ACES Asian Chemical Editorial Society

DOI: 10.1002/asia.201501407

CHEMISTRY AN ASIAN JOURNAL Full Paper

C–H Activation | *Very Important Paper*

Remote C–H Activation of Quinolines through Copper-Catalyzed Radical Cross-Coupling

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Abstract: Achieving site selectivity in carbon–hydrogen (C–H) functionalization reactions is a formidable challenge in organic chemistry. Herein, we report a novel approach to activating remote C–H bonds at the C5 position of 8-aminoquinoline through copper-catalyzed sulfonylation under mild conditions. Our strategy shows high conversion efficiency, a broad substrate scope, and good toleration with different functional groups. Furthermore, our mechanistic investigations suggest that a single-electron-transfer process plays a vital role in generating sulfonyl radicals and subsequently initiating C–S cross-coupling. Importantly, our copper-catalyzed remote functionalization protocol can be expanded for the construction of a variety of chemical bonds, including C–O, C–Br, C–N, C–C, and C–I. These findings provide a fundamental insight into the activation of remote C–H bonds, while offering new possibilities for rational design of drug molecules and optoelectronic materials requiring specific modification of functional groups.

Introduction

Heteroaromatic sulfones are important intermediates that are indispensable to the synthesis of biological and pharmaceutical compounds as well as advanced functional materials.[1] Traditionally, heteroaromatic sulfones are formed via nucleophilic substitution reactions between heteroaryl halides with thiols, followed by the oxidation of corresponding organic sulfides with different oxidants.[2] However, these reactions are often associated with environmental concerns, complex procedure and high remediation costs, particularly on an industrial scale.[3]

From the viewpoint of atom economy and waste reduction, direct sulfonylation of aromatics via metal-catalyzed C–H activation offers a straightforward alternative to the formation of desirable organic sulfides.[4] For example, σ-chelating has been widely applied to synthesize sulfones by employing quinoline derivatives as substrates.[4d–f] Despite their utilities, these methods are usually limited to *ortho*-selectivity. In stark contrast, the preparation of heteroaromatic sulfones by remote C–H sulfonylation of quinolines has been rarely investigated,[5] albeit the promising prospects of using quinolines as building blocks for structural functionalization at the C2, C3 and C8 positions of the quinoline substrates.[6–8] It should be noted that there are few examples of quinoline functionalization at the C5 position. Chlorination, allylation, and sulfuration of quinolines have been reported at the C5 position, but these reactions often require high reaction temperatures (e.g.; 140 or 160 °C).[9] In particular, the chlorination reaction also needs to be conducted under acid conditions together with acetate employed as the solvent and ligand.[9a]

Very recently, two research groups reported similar C–S couplings by using quinoline substrates, however, the underlying mechanism for these reactions remains unclear.[5h,i] Here, we report a convenient method for direct, remote C–H functionalization of quinolines at the C5 position with sulfonyl chlorides to give rise to the corresponding sulfonated products in moderate-to-excellent yields under mild conditions. Our method enables the access to a variety of sulfonated products, which are difficult to be prepared by conventional approaches involving pyridine,[4a,b] 2-pyridinyl isopropyl,[4c] 8-aminoquinolinyl,[4d,e] *N*-oxide,[4f] and oxime acetates[4g,h] as directing groups. More importantly, our investigations also provide fundamental insights into the remote activation of C–H bonds that are largely

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/asia.201501407.

inaccessible by conventional approaches. Corroborated with density functional theory (DFT) simulations, our control experiments under investigation strongly suggest the existence of a radical pathway during the copper-catalyzed cross-coupling. Significantly, this reaction protocol can be extended for the preparation of quinoline derivatives containing C–S, C–O, C–Br, C–N, C–C, and C–I bonds, thereby demonstrating its generality and potential applications in materials synthesis and pharmaceutical industry.

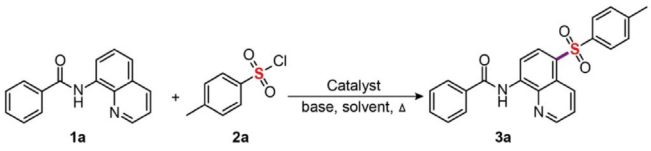
Results and Discussion

Encouraged by previous works on C–S cross-coupling,[10] we commenced our study by reacting 8-aminoquinoline amide **1a** with sulfonyl chloride **2a** as a standardized test. We found that the reaction with 12.5 mol% CuI in CH_3CN under a nitrogen atmosphere for 12 h at 70 °C can afford the desirable product **3a** in 67% yield (Table 1, entry 1), and the structure of the product **3a** was confirmed by X-ray crystallographic analysis (CCDC 1041995), as shown in the Supporting Information. The use of other Cu^I species, such as CuBr and CuCl, led to much lower yields (Table 1, entries 2 and 3). Additionally, the absence of metal catalysts or the use of divalent metal catalysts such as $Cu(OAc)_2$ and $Pd(OAc)_2$ did not show noticeable catalytic activity (Table 1, entries 4–6). Notably, *t*BuOH, 1,2-dichloro-ethane (DCE) or 1,4-dioxane as the solvent improved the yield to 71, 76, and 91%, respectively (Table 1, entries 7–10). However, only a trace amount of the product was obtained under an atmosphere of air or oxygen (Table 1, entry 11). Further variations in pH values or temperatures virtually did not alter the reaction yield (Table 1, entries 12–19).

In a further set of experiments, we proceeded to investigate the substrate scope with various sulfonyl chlorides under the standard conditions listed in Table 1, entry 10. Diversification of the aromatic sulfonyl chlorides afforded a wide range of products (**3a–m**) in moderate-to-excellent isolated yields (45–92%; Table 2). With the exception of **3g**, the reactants with electron-donating substituents generally resulted in the desired products in high yields as compared to those with electron-withdrawing groups. The moderate yield of 45% for product **3h** is likely due to the steric hindrance of the sulfonyl chloride precursor. Critically, aromatic sulfonyl chlorides showed much better tolerance to the reaction conditions than alkyl sulfonyl chlorides.

Subsequently, we inspected the effect of structural variations in 8-aminoquinoline amide on remote sulfonylation (Table 3, entries **3n–y**). The reactions with both aromatic and nonaromatic substituents showed good tolerance to different func-

Table 1. Screening of reaction conditions for remote C–S coupling of quinolines.[a]

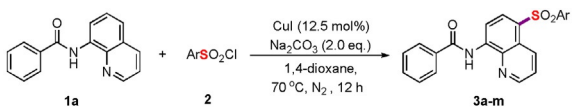


1a 2a 3a

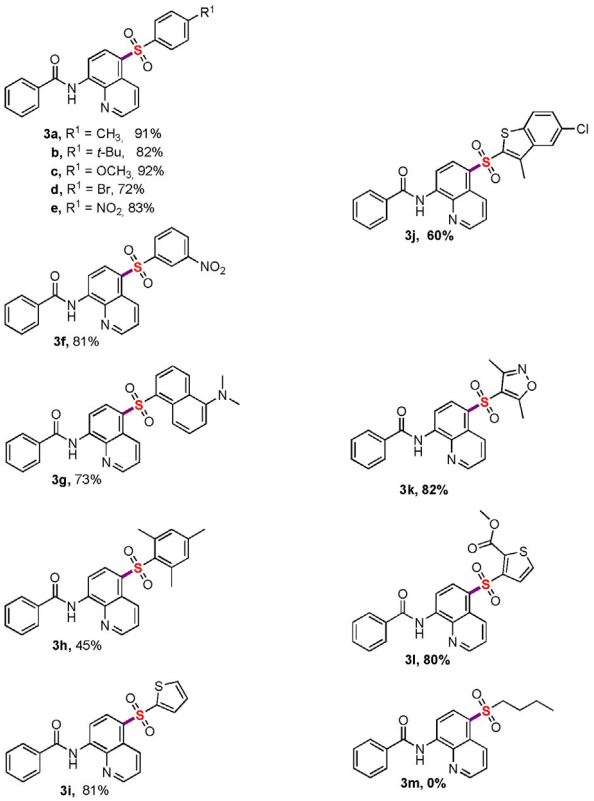
Entry	Catalyst	Base	Solvent	*T* [°C]	Yield [%][b]
1	CuI	Na_2CO_3	CH_3CN	70	67
2	CuBr	Na_2CO_3	CH_3CN	70	42
3	CuCl	Na_2CO_3	CH_3CN	70	29(trace)[c]
4	$Cu(OAc)_2$	Na_2CO_3	CH_3CN	70	trace
5	$Pd(OAc)_2$	Na_2CO_3	CH_3CN	70	0
6	–	Na_2CO_3	CH_3CN	70	0
7	CuI	Na_2CO_3	toluene	70	17
8	CuI	Na_2CO_3	*t*BuOH	70	71
9	CuI	Na_2CO_3	DCE	70	76
10	**CuI**	**Na_2CO_3**	**1,4-dioxane**	**70**	**91**
11	CuI	Na_2CO_3	1,4-dioxane	70	trace[d]
12	CuI	–	1,4-dioxane	70	0
13	CuI	$NaHCO_3$	1,4-dioxane	70	80
14	CuI	NaOH	1,4-dioxane	70	34
15	CuI	K_2CO_3	1,4-dioxane	70	trace
16	CuI	Na_2CO_3	1,4-dioxane	70	84[e]
17	CuI	Na_2CO_3	1,4-dioxane	70	90[f]
18	CuI	Na_2CO_3	1,4-dioxane	50	75
19	CuI	Na_2CO_3	1,4-dioxane	90	89

[a] All the reactions were carried out with **1a** (0.2 mmol), catalyst (12.5 mol%), **2a** (2.0 equiv), base (2.0 equiv), and solvent (2.0 mL) for 12 h under N_2 atmosphere. [b] Isolated yield. [c] $CuCl_2$ instead of CuCl. [d] Under air or O_2 atmosphere. [e] CuI (10%). [f] CuI (15%). DCE = 1,2-dichloroethane.

