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Copper-Mediated Sulfonylation of Aryl C(sp^2)–H Bonds with Sodium and Lithium Sulfinates

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Abstract: A copper-mediated direct sulfonylation of aryl C(sp^2)–H bonds with sodium and lithium sulfinates is reported. Various aryl sulfones were synthesized in moderate to excellent yields with good functional group tolerance.

Keywords: amide-oxazolines; C–H activation; copper; sulfinates; sulfonylation

Aryl sulfones are versatile intermediates in organic chemistry and important target structures in the synthesis of pharmaceuticals and functional materials.[1] Aryl sulfones are found in a variety of biologically active molecules such as Dapsone,[2] Casodex[3] or Pyroxasulfone (Figure 1).[4]

As a result of their interesting properties, efficient and practical methods for the synthesis of sulfones are in high demand. Traditional approaches, such as the oxidation of sulfides or the sulfonylation of arenes in the presence of strong acids tend to suffer from poor functional group compatibility and/or regioselectivity issues.[1] In recent years several efficient reactions of sodium sulfinates in metal-free[5] and metal-catalyzed[6] processes have been reported. These methods have been extended to three-component, one-pot syntheses of sulfones with *in situ* generated lithium, magnesium or zinc sulfinates.[7] However, one common drawback of these methods is the utilization of prefunctionalized coupling partners. The transition-metal catalyzed direct functionalization of C–H bonds has emerged as an attractive, atom-economic alternative.[8] In 2009 Dong and co-workers reported the first Pd-catalyzed C(sp^2)–H bond sulfonylation of 2-arylpyridines with sulfonyl chlorides as an electrophile.[9] Removal of the pyridine directing group is not possible in this case and further improvements would be highly desirable.[10] In the last 15 years, significant advances have been made in the field of oxidative couplings of C–H bonds for the construction of C–C and C–X, so-called cross-dehydrogenative couplings (CDC).[11] In this context several groups have developed oxidative couplings of sodium sulfinates with indoles.[12] Recently, the groups of Tan and Shi reported two copper-mediated/catalyzed C(sp^2)–H sulfonylations of benzoic acids with sodium sulfinates employing either the 8-aminoquinoline (AQ)[13] or 2-pyridinyl isopropyl (PIP)[14] directing group. Herein we wish to report a copper-mediated sulfonylation of aryl C(sp^2)–H bonds with sodium as well as lithium sulfinates directed by the amide-oxazoline directing group (Oxa).

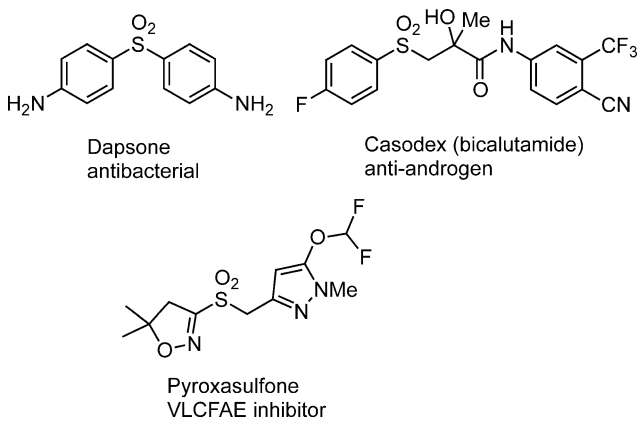
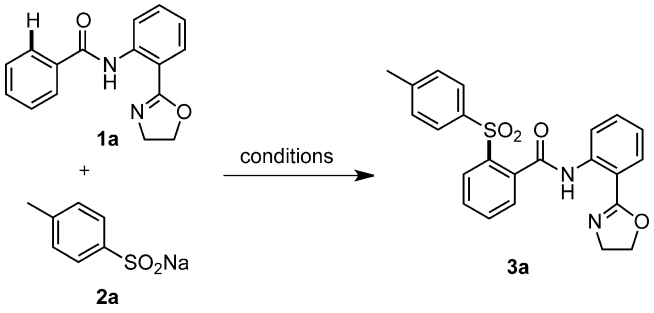


Figure 1. Biologically active aryl sulfones.

