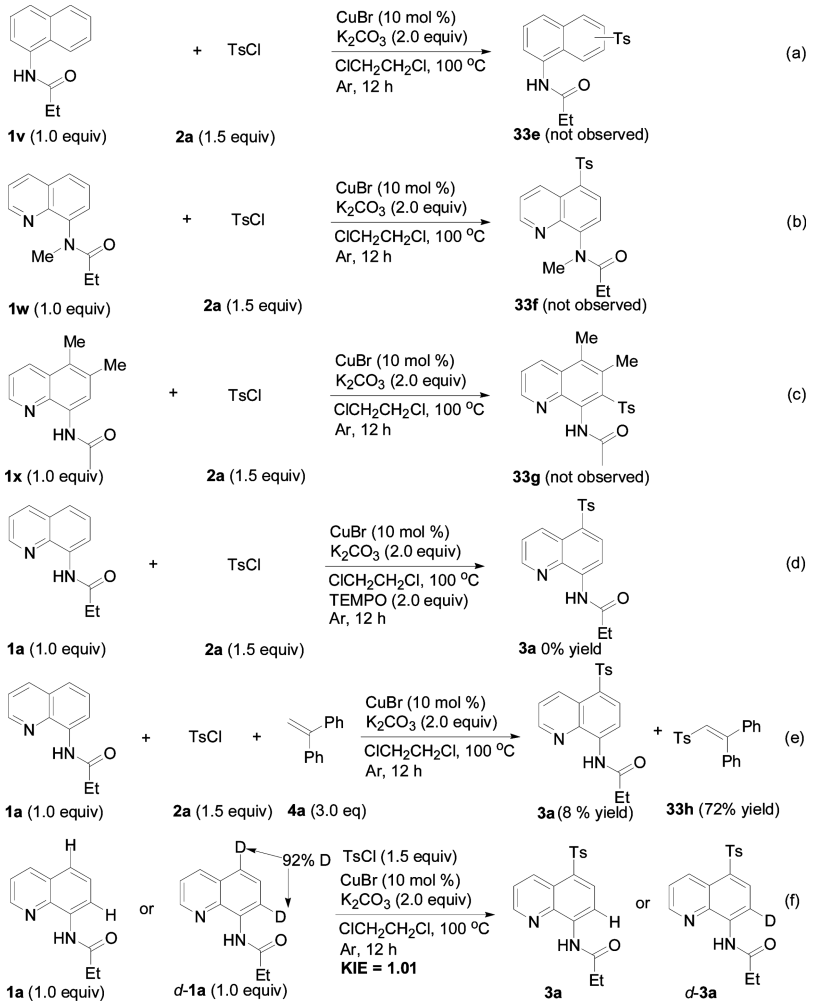
Scheme 2. Several Controlled Experiments about This Transformation



solvent was removed under vacuum, the corresponding resulting residue was then added to 5 mL of saturated aqueous sodium bicarbonate solution and extracted with CH_2Cl_2 (3 × 10 mL). The corresponding combined organic layers were dried over Na_2SO_4 and concentrated. The resulting crude product was purified by flash column chromatography using 25% to 50% (v/v) ethyl acetate in petroleum ether as eluent to afford the desired quinoline substrates (**1s**, **1t**, and **1x**).

*N-(4-Methoxyquinolin-8-yl)acetamide (**1s**).* White solid; mp = 119−120 °C; 173 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.73 (d, J = 7.6 Hz, 1H), 8.59 (d, J = 5.1 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.1 Hz, 1H), 6.73 (d, J = 5.1 Hz, 1H), 4.01 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.6, 149.1, 139.1, 134.2, 126.2, 120.9, 116.8, 115.5, 100.7, 55.8, 25.1; IR (KBr): 3347, 2922, 1680, 1529, 1071, 676 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$: $C_{12}H_{12}N_2NaO_2$: 239.0791, found: 239.0798.

*N-(2-Phenylquinolin-8-yl)acetamide (**1t**).* Yellow liquid; 213 mg, 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.72 (d, J = 7.3 Hz, 1H), 8.03 (dd, J = 14.5, 8.0 Hz, 3H), 7.74 (d, J = 8.5 Hz, 1H), 7.55−7.44 (m, 3H), 7.43−7.34 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 154.9, 138.9, 137.7, 137.1, 134.5, 129.6, 128.9, 127.4, 127.1, 126.7, 121.2, 119.1, 116.6, 25.2; IR (KBr): 3352, 2920, 1735, 1528, 1171, 762 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{17}H_{15}N_2O$: 263.1179, found: 263.1181.

*N-(5,6-Dimethylquinolin-8-yl)acetamide (**1x**).* Brown solid; mp = 80.2−80.3 °C; 177 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.65 (s, 1H), 8.54 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.38−7.31 (m, 1H), 2.41 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 146.4, 137.3, 134.6, 132.3, 132.0, 127.1, 125.0, 121.0, 119.4, 25.1, 21.0, 13.6. IR (KBr): 3444, 2962, 1760, 1442, 1380, 776 cm^{-1}. HRMS (ESI) calcd for $[M + H]^+$: $C_{13}H_{15}N_2O$: 215.1179, found: 215.1188