Table 2. Substrate scope of sulfonyl chlorides.[a]

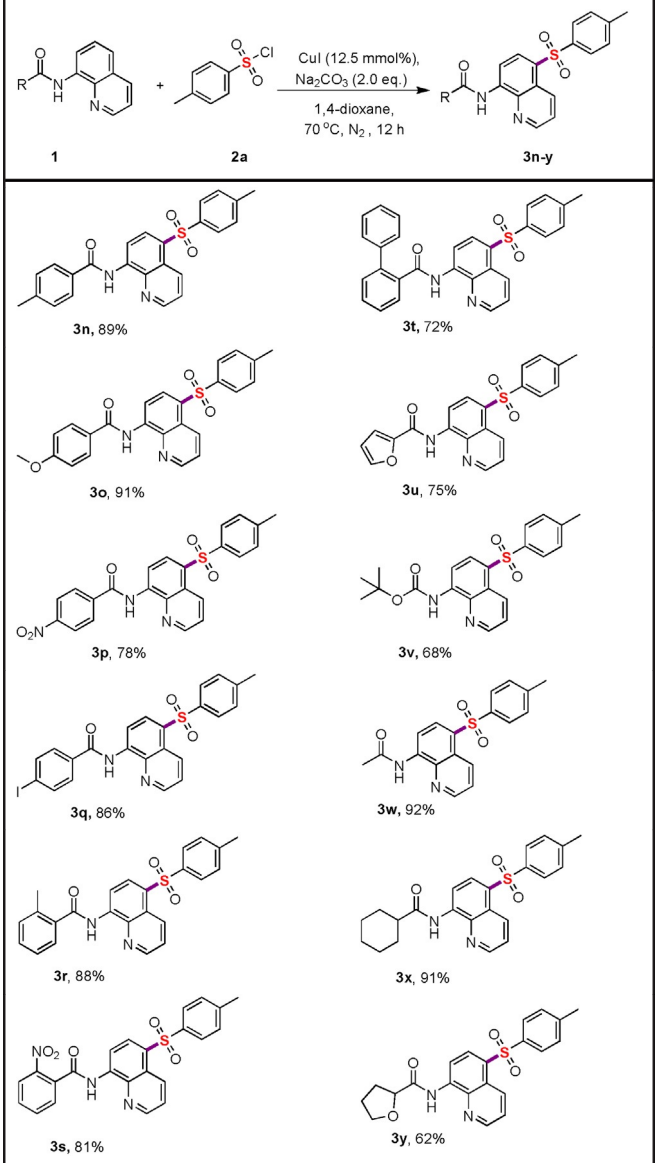


1a 2 3a-m



[a] Reaction conditions: **1a** (0.2 mmol), CuI (12.5 mol%), **2** (2.0 equiv), Na_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), under N_2, 12 h. Note that the yields shown here are isolated yields.

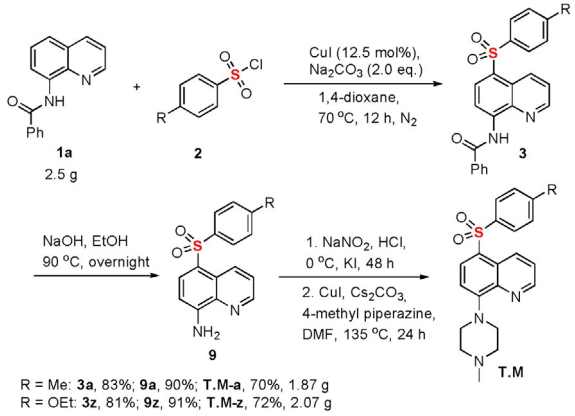
Table 3. Substrate scope of the 8-aminoquinoline reagents.[a]



[a] Reaction conditions: **1** (0.2 mmol), CuI (12.5 mol%), **2a** (2.0 equiv), Na_2CO_3 (2.0 equiv), 1,4-dioxane (2.0 mL), under N_2, 12 h. Note that the yields shown here are isolated yields.

tional groups. The substrates containing either electron-donating or electron-withdrawing groups at the *para*-position of the benzamide showed similar reactivity to **1a**.

With the newly established protocol in hand, we then evaluated the applicability of this methodology to prepare the analogue of the standard radiotracers used for positron emission tomography (PET) (Scheme 1).[11] In a typical experiment, copper(I)-catalyzed sulfonylation of **1a** firstly afforded sulfonylated quinolines compound **3**, and a subsequent hydrolysis reaction led to the corresponding aminoquinolines **9**. Successive diazotization, iodination and C–N coupling reactions gave rise to desired products (**T.M**) in gram scale, thereby providing a feasible solution to the concise synthesis of biologically relevant sulfonates.



Scheme 1. Gram-scale synthesis of analogues of a positron emission tomography (PET) radiotracer by sulfonylation of quinoline ring.

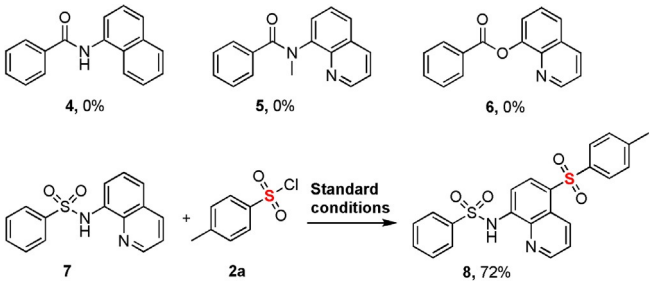
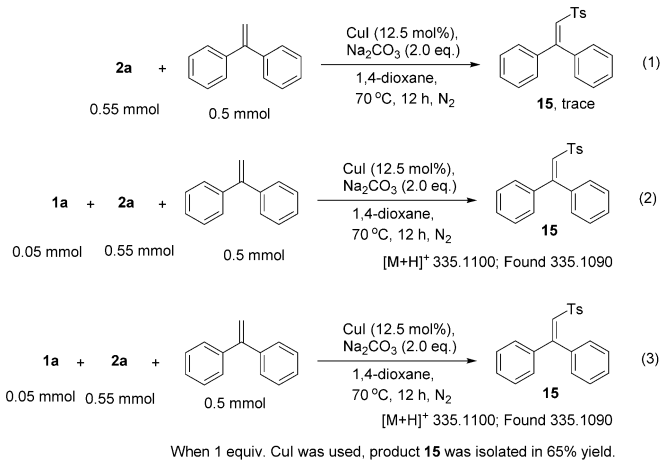


Figure 1. The effect of heteroatoms on remote sulfonylation.

To probe the effect of heteroatoms in 8-aminoquinoline on remote sulfonylation, single factor experiments were conducted based on the type of **3a** analogues (Figure 1). The copper-catalyzed coupling reaction with substrate **4** did not give any sulfonated quinoline product under the standard conditions, thus suggesting that a traditional Friedel–Crafts reaction pathway may be excluded in the reaction process.[12] Similarly, no desired products were obtained either with substrate **5** featuring methylated amide nitrogen or by using substrate **6** substituted with an ester group. However, the reaction between the sulfonamide-based substrate **7** and *p*-tolylsulfonyl chloride **2a** under the standard conditions gave a sulfonated quinoline derivative **8** in 72% yield. These results indicate that the remote sulfonylation under study can be ascribed to a synergistic effect arising from the interplay between the quinoline nitrogen atom and the amide group.

