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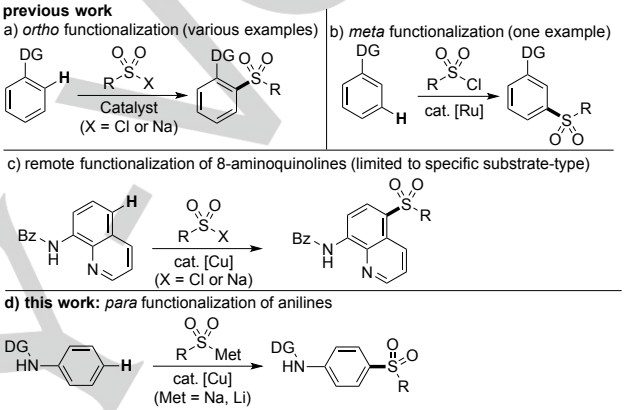
Copper-Catalyzed Remote *para*-C-H Functionalization of Anilines with Sodium and Lithium Sulfinates

Shuai Liang,[a] Michael Bolte,[b] and Georg Manolikakes*[a]

In Memory of Jean F. Normant – A Pioneer of Organocopper Chemistry

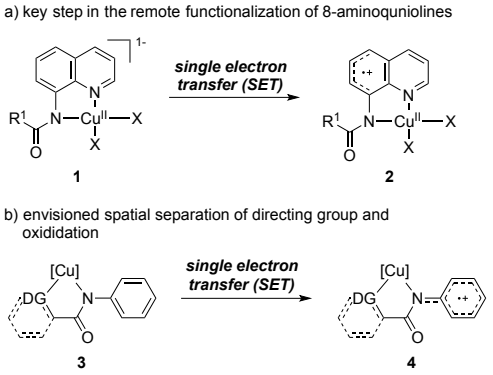
Abstract: A copper-catalyzed, cross-dehydrogenative coupling of anilines with sodium and lithium sulfinates is described. Using a cooperative reaction system with $Mn(OAc)_3$ as stoichiometric cooxidant a highly selective *para*-functionalization of anilines was accomplished. Various functional groups were tolerated and the desired products were obtained in high yields. This method not only provides a novel approach for the synthesis of arylsulfones but also might offer new opportunities for the development of copper-catalyzed *para*-selective C-H functionalizations.

Sulfones are versatile building blocks in organic synthesis and have found diverse applications in agroscience, medicine or materials.[1] Typical methods for the synthesis of sulfones include the oxidation of sulfides, alkylation of sulfinates, addition of sulfonyl-type radicals to alkenes or alkynes or electrophilic sulfonlyation of arenes.[1,2] In the last two decades sulfinic acids and their salts have emerged as useful starting materials for the preparation of sulfones in a variety of different transformations.[3,4] In combination with the in situ generation of sulfinic acids or sulfinates from suitable precursors and different sulfur dioxide sources, these procedures enable the straightforward synthesis of sulfones.[5,6] In recent years, methods for the direct sulfonylation of C-H-bonds have become an attractive alternative to reactions based on prefunctionalized starting materials.[7,8] Controlling the site-selectivity in such reactions with substrates containing multiple C-H-bonds remains a central challenge in this field. The directing group (DG)-assisted C-H-bond activation has been developed as very efficient strategy for the selective *ortho*-functionalization of (hetero)arenes.[7] A variety of methods for the *ortho*-sulfonylation of $C(sp^2)$-H bonds, utilizing this concept, have been reported (Scheme 1a).[8] Although much effort has been devoted to the directing-group assisted *meta*- and *para*-functionalization,[9,10] there is only one report one a ruthenium-catalyzed *meta*-selective sulfonylation of C-H bonds (Scheme 1b).[8g] Recently, we and others have developed methods for the copper-catalyzed remote sulfonylation of 8-aminoquinolines with sulfonyl chlorides or sulfinic acid salts (Scheme 1c).[11] These reactions proceed through an intriguing single-electron transfer (SET) mechanism involving complex between copper and the aminoquinoline.[11,12] Therefore all these methods are limited to functionalization of the 8-aminoquinoline scaffold. Herein we wish to report a copper-catalyzed remote *para*-C-H sulfonylation of anilines, based on a novel concept for site-selective oxidative cross-couplings (Scheme 1d).