*N-[2-(Phenylethynyl)quinolin-8-yl]acetamide (**1u**).* Step 1:[29] Et_3N (3 mmol, 1.5 equiv) in MeCN (4 mL) was added to the solution of 2-chloro-8-nitroquinoline (2 mmol, 1.0 equiv), terminal alkyne (2.2 mmol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (1 mol %), and CuI (3 mol %). The mixture was then refluxed under Ar atmosphere for 16 h at 110 °C. After the solvent was removed under vacuum, and 1 mL of H_2O was added, then the resulting residue was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting residue was further purified by flash column chromatography using 20% (v/v) ethyl acetate in petroleum ether as eluent to afford 8-nitro-2-phenylethynyl-quinoline (**1u-1**) as a brown oil (493 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.3 Hz, 1H), 7.99 (t, J = 8.1 Hz, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.65−7.52 (m, 3H), 7.48−7.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 146.0, 139.6, 136.1, 132.4, 131.7, 129.6, 128.5, 127.7, 126.3, 125.6, 124.3, 121.7, 92.2, 89.1; IR (KBr): 3467, 2921, 2209, 1636, 1145, 756 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{17}H_{11}N_2O_2$: 275.0815, found: 275.0818.

Step 2: Fe (18 mmol, 10.0 equiv) and NH_4Cl (21.6 mmol, 12.0 equiv) were added to the solution of **1u-1** (1.8 mmol, 1.0 equiv) in CH_3CH_2OH/H_2O (2:1), and the mixture was refluxed for 2 h at 100 °C. Then 2 mL of saturated aqueous sodium bicarbonate solution was added, and the corresponding was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concerted in vacuum, the resulting crude products were purified by flash chromatography on silical gel using 25% (v/v) ethyl acetate in

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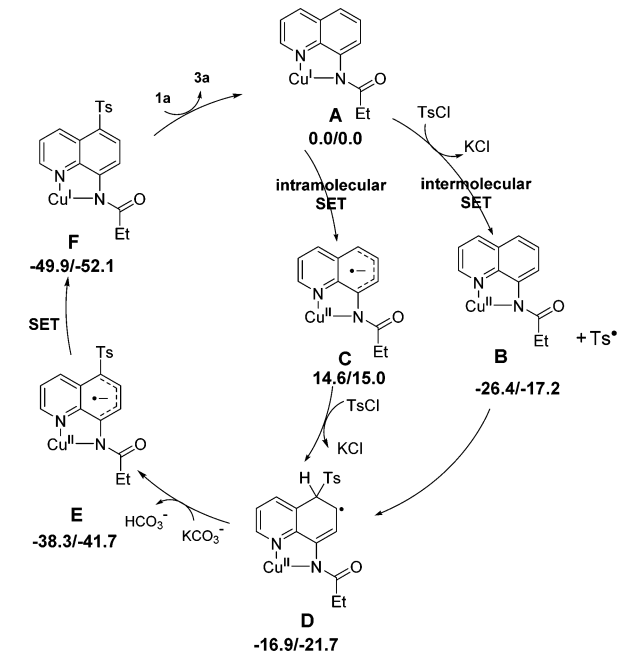
Scheme 3. Proposed Mechanism for the Copper-Catalyzed Sulfonylation of Quinolines[a]



[a]$\Delta G/\Delta H$ are given in kcal/mol; carbonate and counterions are omitted for clarity.

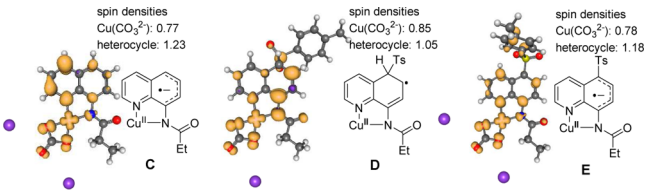


Figure 1. Electronic structures of radical intermediates **C**, **D**, and **E**.

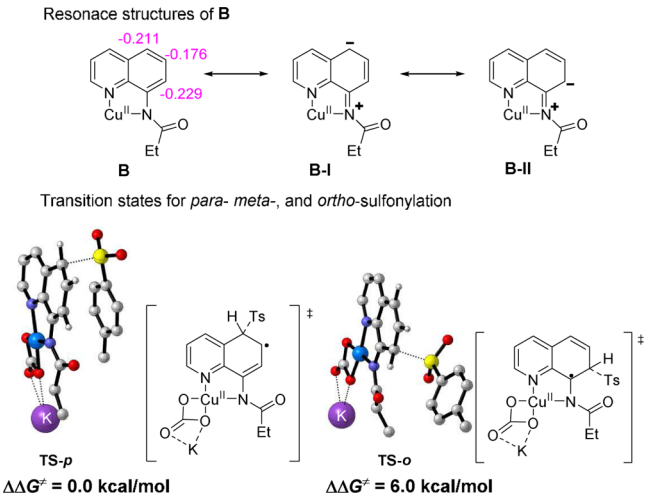


Figure 2. Regioselectivity of copper-catalyzed regioselective sulfonylation of quinolones (Data in purple is NBO charge).

petroleum ether as eluent to afford 2-phenylethynyl-quinolin-8-ylamine (**1u-2**) as a brown oil (246 mg, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 2.5 Hz, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 1.7 Hz, 3H), 7.29 (t, J = 7.9 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 5.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 140.4, 138.4, 136.0, 132.2, 129.1, 128.5, 128.3, 127.8, 124.6, 122.4, 115.6, 110.5, 89.9, 89.2; IR (KBr): 3472, 2921, 2209, 1599, 1155, 752 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{17}H_{13}N_2$: 245.1073, found: 245.1073.