To gain more insights into the reaction mechanism, a series of control experiments were carried out, including radical inhibition and capture, kinetic isotope effect study, and mercury poisoning experiment. We found that the remote sulfonylation reaction was completely suppressed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or hydroquinone as free radical scavengers (see the Supporting Information), implying that a radical step was involved in the reaction process. Then, we tried to trap the sulfonyl radical by using 1,1-diphenylethylene in the absence of amine **1a**. Interestingly, we did not



Scheme 2. Mechanistic investigations of the radical reaction pathway.

obtain the radical coupling product [Scheme 2, Eq. (1)]. When amine **1a** was added, however, the radical coupling product was isolated and fully characterized [Scheme 2, Eq. (2)]. Without the addition of Na_2CO_3, we could also trap the sulfonyl radical [Scheme 2, Eq. (3)]. Taken together, these data suggest that the sulfonyl radical is initiated mainly by the coordination of the amine substrate to CuI. Furthermore, we conducted an intermolecular deuterium labeling experiment to monitor the kinetic isotope effect (see the Supporting Information). A low value of 1.0 for the kinetic isotope effect obtained from the controls indicates that the C–H metalation is unlikely to be the rate determining step.[13] We also found that the addition of a large excess of mercury to the reaction mixture has no marked influence on the formation of **3a**. This result suggests the homogenous dispersion nature of the copper, arising from the chelating effect of the substrate.[14]

Although we initially took into consideration the oxidative addition/reductive elimination mechanism,[5h] our in-depth experimental analysis, however, let us turn our thoughts to a single-electron-transfer process. To validate our hypothesis, DFT computations (SMD-M062X/6-31+G**//M062X/6-31+G**; LANL2DZ basis set for Cu and I) on various aryl-Cu^{II} complex radical intermediates (aryl-Cu^{II}ICl, aryl-Cu^{II}I, aryl-Cu^{II}Cl complexes) were performed. Our findings suggested that only aryl-Cu^{II}Cl complex has a spin density distributed on the quinoline moiety, and this is essential for the desired radical coupling reaction (Figure 2). A control experiment employing an aryl sulfonyl iodide instead of an aryl sulfonyl chloride indeed resulted in a much lower yield with very poor regioselectivity (see Figure S2 in the Supporting Information). These observations indicated that the proposed [aryl-Cu^{II}Cl] complex may play a vital role in the catalysis. The spin density distributions at both the *ortho* and *para* positions in [aryl-Cu^{II}Cl] were similar, but the relative Gibbs free energies (ΔG_{rel}) of the intermediates, presumably formed after the radical coupling at *para*-position of benzamides, proclaims 6.2 kcal mol^{-1} stability higher than that formed at the *ortho* position (see Figure S3 in the Supporting Information). The increased stability can be attributed to the small steric influence at the *para* position, as compared to that

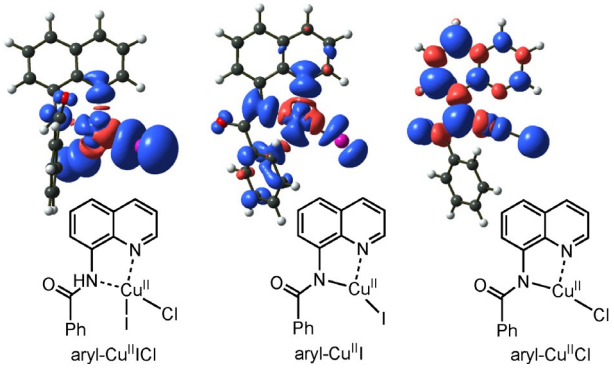


Figure 2. Spin densities of aryl-Cu^{II} complex radical intermediates.

of the *ortho* position with an adjacent electrostatic environment.

Building upon the analysis of the aforementioned results and previous reports,[15] we believe that the quinoline sulfonylation in our study is governed by a single-electron transfer (SET) mechanism (Figure 3). Specifically, substrate **1a** first produces the aryl-Cu^{I} complex **A** in the presence of CuI. Then, the sulfonyl radical **B** can be easily initiated by the oxidation of aryl-Cu^{I} complex **A** to aryl-Cu^{II} complex **C** through a SET process.[16] The deprotonation of the amide group by the carbonate ligand leads to formation of the aryl-Cu^{II} complex **D**. The intermediate **B** subsequently attacks **D** to afford complex **E** by the SET process. Thereafter, the complex **E** turns into **F**, accompanied by the production of sulfonyl radical **B**. After the generation of intermediate **G** through a proton transfer process, product **3a** is obtained via a metal dissociation process. The gen-

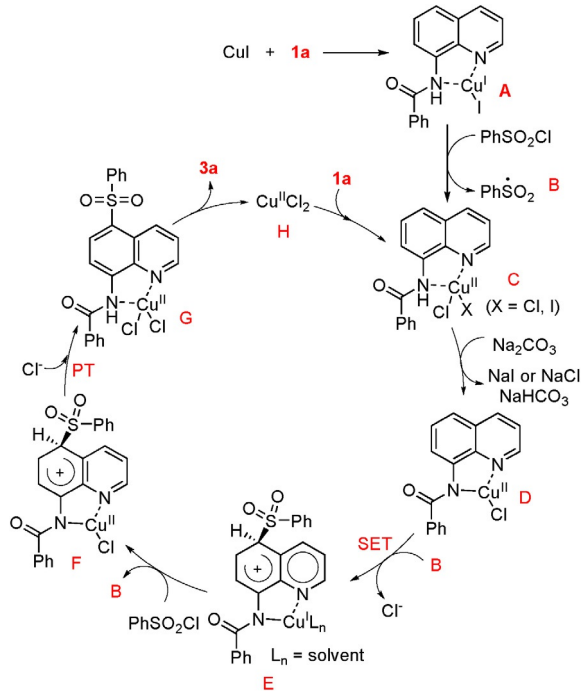
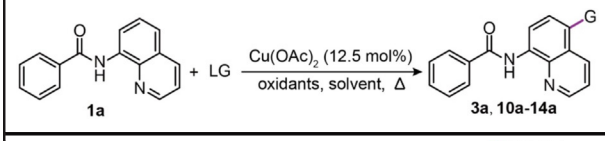


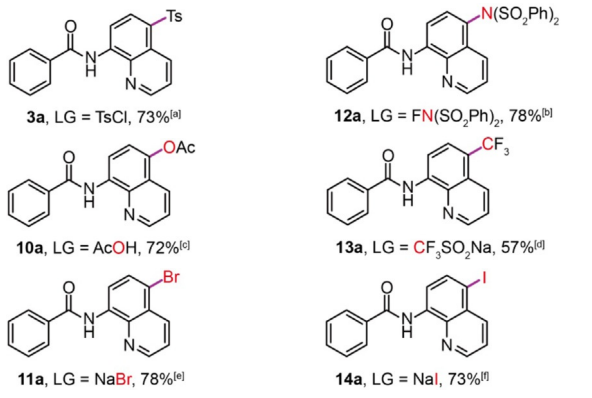
Figure 3. Plausible mechanism for the remote sulfonylation of the quinolines.

eration of aryl-Cu^{II} complex **C** by the coordination of Cu^{II} complex **H** to substrate **1a** completes the catalytic cycle.

To verify the general applicability of our radical cross-coupling approach to quinoline functionalization, we attempted the synthesis of quinoline derivatives comprising different moieties at the C5 position (Table 4).[17] As anticipated, with the help of a copper(II) catalyst the remote C–H activation can be used to construct a variety of chemical bonds, including C–O, C–Br, C–N, C–C, and C–I. The structure of the product **11a** was confirmed by X-ray crystallographic analysis (CCDC 1429311).[18] These results not only demonstrate an easy remote access to quinoline derivatives at the C5 position under relatively mild conditions, but also lend strong support to our proposed mechanism, as illustrated in Figure 3.

Table 4. Versatile remote C–H activation of quinolines based on a free radical mechanism.[a]





Reaction conditions: [a] **1a** (0.2 mmol), $Cu(OAc)_2$ (12.5 mol%), TsCl (2.0 equiv), $K_2S_2O_8$ (2.0 equiv), Na_2CO_3 (2.0 equiv), CH_3CN, air, 120 °C, 12 h. [b] **1a** (0.2 mmol), $Cu(OAc)_2$ (12.5 mol%), $FN(SO_2Ph)_2$ (2.0 equiv), $PhI(OAc)_2$ (2.0 equiv), AcOH (2.0 equiv), 1,4-dioxane, air, 50 °C, 6 h. [c] **1a** (0.2 mmol), $Cu(OAc)_2$ (12.5 mol%), $PhI(OAc)_2$ (2.0 equiv), AcOH, air, 50 °C, 6 h. [d] **1a** (0.2 mmol), $Cu(OAc)_2$ (12.5 mol%), CF_3SO_2Na (2.0 equiv), TBHP (2.0 equiv), CH_3CN, air, 50 °C, 15 min. [e] **1a** (0.2 mmol), $Cu(OAc)_2$ (12.5 mol%), NaI (2.0 equiv), $PhI(OAc)_2$ (2.0 equiv), AcOH (2.0 equiv), DCE, air, 50 °C, 1 h. [f] **1a** (0.2 mmol), $Cu(OAc)_2$ (12.5 mol%), NaBr (2.0 equiv), $PhI(OAc)_2$ (2.0 equiv), AcOH (2.0 equiv), DCE, air, 50 °C, 1 h. TBHP = *tert*-Butyl hydroperoxide. Note that the yields shown here are isolated yields.

