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Copper-catalyzed C5-regioselective C−H sulfonylation of 8-aminoquinoline amides with aryl sulfonyl chlorides

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ABSTRACT

Copper-catalyzed C-H sulfonylation of 8-aminoquinoline scaffolds in the unusual C5 position was developed. The protocol using inexpensive CuI as the catalyst and commercially available aryl sulfonyl chlorides as the sulfonylation reagents, shows broad substrate scope, producing moderate to good yield of sulfone. The developed method was conveniently applied to synthesize a potential fluorinated PET radioligand of 5-HT_6 serotoninergic receptor. Moreover, mechanistic studies revealed that the reactions underwent a radical process.

The quinoline skeleton is one of the most important aromatic heterocycles[1] present in various natural products[2] and pharmaceuticals.[3] Quinolines can also be employed as ligands[4] and directing groups[5] in organic synthesis, as well as fluorescence probes in analytical chemistry.[6] Thus, considerable efforts have been directed toward the formation and modification of quinoline-based scaffolds.[7]

Quinoline rings are often constructed via annulation of anilines and carbonyl compounds by using a variety of classic named reactions (e.g., Friedländer, Combes, Skraup, Gould−Jacobs, Conrad−Limpach, Doebner−Miller, and Povarov syntheses).[8] Nevertheless, these methods usually require harsh acidic or basic conditions and prohibit adequate diversity and substitutes in the quinoline ring system. By contrast, the functionalization of preformed quinoline scaffold is more straightforward for the rapid preparation of diversely substituted quinolines. However, for the electron-deficient property of quinoline ring and the interaction of sp^2-hybridized nitrogen atoms with electrophiles or Lewis acids, direct functionalization of quinolines presents a significant challenge.[9]

In the past decade, significant progress has been made in transition-metal-catalyzed C−H bond functionalization.[10] In contrast to the widely studied C−H functionalization on the phenyl rings, C−H functionalization on the quinoline ring systems remains underdeveloped.[11] Most examples of site-selective C−H functionalization of quinolines focus on the transformation in the C2,[12] C4,[13] and C8[14] positions. However,
efficient approaches toward the C5-functionalization of quinolines are rarely reported.[15] Stahl et al. recently reported the first C5 chlorination of 8-aminoquinoline amides via Cu-catalyzed single-electron-transfer mechanism.[15a] Zeng,[15b] Yin,[15c] and Zhang[15d] subsequently reported the allylation, chlorination, and chacogenation of 8-aminoquinoline amides in the C5 position, respectively.

Heterocyclic aromatic sulfones are ubiquitous structural motifs found in numerous biologically active natural products, pharmaceuticals and functional materials.[16] Direct C−H bond sulfonylation has recently been obtained under transition-metal catalysis or metal-free conditions.[17] No direct method for the sulfonylation of quinolines was available in C5 position via C−H functionalization before this study was conducted. The conventional method for synthesis of quinoline sulfones requires a multi-step operation, involving the de novo synthesis of halogenated quinoline and cross-coupling of the halide with thiol, followed by oxidation to the corresponding sulfone.[16a] During our study, Wei[15e] et al. reported a CuCl-catalyzed direct C5−H bond sulfonylation of 8-aminoquinoline amides with arylsulfonyl chloride. Shortly thereafter, Wu[15f] et al. reported the similar reactions in air by using CuI as the catalyst, and the substrate scope was expanded to cyclic aliphatic sulfonic chlorides. However, the detailed mechanism of this sulfonylation remains unclear. Two different mechanisms, organometallic and radical processes were proposed in the

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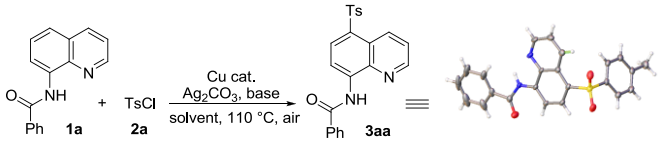
aforementioned study. In the current study, we presented our independent work, with particular focus on the mechanism and practical application of this methodology.[18]