Step 3: The solution of CH_3COCl (1 mmol, 1.0 equiv) in $CHCl_3$ (1 mL) was added dropwise to a solution of **1u-2** (1 mmol, 1.0 equiv) in $CHCl_3$ (2 mL) at 0 °C, and the resulting solution was stirred for 3 h at room temperature. After the solvent was removed under vacuum, 5 mL of saturated aqueous sodium bicarbonate solution was added to the corresponding resulting residue, and the corresponding mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The resulting crude product was purified by flash column chromatography using 25% (v/v) ethyl acetate in petroleum ether as eluent to afford **1u** as a white solid.

*N-[2-(Phenylethynyl)quinolin-8-yl]acetamide (**1u**).* White solid; mp = 102−103 °C; 286 mg, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.79 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.71−7.63 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.42 (dd, J = 14.0, 6.6 Hz, 4H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 141.4, 138.2, 136.4, 134.2, 132.2, 129.4, 128.5, 128.1, 126.8, 124.9, 121.9, 121.2, 117.0, 90.3, 89.3, 25.2; IR (KBr): 3467, 2920, 2190, 1632, 1240, 678 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{15}N_2O$: 287.1179, found: 287.1182.

*General Procedure for the Synthesis of Compounds **3a−3z, 33a, 33b, 33c**, and **33d**.* The reaction mixture of *N*-(quinolin-8-yl) carboxamide **1** (0.1 mmol, 1.0 equiv), arylsulfonyl chlorides **2** (0.15 mmol, 1.5 equiv), K_2CO_3 (0.2 mmol, 2 equiv), and CuBr (0.01 mmol, 10 mol %) in 1.0 mL of DCE in a tube was stirred under Ar atmosphere at 100 °C for 12 h, and the reaction progress was monitored by TLC method. After the starting materials disappeared, the corresponding reaction mixture was then cooled to room temperature, and 1.0 mL of H_2O was added and then extracted with CH_2Cl_2 (3 × 10 mL). The corresponding combined organic layers were dried over Na_2SO_4 and concentrated under vacuum, and the resulting crude products were purified by flash chromatography on silical gel using 25% (v/v) ethyl acetate in petroleum ether as eluent to afford the desired **3**.

*N-(5-Tosylquinolin-8-yl)propionamide (**3a**).* Yellow solid; mp = 153−154 °C; 27.9 mg, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.03 (d, J = 8.6 Hz, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.80 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.57−7.50 (m, 1H), 7.25 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 148.6, 144.2, 139.8, 139.0, 137.9, 133.4, 131.9, 129.9, 129.1, 127.3, 124.2, 123.3, 114.0, 25.2, 21.5; IR (KBr): 3416, 3132, 1648, 1400, 1148, 621 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{19}N_2O_3S$: 355.1111, found: 355.1114.

*N-[5-(Phenylsulfonyl)quinolin-8-yl]propionamide (**3b**).* Yellow solid; mp = 195.5−195.7 °C; 27.5 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.04 (d, J = 8.6 Hz, 1H), 8.90 (d, J = 8.3 Hz, 1H), 8.82 (s, 1H), 8.53 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 7.4 Hz, 2H), 7.54 (dd, J = 12.4, 6.0 Hz, 2H), 7.48 (t, J = 7.2 Hz, 2H), 2.64 (q, J = 7.3 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 148.6, 141.9, 140.1, 137.9, 133.3, 133.1, 132.3, 129.3, 128.5, 127.1, 124.2, 123.3, 114.0, 31.3, 9.5; IR (KBr): 3483, 3129, 1694, 1313, 1147, 723 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{17}N_2O_3S$: 341.0954, found: 341.0960.

*N-[5-(m-Tolylsulfonyl)quinolin-8-yl]propionamide (**3c**).* Yellow solid; mp = 198−198.7 °C; 24 mg, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 9.03 (d, J = 8.5 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.81 (d, J = 2.4 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.70 (s, 1H), 7.55 (dd, J = 8.5, 4.0 Hz, 1H), 7.38−7.30 (m, 2H), 2.62 (q, J = 7.4 Hz, 2H), 2.36 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 148.6, 141.8, 140.0, 139.6, 138.0, 134.0, 133.4, 132.2, 129.1, 128.6, 127.5, 124.3, 123.3, 114.0, 31.3, 21.4, 9.5; IR (KBr):3412, 3129, 1700, 1316, 1145, 699 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{19}N_2O_3S$: 355.1111, found: 355.1117.

*N-[5-(o-Tolylsulfonyl)quinolin-8-yl]propionamide (**3d**).* Yellow solid; mp = 179.7−180.6 °C; 21.9 mg, 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.90 (d, J = 8.3 Hz, 1H), 8.82 (dd, J =

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9.8, 6.2 Hz, 2H), 8.48 (d, J = 8.4 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.50 (dd, J = 8.5, 4.0 Hz, 1H), 7.47−7.34 (m, 2H), 7.19 (d, J = 7.0 Hz, 1H), 2.64 (dd, J = 14.7, 7.2 Hz, 2H), 2.41 (s, 3H), 1.34 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 148.6, 139.9, 139.6, 138.0, 137.9, 133.6, 133.2, 133.0, 132.7, 128.9, 128.1, 126.5, 124.2, 123.2, 113.6, 31.3, 20.1, 9.5; IR (KBr): 3321, 3062, 1697, 1315, 1149, 702 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{19}N_2O_3S$: 355.1111, found: 355.1112.