Conclusions

We have developed a general copper-based catalytic approach for highly regioselective C–H sulfonylation of 8-aminoquinoline and its derivatives at the C5 position. This organic transformation shows high efficiency, a broad substrate scope, and high levels of functional group tolerance. On the basis of mechanistic and experimental investigations, we have proposed a free radical cross-coupling pathway underlying the reaction mechanism. This newly developed protocol could be extended to the preparation of previously inaccessible chemical compounds as potential sulfonyl-based drugs or advanced materials.

Experimental Section

General Information

The reaction product was isolated by short chromatography on a silica gel (200–300 mesh) column using petroleum ether (PE) with a boiling range from 60 to 90 °C and ethyl acetate (EtOAc). ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance 500 MHz spectrometer at ambient temperature with $CDCl_3$ or $[D_6]DMSO$ as a solvent and tetramethylsilane as the internal standard. ^1H NMR data were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, and br = broad), coupling constant (*J* values, Hz). Melting points were determined on an X-5 Data microscopic melting point apparatus. X-ray crystallography was performed on a German Bruker D4 X-ray diffractometer with graphite monochromated $Mo_{K\alpha}$ radiation. Compounds for high resolution mass spectrometry were analyzed by positive mode electrospray ionization using an Agilent 6530 QTOF mass spectrometer. The calculations were performed on Gaussian 09 programs with the density functional theory.[19]

General procedure for Cu^I-catalyzed synthesis of compound 3

To a 25 mL schlenk tube charged with CuI (4.8 mg, 12.5 mol%) and Na_2CO_3 (42.4 mg, 2.0 equiv) in 1,4-dioxane (2.0 mL) was added a mixture of reagent **1** (0.2 mmol) and **2** (2.0 equiv). The mixture was stirred at 70 °C under a nitrogen atmosphere for 12 h. After cooling to room temperature, the mixture was poured into water (10 mL). Then the mixture was extracted with ethyl acetate for three times, and the combined organic layers were gradually washed with brine (10 mL), dried with Na_2SO_4, and filtered through a pad of Celite. The solvent was removed under reduced pressure. The residue was then purified by silica-gel column chromatography using PE/EtOAc as the eluent to afford target compound **3**.

General procedure for Cu^I-catalyzed gram-scale synthesis of compound 3

Following the same synthetic procedure for compound **3**, the reaction of **1a** (2.5 g, 10 mmol), **2** (2.0 equiv), CuI (238.8 mg, 12.5 mol%), and Na_2CO_3 (2.1 g, 2.0 equiv) in 1,4-dioxane (15.0 mL) heated at 70 °C under nitrogen atmosphere for 12.0 h gave rise to product **3a** (83%) or **3z** (81%).

General procedure for gram-scale synthesis of product 9

To a 50 mL schlenk tube equipped with a magnetic stir bar was added a mixture of **3** (8.0 mmol), NaOH (1.0 g, 25 mmol), and EtOH (25.0 mL). Upon completion of the reaction at 90 °C for 12 h, the mixture was cooled to room temperature and then diluted with EtOAc (50 mL). The collected organic layer was washed with brine (100 mL), dried with Na_2SO_4, and filtered through a pad of Celite gradually. The solvent was removed in vacuo by rotary evaporation, and product **9** was isolated by silica-gel column chromatography using PE/DCM (v/v; 1:5) as the eluent.

General procedure for gram-scale synthesis of T.M

To a glass vial charged with compound **9** (7.0 mmol), water (35.0 mL), and concentrated HCl (12.0 mL) at 0 °C was added dropwise to a solution of $NaNO_2$ (690 mg, 10.0 mmol) in water (5.0 mL). After stirring for 30 min, a solution of KI (1.7 g, 10.0 mmol) in water (5.0 mL) was slowly added. Then the mixture was warmed to room temperature and stirred for 48 h. Subsequently, the solution was neutralized by adding 2 N NaOH and the organic phase was extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4, and filtered through a pad of Celite. The solvent was removed to afford iodoquinoline. Note that the iodoquinoline was used without any purification in the following step.

In a 50 mL schlenk tube equipped with a magnetic stir bar, a mixture of as-synthesized iodoquinoline, *N*-methyl piperazine (1.5 g, 15.0 mmol), CuI (267 mg, 20 mol%), Cs_2CO_3 (5.0 g, 15.0 equiv), and DMF (25 mL) was stirred at 135 °C under a nitrogen atmosphere for 24 h. After cooling to room temperature, the mixture was diluted with water (100 mL) and extracted with EtOAc (30 mL) for three times. The combined organic layers were gradually washed with brine (100 mL), dried with Na_2SO_4, filtered through a pad of Celite. Then the solvent was removed under reduced pressure and the residue was purified by silica-gel column chromatography using EtOAc as the eluent to afford **T.M**.

General procedure for mercury poisoning experiment

Following the synthetic procedure for compound **3**, the reaction of **1a** (49.6 mg, 0.2 mmol) and **2a** (76.4 mg, 2.0 equiv) was carried out in the presence of CuI (4.8 mg, 12.5 mol%), Na_2CO_3 (42.4 mg, 2.0 equiv), and mercury (2.0 g, 10 mmol, 400 equiv) in 1,4-dioxane (2.0 mL) at 70 °C under N_2 for 12.0 h.

General procedure for Cu^{II}-catalyzed synthesis of compound 10a

Following the synthetic procedure for compound **3**, the reaction of **1a** (49.6 mg, 0.2 mmol), $Cu(OAc)_2$ (4.6 mg, 12.5 mol%), $PhI(OAc)_2$ (128.8 mg, 2.0 equiv) in AcOH (2.0 mL) at 50 °C under air for 6.0 h afforded **10a**.

General procedure for Cu^{II}-catalyzed synthesis of compound 11a

Following the synthetic procedure for compound **3**, the reaction of **1a** (49.6 mg, 0.2 mmol), NaBr (41.2 mg, 2.0 equiv), $Cu(OAc)_2$ (4.6 mg, 12.5 mol%), $PhI(OAc)_2$ (128.8 mg, 2.0 equiv), and AcOH (24.0 mg, 2.0 equiv) in DCE (2.0 mL) at 50 °C under air for 1.0 h yielded **11a**.

General procedure for Cu^{II}-catalyzed synthesis of compound 12a

Following the synthetic procedure for compound **3**, the reaction of **1a** (49.6 mg, 0.2 mmol), $(PhSO_2)_2NF$ (126.0 mg, 2.0 equiv), $Cu(OAc)_2$ (4.6 mg, 12.5 mol%), $PhI(OAc)_2$ (128.8 mg, 2.0 equiv), and AcOH (24.0 mg, 2.0 equiv) in 1,4-dioxane (2.0 mL) at 50 °C under air for 6.0 h yielded **12a**.

General procedure for Cu^{II}-catalyzed synthesis of compound 13a

Following the synthetic procedure for compound **3**, the reaction of **1a** (49.6 mg, 0.2 mmol), CF_3SO_2Na (62.4 mg, 2.0 equiv), $Cu(OAc)_2$ (4.6 mg, 12.5 mol%), TBHP (51.4 mg, 2.0 equiv) in CH_3CN (2.0 mL) at 50 °C under air for 15 min afforded **13a**.

General procedure for Cu^{II}-catalyzed synthesis of compound 14a

Following the synthetic procedure of compound **3**, the reaction of **1a** (49.6 mg, 0.2 mmol), NaI (60.0 mg, 2.0 equiv), $Cu(OAc)_2$ (4.6 mg, 12.5 mol%), $PhI(OAc)_2$ (128.8 mg, 2.0 equiv) and AcOH (24.0 mg, 2.0 equiv) in DCE (2.0 mL) at 50 °C under air for 1.0 h produced **14a**.

N-(5-tosylquinolin-8-yl)benzamide (3a)

Obtained as a white solid in 91% yield; M.p. 178–179 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.96 (s, 1H), 9.09 (dd, J = 8.7 Hz, 1.5 Hz, 1H), 9.04 (d, J = 8.4 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 7.1 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.64–7.53 (m, 4H), 7.28 (m, 2H), 2.36 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.70, 148.72, 144.15, 139.94, 139.12, 138.50, 134.41, 133.65, 132.44, 132.08, 129.92, 129.49, 128.97, 127.44, 127.32, 124.35, 123.32, 114.35, 21.52 ppm. HRMS (ESI$^+$): Calculated for $C_{23}H_{18}N_2O_3SH$: $[M+H]^+$ 403.1111, Found 403.1114.