Initially, the sulfonylation of *N*-(quinolin-8-yl)benzamide (**1a**) with *p*-tolysulfonyl chloride (**2a**) was chosen as the model reaction for the optimization of the reaction parameters (Table 1). The reaction gave the desired C5-sulfonylated product **3aa** in 42% yield by using $Cu(OAc)_2 \cdot H_2O$ (20 mol%) as the catalyst in the presence of Ag_2CO_3 (0.5 equiv.) and Na_2CO_3 (2.0 equiv.) in 1,4-dioxane for 46 h under air (entry 1). The structure of **3aa** was unequivocally confirmed by X-ray diffraction. No product was detected in the absence of a copper catalyst (entry 2). Without adding Ag_2CO_3, the yield of the product decreased to 30% while 15% C5-chlorinated byproduct was generated (entry 3). Various copper catalysts, such as $CuBr_2$, $Cu(OTf)_2$, CuBr, and CuI were screened to catalyze this transformation, in which CuI gave the best result (entries 4-7). Subsequent base screening showed that K_2CO_3 was superior to other bases, such as Na_2CO_3 and Cs_2CO_3, affording **3aa** in 61% yield (entry 9 vs entries 7-8). Among the solvents (dioxane, DMSO, DMF, DCE and MeCN) screened, dioxane was the best choice (entries 9-13). Increasing the loading of Ag_2CO_3 to 1.0 equiv. gave **3aa** in 69% yield with significantly short reaction time (entry 14). Reducing the loading of CuI to 10 mol% resulted in an increased yield of **3aa** (72% yield, entry 16), and further lowering the loading of CuI to 5 mol% led to a decreased yield and longer reaction time (entry 15). When the amount of *p*-TsCl was reduced from 3.0 equiv. to 1.0 equiv., the yield dropped to 53% (entry 17). Interestingly, replacement of the arylsulfonyl source with *p*-$MePhSO_2Na$ can also give the product **3aa** in 45% yield (entry 18).

Table 1

Optimization of the reaction conditions[a]



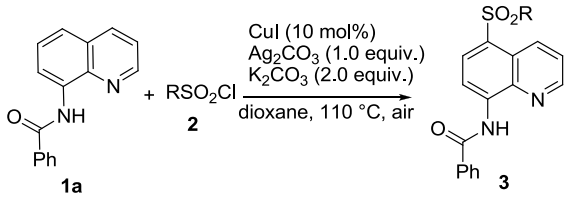
Entry	Catalyst	Base	Solvent	T (h)	Yield (%)
1	$Cu(OAc)_2 \cdot H_2O$	Na_2CO_3	dioxane	46	42
2	-	Na_2CO_3	dioxane	-	N.R.
3[b]	$Cu(OAc)_2 \cdot H_2O$	Na_2CO_3	dioxane	46	30
4	$CuBr_2$	Na_2CO_3	dioxane	46	30
5	$Cu(OTf)_2$	Na_2CO_3	dioxane	48	20
6	CuBr	Na_2CO_3	dioxane	46	35
7	CuI	Na_2CO_3	dioxane	46	55
8	CuI	Cs_2CO_3	dioxane	46	15
9	CuI	K_2CO_3	dioxane	46	61
10	CuI	K_2CO_3	DMSO	-	N.R.
11	CuI	K_2CO_3	DMF	-	N.R.
12	CuI	K_2CO_3	DCE	46	47
13	CuI	K_2CO_3	MeCN	46	50
14[c]	CuI	K_2CO_3	dioxane	12	69
15[c]	CuI[d]	K_2CO_3	dioxane	17	61
16[c]	CuI[e]	K_2CO_3	dioxane	12	72
17[c,f]	CuI[e]	K_2CO_3	dioxane	12	53
18[c,g]	CuI[e]	K_2CO_3	dioxane	24	45

[a] Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (20 mol%), Ag_2CO_3 (0.05 mmol), base (0.2 mmol), and solvent (1 mL) at 110 °C under air; isolated yields.
[b] Without Ag_2CO_3.
[c] 0.1 mmol Ag_2CO_3.
[d] 5 mol% CuI.
[e] 10 mol% CuI.
[f] 1.0 equiv. of TsCl.
[g] *p*-$MePhSO_2Na$ was used instead of TsCl.