Scheme 1. Current methods for directing group(DG)-assisted site-selective sulfonylation of $C(sp^2)$-H bonds.

Key step in the copper-catalyzed remote functionalization of 8-aminoquinolines is a single electron-transfer (SET) onto an imidate copper complex of type **1**, followed by addition of a nucleophile or radical to the formed radical species **2** (Scheme 2a).[11,12] We envisioned, that in principle a spatial separation of the directing group and the oxidation event should be possible, thereby enabling a direct *para*-functionalization of simple anilines (Scheme 2b). A major challenge in the development of such a process would be the identification of a catalyst-oxidant-directing group combination capable of selective single-electron-oxidation of the aniline moiety.



Scheme 2. Rationale for an oxidative *para*-selective C-H functionalization.

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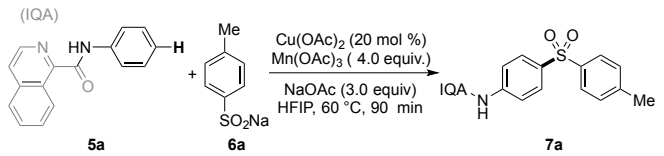
After extensive experimentation we discovered, that, in the presence of 20 mol% of $Cu(OAc)_2$ and stoichiometric amounts of $Mn(OAc)_3 \cdot H_2O$ and NaOAc, aniline **5a**, bearing a isoquinoline carboxamide directing group, reacted with sodium *para*-toluenesulfinate (**6a**) to furnish the desired *para*-sulfonylated aniline **7a** (Table 1, entry 1). The reaction proceeds efficiently in hexafluoroisopropanol (HFIP) and after 90 min at 60 °C the product could be obtained in 80% isolated yield as single regiosiomer.[13,14] The combination of catalytic amounts of $Cu(OAc)_2$ with $Mn(OAc)_3$ as stoichiometric oxidant is crucial for a efficient transformation. Reactions without $Cu(OAc)_2$ or $Mn(OAc)_3$ delivered sulfone **7a** with significantly reduced yields (entries 2 and 3), suggesting some cooperative effect between the copper catalyst and $Mn(OAc)_3$. Substitution of NaOAc with other bases is possible (entry 5). However, control experiments with the sodium salt of HFIP indicate, that in situ formed sodium hexafluoroisopropanolate (NaHFIP) might be the actual base

Table 1. *Para*-selective C-H-sulfonylation of **5a** – influence of the reaction parameters.[a]



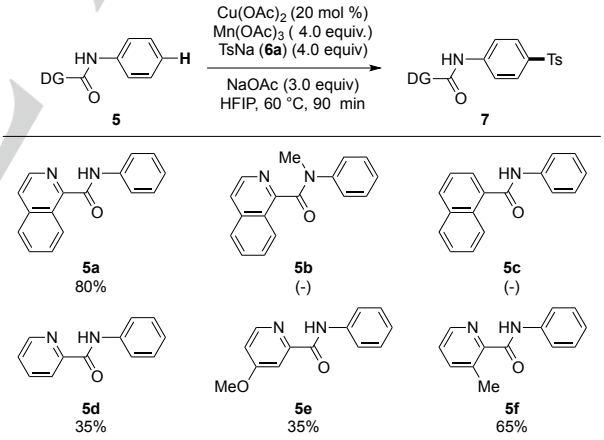
5a **6a** **7a**

entry	Variation from "standard" conditions	Yield [%][b]
1	none	**84** (**80**)[c]
2	without $Cu(OAc)_2$	24
3	with $Cu(OAc)_2$ (4.0 equiv) and without $Mn(OAc)_3$	20
4	without NaOAc	40
5	with NaOH or NaO*t*Bu instead of NaOAc	76-79
6	with NaHFIP instead of NaOAc	**83** (**80**)[c]
7	TFE instead of HFIP	37
8	MeOH or CH_3CN instead of HFIP	< 3
9	$PhI(OAc)_2$ or TBHP instead of $Mn(OAc)_3$	-
10	with $CuCl_2$, $CuBr_2$ or CuI instead of $Cu(OAc)_2$	29-58
11	with $Ni(OAc)_2$ or $Co(OAc)_2$ instead of $Cu(OAc)_2$	23-25
12	reaction performed at 25 °C	73 (71)[c]
13	with **6a** (3 equiv) instead	70
14	with $Mn(OAc)_3$ (3.0 equiv) instead	73
15	with $Cu(OAc)_2$ (5 mol%)	45

