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Selective remote C–H sulfonylation of aminoquinolines with arylsulfonyl chlorides *via* copper catalysis

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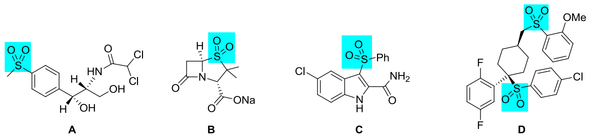
Copper-catalysed direct C–H bond sulfonylation of aminoquinolines using commercially available and inexpensive arylsulfonyl chlorides as the sulfonylation reagents is described. The reactions took place exclusively at the C5–H position of the quinoline rings and tolerated a wide spectrum of functional groups. Moreover, synthetic transformations of the sulfonylated products led to useful compounds.

The synthesis of sulfones is of great importance as these structures exist in a vast range of functional molecules relevant to pharmaceuticals,[1] agrochemicals,[2] and advanced functional materials.[3] For example, compounds **A**[4] and **B**[5] are both famous antibiotics, compounds **C**[6] and **D**[7] are potential drug candidates for the treatment of AIDS/HIV infection and Alzheimer's disease, respectively (Scheme 1). On the other hand, they are valuable synthons in organic synthesis for the preparation of several interesting compounds, as exemplified by Julia olefination[8] and Ramberg-Bäcklund rearrangement.[9] Consequently, several synthetic approaches towards sulfones have successfully been explored. The traditional sulfone preparation processes typically involve oxidation of sulfides[10] and electrophilic substitution[11] of aromatics with sulfonyl halides or sulfonic acids. Although these methods are attractive, the somewhat harsh reaction conditions such as the use of oxidants or strong acids may result in poor functional group compatibility. Besides, cross-coupling reactions are also commonly used methods regarding the sulfone synthesis.[12] Nevertheless, such reactions require the use of prefunctionalized reagents (e.g., halogenated and boron-containing reagents), and will generate large amounts of waste, thus leading to low atom and step economy.

Transition metal-mediated C–H functionalization has been evolved as a useful tool for the construction of new chemical bonds, such as C–C, C–N, and C–O bonds.[13] In contrast to the known



Scheme 1 Representative biologically active molecules containing sulfone moiety.

C-heteroatom bond-forming reactions, the methods with regard to C–S formation from C–H cleavage for the construction of sulfur-containing compounds, sulfones in particular, remain underdeveloped. Recently, Dong realized an elegant Pd-catalysed aryl C–H sulfonylation with arylsulfonyl chlorides.[14] Later, several groups reported the direct C–H sulfonylation of electron-deficient arenes and directing-group containing arenes based on Cu, Pd, and Ru metals or under metal-free conditions.[15] Despite these advances, the C–H sulfonylation remains unsatisfied with regard to substrate scope, selectivity, and reaction efficiency. Herein, we disclose a copper-catalysed efficient method for the construction of a variety of quinoline-derived sulfones from aminoquinolines and commercially available arylsulfonyl chlorides. It is noteworthy that our method, in contrast to the known C2–H and C4–H functionalization of the quinolines,[16] represents a rare example to selectively functionalize the remote C5–H of the quinoline rings.[17]

Our initial aim was to realize Cu-catalysed *ortho* C–H sulfonylation of benzoic acid derivatives with the assistance of 8-aminoquinoline auxiliary.[18] The reaction between benzamide **1a** and commercially available *p*-toluenesulfonyl chloride **2a** was chosen as a model system (Table 1). Strangely, the sulfonylation reaction did not occur at the phenyl group but at the C5–H position of the quinoline ring in the presence of CuI (20 mol%) and NaOAc (2 equiv) at 110 °C in toluene, delivering the corresponding sulfonylated product **3aa** in 10% yield (entry 1). The structure of **3aa** was unambiguously confirmed by single-crystal X-ray diffraction.[19] This finding is unexpected but interesting since it enables the sulfonylation reaction to occur at the remote C–H bond that is inaccessible by conventional methods. Such result prompted us to investigate more reaction parameters to improve the yield. Among the different copper salts, CuCl gave best result while CuI, $Cu(OAc)_2$ and $CuCl_2$ showed lower catalytic activity (entries 1-4). The classic