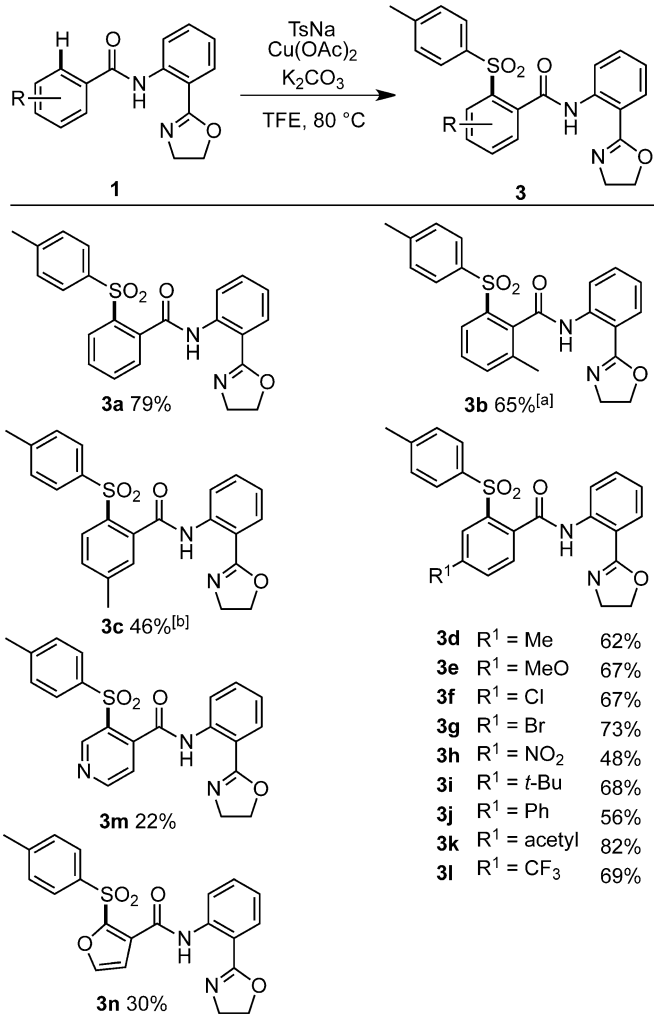
Prompted by the work of Yu on Cu-mediated *ortho*-functionalization using the amide-oxazoline directing group,[15] we subjected amide **1a** to various conditions in the presence of sodium sulfinate **2a** as coupling partner (Table 1). The aryl C(sp^2)–H sulfonylation proceeded in various solvents in the presence of 2 equiv. of TsNa, 1 equiv. of $Cu(OAc)_2 \cdot H_2O$ and 2 equiv. of K_2CO_3 at 80 °C (entries 1–5) Notably, best yields were obtained in trifluoroethanol (TFE).

Table 1. Optimization of the reaction.[a]



Entry	Cu salt [equiv.]	Base	Solvent	Yield [%][b]
1	$Cu(OAc)_2{\cdot}H_2O$ [1]	K_2CO_3	DMSO	34
2	$Cu(OAc)_2{\cdot}H_2O$ [1]	K_2CO_3	DMF	39
3	$Cu(OAc)_2{\cdot}H_2O$ [1]	K_2CO_3	THF	6
4	$Cu(OAc)_2{\cdot}H_2O$ [1]	K_2CO_3	TFE	57
5	$Cu(OAc)_2{\cdot}H_2O$ [1]	K_2CO_3	HFIP[c]	43
6	$Cu(OAc)_2{\cdot}H_2O$ [1]	Na_2CO_3	TFE	28
7	$Cu(OAc)_2{\cdot}H_2O$ [1]	Cs_2CO_3	TFE	54
8	$Cu(OAc)_2{\cdot}H_2O$ [2]	K_2CO_3	TFE	61
9	$Cu(OAc)_2{\cdot}H_2O$ [0.5]	K_2CO_3	TFE	52
10[d]	$Cu(OAc)_2{\cdot}H_2O$ [2]	K_2CO_3	TFE	69
11[d,e]	$Cu(OAc)_2{\cdot}H_2O$ [2]	K_2CO_3	TFE	74
12[d,e]	$CuCl_2$, $CuBr_2$, CuI [2]	K_2CO_3	TFE	<60
13[d,e]	**$Cu(OAc)_2$ [2]**	**K_2CO_3**	**TFE**	**82**
14[d,e,f]	$Cu(OAc)_2$ [2]	K_2CO_3	TFE	25
15[d,e,g]	$Cu(OAc)_2$ [2]	K_2CO_3	TFE	62

[a] Reaction *conditions:* **1a** (0.2 mmol), **2a** (0.3 mmol), Cu catalyst, base (0.4 mmol) in solvent (2 mL) at 80 °C for 20 h.
[b] Yield determined by ^{1}H NMR with CH_2Br_2 as internal standard.
[c] 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP).
[d] With 3 equiv.of TsNa.
[e] Reaction performed in 1 mL of TFE.
[f] Reaction performed at 60 °C.
[g] Reaction performed at 100 °C.