N-{5-[(4-Methoxyphenyl)sulfonyl]quinolin-8-yl}propionamide (**3e**). Yellow solid; mp = 186.2 °C; 30.7 mg, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 9.04 (d, J = 8.6 Hz, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.80 (d, J = 3.1 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.54 (dd, J = 8.7, 4.1 Hz, 1H), 6.92 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 2.62 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 163.3, 148.6, 139.7, 138.0, 133.4, 133.4, 131.7, 129.5, 129.4, 124.1, 123.2, 114.5, 114.0, 55.6, 31.3, 9.5; IR (KBr): 3411, 3129, 1700, 1315, 1144, 699 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{19}N_2O_4S$: 371.1060, found: 371.1063.

N-{5-[(4-Chlorophenyl)sulfonyl]quinolin-8-yl}propionamide (**3f**). Yellow solid; mp = 162.3−162.9 °C; 27 mg, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.99 (d, J = 8.7 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.83 (d, J = 2.8 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 8.6, 4.0 Hz, 1H), 7.43 (d, J = 8.4 Hz, 2H), 2.63 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 148.7, 140.5, 140.3, 139.8, 138.0, 133.1, 132.5, 129.6, 128.6, 128.0, 124.2, 123.5, 114.0, 31.3, 9.5; IR (KBr): 3442, 3133, 1670, 1314, 1140, 703 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{16}ClN_2O_3S$: 375.0565, found: 375.0567.

N-{5-[(4-Bromophenyl)sulfonyl]quinolin-8-yl}propionamide (**3g**). Yellow solid; mp = 167.6−167.7 °C; 32 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.98 (d, J = 8.6 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 8.82 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 16.1, 6.3 Hz, 3H), 2.63 (q, J = 7.5 Hz, 2H), 1.33 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 148.7, 141.1, 140.3, 138.0, 133.1, 132.6, 132.5, 128.7, 128.3, 127.9, 124.1, 123.5, 114.0, 31.3, 9.5; IR (KBr): 3405, 3089, 1699, 1313, 1142, 686 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{16}BrN_2O_3S$: 419.0060, found: 419.0059.

N-[5-(Naphthalen-2-ylsulfonyl)quinolin-8-yl]propionamide (**3h**). Yellow solid; mp = 160.4 °C; 29.2 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.07 (d, J = 8.7 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.74 (s, 1H), 8.65−8.46 (m, 2H), 7.93 (d, J = 5.9 Hz, 1H), 7.79 (dd, J = 26.7, 8.6 Hz, 3H), 7.55 (s, 2H), 7.49 (dd, J = 8.2, 3.7 Hz, 1H), 2.61 (q, J = 7.4 Hz, 2H), 1.31 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 148.6, 140.1, 138.8, 137.9, 134.9, 133.2, 132.4, 132.1, 129.7, 129.3, 129.2, 128.4, 127.9, 127.7, 124.2, 123.4, 122.3, 114.0, 31.3, 9.5; IR (KBr): 3414, 3113, 1699, 1314, 1146, 682 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{22}H_{19}N_2O_3S$: 391.1111, found: 391.1116.

N-{5-[4-(Trifluoromethyl)phenyl)sulfonyl]quinolin-8-yl}-propionamide (**3i**). Yellow solid; mp = 196.4−197.1 °C; 22 mg, 54% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.09 (s, 1H), 9.01 (d, J = 8.6 Hz, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.85 (d, J = 2.7 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.59 (dd, J = 8.6, 4.1 Hz, 1H), 2.65 (q, J = 7.5 Hz, 2H), 1.35 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 148.8, 145.6, 140.6, 138.0, 133.0, 132.9, 127.7, 127.2, 126.5, 126.5, 126.4, 126.4, 124.3, 123.6, 114.0, 31.3, 9.4; IR (KBr): 3409, 3126, 1756, 1318, 1139, 706 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{16}F_3N_2O_3S$: 409.0828, found: 409.0833.

N-[5-(4-Nitrophenyl)sulfonyl)quinolin-8-yl]propionamide (**3j**). Yellow solid; mp = 204.6−205 °C; 20 mg, 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 9.01 (d, J = 8.6 Hz, 1H), 8.96 (d, J = 8.5 Hz, 1H), 8.88 (s, 1H), 8.58 (d, J = 8.5 Hz, 1H), 8.32 (d, J = 7.3 Hz, 2H), 8.13 (d, J = 7.5 Hz, 2H), 7.64−7.58 (m, 1H), 2.70−2.61 (m, 2H), 1.35 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 150.2, 148.9, 147.8, 140.9, 138.0, 133.4, 132.8, 128.4, 126.6, 124.5, 124.3, 123.7, 114.1, 31.3, 9.4; IR (KBr): 3412, 3115, 1623, 1318, 1146, 618 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{16}N_3O_5S$: 386.0805, found: 386.0804.

N-(5-Tosylquinolin-8-yl)acetamide (**3k**). Yellow solid; mp = 175.1−175.4 °C; 24 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.03 (d, J = 8.6 Hz, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.80 (d, J = 2.1 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.57−7.50 (m, 1H), 7.25 (d, J = 8.0 Hz, 2H), 2.37 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 148.6, 144.2, 139.8, 139.0, 137.9, 133.4, 131.9, 129.9, 129.1, 127.3, 124.2, 123.3, 114.0, 25.2, 21.5; IR (KBr): 3340, 3118, 1698, 1314, 1146, 685 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{17}N_2O_3S$: 341.0954, found: 341.0955.