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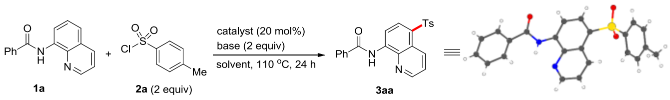
Table 1 Reaction optimization[a]



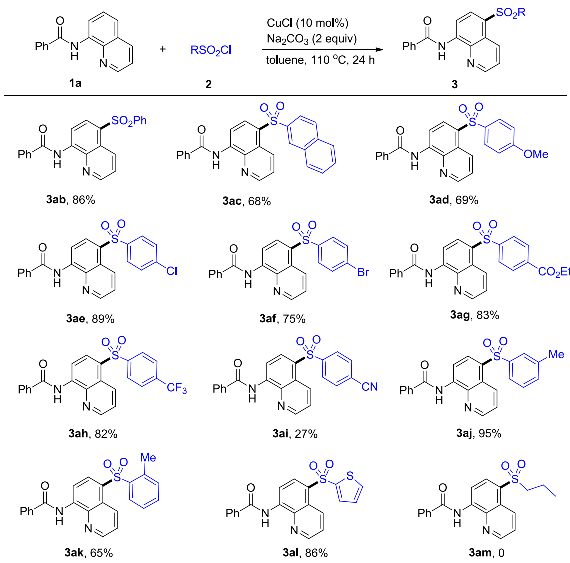
Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	CuI	NaOAc	toluene	10
2	CuCl	NaOAc	toluene	27
3	$Cu(OAc)_2$	NaOAc	toluene	13
4	$CuCl_2$	NaOAc	toluene	20
5	$FeCl_3$	NaOAc	toluene	0
6	$AuCl_3$	NaOAc	toluene	0
7	$Ni(OTf)_2$	NaOAc	toluene	0
8	$Zn(OTf)_2$	NaOAc	toluene	0
9	$Pd(OAc)_2$	NaOAc	toluene	0[c]
10	$[Cp^*RhCl_2]_2$	NaOAc	toluene	0
11	CuCl	PhCOOK	toluene	20
12	CuCl	$NaHCO_3$	toluene	16
13	CuCl	K_2HPO_4	toluene	15
14	CuCl	K_2CO_3	toluene	51
15	CuCl	Na_2CO_3	toluene	59
16	CuCl	Na_2CO_3	DMSO	0
17	CuCl	Na_2CO_3	DMF	0
18	CuCl	Na_2CO_3	dioxane	3
19	CuCl	Na_2CO_3	toluene	86[d]
20	CuCl	Na_2CO_3	toluene	trace[e]

[a] All the reactions were performed on a 0.2 mmol scale under Ar: **1a** (0.2 mmol), **2a** (2 equiv), catalyst (20 mol%), base (2 equiv), solvent (1 mL), 110 °C, 24 h. [b] Isolated yields. [c] *Ortho*-aryl C–H sulfonylation was observed. [d] 10 mol% of CuCl and 3 equiv of **2a** were used. [e] The reaction was run under air atmosphere.

Lewis acids including $FeCl_3$, $AuCl_3$, $Ni(OTf)_2$, and $Zn(OTf)_2$ all inhibited the reaction, suggesting that the formation of **3aa** through Lewis acid-catalysed Friedel–Crafts-type reaction seem unlikely (entries 5-8). **3aa** was not formed with $Pd(OAc)_2$ or $[Cp^*RhCl_2]_2$ as the catalyst (entries 9-10). However, a significant amount of sulfone generated from *ortho*-aryl C–H sulfonylation was observed in the presence of $Pd(OAc)_2$ (entry 9).[20] We also studied several inorganic bases such as PhCOOK, $NaHCO_3$, K_2HPO_4, K_2CO_3, and Na_2CO_3 (entries 11-15). The results indicated that the use of carbonate salts was beneficial to the reaction, of which a 59% yield being obtained using Na_2CO_3 as the base. The reaction either did not occur at all or provided **3aa** in a very low yield in polar solvents (entries 16-18). Pleasingly, **3aa** was obtained in 86% yield in the presence of 3 equiv of **2a** with only 10 mol% of CuCl as the catalyst (entry 19). Note that the reaction was almost inhibited under air atmosphere (entry 20).