With the optimal reaction conditions in hand, we evaluated the scope of the reaction with respect to the sulfonyl component (Table 2). The results showed that various aryl sulfonyl chlorides bearing electron-withdrawing, -neutral or -donating groups in the benzene ring readily participate in this selective sulfonylation reaction. Substrates with electron-donating methyl groups in the *para*-, *meta*- and *ortho*-positions were compatible under these reaction conditions, with the yields being 72%, 65% and 32%, respectively (**3aa**−**3ac**). The relatively lower yield of the *ortho*-substituted product may be a steric effect. Benzene sulfonyl chloride afforded the corresponding sulfone in 79% yield (**3ad**). The arylsulfonyl chloride with electron-donating groups such as 4-OMePh and 4-*t*BuPh, provided the desired products in 53% and 77% yields, respectively (**3ae**-**3af**). Electron-withdrawing substituted sulfonyl chlorides were also suitable substrates. When trifluoromethyl and fluoro groups were substituted in the *p*-position, 75% or 74% yields were obtained, respectively (**3ag**-**3ah**). Notably, 4-bromophenylsulfonyl chloride gave the highest yield of 91% (**3ai**). These halogen-substituted products are useful intermediates, owing to their ability to undergo further transformations via transition-metal catalyzed coupling reactions (see Scheme 1). In addition, 2-naphthylsulfonyl chloride was also tolerated, affording **3aj** in 59% yield. However, the use of aliphatic methanesulfonyl chloride resulted in no conversion in this system (**3ak**).

Table 2

Investigation on the scope of arylsulfonyl chlorides[a]



R = *p*-MePh	**3aa** 72% (12 h)
R = *m*-MePh	**3ab** 65% (32 h)
R = *o*-MePh	**3ac** 32% (32 h)
R = Ph	**3ad** 79% (12 h)
R = *p*-OMePh	**3ae** 53% (32 h)
R = *p*-*t*-BuPh	**3af** 77% (32 h)
R = *p*-FPh	**3ag** 74% (10 h)
R = *p*-CF_3Ph	**3ah** 75% (32 h)
R = *p*-BrPh	**3ai** 91% (10 h)
R = 2-naphthyl	**3aj** 59% (32 h)
R = Me	**3ak** 0%

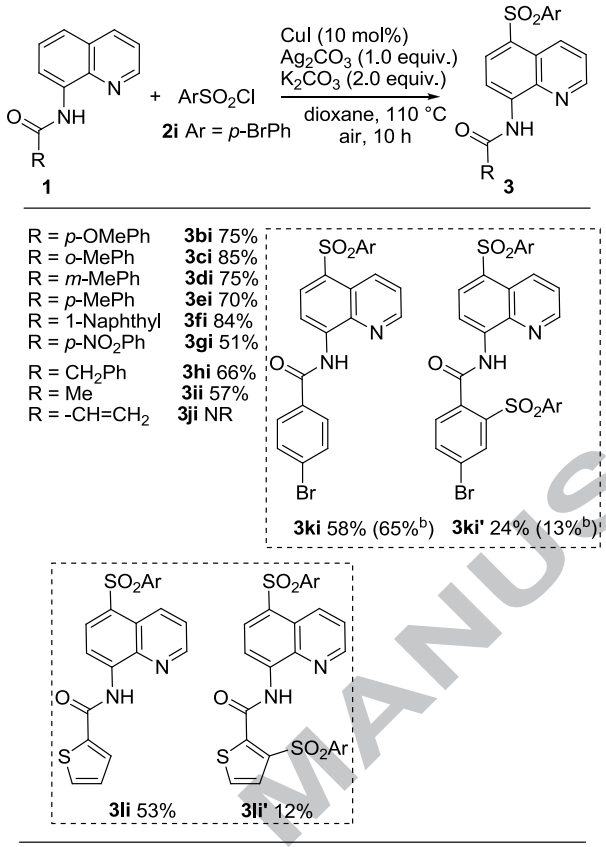
[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), CuI (0.01 mmol), Ag_2CO_3 (0.1 mmol), K_2CO_3 (0.2 mmol), 1,4-dioxane (1.0 mL), 110 °C under air; isolated yields.

