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Advanced Synthesis & Catalysis

Copper-Catalyzed Remote C–H Functionalization of 8-Aminoquinolines with Sodium and Lithium Sulfinates

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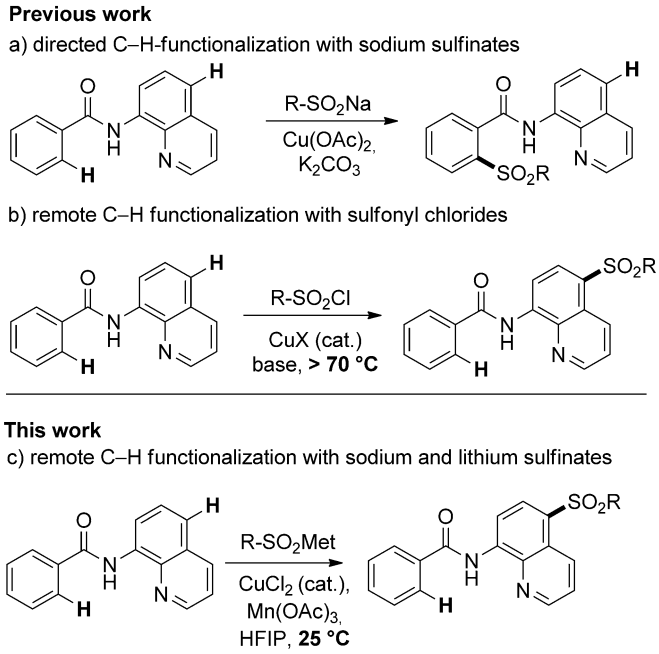
Abstract: A simple and mild copper-catalyzed sulfonylation of 8-aminoquinolines with sodium and lithium sulfinates is reported. In the presence of manganese(III) acetate [$Mn(OAc)_3$] as cooxidant a highly site-selective C–H functionalization at the C-5 position takes place. The reaction proceeds readily at room temperature in air and various sulfones were synthesized in moderate to high yields. Moreover, a straightforward procedure for the conversion of organolithium reagents and sulfur dioxide into C-5 sulfonylated quinolines was developed.

Keywords: C–H activation; copper; manganese; sulfinates; sulfones; sulfonylation

Sulfones are important building blocks in organic synthesis and common structural motifs found in numerous pharmaceuticals, agrochemicals and functional materials.[1] Among them, heteroaromatic sulfones have attracted particular interest as lead structures for the development of potential drugs against various diseases, such as HIV[2] or neurological disorders.[3]

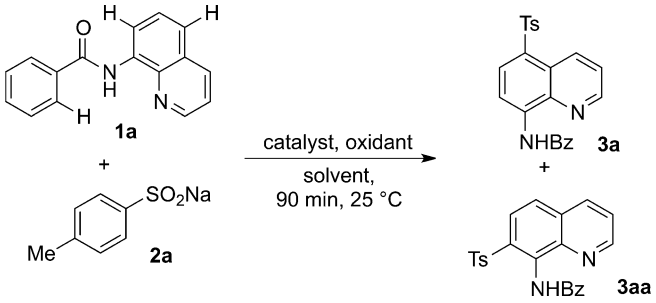
Traditional approaches for the synthesis of sulfones include the oxidation of sulfides, the alkylation of sulfinates, Friedel–Crafts-type sulfonylation of arenes with sulfonyl chlorides or addition reactions of sulfonyl-based radicals to olefins and alkynes.[1,4] Often these classical methods are limited by their harsh reaction conditions or inherent reactivities governed by electronic effects of the starting materials. During the past two decades new metal-catalyzed[5] and metal-free[6] coupling reactions of sodium sulfinates have been developed as milder, regioselective alternatives. Extension of these procedures to *in situ* generated metal sulfinates has led to the development of efficient multicomponent, one-pot sequences for the synthesis of sulfones.[7] Although quite straightforward, these processes rely extensively on prefunctionalized starting materials. In this context, the direct functionalization of C–H bonds offers an economically and ecologically attractive alternative.[8] In the last five years, considerable effort has been devoted to the development of new approaches for the synthesis of sulfones *via* selective functionalization of C–H bonds. Since the first report from Dong and co-workers on the palladium-catalyzed sulfonylation of phenylpyridines,[9a] various metal-catalyzed and metal-free procedures for the direct sulfonylation of C–H bonds have been described.[9] Recently, Tan and Shi as well as our group have reported copper-mediated or copper-catalyzed C(sp^2)–H sulfonylations of benzoic acid derivatives with sulfinic acid salts employing different removable directing groups (Scheme 1a).[10] Regioselective sulfonylation in an *ortho*-position of the directing group is observed in all three cases. Interestingly the copper-catalyzed sulfonylation of benzoic acids bearing the 8-aminoquinoline auxiliary[11] with sulfonyl chlorides does not occur at the phenyl ring. Instead a remote C-5–H sulfonylation of the quinoline ring takes place (Scheme 1b).[12,13] Herein, we report a copper-catalyzed remote C–H sulfonylation of 8-aminoquinolines with sodium and lithium sulfinates, which proceeds readily at room temperature.