N-(5-Tosylquinolin-8-yl)butyramide (**3l**). Yellow solid; mp = 150.2−150.3 °C; 24.3 mg, 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 9.04 (d, J = 8.7 Hz, 1H), 8.88 (d, J = 8.4 Hz, 1H), 8.81 (d, J = 2.1 Hz, 1H), 8.49 (d, J = 8.3 Hz, 1H), 7.81 (d, J = 7.7 Hz, 2H), 7.54 (dd, J = 8.3, 3.7 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.85 (dd, J = 14.7, 7.3 Hz, 2H), 1.05 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 148.6, 144.1, 139.9, 139.1, 138.0, 133.4, 132.0, 129.9, 129.0, 127.3, 124.2, 123.2, 114.0, 40.1, 21.5, 18.9, 13.7; IR (KBr): 3337, 2923, 1697, 1315, 1146, 688 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{20}H_{21}N_2O_3S$: 369.1267, found: 369.1271.

N-(5-Tosylquinolin-8-yl)isobutyramide (**3m**). Yellow solid; mp = 186.4−187 °C; 25 mg, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 9.04 (d, J = 8.7 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.82 (d, J = 3.6 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.55 (dd, J = 8.6, 4.0 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 2.78 (dt, J = 13.7, 6.8 Hz, 1H), 2.36 (s, 3H), 1.35 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 148.6, 144.1, 140.0, 139.1, 138.2, 133.5, 132.1, 129.9, 129.0, 127.2, 124.2, 123.2, 114.1, 37.2, 21.5, 19.5; IR (KBr): 3442, 3136, 1667, 1333, 1149, 674 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{20}H_{21}N_2O_3S$: 369.1267, found: 369.1279.

3-Methyl-N-(5-tosylquinolin-8-yl)butanamide (**3n**). Yellow oil; 27.1 mg, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.04 (d, J = 8.7 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.81 (d, J = 4.0 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.54 (dd, J = 8.6, 4.0 Hz, 1H), 7.25 (d, J = 7.9 Hz, 2H), 2.45 (d, J = 7.1 Hz, 2H), 2.35 (s, 3H), 2.29 (dd, J = 13.3, 6.7 Hz, 1H), 1.06 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 148.6, 144.1, 139.8, 139.1, 138.0, 133.4, 132.0, 129.9, 129.0, 127.3, 124.2, 123.2, 114.1, 47.5, 26.2, 22.5, 21.5; IR (KBr): 3342, 3130, 1695, 1315, 1145, 684 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{21}H_{23}N_2O_3S$: 383.1424, found: 383.1426.

N-(5-Tosylquinolin-8-yl)pivalamide (**3o**). Yellow solid; mp = 179.2−179.4 °C; 26 mg, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 9.04 (d, J = 8.7 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.84 (d, J = 3.4 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 7.7 Hz, 2H), 7.56 (dd, J = 8.5, 3.9 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 148.7, 144.1, 140.1, 139.1, 138.5, 133.4, 132.0, 129.9, 128.9, 127.9, 127.2, 124.2, 123.3, 113.9, 40.6, 27.6, 21.5; IR (KBr): 3340, 3123, 1681, 1311, 1145, 690 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{21}H_{23}N_2O_3S$: 383.1424, found: 383.1427.

2-Chloro-N-(5-tosylquinolin-8-yl)acetamide (**3p**). Yellow solid; mp = 165.3−165.6 °C; 26.2 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1H), 9.05 (d, J = 8.7 Hz, 1H), 8.89−8.80 (m, 2H), 8.48 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.56 (dd, J = 8.5, 4.0 Hz, 1H), 7.26 (d, J = 7.5 Hz, 2H), 4.32 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 149.1, 144.3, 138.8, 138.8, 138.5, 133.4, 131.6, 130.5, 129.9, 127.3, 124.2, 123.4, 114.4, 43.3, 21.5; IR (KBr): 3355, 3052, 1685, 1325, 1175, 682 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{16}ClN_2O_3S$: 375.0565, found: 375.0568.

N-(5-Tosylquinolin-8-yl)benzamide (**3q**). Yellow solid; mp = 168.1−168.6 °C; 28.1 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 9.05 (dd, J = 16.7, 8.5 Hz, 2H), 8.86 (d, J = 2.5 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 7.1 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.58 (dd, J = 14.9, 6.9 Hz, 4H), 7.26 (d, J = 7.7 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 148.8, 144.2, 139.9, 139.0, 138.5, 134.3, 133.5, 132.5, 132.0, 129.9, 129.4, 129.0, 127.4, 127.3, 124.3, 123.4, 114.2, 21.5; IR (KBr): 3442, 3118, 1698, 1314, 1147, 686 cm $^{-1}$; HRMS (ESI) calcd for $[M + H]^+$: $C_{23}H_{19}N_2O_3S$: 403.1111, found: 403.1114.

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*4-Methoxy-N-(5-tosylquinolin-8-yl)benzamide (**3r**).* Yellow solid; mp = 186.9−187.1 °C; 34.6 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.89 (s, 1H), 9.07 (d, J = 8.7 Hz, 1H), 9.01 (d, J = 8.4 Hz, 1H), 8.87 (s, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 7.8 Hz, 2H), 7.57 (dd, J = 8.4, 3.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.3 Hz, 2H), 3.89 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 163.0, 148.7, 144.1, 140.2, 139.1, 138.4, 133.5, 132.1, 129.9, 129.4, 129.0, 127.3, 126.5, 124.3, 123.3, 114.2, 114.0, 55.5, 21.5; IR (KBr): 3442, 3128, 1676, 1315, 1145, 684 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{24}H_{21}N_2O_4S$: 433.1217, found: 433.1213.