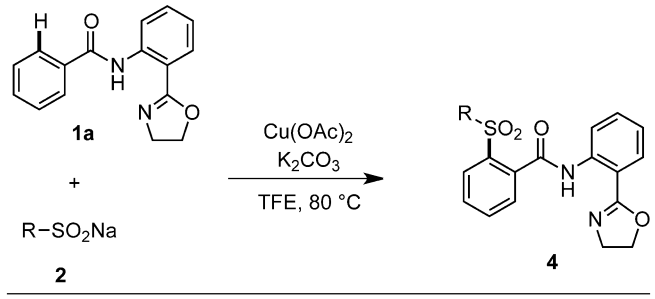


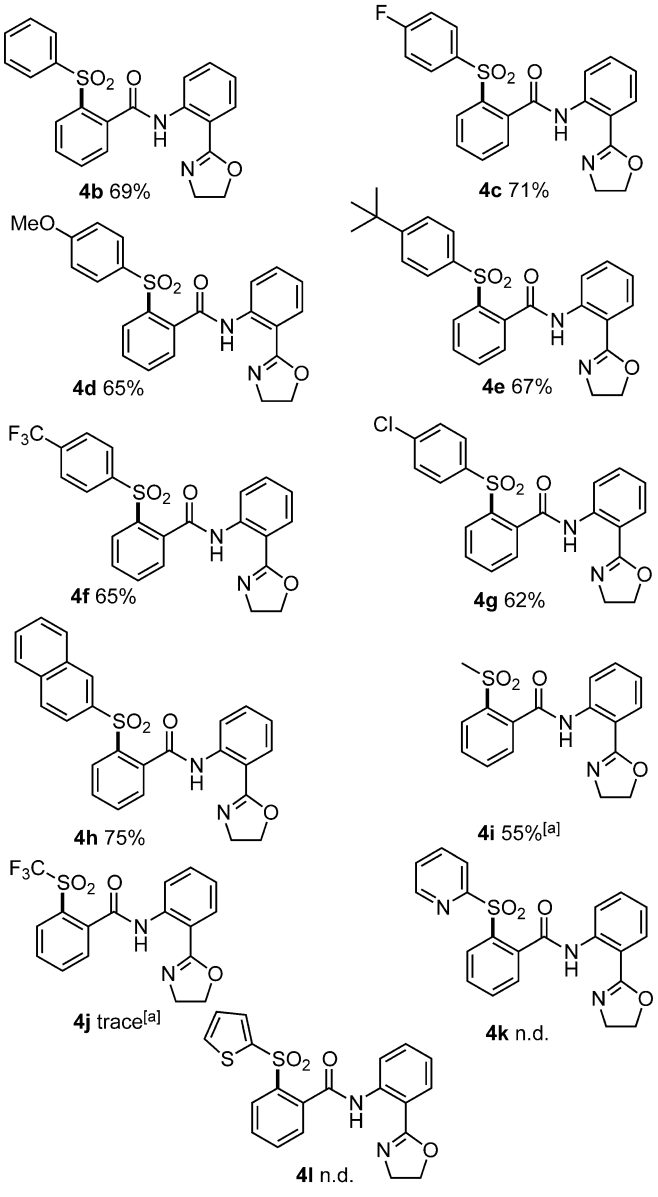
Scheme 1. Scope of benzamides. *Reaction conditions:* **1** (0.2 mmol), **2a** (0.6 mmol), $Cu(OAc)_2$ (0.4 mmol), K_2CO_3 (0.4 mmol) in TFE (1 mL) at 80 °C for 20 h under air.

