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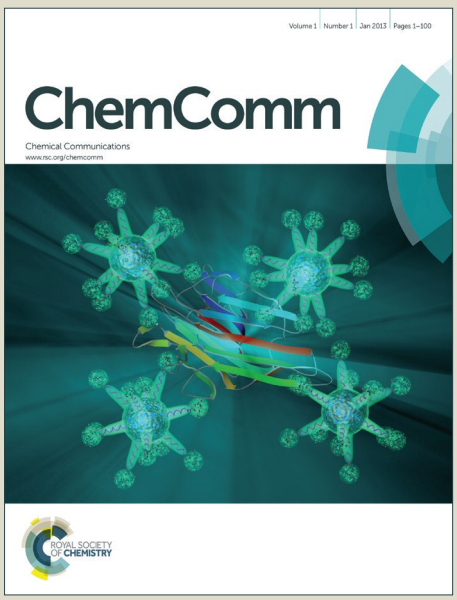

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ARTICLE TYPE

Copper-mediated *ortho* C-H sulfonylation of benzoic acid derivatives with sodium sulfinates

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Copper-mediated direct *ortho* C-H bond sulfonylation of benzoic acid derivatives with sodium sulfinates was achieved by employing an 8-aminoquinoline moiety as the bidentate directing group. **Various aryl sulfones were synthesized in good yields with excellent regioselectivity**.

Sulfones are a group of important molecules in organic chemistry[1] and they are valuable intermediates[2] in classic organic transformations such as the Ramberg-Backlund reaction[3] and Julia olefination.[4] In addition, the sulfone moiety has also been found in various drugs, natural products and medicinally active agents (Fig. 1).[5,6] Among the various sulfones, the synthesis of alkyl sulfones is rather straight forward since they can be conveniently synthesized *via* the classic nucleophilic substitution reaction of an alkyl halide with an alkyl thiol followed by oxidation.[1,7] In contrast, the synthesis of aryl containing sulfones can be more complicated since S_N2 reactions cannot be applied to aryl electrophiles. Among the methods developed for their syntheses, the sulfonylation of arenes in the presence of strong acids is frequently utilized. Though highly efficient, it tends to suffer from regioselectivity issues and functional group compatibility problems due to harsh reaction conditions.[8] In order to overcome these problems, several alternative strategies have been developed. For example, Pd- or Cu-catalyzed cross-coupling reaction of sodium sulfinates with alkyl or aryl halides has proven to be an effective route to construct aryl sulfones.[9] Besides aryl halides, aryl boronic acids[10] and diaryliodonium salts[11] can also be used as coupling reagents with or without metal catalyst. Although these strategies can serve as promising approaches for the synthesis of aryl sulfones, they all suffer from the need to use prefunctionalized starting materials such as aryl halides. On the other hand, direct sulfonylation *via* transition metal mediated or catalyzed C-H functionalization using the parent arenes as the starting materials could be appealing since no prefunctionalization is required. Along this line, Dong in 2009 developed an elegant palladium-catalyzed direct C-H bond sulfonylation of 2-aryl pyridines with arylsulfonyl chlorides.[12] However, substrate types of these recent developments are rather limited. Thus there remains much room to be improved in the field of selective sulfonylation of arenes.

Over the past several years, transition-metal-catalyzed or -mediated functionalization of C-H bonds has emerged as a powerful tool for the formation of carbon-carbon and carbon-heteroatom bonds.[13] Among the various metals employed, copper has gained significant attention owing to its abundance, inexpensiveness and versatile reactivity.[14] Since the pioneering work of Daugulis on the introduction of picolinic acid and 8-aminoquinoline auxiliaries as removable directing groups in transition metal catalyzed C-H bond activations,[15] combination of copper salts with these bidentate directing groups has emerged as an innovative strategy for the construction of carbon-carbon or carbon-heteroatom bonds through C-H bond cleavage.[16] Recently, copper-catalyzed or mediated chelation-assisted C-H bond activation to construct C-C bond and C-X bonds (X = S, O, N, F) with the aid of a bidentate directing group have been developed by the groups of Daugulis,[17] Miura,[18] Yu,[19] Shi,[20] Niu,[21] Stahl[22] and others.[23] Inspired by these studies as well as our continuing effort in this area,[23g] we were tempted to test the possibility of