During our initial studies on the copper-mediated sulfonylation of C(sp^2)–H bonds with sulfinates[10c] we made an interesting observation. Reaction of benzoic acid derivative **1a**, bearing an 8-aminoquinoline auxiliary, with sodium *para*-toluenesulfinate (**2a**) in the presence of 3 equivalents of $Cu(OAc)_2$ in hexafluoroisopropyl alcohol (HFIP) did not lead to the expected *ortho*-functionalization. Instead sulfonylation occurred at the aminoquinoline ring, furnishing the C-5 and the C-7 substituted products **3a** and **3aa** in 42% and 11% yields within 90 min at room temperature (Table 1, entry 1). This result is in stark contrast to the previous report by Tan,[10a] which showed that regioselective *ortho*-sulfonylation occurs under basic



Scheme 1. Directed *vs.* remote C–H sulfonylation of 8-aminoquinoline.

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Oxidant	Solvent	Yield [%][b] (**3a**+**3aa**)
1[c]	$Cu(OAc)_2$	–	HFIP	42+11
2	$CuCl_2$	$Mn(OAc)_3$	HFIP	77+17
3	$CuCl_2$	TBHP	HFIP	–
4	$CuCl_2$	$PhI(OAc)_2$	HFIP	–
5	–	$Mn(OAc)_3$	HFIP	27+10
6	$CuCl_2$	$Mn(OAc)_3$	TFE	54+31
7	$CuCl_2$	$Mn(OAc)_3$	*i*-PrOH	26
8	$CuCl_2$	$Mn(OAc)_3$	CH_3CN	<5
9[d]	$CuCl_2$	$Mn(OAc)_3$	HFIP	56+20
10[e]	$CuCl_2$	$Mn(OAc)_3$	HFIP	51+10
11[f]	$CuCl_2$	$Mn(OAc)_3$	HFIP	53+14

[a] *Reactions conditions:* **1a** (0.2 mmol), **2a** (3.0 equiv., 0.6 mmol), catalyst (20 mol%), oxidant (3.0 equiv., 0.6 mmol), solvent (2 mL), 25 °C, 90 min.
[b] Isolated yield.
[c] 3.0 equiv. $Cu(OAc)_2$.
[d] With 1.5 equiv. of $Mn(OAc)_3 \cdot 2H_2O$.
[e] With 1.5 equiv. of **2a**.
[f] With 5 mol% $CuCl_2$.

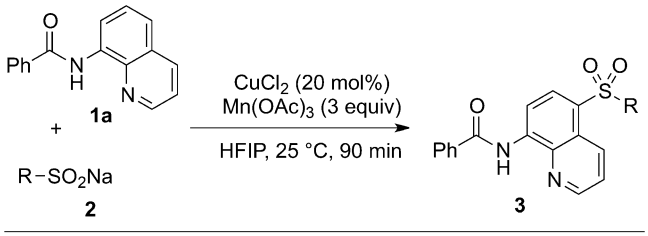
conditions (Scheme 1). So far selective sulfonylation of the 8-aminoquinoline motif is only possible using harsh reaction conditions and high temperatures.[12] The novel reactivity, discovered during our initial work, could provide a milder approach to C-5 sulfonylated quinolines. In addition, this transformation represents an unusual, condition-dependent switch in the regioselectivity of copper(II)-mediated C–H functionalizations, which warrants further examination. Therefore we decided to investigate this transformation in more detail.