Among various bases screened, K_2CO_3 gave the highest yields (entries 6 and 7). The yield increased to 69% when 2 equiv. of $Cu(OAc)_2{\cdot}H_2O$ and 3 equiv. of TsNa were employed (entries 8 and 10). Reducing the amount of copper catalyst lead to a decreased yield (entry 9). Further evaluation of the reaction conditions revealed that the yield could be increased to 82% by using anhydrous $Cu(OAc)_2$ and performing the reaction at higher concentrations (entries 11 and 13). Other copper salts displayed reduced reactivity and changes of the temperature resulted in lower yields (entries 12, 14, and 15).

With the optimized conditions in hand, we explored the reaction scope in terms of the benzamide component (Scheme 1). In general, both electron-withdrawing and electron-donating substituents in the *para*-position (**3d–3l**) were well tolerated. Reactions with benzamides bearing a halogen (**3f**, **3g**), trifluoromethyl (**3l**), keto (**3k**) or nitro (**3h**) group proceeded smoothly, affording the desired diaryl sulfones in 48–82% yield. The method is somewhat sensitive to steric hindrance. Reaction of benzamide **1b** bearing a methyl group in *ortho* positions (**3b**) required higher temperatures of 100 °C to obtain the sulfone in 65% yield. In the case of *meta*-substituted benzamide **3c**, even higher temperatures were required to achieve reasonable conversion rates. Even so the sulfone was obtained in only 46% yield. Heterocycles such as pyridine (**3m**) or furan (**3n**) could also be sulfonylated albeit in lower yields (22–30%).

Subsequently the scope of the sodium sulfinate component was investigated (Scheme 2). A range of *para*-substituted arylsulfinic acids sodium salts delivered the desired products in high yields. Sodium ben-



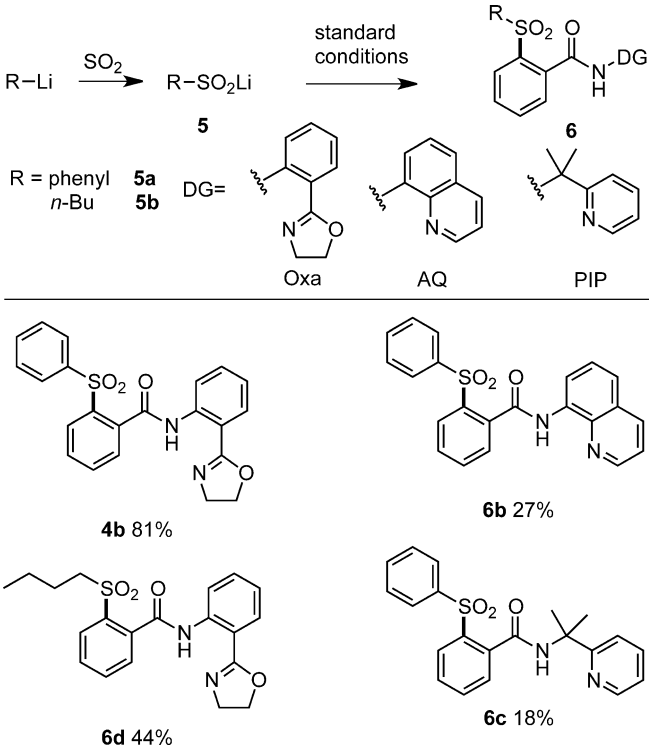


[a] With 5 equiv. of sulfinate.

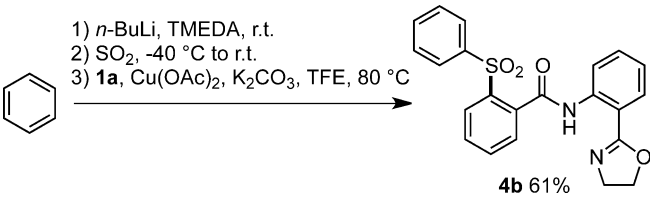
Scheme 2. Scope of sulfinates. *Reaction conditions:* **1a** (0.2 mmol), sulfinate **2** (0.6 mmol), $Cu(OAc)_2$ (0.4 mmol), K_2CO_3 (0.4 mmol) in TFE (1 mL) at 80 °C for 20 h under air.

zenesulfinates bearing fluoro (**4c**), chloro (**4g**), trifluoromethyl (**4f**) or electron-donating (**4d**, **4e**) groups were well tolerated. Reaction with sodium methyl sulfonate afforded alkyl aryl sulfone **4i** in 55% yield. In the cases of heterocyclic sulfones (**4k**, **4l**) and trifluoromethylsulfinate (**4j**), no desired products could be obtained.