[a] *Reaction conditions*: **5a** (0.2 mmol), **6a** (0.8 mmol), $Cu(OAc)_2$ (20 mol%), $Mn(OAc)_3 \cdot 2H_2O$ (0.8 mmol), NaOAc (0.6 mmol), HFIP (2 mL), 60 °C, 90 min. [b] Yield determined by 1H-NMR with CH_2Br_2 as internal standard. [c] Isolated yield of analytical pure product.

(entry 6). The choice of HFIP as solvent is essential for a successful reaction.[15] Whereas the reaction in trifluoroethanol (TFE) delivered the desired sulfone **7a** in only 37% yield (entry 7), no or only trace amounts of product were observed in non-fluorinated alcohols or acetonitrile (entry 8). The use of other oxidants, such as $PhI(OAc)_2$ or *tert*-butyl hydroperoxide (TBHP) did not afford the sulfonylated aniline (entry 9). Best yields were obtained with $Cu(OAc)_2$ as catalyst. Other copper salts did not catalyze this transformation with a similar efficiency (entry 10). Substitution of the copper catalyst with other metal salts, e.g. $Ni(OAc)_2$ or $Co(OAc)_2$ was not possible (entry 11). Reduction of the reaction temperature or the amount of catalyst, $Mn(OAc)_3$ or the sulfinate **6a** led to reduced yields (entries 12-15).

A survey of different amide-linked directing groups underlined the pivotal role of this group (Scheme 3). Whereas the reaction of aniline derivative **5a** did furnish the *para*-sulfonylated product in 80% yield, N-methylated amide **5b** and the simple naphthyl amide **5c** did not undergo the desired C-H functionalization. These results indicate the critical role of both the amide and heterocyclic nitrogen, most likely as bidentate binding site for a metal atom. Since reaction of **5c** did not furnish any product, we can also exclude a reaction pathway via electrophilic aromatic substitution. Under the standard conditions, anilines **5d** and **5e**, bearing a picolinamide directing group, did react, albeit with a low yield of 35%. Only the reaction of **5f**, bearing a bulky substituent in *ortho*-position to the amide linker, furnished the sulfonylated product in comparable high yields.



Scheme 3. Influence of the directing group. Yields of isolated products of type **7** are given.

With the optimized reaction conditions at hand, we explored the substrate scope. At first reactions with various sodium sulfinates **6** with aniline derivative **5a** were studied (Scheme 4). Electron-rich, electron-poor and halogen-substituted sodium arylsulfinates or naphthylsulfinate were well tolerated and afforded the diarylsulfones **7a**-**7j** in 63-87% yield. The reaction with sodium methylsulfinate furnished alky sulfone **7k** in 67% yield. In all cases a highly selective *para*-sulfonylation was observed. In trace amounts (< 3%) of the *ortho*-functionalized product or no

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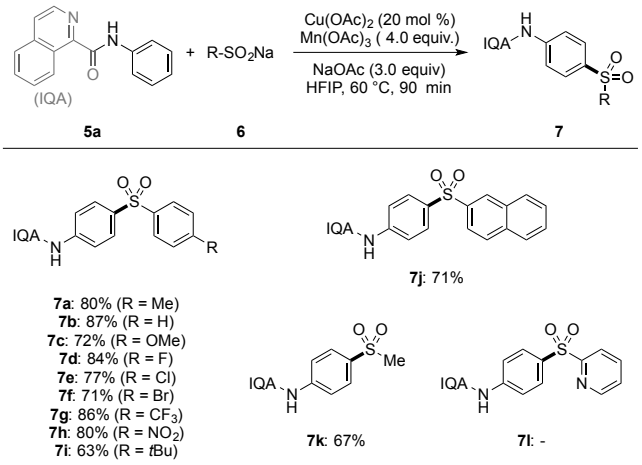
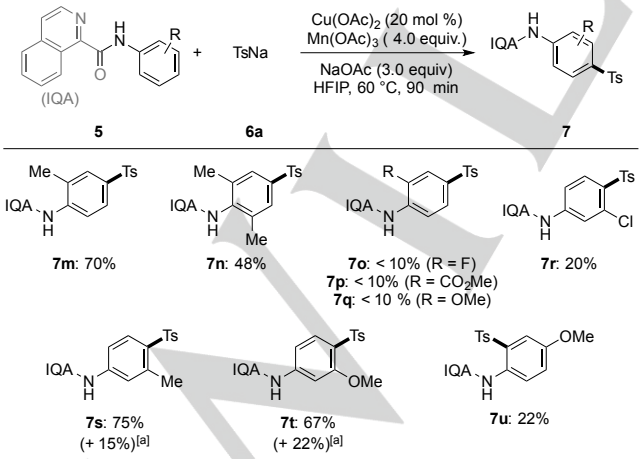