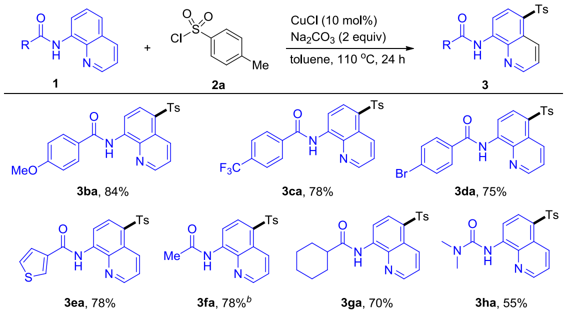
With the optimized reaction conditions in hand, we subsequently explored the substrate scope with respect to the sulfonyl chlorides (Table 2). Benzenesulfonyl chloride, naphthalenesulfonyl chloride and arylsulfonyl chlorides bearing methoxy, chloro, bromo, ester, and trifluoromethyl groups all exhibited good reactivity, affording the corresponding products in moderate to good yields (**3ab**-**3ah**, and **3aj**). However, the reaction of arylsulfonyl chloride with a cyano group only gave rise to **3ai** in 27% yield. Besides, the sulfonylation reaction between *ortho* methyl-substituted arylsulfonyl chloride **2k** and **1a** furnished the sulfone **3ak** in 65% yield. Significantly, thiophene-derived sulfonyl chloride also smoothly participated in the reaction to afford **3al** in 86% yield. Unfortunately, attempts to utilize 1-propanesulfonyl chloride failed most likely due to its thermal instability under the reaction conditions (**3am**).

Table 2 Substrate scope of arylsulfonyl chlorides[a]



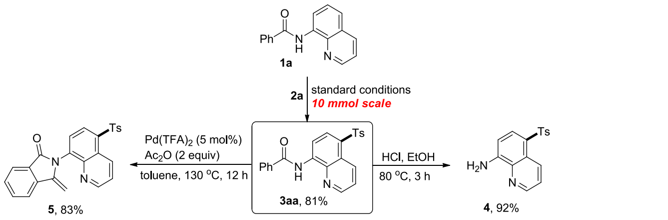
[a] All the reactions were performed on a 0.2 mmol scale under Ar: **1** (0.2 mmol), **2** (3 equiv), CuCl (10 mol%), Na_2CO_3 (2 equiv), toluene (1 mL), 110 °C, 24 h. Isolated yields are indicated.

Table 3 Substrate scope of aminoquinoline amides[a]



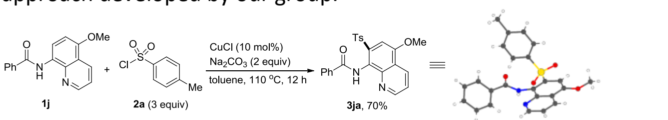
[a] All the reactions were performed on a 0.2 mmol scale under Ar: **1** (0.2 mmol), **2a** (3 equiv), CuCl (10 mol%), Na_2CO_3 (2 equiv), toluene (1 mL), 110 °C, 24 h. Isolated yields are indicated. [b] 20 mol% of CuCl was used.

The generality of this Cu-catalysed C–H sulfonylation was further demonstrated by the reactions of a variety of aminoquinoline amides with **2a** (Table 3). Various functionalities, such as methoxy (**3ba**), trifluoromethyl (**3ca**), and bromo (**3da**) groups were tolerated. Moreover, thiophenecarboxylic acid derived substrate was also suitable for the transformations, furnishing the corresponding sulfone in 78% yield (**3fa**). This method was also amenable to alphatic acid and carbamic acid derived substrates, which were indicated by the results of **3fa**, **3ga**, and **3ha**. However, 8-aminoquinoline and *N*-methylquinolin-8-amine were unreactive in the reactions.



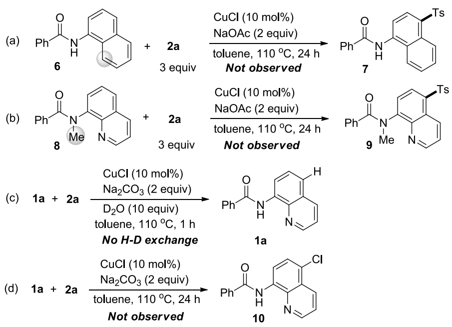
Scheme 2 Gram scale route to sulfone **3aa** and its synthetic transformations.