A variety of 8-aminoquinoline amides were subsequently investigated to evaluate the generality of the current reaction (Table 3). The substrates bearing electron-donating groups such as 4-OMe, 2-Me, 3-Me, and 4-Me on the benzamides reacted smoothly with 4-bromobenzenesulfonyl chloride **2i** and afforded the corresponding sulfones in good yields (**3bi**-**3ei**). 1-Naphthoic acid amide was also a suitable substrate, affording **3fi** in 84% yield. The highly electron-deficient 4-nitroaromatic amide could also generate product **3gi** in 51% yield. Moreover, aliphatic acid amides, such as phenylacetic amide and acetamide were also tolerated, affording the corresponding products **3hi** and **3ii** in moderate yields. Unfortunately, attempts to utilize acrylamide failed to afford the corresponding product **3ji**. The reactions of 4-bromobenzamide with arylsulfonyl chloride provided both mono- and bis-sulfonylated products in 58% and 24% yields, respectively (**3ki** and **3ki'**). Reducing the loading of arylsulfonyl chloride to 1.5 equiv. cause the yield of C5-substituted product **3ki** to increase to 65%. Similarly, 2-thiophenecarboxylic acid amide was also converted to both mono- and bis-sulfonylated products in 53% and 12% yields, respectively (**3li**-**3li'**).

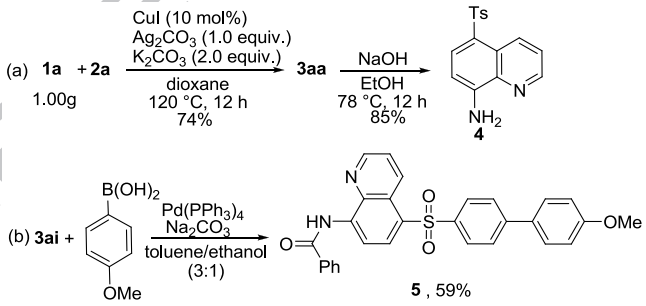
Based on the above results, we explored the applications of this sulfonylation protocol (Scheme 1). This C5-sulfonylation of **1a** with **2a** was successfully scaled up to gram-scale under the same reaction conditions, and **3aa** was obtained in 74% yield. **3aa** was then transformed to the corresponding amine **4** under basic conditions (Scheme 1a). As previously mentioned, the bromo-substituted sulfone **3ai** was allowed for further modification via palladium-catalyzed Suzuki cross-coupling reactions (Scheme 1b).

Table 3

Investigation on the scope of aromatic amides[a]

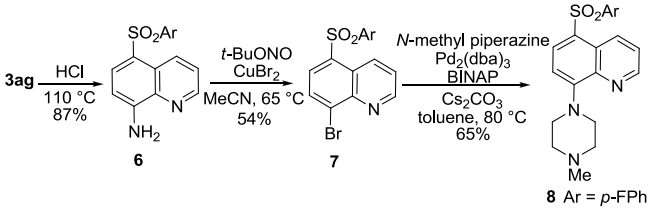


[a] Reaction conditions: **1** (0.1 mmol), **2i** (0.3 mmol), CuI (0.01 mmol), Ag_2CO_3 (0.1 mmol), K_2CO_3 (0.2 mmol), 1,4-dioxane (1.0 mL), 110 °C, under air, 10 h; isolated yields.
[b] 0.15 mmol aryl sulfonyl chloride was used.