N-(5-((4-(tert-butyl)phenyl)sulfonyl)quinolin-8-yl)benzamide (3b)

Obtained as a white solid in 82% yield; M.p. 208–209 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.95 (s, 1H), 9.12 (d, J = 8.4 Hz, 1H), 9.02 (d, J = 8.4 Hz, 1H), 8.86 (d, J = 3.1 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 7.4 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.58 (dd, J = 8.3, 4.3 Hz, 2H), 7.53 (t, J = 7.4 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 1.26 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.61, 157.10, 148.80, 139.91, 138.92, 138.44, 134.27, 133.59, 132.46, 132.07, 129.41, 128.96, 127.39, 127.13, 126.35, 124.34, 123.43, 114.22, 35.17, 30.99 ppm. HRMS (ESI$^+$): Calculated for $C_{26}H_{24}N_2O_3SH$: $[M+H]^+$ 444.1581, Found 444.1569.

N-(5-((4-methoxyphenyl)sulfonyl)quinolin-8-yl)benzamide (3c)

Obtained as a white solid in 92% yield; M.p. 205–206 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.95 (s, 1H), 9.10 (dd, J = 8.7, 1.5 Hz, 1H), 9.02 (d, J = 8.4 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.13–8.02 (m, 2H), 7.93–7.86 (m, 2H), 7.63–7.53 (m, 4H), 6.94 (d, J = 9.0 Hz, 2H), 3.81 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.53, 163.18, 148.57, 139.65, 138.40, 134.28, 133.46, 133.38, 132.28, 131.61, 129.77, 129.38, 128.82, 127.27, 124.09, 123.14, 114.38, 114.15, 55.49 ppm. HRMS (ESI$^+$): Calculated for $C_{23}H_{18}N_2O_4SH$: $[M+H]^+$ 419.1060, Found 419.1062.

N-(5-((4-bromophenyl)sulfonyl)quinolin-8-yl)benzamide (3d)

Obtained as a white solid in 72% yield; M.p. 210–211 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.97 (s, 1H), 9.04 (dd, J = 13.9, 5.0 Hz, 2H), 8.89 (dd, J = 4.2, 1.4 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.10–8.03 (m, 2H), 7.81 (d, J = 8.7 Hz, 2H), 7.64–7.53 ppm (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.68, 148.89, 141.15, 140.40, 138.50, 134.29, 133.27, 132.60, 132.58, 132.51, 128.99, 128.73, 128.38, 128.35,

127.43, 124.29, 123.54, 114.28 ppm. HRMS (ESI$^+$): Calculated for $C_{22}H_{15}BrN_2O_3SH$: $[M+H]^+$ 467.0060, Found 467.0054.

N-(5-((4-nitrophenyl)sulfonyl)quinolin-8-yl)benzamide (3e)

Obtained as a yellow solid in 83% yield; M.p. 209–210 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.00 (s, 1H), 9.10 (d, J = 8.5 Hz, 1H), 9.03 (dd, J = 8.7, 1.4 Hz, 1H), 8.92 (dd, J = 4.2, 1.4 Hz, 1H), 8.63 (d, J = 8.5 Hz, 1H), 8.30 (d, J = 8.9 Hz, 2H), 8.13 (d, J = 8.9 Hz, 2H), 8.09–8.05 (m, 2H), 7.65–7.60 (m, 2H), 7.57 ppm (t, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.98, 150.55, 149.32, 148.06, 141.29, 138.73, 134.42, 133.68, 133.21, 132.88, 129.28, 128.71, 127.70, 127.30, 124.78, 124.66, 124.06, 114.61 ppm. HRMS (ESI$^+$): Calculated for $C_{22}H_{15}N_3O_5SH$: $[M+H]^+$ 434.0805, Found 434.0808.

N-(5-((3-nitrophenyl)sulfonyl)quinolin-8-yl)benzamide (3f)

Obtained as a yellow solid in 81% yield; M.p. 199–200 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.99 (s, 1H), 9.13–9.04 (m, 2H), 8.92 (dd, J = 4.1, 1.3 Hz, 1H), 8.80 (t, J = 1.8 Hz, 1H), 8.63 (d, J = 8.5 Hz, 1H), 8.41–8.33 (m, 1H), 8.25 (d, J = 7.9 Hz, 1H), 8.06 (d, J = 7.3 Hz, 2H), 7.70 (t, J = 8.0 Hz, 1H), 7.67–7.60 (m, 2H), 7.57 ppm (t, J = 7.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.72, 149.09, 148.43, 144.45, 141.01, 138.49, 134.19, 133.40, 132.96, 132.65, 132.62, 130.78, 129.03, 127.62, 127.45, 127.19, 124.37, 123.89, 122.34, 114.38 ppm. HRMS (ESI$^+$): Calculated for $C_{22}H_{15}N_3O_5SH$: $[M+H]^+$ 434.0805, Found 434.0808.

N-(5-((5-(dimethylamino)naphthalen-1-yl)sulfonyl)quinolin-8-yl)benzamide (3g)

Obtained as a white solid in 73% yield; M.p. 220–221 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.94 (s, 1H), 9.05 (d, J = 8.4 Hz, 1H), 8.99 (dd, J = 8.7, 1.4 Hz, 1H), 8.81 (dd, J = 4.2, 1.4 Hz, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.56 (t, J = 8.0 Hz, 2H), 8.24 (d, J = 8.7 Hz, 1H), 8.05–8.02 (m, 2H), 7.63–7.57 (m, 2H), 7.53 (t, J = 7.4 Hz, 2H), 7.50 (dd, J = 8.8, 4.2 Hz, 1H), 7.46–7.42 (m, 1H), 7.08 (d, J = 7.5 Hz, 1H), 2.80 ppm (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.69, 151.94, 148.66, 139.79, 138.38, 136.60, 134.31, 133.49, 132.41, 132.13, 131.49, 129.91, 129.83, 129.53, 129.43, 128.93, 128.53, 127.36, 124.35, 123.22, 123.19, 118.71, 115.34, 113.97, 45.33 ppm. HRMS (ESI+): Calculated for $C_{28}H_{23}N_3O_3SH$: $[M+H]^+$ 482.1533, Found 482.1543.

N-(5-(mesitylsulfonyl)quinolin-8-yl)benzamide (3h)

Obtained as a white solid in 45% yield; M.p. 185–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.95 (s, 1H), 8.93 (d, J = 8.4 Hz, 1H), 8.87 (d, J = 4.2 Hz, 1H), 8.83 (dd, J = 8.7, 0.9 Hz, 1H), 8.06 (d, J = 8.0 Hz, 3H), 7.59 (d, J = 7.2 Hz, 1H), 7.58–7.51 (m, 3H), 6.96 (s, 2H), 2.57 (s, 6H), 2.30 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.69, 148.80, 143.58, 140.02, 139.04, 138.45, 134.45, 134.30, 133.31, 132.45, 132.38, 132.08, 129.35, 128.95, 127.39, 124.04, 123.11, 113.79, 22.80, 21.04 ppm. HRMS (ESI$^+$): Calculated for $C_{25}H_{22}N_2O_3SH$: $[M+H]^+$ 431.1424, Found 431.1438.

N-(5-(thiophen-2-ylsulfonyl)quinolin-8-yl)benzamide (3i)

Obtained as a pale yellow solid in 81% yield; M.p. 180–181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.98 (s, 1H), 9.25 (dd, J = 8.7, 1.6 Hz, 1H), 9.03 (d, J = 8.4 Hz, 1H), 8.91 (dd, J = 4.2, 1.5 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 8.09–8.02 (m, 2H), 7.73 (dd, J = 3.8, 1.3 Hz, 1H),7.67–7.52 (m, 5H),7.04 ppm (dd, J = 4.9, 3.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.66, 147.84, 142.85, 139.21, 137.43, 133.33, 132.52, 132.43, 132.03, 131.45, 130.94, 128.83, 127.96, 126.67, 126.40, 123.24, 122.43, 113.32 ppm. HRMS (ESI$^+$): Calculated for $C_{20}H_{14}N_2O_3S_2H$: $[M+H]^+$ 395.0519, Found 395.0515.

N-(5-((5-chloro-3-methylbenzo[b]thiophen-2-yl)sulfonyl)quinolin-8-yl)benzamide (3j)

Obtained as a pale yellow solid in 60% yield; M.p. 204–205 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.99 (s, 1H), 9.24 (dd, J = 8.7, 1.5 Hz, 1H), 9.07 (d, J = 8.5 Hz, 1H), 8.88 (dd, J = 4.2, 1.4 Hz, 1H), 8.61 (d, J = 8.5 Hz, 1H), 8.10–8.04 (m, 2H), 7.70 (dd, J = 18.8, 5.3 Hz, 2H), 7.64–7.59 (m, 2H), 7.56 (t, J = 7.4 Hz, 2H), 7.39 (dd, J = 8.7, 1.9 Hz, 1H), 2.52 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.74, 148.98, 140.97, 140.52, 139.19, 138.42, 137.94, 137.48, 134.31, 133.65, 132.54, 132.48, 131.76, 129.01, 128.97, 128.19, 127.45, 124.41, 123.79, 123.56, 123.42, 114.00, 12.25 ppm. HRMS (ESI$^+$): Calculated for $C_{25}H_{17}ClN_2O_3S_2H$: $[M+H]^+$ 493.0442, Found 493.0439.