Given the easy accessibility of the starting materials and exceptionally simple catalytic system of this method, we performed the reaction on a gram scale (Scheme 2). Thus, a mixture of **1a** (10 mmol, 2.48 g), **2a** (30 mmol, 5.7 g), Na_2CO_3 (20 mmol, 2.12 g), and CuCl (1 mmol, 0.099 g) in toluene was stirred at 110 °C for 24 h to afford 3.26 g of **3aa** (81% yield), demonstrating the good scalability of our method. Furthermore, the obtained sulfone **3aa** was easily converted into some interesting compounds. After hydrolysis, **3aa** was transformed into C5 sulfonylated 8-aminoquinoline **4**[21] in 92% yield. In addition, **3aa** can be efficiently transformed into isoindolinone **5** using Pd-catalysed C–H functionalization/annulation approach developed by our group.[22]



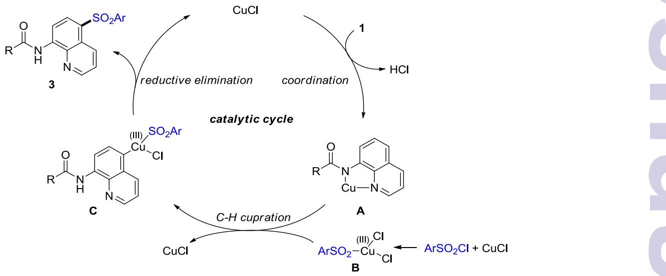
Scheme 3 Copper-catalysed C7–H bond sulfonylation.

During the course of these studies, we discovered that the sulfonylation reaction exclusively took place at the C7–H position of the quinoline ring under the standard reaction conditions if the C5–H position was blocked by a methoxy group (Scheme 3).[23] In the reaction, the amide functionality might act as a directing group to assist the C7–H bond cleavage. Unfortunately, the substrate scope with respect to the aminoquinoline amides and arylsulfonyl chlorides was very limited in this transformation.



Scheme 4 Mechanistic studies.

In order to gain insight into the reaction mechanism, some experiments were conducted (Scheme 4). Arylamide **6** derived from benzoic acid and 1-aminonaphthalene did not participate in the sulfonylation reaction at all (Scheme 4a). No sulfonylated product was observed in the reaction of *N*-methyl aminoquinoline amide **8** with **2a** (Scheme 4b). These two reactions suggested that the formation of a chelated complex between copper salt and aminoquinoline was crucial to the C–H sulfonylation. In addition, no deuterium was incorporated into the recovered starting material, which indicated that an irreversible C–H cleavage event occurred during the reaction (Scheme 4c). The product **10** derived from C5–H chlorination was not observed by GC-MS (Scheme 4d). Furthermore, **10** cannot be transformed into **3aa** under standard reaction conditions. These results indicated that an intermediate of C5 chloride was not involved in the reaction.



Scheme 5 Proposed mechanism of Cu-catalysed C–H sulfonylation.

Although the exact mechanism remains unclear, based on experimental results and the Cu-mediated C–H sulfonylation reactions,[15b,g] we proposed a mechanistic hypothesis for the Cu-catalysed selective C5–H sulfonylation of aminoquinolines with arylsulfonyl chlorides (Scheme 5). First, CuCl reacts with aminoquinoline amides **1** to produce a chelated complex **A** that may influence the electron density distribution of the C5–H position of the quinoline ring. Then, the intermediate **A** undergoes C–H cupration with a Cu(III) intermediate **B**[24] generated by an oxidative addition of the arylsulfonyl chloride to the CuCl. Finally, the formed intermediate **C** delivers the target product **3** and the CuCl via reductive elimination.[25,26]

In conclusion, we have established a site-selective C–H sulfonylation approach for the construction of a variety of quinoline-derived sulfones. The reactions use commercially available and inexpensive arylsulfonyl chlorides as the sulfonylation agents and cheap copper chloride as the catalyst. More importantly, our work complements the research area concerning the functionalization of remote C–H bonds. Further studies will be focused on the expansion of the transition metal-catalysed C–H sulfonylation strategy to a wide range of substrates.

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