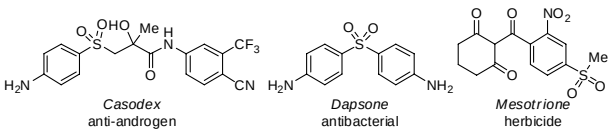
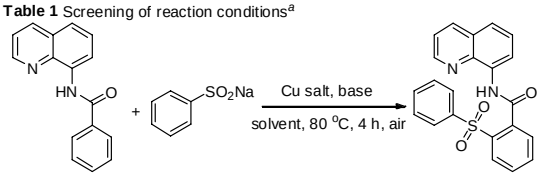


Fig. 1 Representive biological acitive aryl sulfone motif.

Table 1 Screening of reaction conditions[a]



1a 2a 3a

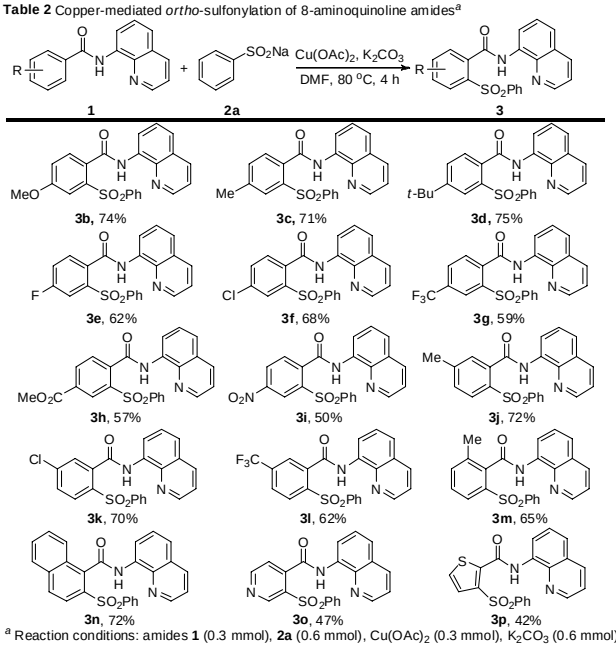
Entry	Cu salt	Base	Solvent	Yield[b] (%)
1	$Cu(OAc)_2$	None	DMF	25
2	$Cu(OAc)_2$	NaOAc	DMF	37
3	$Cu(OAc)_2$	$NaHCO_3$	DMF	40
4	$Cu(OAc)_2$	KOAc	DMF	44
5	$Cu(OAc)_2$	Li_2CO_3	DMF	52
6	$Cu(OAc)_2$	Cs_2CO_3	DMF	55
7	$Cu(OAc)_2$	Na_2CO_3	DMF	64
8	$Cu(OAc)_2$	K_2CO_3	DMF	76
9	CuI	K_2CO_3	DMF	18
10	$CuCl_2$	K_2CO_3	DMF	trace
11	$Cu(OTf)_2$	K_2CO_3	DMF	21
12	$Cu(OAc)_2{\cdot}H_2O$	K_2CO_3	DMF	68
13	–	K_2CO_3	DMF	0
14	$Cu(OAc)_2$	K_2CO_3	DMSO	56
15	$Cu(OAc)_2$	K_2CO_3	MeOH	42
16	$Cu(OAc)_2$	K_2CO_3	toluene	24
17	$Cu(OAc)_2$	K_2CO_3	CH_3CN	27
18	$Cu(OAc)_2$	K_2CO_3	dioxane	22
19	$Cu(OAc)_2$	K_2CO_3	DCE	18
20[c]	$Cu(OAc)_2$	NaOAc	DMF	12
21[c,d]	$Cu(OAc)_2$	NaOAc	DMF	15

[a] Reaction conditions: amide **1a** (0.3 mmol), **2a** (0.6 mmol), Cu salt (0.3 mmol), base (0.6 mmol), DMF (1 mL) under air for 4 h. [b] Isolated yield. [c] 0.2 equiv. of $Cu(OAc)_2$ was used. [d] $PhSO_2H$ was used as sulfonylation reagent.

sulfonylation of **1a** using sodium sulfinates as the source of sulfones. We herein wish to disclose a copper-mediated, 8-aminoquinoline directed *ortho* C-H sulfonylation of benzoic acid derivatives with sodium sulfinates to synthesize various arylsulfones.