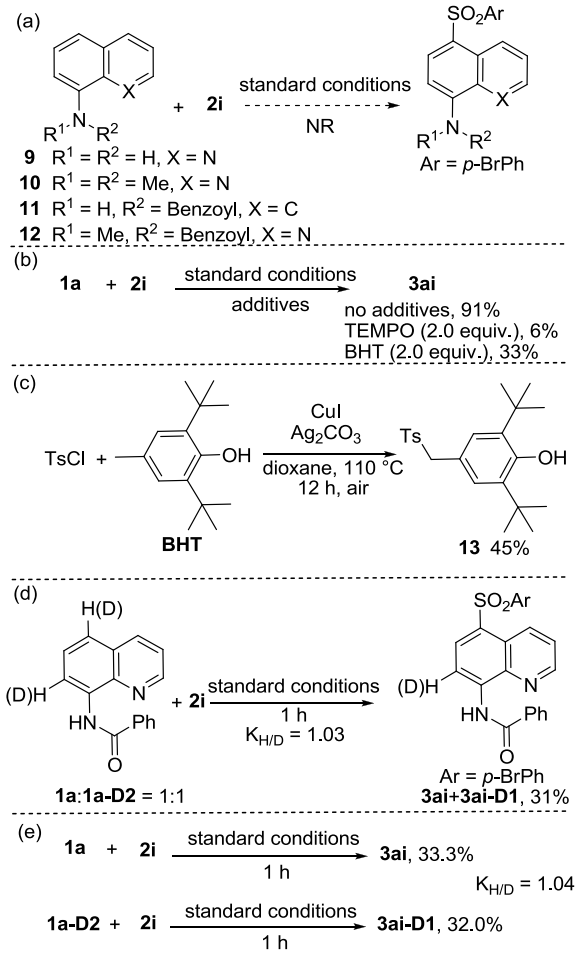
Scheme 1 Synthetic applications

The synthetic utility of this method was further demonstrated by the efficient synthesis of **8**, a potential fluorinated PET radioligand of 5-HT_6 serotoninergic receptor. **8** was initially prepared from 8-chloroquinoline in 4 steps, and the sulfone group was introduced using a two-step strategy, including the coupling of thiol with iodoquinoline and the oxidation of the resulting sulfide.[16a] By applying our new method, sulfone **3ag** can be prepared directly from **1a** and 4-fluorobenzenesulfonyl chloride **2g**. After deprotection, bromination and subsequent coupling with *N*-methylpiperazine, **8** was obtained in 31% overall yield (Scheme 2).



Scheme 2 Synthesis of **8**

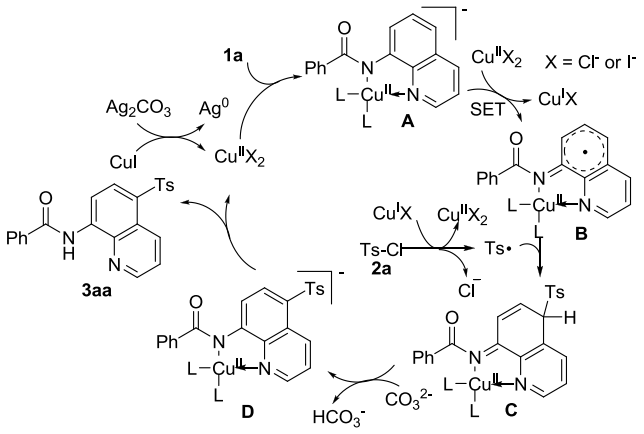
A number of control experiments were conducted under the optimized conditions to gain a mechanistic insight into these copper-catalyzed sulfonylation reactions (Scheme 3). Amino quinoline **9** and dimethylamino quinoline **10** failed to give the corresponding sulfones (Scheme 3a). Meanwhile, no sulfonylated product was detected in the reactions of *N*-naphthylamide **11** and **2i** (Scheme 3a). *N*-Methyl-protected amide **12** cannot give rise to the desired sulfone (Scheme 3a). These results of the investigation on the scope of quinolines indicate that chelation of copper with *N*,*N*′-bidentate 8-aminoquinoline plays an important role in promoting the reaction. The reaction was inhibited when the radical scavenger TEMPO or BHT was added, and the yield was sharply decreased to trace or 33% (Scheme 3b). Meanwhile, the reaction of TsCl with BHT gave product **13** in 45% yield, suggesting that *p*-tolylsulfonyl radical was formed and could be captured by BHT under the reaction condition (Scheme 3c).



Scheme 3 Control experiments

Moreover, kinetic isotope effect (KIE) experiments were performed to gain further mechanistic insight.[17] No KIEs were observed from both intermolecular competition ($k_{H/D}$ = 1.03) and two parallel reactions ($k_{H/D}$ = 1.04) (Scheme 3d and 3e), indicating that the cleavage of aromatic C−H bond is not the rate-determining step.