*4-Bromo-N-(5-tosylquinolin-8-yl)benzamide (**3s**).* Yellow solid; mp = 185.9−186.2 °C; 36.5 mg, 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 9.08 (d, J = 8.7 Hz, 1H), 8.99 (d, J = 8.3 Hz, 1H), 8.87 (s, 1H), 8.54 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H), 7.58 (dd, J = 8.0, 3.8 Hz, 1H), 7.27 (d, J = 6.9 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 148.8, 144.2, 139.6, 139.0, 138.4, 133.6, 133.2, 132.2, 132.0, 129.9, 129.7, 129.0, 127.3, 124.3, 123.4, 114.4, 21.5; IR (KBr): 3442, 3131, 1681, 1318, 1145, 682 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{23}H_{18}BrN_2O_3S$: 481.0216, found: 481.0211.

*4-Nitro-N-(5-tosylquinolin-8-yl)benzamide (**3t**).* Yellow solid; mp = 169.5−169.7 °C; 33.5 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (s, 1H), 9.11 (d, J = 8.7 Hz, 1H), 9.00 (d, J = 8.3 Hz, 1H), 8.89 (d, J = 3.9 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.41 (d, J = 8.1 Hz, 2H), 8.23 (d, J = 8.3 Hz, 2H), 7.84 (d, J = 7.9 Hz, 2H), 7.61 (dd, J = 8.5, 4.0 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 150.1, 149.0, 144.4, 139.8, 139.1, 138.8, 138.4, 133.8, 131.8, 130.5, 130.0, 128.6, 127.4, 124.3, 124.2, 123.5, 114.7, 21.5; IR (KBr):3442, 3125, 1691, 1316, 1146, 684 cm^{-1}; HRMS (ESI) calcd for $[M + Na]^+$: $C_{23}H_{17}N_3NaO_5S$: 470.0781, found: 470.0787.

*N-Benzyl-5-tosylquinolin-8-amine (**3v**).* Yellow solid; mp = 161.1−161.3 °C; 30.6 mg, 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 2.2 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.57 (t, J = 6.8 Hz, 3H), 7.38 (t, J = 7.7 Hz, 1H), 7.29 (dd, J = 8.2, 4.0 Hz, 1H), 7.14 (dd, J = 17.0, 7.7 Hz, 7H), 5.21 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 145.1, 142.7, 137.3, 137.3, 136.2, 135.4, 134.2, 129.3, 128.9, 128.7, 128.6, 128.1, 128.0, 127.3, 126.1, 121.0, 54.8, 21.5; IR (KBr): 3442, 3137, 1667, 1400, 1153, 678 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{23}H_{21}N_2O_2S$: 389.1318, found: 389.1315.

*N-Methyl-5-tosylquinolin-8-amine (**3w**).* Yellow oil; 25.9 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 7.0 Hz, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.54 (t, J = 7.6 Hz, 1H), 7.37−7.31 (m, 1H), 7.19 (d, J = 7.6 Hz, 2H), 3.50 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 145.3, 142.9, 138.5, 136.4, 136.1, 131.3, 129.5, 129.0, 128.5, 128.0, 126.2, 121.2, 39.3, 21.5; IR (KBr): 3341, 3115, 1696, 1315, 1149, 685 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{17}H_{17}N_2O_2S$: 313.1005, found: 313.1013.

*N-(2-Methyl-5-tosylquinolin-8-yl)acetamide (**3x**).* Yellow solid; mp = 193.3−193.6 °C; 27.3 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.89 (d, J = 8.8 Hz, 1H), 8.80 (d, J = 8.3 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 2H), 2.71 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 158.0, 144.0, 139.2, 137.4, 133.3, 130.8, 129.8, 129.0, 127.2, 124.1, 122.3, 114.0, 25.2, 25.0, 21.5; IR (KBr): 3442, 3129, 1695, 1306, 1147, 695 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{19}N_2O_3S$: 355.1111, found: 355.1110.

*N-(6-Methyl-5-tosylquinolin-8-yl)acetamide (**3y**).* Yellow solid; mp = 197.4−198.2 °C; 27.3 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.53 (dd, J = 9.0, 1.4 Hz, 1H), 8.74 (dd, J = 4.1, 1.3 Hz, 1H), 8.68 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.51 (dd, J = 9.0, 4.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 2.90 (s, 3H), 2.36 (d, J = 1.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 147.5, 143.9, 143.8, 140.6, 138.8, 136.8, 134.0, 129.7, 126.4, 126.1, 126.1, 123.0, 120.1, 25.2, 24.0, 21.5; IR (KBr): 3316, 2922, 2853, 1695, 1297, 679 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{19}H_{19}N_2O_3S$: 355.1111, found: 355.1113.

*N-(2-Chloro-5-tosylquinolin-8-yl)acetamide (**3z**).* Yellow solid; mp = 223.1−224 °C; 28.0 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 9.03 (d, J = 9.0 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.44 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 7.8 Hz, 2H), 7.51 (d, J = 9.0 Hz, 1H), 7.27 (d, J = 7.8 Hz, 2H), 2.38 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 150.2, 144.4, 138.9, 138.7, 137.8, 136.4, 131.9, 130.0, 129.6, 127.3, 124.6, 122.9, 115.5, 25.3, 21.5; IR (KBr):3362, 2923, 2854, 1701, 1322, 691 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{16}ClN_2O_3S$: 375.0565, found: 375.0561.