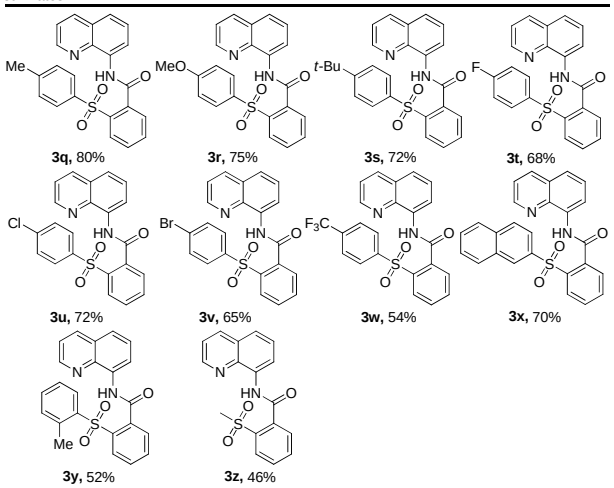
We commenced our studies by reacting benzoic acid derivatives **1a** with sodium benzenesulfinate in DMF in the presence of anhydrous $Cu(OAc)_2$ at 80 °C for 4 hours, and to our delight, the desired monosulfonylated product **3a** was obtained in 25% yield (Table 1, entry 1). The yield of **3a** could be increased up to 37% by employing 2 equiv of NaOAc as the base (Table 1, entry 2). We surmise that the addition of base may help with the cyclocupration process (see the mechanistic discussion part). Extensive screening studies showed that among the various bases such as $NaHCO_3$, KOAc, Li_2CO_3, Cs_2CO_3, Na_2CO_3, K_2CO_3 examined, K_2CO_3 was found to be the most effective base (Table 1, entries 2-8) and a 76% yield could be achieved. When the copper source was switched to CuI, $CuCl_2$, $Cu(OTf)_2$ or $Cu(OAc)_2{\cdot}H_2O$, the desired product **3a** was isolated in lower yields (Table 1, entries 9-12) and the reaction did not work in the absence of copper salts (Table 1, entries 13). Other organic solvents such as DMSO, MeOH, toluene, CH_3CN, dioxane, DCE were less effective for the reaction to preceed. Since it is well known that Cu(I) can be easily oxidized to Cu(II) under air, we tried to conduct this reaction by using a catalytic amount of $Cu(OAc)_2$ (20mol%) (Table 1, entry 20). Howerer, the desired product **3a** was only obtained in 12% yield. Using sulfinic acid as the starting material instead of the sodium salt did not improve the reaction yield much either (Table 1, entry 21). (see SI for more extensive screening results). Consequently, we decided to set reacting **1a** with 1 equiv of $Cu(OAc)_2$, 2 equiv of sodium sulfinates and 2 equiv of K_2CO_3 in DMF at 80 °C as the standard conditions. *It is worthwhile to mention that the same type of product can not be accessible through thiolation (Daugulis's procedure) followed by oxidation since disubstitution products predominate in the step of thioether formation.*[17a]

Table 2 Copper-mediated *ortho*-sulfonylation of 8-aminoquinoline amides[a]



[a] Reaction conditions: amides **1** (0.3 mmol), **2a** (0.6 mmol), $Cu(OAc)_2$ (0.3 mmol), K_2CO_3 (0.6 mmol), DMF (1 mL) under air for 4 h.

Table 3 Copper-mediated *ortho*-sulfonylation of 8-aminoquinoline amides with various sodium sulfinates[a]



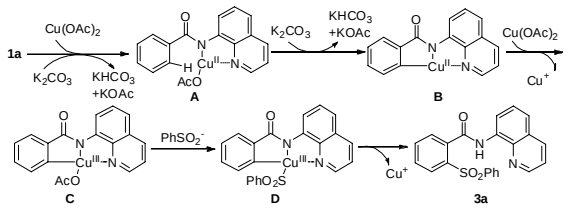
[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $Cu(OAc)_2$ (0.3 mmol), K_2CO_3 (0.6 mmol), DMF (1 mL) under air for 4 h.