N-(5-((3,5-dimethylisoxazol-4-yl)sulfonyl)quinolin-8-yl)benzamide (3k)

Obtained as a white solid in 82% yield; M.p. 179–180 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.99 (s, 1H), 9.05 (dd, J = 8.4, 4.8 Hz, 1H), 8.92 (dd, J = 7.8, 2.1 Hz, 2H), 8.46 (dd, J = 8.4, 4.0 Hz, 1H), 8.10–8.04 (m, 2H), 7.64–7.61 (m, 2H), 7.59–7.55 (m, 2H), 2.78 (s, 3H), 2.23 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.39, 165.70, 157.49, 149.07, 140.50, 138.38, 134.18, 132.57, 132.53, 132.13, 129.00, 128.72, 127.42, 124.17, 123.58, 117.82, 113.77, 12.97, 10.79 ppm. HRMS (ESI$^+$): Calculated for $C_{21}H_{17}N_3O_4SH$: $[M+H]^+$ 408.1013, Found 408.1007.

Methyl-3-((8-benzamidoquinolin-5-yl)sulfonyl)thiophene-2-carboxylate (3l)

Obtained as a white solid in 80% yield; M.p. 186–187 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.00 (s, 1H), 9.08 (d, J = 8.5 Hz, 1H), 8.92 (dd, J = 8.7, 1.5 Hz, 1H), 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.68 (d, J = 8.5 Hz, 1H), 8.10–8.05 (m, 2H), 7.86 (d, J = 5.3 Hz, 1H), 7.62–7.54 (m, 5H), 3.78 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.69, 159.20, 148.55, 144.93, 140.09, 138.17, 134.96, 134.41, 134.01, 133.17, 132.45, 130.98, 130.03, 128.98, 128.23, 127.42, 124.51, 123.29, 113.77, 52.87 ppm. HRMS (ESI$^+$): Calculated for $C_{22}H_{16}N_2O_5S_2H$: $[M+H]^+$ 453.0573, Found 453.0566.

4-methyl-*N*-(5-tosylquinolin-8-yl)benzamide (3n)

Obtained as a white solid in 89% yield; M.p. 188–189 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.93 (s, 1H), 9.08 (dd, J = 8.7, 1.3 Hz, 1H), 9.03 (d, J = 8.4 Hz, 1H), 8.86 (dd, J = 4.1, 1.3 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 8.7, 4.2 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 5.7 Hz, 2H), 2.45 (s, 3H), 2.36 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.67, 148.69, 144.12, 143.12, 140.09, 139.16, 138.53, 133.57, 132.12, 131.61, 129.90, 129.64, 129.24, 127.46, 127.31, 124.34, 123.28, 114.20, 21.59, 21.52 ppm. HRMS (ESI$^+$): Calculated for $C_{24}H_{20}N_2O_3SH$: $[M+H]^+$ 417.1267, Found 417.1265.

4-methoxy-*N*-(5-tosylquinolin-8-yl)benzamide (3o)

Obtained as a white solid in 91% yield; M.p. 178–179 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.88 (s, 1H), 9.06 (dd, J = 8.7, 1.4 Hz, 1H), 9.00 (d, J = 8.4 Hz, 1H), 8.85 (dd, J = 4.2, 1.4 Hz, 1H), 8.53 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.56 (dd, J = 8.7, 4.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 8.8 Hz,

2H), 3.88 (s, 3H), 2.35 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.14, 163.04, 148.66, 144.10, 140.18, 139.17, 138.48, 133.52, 132.11, 129.89, 129.38, 129.02, 127.27, 126.60, 124.31, 123.27, 114.19, 114.02, 55.53, 21.51 ppm. HRMS (ESI$^+$): Calculated for $C_{24}H_{20}N_2O_4SH$: $[M+H]^+$ 433.1217, Found 433.1212.

4-nitro-*N*-(5-tosylquinolin-8-yl)benzamide (3p)

Obtained as a yellow solid in 78% yield; M.p. 206–207 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.02 (s, 1H), 9.11 (ddd, J = 7.0, 5.6, 1.4 Hz, 1H), 9.00 (d, J = 8.4 Hz, 1H), 8.89 (dd, J = 4.2, 1.4 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 8.40 (dd, J = 11.4 Hz, 5.4 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.63–7.55 (m, 1H), 7.28 (d, J = 8.2 Hz, 2H), 2.37 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.53, 150.17, 149.00, 144.35, 139.79, 139.12, 138.88, 138.45, 133.80, 131.82, 130.54, 129.98, 128.63, 127.39, 124.32, 124.20, 123.54, 114.70, 21.54 ppm. HRMS (ESI$^+$): Calculated for $C_{23}H_{17}N_3O_5SH$: $[M+H]^+$ 448.0962, Found 448.0951.

4-iodo-*N*-(5-tosylquinolin-8-yl)benzamide (3q)

Obtained as a white solid in 86% yield; M.p. 242–243 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.93 (s, 1H), 9.09 (dd, J = 8.7 Hz, 1.5 Hz, 1H), 9.00 (d, J = 8.4 Hz, 1H), 8.87 (dd, J = 4.2 Hz, 1.5 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.59 (dd, J = 8.7, 4.2 Hz, 1H), 7.28 (s, 2H), 2.37 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.95, 148.79, 144.23, 139.60, 138.93, 138.42, 138.24, 133.78, 133.66, 131.99, 129.93, 129.71, 128.92, 127.33, 124.29, 123.41, 114.40, 99.77, 21.56 ppm. HRMS (ESI+): Calculated for $C_{23}H_{17}IN_2O_3SH$: $[M+H]^+$ 529.0078, Found 529.0065.

2-methyl-*N*-(5-tosylquinolin-8-yl)benzamide (3r)

Obtained as a white solid in 88% yield; M.p. 186–187 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.46 (s, 1H), 9.10–9.01 (m, 2H), 8.79 (dd, J = 4.1, 1.4 Hz, 1H), 8.55 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 7.6 Hz, 1H), 7.55 (dd, J = 8.7, 4.2 Hz, 1H), 7.41 (dd, J = 11.2, 3.7 Hz, 1H), 7.32 (t, J = 7.6 Hz, 2H), 7.28–7.25 (m, 2H), 2.59 (s, 3H), 2.36 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.30, 148.72, 144.15, 140.06, 139.10, 138.35, 137.07, 135.72, 133.50, 132.01, 131.63, 130.88, 129.90, 129.51, 127.29, 127.27, 126.15, 124.31, 123.29, 114.19, 21.51, 20.24 ppm. HRMS (ESI$^+$): Calculated for $C_{24}H_{20}N_2O_3SH$: $[M+H]^+$ 417.1267, Found 417.1265.

2-nitro-*N*-(5-tosylquinolin-8-yl)benzamide (3s)

Obtained as a yellow solid in 81% yield; M.p. 221–222 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 11.12 (s, 1H), 9.00 (dd, J = 8.8, 1.5 Hz, 1H), 8.96–8.91 (m, 2H), 8.63 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 7.89 (dd, J = 9.6, 4.6 Hz, 3H), 7.85 (dd, J = 7.6, 1.5 Hz, 1H), 7.79 (dd, J = 8.7, 4.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 2.31 ppm (s, 3H). ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 165.87, 150.16, 146.61, 144.78, 140.52, 138.90, 138.61, 134.86, 133.12, 132.66, 132.05, 131.70, 130.62, 129.99, 129.41, 127.55, 124.80, 124.56, 124.01, 115.92, 21.41 ppm. HRMS (ESI$^+$): Calculated for $C_{23}H_{17}N_3O_5SH$: $[M+H]^+$ 448.0962, Found 448.0951.

2-phenyl-*N*-(5-tosylquinolin-8-yl)benzamide (3t)

Obtained as a white solid in 72% yield; M.p. 185–186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.95 (s, 1H), 8.94 (dd, J = 8.7 Hz, 1.5 Hz, 1H), 8.91 (d, J = 8.4 Hz, 1H), 8.48 (dd, J = 4.2 Hz, 1.5 Hz, 1H), 8.45 (d, J = 8.4 Hz, 1H), 7.92 (dd, J = 7.7 Hz, 1.1 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.57 (td, J = 7.5 Hz, 1.3 Hz, 1H), 7.52–7.45 (m, 4H), 7.42 (dd, J = 8.7, 4.2 Hz, 1H), 7.28–7.23 (m, 4H), 7.14 (t, J = 7.5 Hz, 1H), 2.34 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.12, 148.10, 144.13, 140.44, 139.78, 139.74, 139.04, 138.07, 135.23, 133.10, 131.87, 131.09, 130.87, 129.88, 129.56, 129.17, 129.04, 128.49, 127.85, 127.79, 127.31, 123.98, 123.01, 113.91, 21.52 ppm. HRMS (ESI$^+$): Calculated for $C_{29}H_{22}N_2O_3SH$: $[M+H]^+$ 479.1424, Found 479.1435.