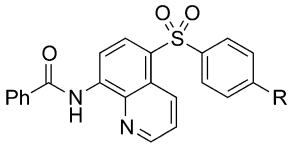
We started our studies with the optimization of the reaction conditions (Table 1). After screening a range of copper(II) salts, cooxidants, solvents and additives, we could identify the optimal conditions. Best yields were obtained with 20 mol% of $CuCl_2$, stoichiometric amounts of $Mn(OAc)_3$ (used as dihydrate) as cooxidant in HFIP as solvent (entry 2). Other oxidizing agents, such as $PhI(OAc)_2$ or *tert*-butyl hydroperoxide (TBHP), did not lead to the formation of the desired sulfonylated products (entries 3 and 4). Interestingly, $Mn(OAc)_3$ alone can promote the C–H functionalization, albeit in lower yields (entry 5).[14,15] Performing the reaction in trifluoroethanol furnished the products **3a** and **3aa** in a similar overall yield (85% *vs.* 94%), however with a diminished regioselectivity (1.7:1 *vs.* 4.5:1) (entry 6). Other solvents, including non-fluorinated alcohols or acetonitrile, did not prove as effective as HFIP (entries 7 and 8). Decreasing the amount of catalyst, sulfinate or $Mn(OAc)_3$ led to a significantly reduced yield (entries 9–11).

With the optimized conditions at hand, we explored the substrate scope in terms of the sodium sulfinate (Table 2). In general, both electron-rich or electron-poor arylsulfinic acid salts were well tolerated and the desired C-5 sulfonylated products could be obtained in good to excellent yields (**3a**–**3i**). In most cases the minor C-7 regioisomer was formed only in trace amounts or could not be detected at all. Only in the case of **3e** could the side product be isolated in 15% yield. Reactions with heterocyclic sulfinates, such as sodium pyridine-2-sulfinate, did not afford the desired sulfones (**3j**). Treatment of **1a** with sodium methylsulfinate (**2k**) furnished the corresponding alkyl sulfone **3k** in 58% yield. In this case a larger excess of the alkyl sulfinate was necessary to achieve a good yield.

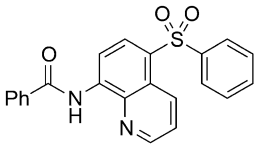
Subsequently, we investigated the effect of structural variations in the 8-aminoquinoline on the C-5 sulfonylation (Table 3). Reactions with substituted benzamides bearing electron-withdrawing or electron-donating substituents in the *para*-position as well as with heterocyclic amides proceeded smoothly, affording the diaryl sulfones **3l**–**3n** and **3q** in 73–96% yield. As before, the C-7 regioisomer was observed only in small amounts (<3%). Treatment of an acetamide-protected 8-aminoquinoline with 4-chlorophenylsulfinate furnished the desired product **3o** in 91% yield.

Table 2. Substrate scope of sodium sulfinates.[a]

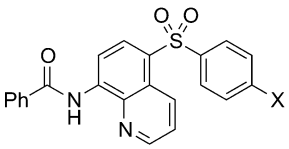




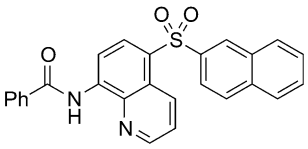
3a (R = Me) 77%
3b (R = CF_3) 96%
3c (R = OMe) 86%%
3d (R = *t*-Bu) 76%[b]



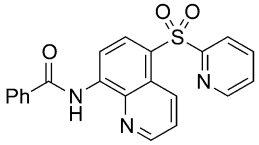
3e 78%



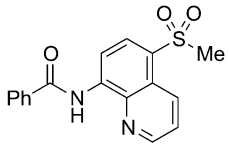
3f (X = F) 92%
3g (X = Cl) 95%
3h (X = Br) 85%