*N-(6-Chloro-5-tosylquinolin-8-yl)acetamide (**33a**).* Yellow solid; mp = 229−230 °C; 26.2 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.92 (d, J = 9.0 Hz, 1H), 8.82 (d, J = 4.3 Hz, 2H), 7.83 (d, J = 7.9 Hz, 2H), 7.65 (dd, J = 8.9, 3.9 Hz, 1H), 7.27 (d, J = 6.7 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 148.2, 144.3, 139.5, 139.4, 138.1, 136.4, 134.2, 129.5, 127.4, 127.2, 126.3, 123.8, 118.7, 25.2, 21.6; IR (KBr): 3389, 2921, 1704, 1307, 1150, 678 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{18}H_{16}ClN_2O_3S$: 375.0565, found: 375.0568.

*N-[4-Methoxy-5-(thiophen-2-ylsulfonyl)quinolin-8-yl]acetamide (**33b**).* Yellow solid; mp = 233.3−233.6 °C; 25.7 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.80 (d, J = 8.4 Hz, 1H), 8.64 (d, J = 4.4 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.56 (s, 2H), 7.06 (s, 1H), 6.90 (d, J = 4.3 Hz, 1H), 3.88 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 162.1, 149.6, 145.3, 140.0, 139.6, 133.0, 131.3, 131.0, 129.9, 127.0, 118.1, 114.0, 104.2, 55.5, 25.2; IR (KBr): 3469, 3105, 2920, 1683, 1313, 671 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{16}H_{15}N_2O_4S_2$: 363.0468, found: 363.0478.

*N-[2-Phenyl-5-(thiophen-2-ylsulfonyl)quinolin-8-yl]acetamide (**33c**).* Yellow solid; mp = 206.6−207.3 °C; 28.5 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 9.27 (d, J = 9.0 Hz, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.14−8.01 (m, 3H), 7.74 (d, J = 3.1 Hz, 1H), 7.61−7.52 (m, 4H), 7.05 (t, J = 4.2 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 155.9, 143.9, 139.2, 135.3, 134.9, 134.2, 133.4, 133.0, 129.2, 129.0, 127.7, 127.5, 127.2, 126.8, 121.3, 119.4, 116.7, 25.2; IR (KBr): 3502, 3106, 2919, 1633, 1335, 690 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{21}H_{17}N_2O_3S_2$: 409.0675, found: 409.0678.

*N-[2-(Phenylethynyl)-5-tosylquinolin-8-yl]acetamide (**33d**).* Yellow solid; mp = 210.7−210.9 °C; 32.1 mg, 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 9.05 (d, J = 8.9 Hz, 1H), 8.91 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.9 Hz, 2H), 7.72 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 7.7 Hz, 2H), 7.45 (t, J = 6.5 Hz, 3H), 7.30 (s, 2H), 2.43 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 144.3, 142.1, 139.3, 138.9, 138.0, 133.5, 132.2, 129.9, 129.7, 129.2, 128.6, 127.3, 126.6, 123.1, 121.5, 114.7, 91.8, 88.4, 25.4, 21.5; IR (KBr): 3469, 3105, 2236, 1728, 1303, 733 cm^{-1}; HRMS (ESI) calcd for $[M + H]^+$: $C_{26}H_{21}N_2O_3S$: 441.1267, found: 441.1268.

*5-(Phenylsulfonyl)quinolin-8-amine (**3b-1**).* To a solution of **3b** (0.1 mmol) in 2 mL of EtOH and H_2O (v/v = 3:1) was added 0.5 mL of hydrochloric acid (1 M). The mixture was refluxed for 5 h, and then 5 mL of saturated aqueous sodium bicarbonate solution and 10 mL of ethyl acetate were added. The corresponding organic layer was separated and concentrated under reduced pressure. The resulting crude product was purified by flash chromatography on silica gel using 50% (v/v) ethyl acetate in petroleum ether as eluent to afford the product **3b-1** as white solid. mp = 159−160 °C; 26 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 8.7, 1.5 Hz, 1H), 8.70 (dd, J = 4.1, 1.4 Hz, 1H), 8.32 (d, J = 8.3 Hz, 1H), 7.94−7.86 (m, 2H), 7.49−7.40 (m, 4H), 6.88 (d, J = 8.4 Hz, 1H), 5.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 147.6, 143.1, 137.3, 133.1, 132.7, 132.6, 129.1, 126.8, 125.5, 123.3, 120.9, 106.5. IR (KBr): 3500, 3015, 1622, 1588, 1153, 776 cm^{-1}. HRMS (ESI) calcd for $[M + H]^+$: $C1_5H_{13}N_2O_2S$, 285.0692, found: 285.0691.

*Procedure for the Synthesis of the Isotopically Labeled Substrate **D-1a**.* The mixture of propionic acid (2 mmol, 1.0 equiv) and $SOCl_2$ (3 mmol, 1.5 equiv) was stirred in $CHCl_3$ (2.0 mL) at 80 °C for 2 h under Ar atmosphere in a sealed reaction tube. After cooling to room temperature, Et_3N (2 mmol, 1.0 equiv) and 8-amino-5,7-dideuteroquinoline (***D*-1**) (2 mmol, 1.0 equiv) were added to the reaction mixture. Then the corresponding mixture was stirred at 25 °C for 3 h.