N-(5-tosylquinolin-8-yl)furan-2-carboxamide (3u)

Obtained as a white solid in 75% yield; M.p. 193–194 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.97 (s, 1H), 9.06 (dd, J = 8.7 Hz, 1.4 Hz, 1H), 8.96 (d, J = 8.4 Hz, 1H), 8.88 (dd, J = 4.1 Hz, 1.4 Hz, 1H), 8.51 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.3 Hz, 2H), 7.63 (s, 1H), 7.57 (dd, J = 8.7, 4.2 Hz, 1H), 7.33 (d, J = 3.4 Hz, 1H), 7.29–7.26 (m, 2H), 6.60 (dd, J = 3.4, 1.7 Hz, 1H), 2.36 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.45, 148.83, 147.76, 145.05, 144.16, 139.60, 139.03, 138.36, 133.43, 131.89, 129.91, 129.53, 127.31, 124.29, 123.33, 116.17, 114.28, 112.72, 21.51 ppm. HRMS (ESI$^+$): Calculated for $C_{21}H_{16}N_2O_4SH$: $[M+H]^+$ 393.0904, Found 393.0921.

Tert-butyl (5-tosylquinolin-8-yl)carbamate (3v)

Obtained as a white solid in 68% yield; M.p. 171–172 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.31 (s, 1H), 9.00 (dd, J = 8.7 Hz, 1.4 Hz, 1H), 8.78 (dd, J = 4.1, 1.4 Hz, 1H), 8.57–8.47 (m, 2H), 7.81 (d, J = 8.1 Hz, 2H), 7.54–7.49 (m, 1H), 7.27–7.21 (m, 2H), 2.34 (s, 3H), 1.59 ppm (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.26, 148.44, 143.98, 140.92, 139.24, 137.80, 133.21, 132.00, 129.84, 127.61, 127.15, 124.28, 123.25, 111.99, 81.50, 28.27, 21.49 ppm. HRMS (ESI$^+$): Calculated for $C_{21}H_{22}N_2O_4SH$: $[M+H]^+$ 399.1373, Found 399.1368.

N-(5-tosylquinolin-8-yl)acetamide (3w)

Obtained as a white solid in 92% yield; M.p. 163–164 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.01 (s, 1H), 9.07–9.02 (m, 1H), 8.87–8.83 (m, 1H), 8.81 (dd, J = 4.0, 1.6 Hz, 1H), 8.50–8.45 (m, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.56–7.53 (m, 1H), 7.25 (m, 2H), 2.37 (s, 3H), 2.35 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.19, 148.51, 144.15, 139.75, 139.01, 137.85, 133.54, 131.98, 129.88, 129.23, 127.27, 124.21, 123.22, 114.15, 25.19, 21.50 ppm. HRMS (ESI$^+$): Calculated for $C_{18}H_{16}N_2O_3SH$: $[M+H]^+$ 341.0955, Found 341.0953.

N-(5-tosylquinolin-8-yl)cyclohexanecarboxamide (3x)

Obtained as a white solid in 91% yield; M.p. 188–189 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.12 (s, 1H), 9.04 (dd, J = 8.7, 1.3 Hz, 1H), 8.89 (d, J = 8.4 Hz, 1H), 8.82 (dd, J = 4.1 Hz, 1.3 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.3 Hz, 2H), 7.54 (dd, J = 8.7, 4.2 Hz, 1H), 7.25 (d, J = 8.2 Hz, 2H), 2.53–2.46 (m, 1H), 2.35 (s, 3H), 2.07 (d, J = 11.5 Hz, 2H), 1.91–1.83 (m, 2H), 1.75–1.58 (m, 2H), 1.42–1.26 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 175.25, 148.56, 144.07, 140.02, 139.12, 138.17, 133.44, 132.05, 129.85, 128.90, 127.22, 124.23, 123.19, 114.08, 46.84, 29.61, 25.69, 25.62, 21.49 ppm. HRMS (ESI$^+$): Calculated for $C_{23}H_{24}N_2O_3SH$: $[M+H]^+$ 409.1580, Found 409.1583.

N-(5-tosylquinolin-8-yl)tetrahydrofuran-2-carboxamide (3y)

Obtained as a white solid in 62% yield; M.p. 145–146 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.13 (s, 1H), 9.04 (dd, J = 8.7, 1.5 Hz, 1H), 8.90 (d, J = 8.4 Hz, 1H), 8.87 (dd, J = 4.2 Hz, 1.5 Hz, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.54 (dd, J = 8.8 Hz, 4.2 Hz, 1H), 7.25 (d, J = 8.1 Hz, 2H), 4.61 (dd, J = 8.4, 5.7 Hz, 1H), 4.21–4.17 (m,

1H), 4.05 (dd, J=15.2, 7.0 Hz, 1H), 2.45–2.39 (m, 1H), 2.35 (s, 3H), 2.28–2.20 (m, 1H), 2.20–1.95 ppm (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=172.79, 149.04, 144.12, 139.31, 139.04, 138.66, 133.21, 131.77, 129.87, 129.64, 127.25, 124.30, 123.21, 114.21, 79.13, 69.85, 30.42, 25.54, 21.49 ppm. HRMS (ESI$^+$): Calculated for $C_{21}H_{20}N_2O_4SH$: $[M+H]^+$ 397.1217, Found 397.1225.

N-(5-tosylquinolin-8-yl)benzenesulfonamide (8)

Obtained as a white solid in 72% yield; M.p. 183–184 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.59 (s, 1H), 8.97 (dd, J=8.7 Hz, 1.5 Hz, 1H), 8.79 (dd, J=4.2, 1.5 Hz, 1H), 8.37 (d, J=8.3 Hz, 1H), 7.99–7.96 (m, 2H), 7.83 (d, J=8.3 Hz, 1H), 7.78 (d, J=8.3 Hz, 2H), 7.55–7.51 (m, 2H), 7.46 (d, J=7.9 Hz, 2H), 7.26–7.24 (m, 2H), 2.35 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=149.06, 144.32, 139.26, 139.06, 138.75, 137.85, 133.54, 133.48, 131.18, 129.94, 129.30, 128.51, 127.30, 127.21, 124.50, 123.66, 111.25, 21.51 ppm. HRMS (ESI$^+$): Calculated for $C_{22}H_{18}N_2O4S_2H$: $[M+H]^+$ 439.0781, Found 439.0791.

N-(5-((4-ethoxyphenyl)sulfonyl)quinolin-8-yl)benzamide (3z)

Obtained as a white solid in 81% yield; M.p. 213–214 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.93 (s, 1H), 9.08 (dd, J=8.5, 1.5 Hz, 1H), 8.99 (d, J=8.2 Hz, 1H), 8.85 (dd, J=4.0 Hz, 1.5 Hz, 1H), 8.48 (d, J=8.2 Hz, 1H), 8.21–8.00 (m, 2H), 7.88–7.86 (m, 2H), 7.59–7.52 (m, 4H), 6.91 (d, J=9.0 Hz, 2H), 3.98 (q, J=7.0 Hz, 2H), 1.33 ppm (t, J=7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=165.58, 163.23, 148.62, 139.76, 138.51, 134.39, 133.51, 133.30, 132.33, 131.66, 129.99, 129.43, 128.87, 127.32, 124.14, 123.19, 114.43, 114.20, 59.89, 14.33 ppm. HRMS (ESI$^+$): Calculated for $C_{24}H_{20}N_2O_4SH$: $[M+H]^+$ 433.1217, Found 433.1229.

5-tosylquinolin-8-amine (9a)

Obtained as a brown solid in 90% yield; M.p. 167–168 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.90 (dd, J=8.7, 1.3 Hz, 1H), 8.69 (dd, J=4.1, 1.3 Hz, 1H), 8.29 (d, J=8.3 Hz, 1H), 7.78 (d, J=8.3 Hz, 2H), 7.43 (dd, J=8.7, 4.2 Hz, 1H), 7.21 (d, J=8.2 Hz, 2H), 6.87 (d, J=8.3 Hz, 1H), 5.76 (s, 2H), 2.32 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=149.80, 147.33, 143.41, 140.17, 137.04, 133.07, 132.90, 129.68, 126.85, 125.47, 123.14, 121.46, 106.73, 21.43 ppm. HRMS (ESI$^+$): Calculated for $C_{16}H_{14}N_2O_2SH$: $[M+H]^+$ 299.0849, Found 299.0859.