3i 89%



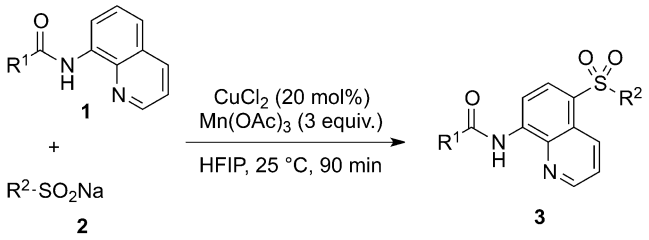
3j –

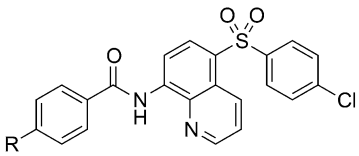


3k 58%[b]

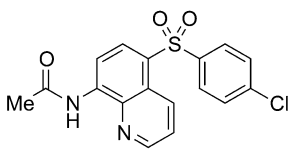
[a] *Reactions conditions:* **1a** (0.2 mmol), **2** (3.0 equiv., 0.6 mmol), $CuCl_2$ (20 mol%), $Mn(OAc)_3{\cdot}2H_2O$ (3.0 equiv., 0.6 mmol), HFIP (2 mL), 25 °C, 90 min.
[b] With 5.0 equiv. sulfinate.

Table 3. Substrate scope of sodium sulfinates.[a]

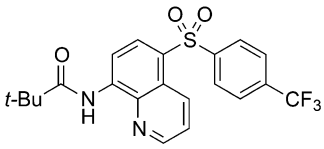




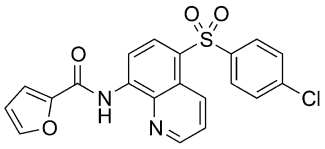
3l (R = OMe) 96%
3m (R = CO_2Me) 73%
3n (R = Cl) 95%



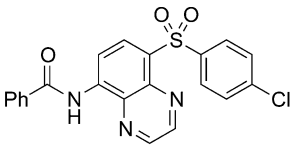
3o 91%



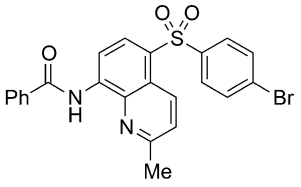
3p 25%[b]



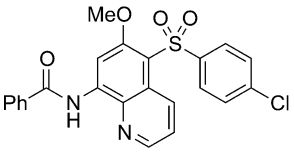
3q 91%



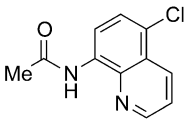
3r 22%



3s 41%



3t 89%



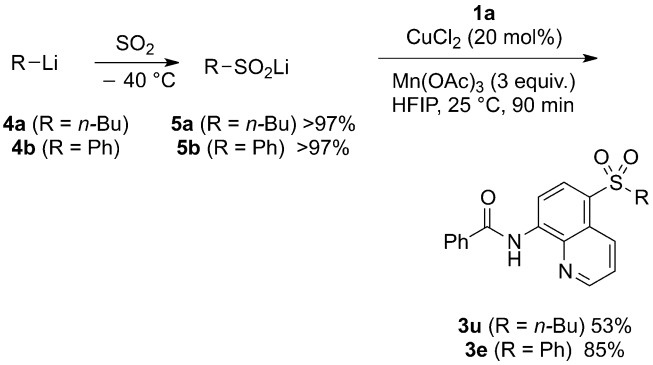
1k no reaction

[a] *Reactions conditions:* **1** (0.2 mmol), **2** (3.0 equiv., 0.6 mmol), $CuCl_2$ (20 mol%), $Mn(OAc)_3{\cdot}2H_2O$ (3.0 equiv., 0.6 mmol), HFIP (2 mL), 25 °C, 90 min.
[b] Reaction performed at 80 °C for 20 h.