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The mixture was cooled to room temperature, 5 mL of saturated aqueous sodium bicarbonate solution was added, and then the mixture was extracted with CH_2Cl_2 (3 × 10 mL). After the combined organic layers were dried over Na_2SO_4, the resulting crude product was purified by flash chromatography on silical gel using 25% (v/v) ethyl acetate in petroleum ether as eluent to afford the deuterated propionamide (***D*-1a**) as a yellow liquid (360 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.78 (d, J = 3.0 Hz, 1H), 8.13 (d, J = 8.1 Hz, 1H), 7.52 (s, 1H), 7.48 (s, 0.10H), 7.46 (s, 0.08H), 7.46−7.39 (m, 1H), 2.59 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 148.1, 138.4, 136.3, 134.5, 127.9, 127.2, 121.5, 121.3, 116.4, 31.2, 9.8; IR (KBr): 3302, 3100, 2962, 1680, 1450, 1375 cm^{-1}. HRMS (ESI) calcd for $[M + H]^+$: $C_{12}H_{11}N_2OD_2$: 203.1148, found: 203.1146.

Mechanistic Studies for Copper-Catalyzed Regioselective C−H Sulfonylation of 8-Aminoquinolines. *Trapping of the Possible Radical Intermediates for This Reaction.* The mixture of *N*-(quinolin-8-yl)propionamide **1a** (0.1 mmol, 1.0 equiv), arylsulfonyl chlorides **2a** (0.15 mmol, 1.5 equiv), K_2CO_3 (0.2 mmol, 2 equiv), CuBr (0.01 mmol, 10 mol %), and 1,1-diphenylethylene **4a** (0.3 mmol, 3.0 equiv) was stirred in DCE (1.0 mL) at 100 °C for 12 h under Ar atmosphere in a sealed reaction tube. Then the corresponding reaction mixture was cooled to room temperature, and 1.0 mL of H_2O was added and then extracted with CH_2Cl_2 (3 × 10 mL). The corresponding combined organic layers were dried over Na_2SO_4 and concentrated under vacuum, and the resulting crude products were purified by flash chromatography on silical gel using 50% (*v*/*v*) ethyl acetate in petroleum ether as eluent to afford the compounds **3a** (8% yield) and **33h**[30] (72% yield).

*1-(2,2-Diphenyl-ethenesulfonyl)-4-methyl-benzene (**33h**).*[30] Brown solid; mp = 94−95 °C; 24 mg, 72% yield; ^{1}H NMR (400 MHz, CDCl3) δ 7.47 (d, J = 8.3 Hz, 2H), 7.39−7.33 (m, 2H), 7.29 (ddd, J = 7.0, 5.3, 1.3 Hz, 4H), 7.19 (dd, J = 5.3, 3.4 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.12−7.06 (m, 2H), 6.99 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 154.7, 143.8, 139.3, 138.7, 135.6, 130.2, 129.8, 129.3, 129.0, 128.8, 128.6, 128.2, 127.8, 127.7, 21.6; IR (KBr): 3011, 2980, 1625, 1428, 1138, 810 cm^{-1}. MS (ESI): m/z = 333.85 [M$^+$].

Kinetic Isotope Effect Experiments.[31] Parallel individual reactions of **1a** and **D-1a**: *N*-(quinolin-8-yl)propionamide **1a** (0.1 mmol, 1.0 equiv) or the isotopically labeled substrate **D-1a** (0.1 mmol, 1.0 equiv), arylsulfonyl chlorides **2a** (0.15 mmol, 1.5 equiv), K_2CO_3 (0.2 mmol, 2 equiv), and CuBr (0.01 mmol, 10 mol %) were dissolved in 2.5 mL of DCE in a tube, and then the tube was sealed under Ar and heated at 100 °C in an oil bath. Then aliquots (0.5 mL) were taken at 2 h intervals after the reaction was performed for 3 h. Each aliquot was removed the solvent under reduced pressure and analyzed by ^{1}H NMR. The ^{1}H NMR raw data of the reactions of **1a** and **D-1a** is displayed in the SI (see Figures S5 and S10). Comparison of the reaction progress indicated that the corresponding KIE value is 1.01 (see the SI, Figure S11).

Computational Details. All calculations were performed with the Gaussian 09 program.[32] DFT[33] calculations using the M06-L functional[34] were used to locate all the stationary points involved. The 6-31G(d,p)[35] basis set is applied for all nonmetal elements, and the SDD pseudopotential[36] is used for Cu and K, which denotes as basis set 1 (BS1). Frequency calculations at the same level have been carried out to confirm each stationary point to be either a minimum or a transition state. In order to confirm the connection of each transition state to its corresponding reactant and product, intrinsic reaction coordinate (IRC)[37] calculations were performed. Based on the optimized structures at BS1, we calculated the solvated single-point energies at a larger basis set BS2 (the SDD for K, the SDD pseudopotential with outer p functions and a set of f-polarization functions for Cu, and the 6-311++G (2d,2p) for the other atoms) to further refine the energetics. Both structure optimizations and single-point calculations were carried out with the integral equation formalism polarizable continuum medium (IEF-PCM) model.[38] The parameters for 1,2-dichloroethane (DCE, ε = 10.36) are used corresponding to the experimental conditions. The radii from the UFF force field with an explicit hydrogen radius were used in these calculations. The solvation free energies were obtained at the M06-L/BS2/IEF-PCM//M06-L/BS1/IEF-PCM level of theory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02509.

NMR spectra and computational data (PDF)

single crystal data of **3b** (CIF)

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Notes

The authors declare no competing financial interest.

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