5-((4-ethoxyphenyl)sulfonyl)quinolin-8-amine (9z)

Obtained as a brown solid in 91% yield; M.p. 209–210 °C. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ=8.83 (dd, J=8.7, 1.5 Hz, 1H), 8.80 (dd, J=4.1, 1.5 Hz, 1H), 8.23 (d, J=8.5 Hz, 1H), 7.86–7.82 (m, 2H), 7.67–7.64 (m, 1H), 7.15 (s, 2H), 7.05–7.02 (m, 2H), 6.99 (d, J=8.5 Hz, 1H), 4.02 (t, J=7.0 Hz, 2H), 1.28 ppm (t, J=7.0 Hz, 3H). ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ=161.65, 151.39, 147.38, 136.37, 134.38, 132.65, 131.97, 128.66, 124.80, 123.49, 118.61, 114.87, 105.78, 63.70, 14.33 ppm. HRMS (ESI$^+$): Calculated for $C_{17}H_{16}N_2O_3SH$: $[M+H]^+$ 329.0955, Found 329.0965.

8-(4-methylpiperazin-1-yl)-5-tosylquinoline (T.M-a)

Obtained as a brown oil in 70% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.72 (d, J=9.6 Hz, 1H), 8.09 (d, J=7.3 Hz, 1H), 7.88 (d, J=8.3 Hz, 1H), 7.79 (d, J=8.2 Hz, 2H), 7.60 (d, J=8.0 Hz, 1H), 7.24 (d, J=8.1 Hz, 2H), 7.01 (d, J=9.6 Hz, 1H), 3.80–3.78 (m, 4H), 2.61–2.59 (m, 4H), 2.38 (s, 3H), 2.35 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=156.74, 148.72, 144.02, 138.98, 136.06, 133.70, 133.30, 129.78, 127.97, 127.28, 125.13, 118.64, 110.94, 54.46, 45.64, 44.17, 21.52 ppm. HRMS (ESI$^+$): Calculated for $C_{21}H_{23}N_3O_2SH$: $[M+H]^+$ 382.1584, Found 382.1576.

5-((4-ethoxyphenyl)sulfonyl)-8-(4-methylpiperazin-1-yl)quinolone (T.M-z)

Obtained as a brown oil in 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.74 (d, J=9.6 Hz, 1H), 8.05 (dd, J=7.4, 1.1 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.85–7.82 (m, 2H), 7.58 (dd, J=8.3, 7.6 Hz, 1H), 7.01 (d, J=9.7 Hz, 1H), 6.89 (d, J=8.9 Hz, 2H), 4.00 (q, J=7.0 Hz, 2H), 3.75–3.73 (m, 4H), 2.50–2.48 (m, 4H), 2.32 (s, 3H), 1.37 ppm (t, J=7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=162.62, 156.89, 148.83, 136.56, 133.65, 133.09, 129.50, 129.29, 127.91, 124.71, 118.50, 114.78, 110.94, 63.99, 54.86, 46.16, 44.61, 14.56 ppm. HRMS (ESI$^+$): Calculated for $C_{22}H_{25}N_3O_3SH$: $[M+H]^+$ 412.1689, Found 412.1675.

8-benzamidoquinolin-5-yl acetate (10a)

Obtained as as a white solid in 72% yield; M.p. 176–177 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.64 (s, 1H), 8.94 (d, J=8.5 Hz, 1H), 8.86 (dd, J=2.8, 1.4 Hz, 1H), 8.19 (d, J=8.4 Hz, 1H), 8.08–8.05 (m, 2H), 7.58–7.52 (m, 3H), 7.50 (m, 1H), 7.36 (d, J=8.5 Hz, 1H), 2.44 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=169.54, 165.37, 148.70, 140.73, 138.99, 134.99, 132.87, 131.95, 130.49, 128.85, 127.30, 121.98, 121.94, 119.38, 115.89, 20.93 ppm. HRMS (ESI$^+$): Calculated for $C_{18}H_{14}N_2O_3H$: $[M+H]^+$ 307.1077, Found 307.1078.

N-(5-bromoquinolin-8-yl)benzamide (11a)

Obtained as a white solid in 78% yield; M.p. 114–115 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.68 (s, 1H), 8.86–8.83 (m, 1H), 8.81 (d, J=8.4 Hz, 1H), 8.51 (dd, J=8.5, 1.5 Hz, 1H), 8.07–8.05 (m, 2H), 7.82 (*d*, J=8.4 Hz, 1H), 7.58–7.53 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=165.39, 148.75, 139.39, 136.04, 134.84, 134.49, 132.04, 130.98, 128.86, 127.30, 127.25, 122.75, 117.06, 114.44 ppm. HRMS (ESI+): Calculated for $C_{16}H_{11}BrN_2OH$: $[M+H]^+$ 327.0128, Found 327.0123.

N-(5-(*N*-(phenylsulfonyl)phenylsulfonamido)quinolin-8-yl)-benzamide (12a)

Obtained as as a white solid in 78% yield; M.p. 190–191 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.87 (s, 1H), 8.88 (d, J=8.4 Hz, 1H), 8.82 (dd, J=4.1, 1.5 Hz, 1H), 8.10–8.06 (m, 2H), 7.93–7.89 (m, 5H), 7.70 (t, J=7.5 Hz, 2H), 7.56 (m, 7H), 7.33 (dd, J=8.5, 4.2 Hz, 1H), 7.16 ppm (d, J=8.4 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=165.71, 148.73, 139.00, 138.74, 137.01, 134.67, 134.34, 133.01, 132.28, 132.23, 129.16, 128.97, 128.91, 128.23, 127.38, 124.25, 122.50, 115.27 ppm. HRMS (ESI$^+$): Calculated for $C_{28}H_{21}N_3O_5S_2H$: $[M+H]^+$ 544.0995, Found 544.0995.

N-(5-(trifluoromethyl)quinolin-8-yl)benzamide (13a)

Obtained as as a white solid in 57% yield; M.p. 124–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.93 (s, 1H), 8.96 (d, J=8.2 Hz, 1H), 8.93 (dd, J=4.1, 1.3 Hz, 1H), 8.56–8.51 (m, 1H), 8.11–8.07 (m, 2H), 7.97 (d, J=8.2 Hz, 1H), 7.64–7.60 (m, 2H), 7.59–7.55 ppm (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ=165.70, 148.75, 138.58, 138.11, 134.60, 133.30 (q, J=1.7 Hz), 132.30, 128.94, 127.39, 126.68, 125.36, 124.15 (q, J=275.4 Hz), 122.92, 119.72 (q, J=31.5 Hz), 114.22 ppm. ^{19}F NMR (471 MHz, $CDCl_3$): δ=−58.70 ppm (s). HRMS (ESI$^+$): Calculated for $C_{17}H_{11}F_3N_2OH$: $[M+H]^+$ 317.0896, Found 317.0897.

N-(5-iodoquinolin-8-yl)benzamide (14a)

Obtained as as a white solid in 73% yield; M.p. 150–151 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.71 (s, 1H), 8.80 (dd, J = 4.1, 1.1 Hz, 1H), 8.70 (d, J = 8.3 Hz, 1H), 8.37 (dd, J = 8.5, 1.1 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 7.2 Hz, 2H), 7.55 ppm (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.38, 148.81, 140.80, 139.32, 138.35, 135.51, 134.89, 132.01, 129.68, 128.84, 127.31, 123.19, 117.96, 89.49 ppm. HRMS (ESI$^+$): Calculated for $C_{16}H_{11}IN_2OH$: $[M+H]^+$ 374.9989, Found 374.9979.

(2-tosylethene-1,1-diyl)dibenzene (15)

Obtained as as a white solid in 65% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.3 Hz, 2H), 7.38–7.32 (m, 2H), 7.30–7.26 (m, 4H), 7.21–7.18 (m, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.11–7.07 (m, 2H), 6.99 (s, 1H), 2.36 ppm (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.74, 143.82, 139.24, 138.63, 135.61, 130.29, 129.80, 129.39, 129.00, 128.88, 128.62, 128.24, 127.84, 127.71, 21.60 ppm. HRMS (ESI$^+$): Calculated for $C_{21}H_{18}O_2SH$: $[M+H]^+$ 335.1100, Found 335.1090.

Acknowledgements

We thank the funding support from the National Natural Science Foundation of China (No. 21376058, 21302171), Zhejiang Provincial Natural Science Foundation of China (No. LZ13B 020001) and the Key-Sci-Tech Innovation Team of Zhejiang Province (No. 2010R50017).

Keywords: cross-coupling · remote C–H functionalization · radicals · sulfonylation

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Manuscript received: December 17, 2015
Accepted Article published: January 12, 2016
Final Article published: February 4, 2016