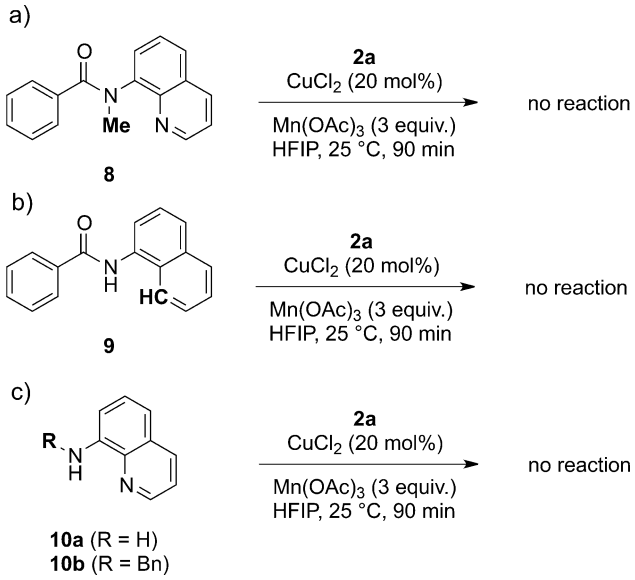
The method is somewhat sensitive to steric hindrance. Reaction of an 8-aminoquinoline bearing a sterically demanding pivaloyl amide required higher temperatures and longer reaction times and sulfone **3p** was isolated in only 25% yield. Structural modifications on the 8-aminoquinoline core are also possible to a certain extent. Substituents in the 2- or 6-position are tolerated and the desired products **3s** and **3t** were obtained in 41% and 89%. In the case of a quinoxaline-based starting material the heteroaryl sulfone is obtained in only 22% yield. Interestingly, no reaction, even no C-7 functionalization, is observed with 8-aminoquinolines bearing already a substituent in the 5-position, such as the chloro-derivative **1k**.

To increase the scope and applicability of our reactions, we next investigated a possible incorporation of lithium sulfinates. Sulfinic acid lithium salts, easily prepared from the reaction of organolithium reagents with sulfur dioxide,[1] are an attractive alternative to sodium sulfinates.[7] Due to the broad availability of organolithium reagents[16] a wide range of these lithium salts can be accessed. Therefore, both lithium phenyl- and *n*-butylsulfinates **5a** and **5b** were prepared in nearly quantitative yields from the corresponding lithium reagents and sulfur dioxide (Scheme 2). To our delight, lithium sulfinates are compatible with our copper-catalyzed remote sulfonylation and the reaction with aminoquinoline **1a** afforded the desired sulfones **3e** and **3u** in 85% and 53% yields.

For further applications of our transformation in the synthesis of complex sulfones, we explored the



Scheme 2. Synthesis of sulfones starting from organolithium reagents.

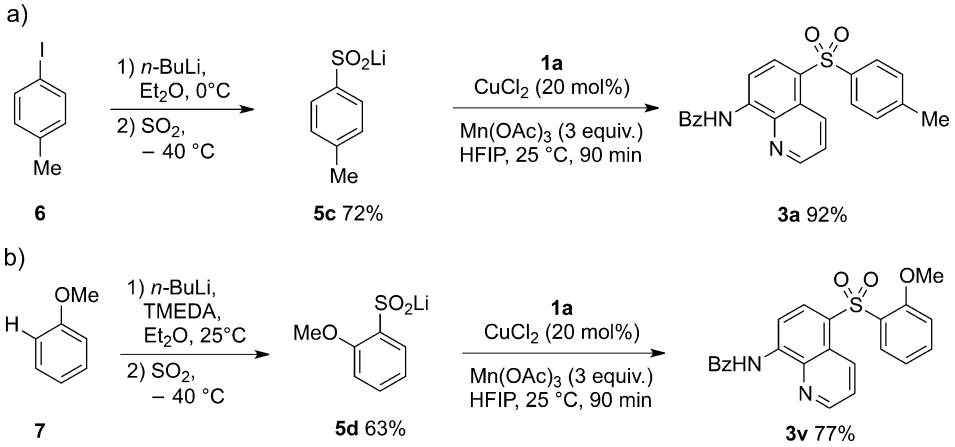


Scheme 4. Unsuccessful starting materials for the copper-catalyzed sulfonylation.