Scheme 4. Substrate scope of sodium sulfinates. Yields of isolated products are given. IQA = 1-isochinolinecarboxamide.

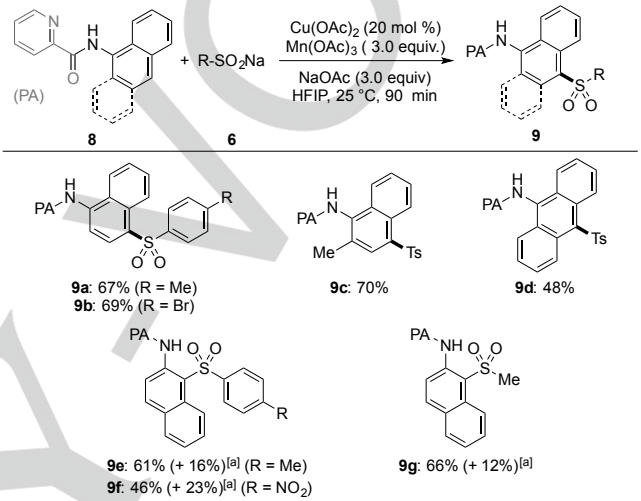
minor regioisomer at all were formed. Heterocyclic sulfinates, such as sodium 2-pyridine sulfinate, did not undergo the desired transformation (**7l**).

Subsequently reactions with aniline derivatives **5** were investigated (Scheme 5). Interestingly, our method proved to be quite sensitive to structural variations on the aniline core. Reactions of anilines with one or two methyl groups in the *ortho* position(s) proceeded more or less efficiently, and delivering sulfones **7m** and **7n** in 70% and 48% yield. However, substrates bearing either electron-withdrawing or -donating substituents in the *ortho*-position did not undergo the C-H-suflonylation. Treatment of *meta*-substituted anilines with **6a** afforded the *para*-functionalized products **7r**-**7t** in 20-75% yield, together with considerable amounts of undesired regioisomers. In the case of anisidine derivate **5u**, where the *para* position is blocked by a methoxy group, a selective *ortho*-sulfonylation takes place, albeit in only 22% yield (**7u**).



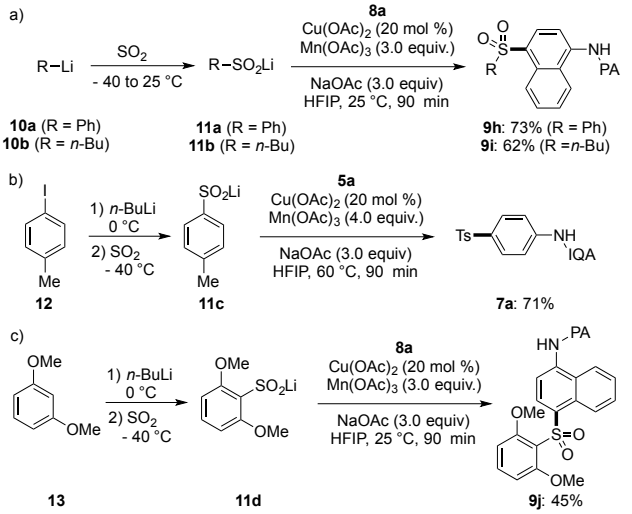
Scheme 5. Substrate scope of aniline derivatives. Yields of isolated products are given. [a]Combined yield of others regioisomers as determined by crude NMR. IQA = 1-isochinolinecarboxamide.