On the basis of the aforementioned experimental results and the literatures,[15a,15d,18] a radical process probably occurred in the reaction course. A proposed mechanism is depicted in Scheme 4. $Cu^{I}I$ is first oxidized to $Cu^{II}X_2$ (X = Cl or I) by Ag_2CO_3.[19] *N*-(Quinolin-8-yl)benzamide **1a** chelates with $Cu^{II}X_2$ to form complex **A**, and then the radical complex **B** is formed through the intermolecular SET between the electron-rich imidoquinoline moieties and the highly oxidative $Cu^{II}X_2$. Meanwhile, the *p*-tolylsulfonyl radical is generated.[20] The transfer of the *p*-tolylsulfonyl radical to **B** produces the imino−Cu^{II} complex **C**. Complex **D** is then provided under a deprotonation process of **C**. Complex **D** undergoes elimination to afford product **3aa**, and $Cu^{II}X_2$ is regenerated for the catalytic cycle.



Scheme 4 Proposed mechanism of Cu-catalyzed C–H sulfonylation

Conclusion

In summary, we developed an efficient reaction of copper-catalyzed C5-regioselective C−H sulfonylation of quinolineamide scaffolds using commercially available arylsulfonyl chlorides. The developed method was conveniently applied to synthesize a potential fluorinated PET radioligand **8**. Our insight into mechanistic studies suggested that sulfonylation of the quinoline ring undergo a radical process. Further studies focusing on the applications of this selective sulfonylation are currently underway.

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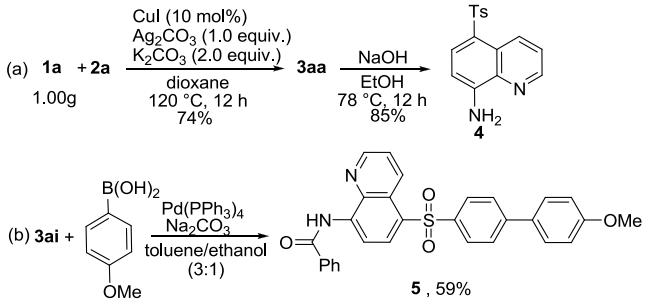
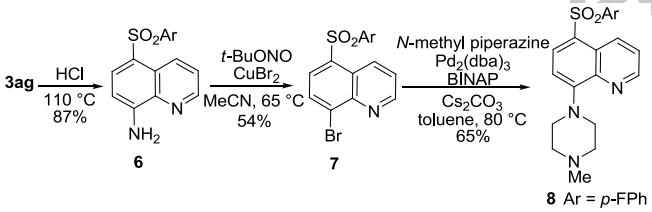
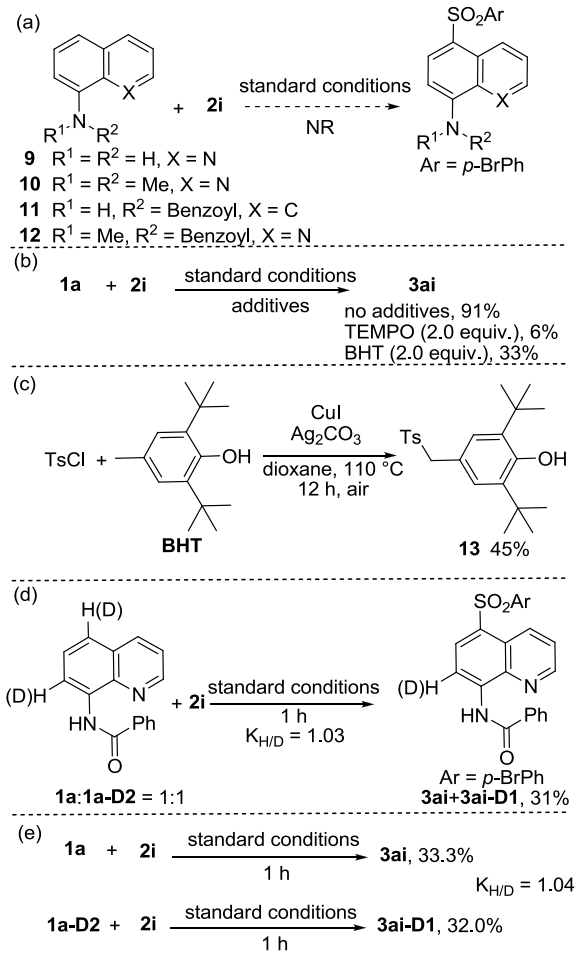