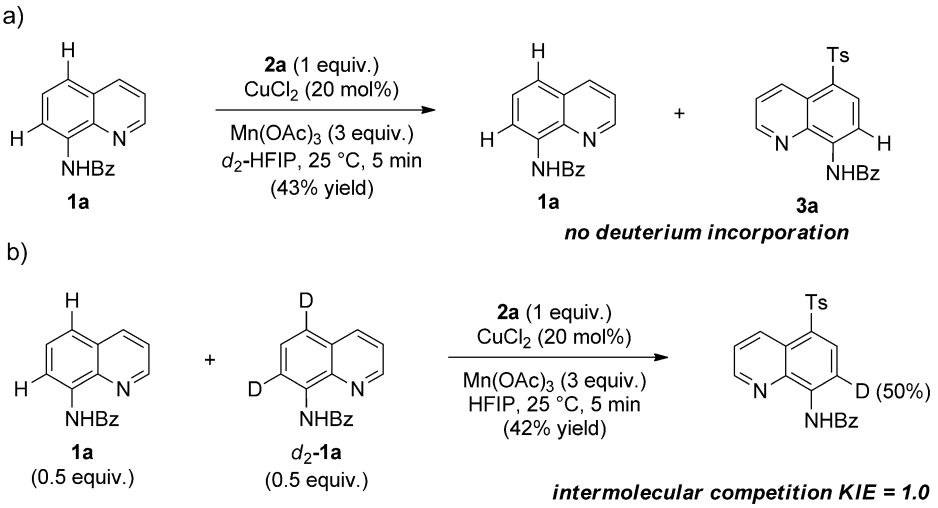
possible merger of our method with common procedures for the generation of organolithium compounds. To our delight, the two most common methods used for the preparation of complex organolithium reagents, lithium–halogen exchange and deprotonation,[16] are compatible with our copper-catalyzed C–H-sulfonylation. Lithium *para*-toluenesulfinate (**5c**) was synthesized in 72% yield starting from 4-iodotoluene (**6**) *via* lithium–iodine exchange with *n*-Buli followed by reaction of the corresponding lithium reagent with sulfur dioxide (Scheme 3a). Copper-catalyzed coupling of sulfinate **5c** with 8-aminoquinoline derivative **1a** under standard conditions afforded the desired C-5 sulfonylated product **3a** in 92% yield. Deprotonation of anisole (**7**) and subsequent trapping with sulfur dioxide gave *ortho*-methoxyphenylsulfinate (**5d**) in 63% yield. Reaction of sulfinate **5d** with **1a** led to the formation of diaryl sulfone **3v** in 77% yield.

To gain more insight into the reaction mechanism, a series of control experiments was performed. The copper-catalyzed coupling of *N*-methylated quinoline **8**, a substrate where bidentate chelation between both nitrogen atoms is blocked, did not afford any sulfonylated products under the standard conditions (Scheme 4a). In a similar manner reaction of the more electron-rich naphthalene derivative **9**, also not capable of bidentate coordination to metal centers, did not furnish any product at all (Scheme 4b). These results rule out a pathway *via* electrophilic aromatic substitution and indicate that a chelation complex between both nitrogens of the 8-aminoquinoline and copper might be crucial for the C–H sulfonylation. Interestingly, an acyl group on the 8-amino moiety is necessary for an efficient sulfonylation. Reactions of the parent free 8-aminoquinoline **10a** or an alkylated derivative **10b** did not afford the desired sulfonylated products (Scheme 4c).

Next reactions with isotopically labelled substrates were performed (Scheme 5). When the sulfonylation of **1a** was performed in d_2-HFIP no deuterium incor-



Scheme 3. Lithium–halogen exchange and direct lithiation approach to sulfones.