With the optimized conditions in hand, we next set out to explore the substrate scope of 8-aminoquinoline amides and the results were summarized in Table 2. As shown in Table 2, a variety of benzamide substrates were compatible with this transformation, both electron-rich (**3b-3d**) and electron-poor (**3g-3i**) functional groups on the *para*-position of the benzene ring of benzamides were well tolerated in this reaction. Benzamides bearing halides (**3e-3f**) such as fluoro, chloro groups proceeded smoothly to give the corresponding sulfonylated products in good yields. In addition, substrate bearing a methyl group at the *ortho*-position could also be used as a viable substrate to deliver the desired product **3m**, showing the reaction is not sensitive to steric hindrance. Moreover, pyridine and thiophene derivatives could also be sulfonylated in 47% and 42% yields, respectively (**3o**, **3p**). It is important to point out that monosulfonylated products were exclusively obtained in all cases.

The scope of the sodium sulfinate substrates was also investigated under the optimized conditions (Table 3). Various 4-substituted electron-rich arylsulfinic acid sodium salts could smoothly react with **1a** to generate 2-arylsulfonyl benzamides in 72-80% yields (**3q-3s**). Sodium benzenesulfinates bearing halides such as fluoro, chloro, bromo groups could also be used in this reaction, giving the desired products in good yields (**3t-3v**). However, the yield for substrate with electron-withdrawing CF_3 group fell to 54% (**3w**). 2-Naphthylsulfinic acid sodium salt (**3x**) and 2-methyl benzenesulfinate (**3y**) could also participate in the coupling as well, furnishing the desired products in 70% and 52% yield, respectively. Finally, sodium methanesulfinate, an aliphatic sodium sulfinate, reacted with **1a** to produce the desired product in 46% yield (**3z**).

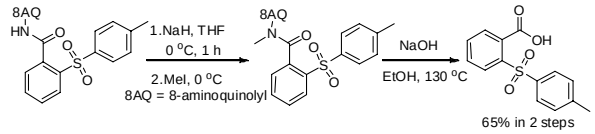
To shed some light on the mechanism of this new transformation, a series of control experiments were conducted. When radical inhibitor 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) was employed in the standard reaction, the yield was only slightly decreased, suggesting that the reaction does not involve radical steps. The intermolecular k_H/k_D of **1a** to **1a-*d*$_5$** was determined to be 3.0 and a similar KIE was also obtained from the intramolecular H/D competition experiment (k_H/k_D = 3.5). These results clearly indicated that the *ortho* C-H bond cleavage

of benzamide was involved in the rate-determining step of the sulfonylation (see SI for details).



Scheme 1 Plausible mechanism.

Though the mechanism of this reaction is still unclear at this moment, based on the above investigations and literature precedents,[18a,22,23] a tentative reaction mechanism is proposed in Scheme 1. Firstly, Coordination of **1a** to $Cu(OAc)_2$ followed by ligand exchange provides intermediate **A** which undergoes C-H activation to form the aryl/Cu^{II} species **B**. Next copper(III) complex **C** is formed *via* $Cu(OAc)_2$-promoted oxidation of **B**.[18a,22] **C** will next react with sodium sulfinate to afford copper complex **D**.[19,23] Subsequent reductive elimination of **D** provides the desired sulfonylated product **3a**.



Scheme 2 Removal of 8-Aminoquinoline directing group.

To demonstrate the synthetic utility of our procedure, we attempted to remove the 8-aminoquinoline directing group. As shown in Scheme 2, *N*-methylation of the secondary amide followed by base hydrolysis gave 2-tosylbenzoic acid in a good overall yield of 65%.

In conclusion, we have developed a novel copper-mediated auxiliary-assisted *ortho* C-H bond sulfonylation of benzoic acid derivative with a variety of sodium sulfinates. Notable features of this newly developed protocol include high monosulfonylation selectivity, excellent *ortho*-sulfonylation selectivity and broad functional group compatibility. Exploration on extending this strategy for the synthesis of complex sulfones is currently underway in our lab and the results will be reported in due course.

Notes and references

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† Electronic Supplementary Information (ESI) available: [Detail experimental procedures, analytical data]. See DOI: 10.1039/b000000x/

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