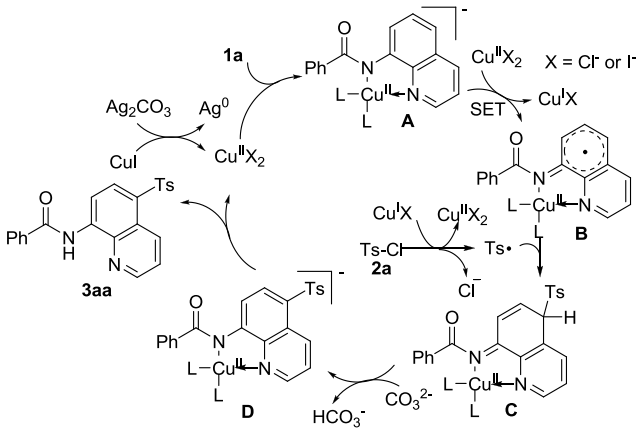
Scheme 1 Synthetic applications



Scheme 2 Synthesis of **8**



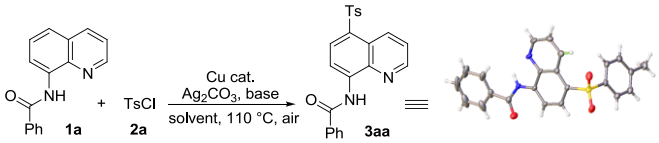
Scheme 3 Control experiments



Scheme 4 Proposed mechanism of Cu-catalyzed C–H sulfonylation

Table 1

Optimization of the reaction conditions[a]

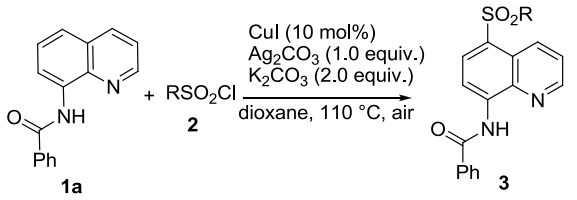


Entry	Catalyst	Base	Solvent	T (h)	Yield (%)
1	$Cu(OAc)_2{\cdot}H_2O$	Na_2CO_3	dioxane	46	42
2	-	Na_2CO_3	dioxane	-	N.R.
3[b]	$Cu(OAc)_2{\cdot}H_2O$	Na_2CO_3	dioxane	46	30
4	$CuBr_2$	Na_2CO_3	dioxane	46	30
5	$Cu(OTf)_2$	Na_2CO_3	dioxane	48	20
6	CuBr	Na_2CO_3	dioxane	46	35
7	CuI	Na_2CO_3	dioxane	46	55
8	CuI	Cs_2CO_3	dioxane	46	15
9	CuI	K_2CO_3	dioxane	46	61
10	CuI	K_2CO_3	DMSO	-	N.R.
11	CuI	K_2CO_3	DMF	-	N.R.
12	CuI	K_2CO_3	DCE	46	47
13	CuI	K_2CO_3	MeCN	46	50
14[c]	CuI	K_2CO_3	dioxane	12	69
15[c]	CuI[d]	K_2CO_3	dioxane	17	61
16[c]	CuI[e]	K_2CO_3	dioxane	12	72
17[c,f]	CuI[e]	K_2CO_3	dioxane	12	53
18[c,g]	CuI[e]	K_2CO_3	dioxane	24	45

[a] Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (20 mol%), Ag_2CO_3 (0.05 mmol), base (0.2 mmol), and solvent (1 mL) at 110 °C under air; isolated yields.
[b] Without Ag_2CO_3.
[c] 0.1 mmol Ag_2CO_3.
[d] 5 mol% CuI.
[e] 10 mol% CuI.
[f] 1.0 equiv. of TsCl.
[g] *p*-$MePhSO_2Na$ was used instead of TsCl.