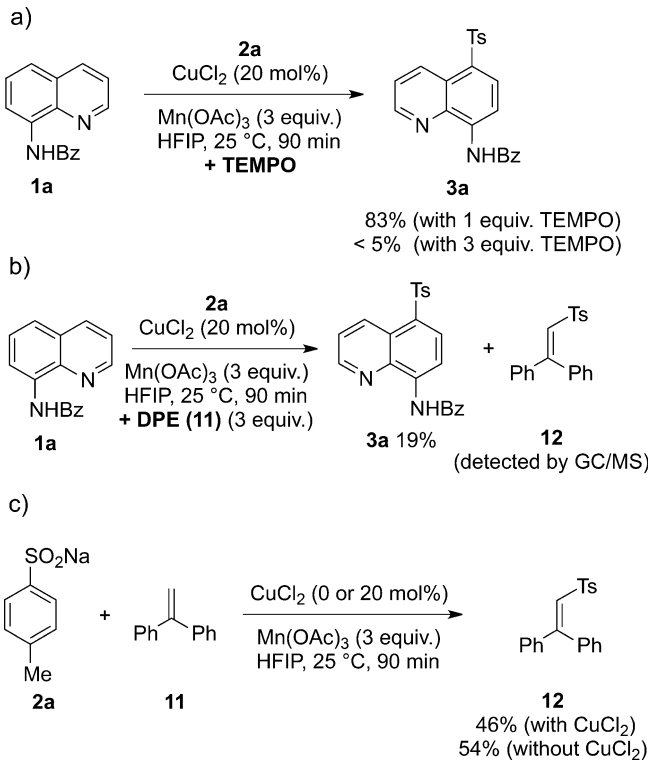


Scheme 5. Deuteration and isotope effect experiments.

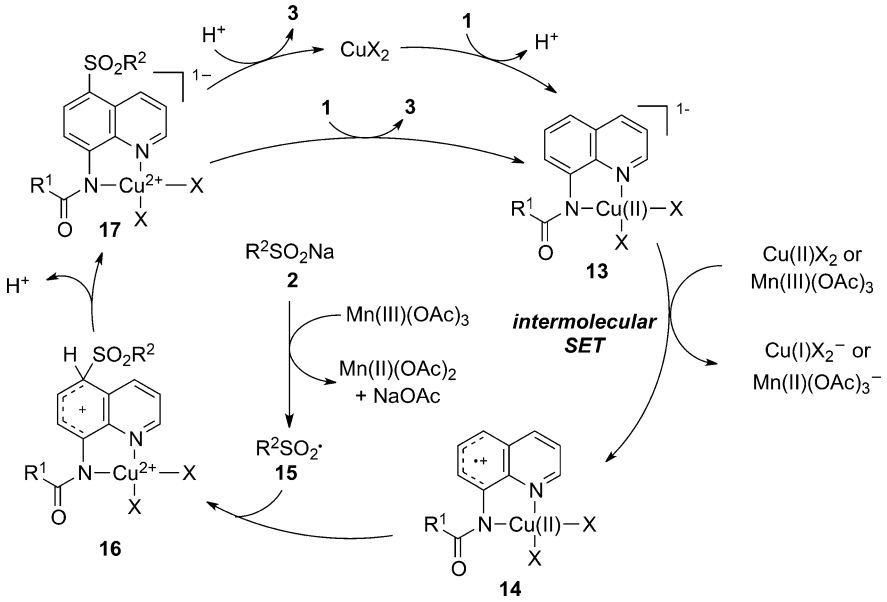
poration was observed in the product or the recovered starting material, suggesting an irreversible cleavage of the C–H bond (Scheme 5a). No kinetic isotope effect (KIE) was observed in an intermolecular competition experiment between amide **1a** and the dideuterated substrate d_2-**1a** (Scheme 5b). These results indicate that the cleavage of the C–H bond is not the rate-limiting step.