Further investigation revealed, that benzanelated anilines (**8**), such as 1-naphthylderivative **8a**, undergo a facile C-H-sulfonylation (Scheme 6). The reactions take place already at room temperature and require less excess of oxidant and sulfinate and in addition only the simple picolinamide (PA) directing group.[16] Sulfones **9a**- **9d** were isolated in 48-70% yield as single regiosiomer. Reactions of 2-naphtylamine derivatives proceeded with similar ease, affording the C1-sulfonylated or *ortho*-substituted products **9e**-**9g** in 46-61% yield together with 12-23% other regioisomers.



Scheme 6. Substrate scope of benzanelated aniline derivatives. Yields of isolated products are given. [a]Combined yield of others regioisomers as determined by crude NMR. PA = picolinamide.

In order to increase the scope of our method, we examined reactions with lithium sulfinates, readily accessible from the reaction of organolithium compounds with sulfur dioxide.[1,17] Thus, the benzene- and *n*-butanesulfinic acid lithium salts **11a** and **11b** were prepared from phenyl- and *n*-butyllithium **10a** and **10b** in quantitative yields (Scheme 7a). Gratifyingly, the crude lithium sulfinates undergo an efficient oxidative coupling with naphthylamine **8a**, thereby affording the desired sulfones **9h** and **9i** in 73% and 62% yield. As further extension sulfones **7v** and **9j** were synthesized from simple starting materials, using standard organolithium chemistry. *para*-Toluenesulfinic acid lithium salt (**11c**) was prepared from 4-iodotolune (**12**) via lithium-halide exchange and subsequent trapping of the formed *para*-tolyllithium with sulfur dioxide (Scheme 7b). Reaction of the lithium sulfinate **11c** with aniline derivative **5a** under the standard conditions furnished the C-H-sulfonylated product **7a** in 71% yield. In a similar manner lithium sulfinate **11d** was synthesized starting from 1,3-dimethoxybenzene (**13**) via deprotonation with *n*-BuLi, followed by reaction with sulfur dioxide (Scheme 7c). Oxidative coupling with **8a** furnished sulfone **9j** in 45% yield. These experiments show, that by merging classical organolithium chemistry with our oxidative coupling reaction, interesting sulfone scaffolds are accessible in a straightforward manner from two simple starting materials and sulfur dioxide.



Scheme 7. Synthesis and oxidative coupling of lithium sulfinates. Yields of isolated products are given. IQA = 1-Isoquinolinecarboxamide. PA = picolinamide..

In summary, we have developed *para*-selective, cross-dehydrogenative coupling of anilines with sulfinic acid salts. This efficient, remote C-H functionalization could be achieved by a cooperative reaction system consisting of $Cu(OAc)_2$ as catalyst and $Mn(OAc)_3$ as oxidant in combination with the 1-isocuinoline carboxamide directing group. This system overrides the usual *ortho*-selectivity of directing group-assisted copper-catalyzed C-H functionalizations. The reaction conditions are quite mild and tolerate range of functional groups. Moreover we could show, that, through the combination of organolithium chemistry and the oxidative C-H sulfonylation, a variety of interesting arylsulfones is accessible from simple building blocks. Although the reaction mechanism is not clarified so far,[18] our approach offers a new opportunity for copper-catalyzed *para*-selective oxidative C-H functionalization of arenes. Application of our concept in other cross-dehydrogenative couplings is currently under investigation in our laboratory.

Acknowledgements

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Keywords: sulfone • C-H functionalization • copper • manganese • site-selectivity

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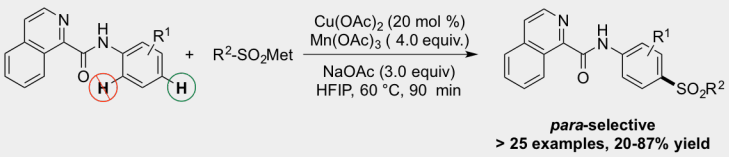

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Para* not *ortho: A cross-dehydrogenative coupling of anilines with sulfinic acid salts is reported. The cooperative reaction system with $Cu(OAc)_2$ as catalyst and $Mn(OAc)_3$ as stoichiometric cooxidant overrides the usual *ortho*-selectivity of copper-catalyzed, directing group-assisted C-H-functionalizations and allows remote *para*-selective C-H-sulfonylation of anilines.