Table 2

Investigation on the scope of arylsulfonyl chlorides[a]

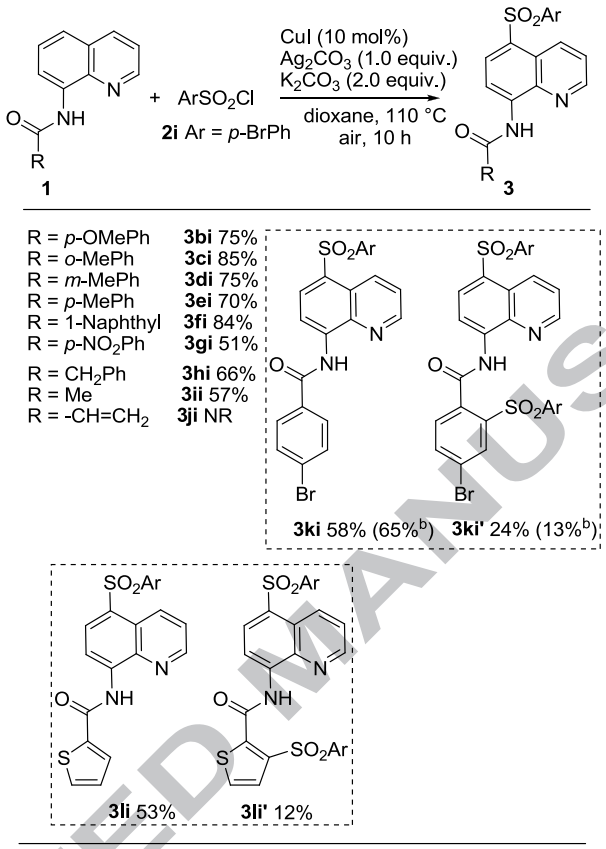


R = *p*-MePh	**3aa** 72% (12 h)
R = *m*-MePh	**3ab** 65% (32 h)
R = *o*-MePh	**3ac** 32% (32 h)
R = Ph	**3ad** 79% (12 h)
R = *p*-OMePh	**3ae** 53% (32 h)
R = *p*-*t*-BuPh	**3af** 77% (32 h)
R = *p*-FPh	**3ag** 74% (10 h)
R = *p*-CF_3Ph	**3ah** 75% (32 h)
R = *p*-BrPh	**3ai** 91% (10 h)
R = 2-naphthyl	**3aj** 59% (32 h)
R = Me	**3ak** 0%

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.3 mmol), CuI (0.01 mmol), Ag_2CO_3 (0.1 mmol), K_2CO_3 (0.2 mmol), 1,4-dioxane (1.0 mL), 110 °C under air; isolated yields.

Table 3

Investigation on the scope of aromatic amides[a]



[a] Reaction conditions: **1** (0.1 mmol), **2i** (0.3 mmol), CuI (0.01 mmol), Ag_2CO_3 (0.1 mmol), K_2CO_3 (0.2 mmol), 1,4-dioxane (1.0 mL), 110 °C, under air, 10 h; isolated yields.

[b] 0.15 mmol aryl sulfonyl chloride was used.

Graphical Abstract

Copper-catalyzed C5-regioselective C−H sulfonylation of 8-aminoquinoline amides with aryl sulfonyl chlorides

Jun-Ming Li, Jiang Weng, Gui Lu and Albert S. C. Chan

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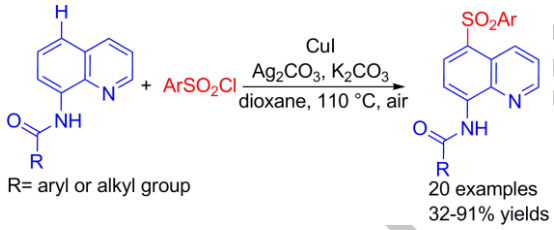

Highlights

- A copper-catalyzed C-H sulfonylation of 8-aminoquinoline on unusual C5 position was developed.
- The protocol showed broad substrates scope, giving the sulfones in good to excellent yields.
- With this method as the key step, a potential fluorinated PET radioligand was synthesized.
- Possible mechanism reveals that the reaction might undergo a radical process.