Performing the model reaction in the presence of the radical scavenger, 2,2,6,6-tetramethylpiperin-1-yl oxyl (TEMPO) did not affect the yield, if only one equivalent of TEMPO was used (Scheme 6a). Addition of three equivalents of the TEMPO completely shut down the reaction. Since TEMPO can either scavenge radical intermediates or deactivate the copper catalyst or $Mn(OAc)_3$ through redox processes or the formation of metal complexes, this result does not unambiguously prove the involvement of single electron transfer (SET) processes or radical intermediates. Therefore, additional experiments with 1,1-diphenylethylene (DPE) (**11**) as radical trap were conducted. Addition of 3 equivalents of DPE (**11**) to our model reaction led to sharp decrease in yield to 19%. Interestingly the coupling product **12** could be detected as side product (Scheme 6b). Reaction of sulfinate **2a** with DPE (**11**) in the absence of the aminoquinoline **1a** furnished vinyl sulfone **12** in 46–54% yield in the presence or absence of the copper catalyst (Scheme 6c). Formation of the addition product **12** suggests the involvement of a sulfonyl radical, which could be easily generated upon single-electron oxidation of the sulfinate salt.[1]

Considering our overall results and the recent reports by Stahl and others on remote C–H functionalizations of 8-aminoquinolines under acidic conditions,[13] the most plausible reaction pathway should proceed *via* single-electron transfer processes. Therefore we propose the following tentative mechanism (Scheme 7). Complexation of a copper(II) salt with 8-aminoquinoline **1** gives anionic imidate-copper(II) complex **13**. Recent theoretical calculations have shown that coordination of the substrate **1** to copper lowers the energy barrier for oxidation of the aminoquinoline and facilitates an intermolecular SET.[13a,d] Subsequently, the intermolecular SET between the amidoquinoline and either copper(II) or manganese(III) furnishes the radical complex **14**. Al-



Scheme 6. Radical-trapping experiments.



Scheme 7. Proposed mechanism.

though both Cu^{2+} and Mn^{3+} are competent oxidants for this reaction, oxidation by $Mn(OAc)_3$ is more likely to occur, due to the higher oxidation potential of Mn^{3+}.[17] This high oxidation potential might be the cause for the observed fast C–H functionalization at room temperature.[18] Single-electron oxidation of the sulfinate **2**, most likely again with $Mn(OAc)_3$,[19] leads to the formation of sulfonyl radical **15**. Addition of the radical **15** to intermediate **14** yields complex **16**. Loss of a proton, presumably *via* base-assisted deprotonation gives the anionic copper complex **17**, which can undergo protonation to yield the desired product **3** and the regenerated catalyst. Alternatively a direct ligand exchange of **18** with starting material **1** could lead to complex **13**, which can reenter the catalytic cycle. Reaction of intermediate **14** with sulfonyl radical **15** at the C-7 position would furnish the observed side-product of type **3aa**.

In summary, we have developed a novel, mild and efficient method for the remote sulfonylation of aminoquinolines with sodium sulfinates. The copper-catalyzed reaction is simple to perform and proceeds readily at room temperature. Various functional groups are tolerated and the desired C-5 sulfonylated aminoquinolines were obtained in high yields and regioselectivities. In addition, the use of lithium sulfinates, easily accessible from sulfur dioxide and organolithium reagents, enables the rapid synthesis of sulfones in two or three steps starting from simple building blocks. Essential for the rapid C–H functionalization at room temperature is the cooxidant, $Mn(OAc)_3$. This facile manganese-mediated oxidation offers new opportunities for the development of novel, mild C–H activations. Further applications of $Mn(OAc)_3$ in other oxidative C–H functionalizations are currently under investigation in our laboratory.

Experimental Section

Typical Procedure

An oven-dried 10-mL tube was charged with a magnetic stirring bar, aminoquinoline derivative **1** (1.0 equiv., 0.2 mmol), sodium sulfinate **2** (3.0 equiv., 0.6 mmol), $CuCl_2$ (5.4 mg, 0.2 equiv., 0.04 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (160.8 mg, 3.0 equiv., 0.6 mml) and HFIP (0.1 M referring to aminoquinoline derivative, 2 mL). The tube was closed with a rubber septum and the resulting reaction mixture was stirred at room temperature for 90 min. After completion of the reaction, the mixture was diluted with ethyl acetate and filtered through a short plug of celite and silica gel. The filter pad was rinsed with additional ethyl acetate and the combined filtrates were concentrated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.[20]

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