Although the scope of this oxidative coupling is quite broad, this method is inherently limited by the restricted access to the required sodium sulfinates.[16] The group of Willis and we have shown that lithium, magnesium or zinc sulfinates, generated from the reaction of an organometallic reagent and an appropriate sulfur dioxide source, are attractive and readily available alternatives to sodium sulfinates and suitable reagents for a variety of transformations.[7] Therefore we investigated the reaction with benzenesulfinic acid lithium salt **5a** as sulfonylating reagent in our transformation. The lithium salt was readily prepared from commercial available phenyllithium and sulfur dioxide. To our delight, the copper-mediated reaction of the lithium sulfinate with benzamide **1a**, bearing the Oxa directing group, furnished the desired sulfone **4b** in 81% yield (Scheme 3).[17] Similar reactions with benzamides bearing the AQ or PIP directing group and employing the reaction conditions reported by Tan[13] and Shi[14] delivered the sulfonylated



Scheme 3. Sulfonylation of benzoic acids bearing different directing groups with lithium sulfinates. *Reaction conditions:* all reactions are carried out using conditions as reported in ref.[13] (AQ), ref.[14] (PIP) and herein (Oxa).



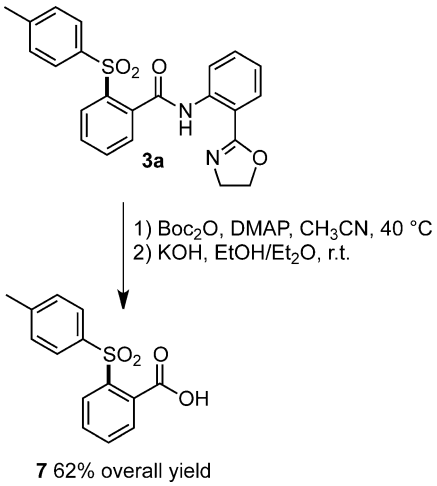
Scheme 4. Synthesis of diaryl sulfone **4b**.

products in only 27% and 18% yield (**6b**, **6c**), highlighting the superior directing effect of the Oxa group. The reaction of butanesulfinic acid lithium salt **5b**, derived from *n*-BuLi, with benzamide **1a** afforded alkyl aryl sulfone **6d** in 44% yield.

One of the most atom-economical routes to organolithium reagents is the direct deprotonation of acidic C–H functionalities.[18] In order to explore the compatibility of our oxidative coupling with the *in situ* generation of organolithium reagents, benzene was deprotonated with *n*-BuLi/TMEDA (Scheme 4). Reaction of the resulting organolithium compound with sulfur dioxide furnished lithium benzenesulfinate. After removal of solvents and excess sulfur dioxide, the crude sulfinate was subjected directly to the copper-mediated coupling affording diaryl sulfone in 61% yield. This three-step protocol allows the direct synthesis of diaryl sulfones *via* stepwise functionalization of two aryl C(sp^2)–H bonds and should find further application in the preparation of more complex sulfones.

Finally, removal of the Oxa-directing group can be achieved by a standard deprotection procedure (Scheme 5).[15b]

In summary, we have developed an efficient copper-mediated sulfonylation of aryl C(sp^2)–H bonds assisted by an amide-oxazoline directing group. The reaction scope is very broad and both sodium as well as lithium sulfinates are well tolerated. In combination with the generation of lithium sulfinates from organolithium reagents and sulfur dioxide, this novel methods allows the rapid construction of aryl sulfones from readily available starting materials. Currently we are investigating the extension of this strategy to other organometallic compounds as well as the activation of C(sp^3)–H bonds.[19]



Scheme 5. Removal of the directing group.

Experimental Section

Typical Procedure for the Coupling of Sodium Sulfinates

A sealed 10-mL screw cap glass vial was charged with a magnetic stirring bar, benzoic acid derivative **1** (1.0 equiv., 0.2 mmol), sodium sulfinate **2** (3.0 equiv., 0.6 mmol), $Cu(OAc)_2$ (72.8 mg, 2.0 equiv., 0.4 mmol), K_2CO_3 (55 mg, 2.0 equiv., 0.4 mmol) and TFE (0.2 M referred to benzoic acid derivative, 1 mL). The vial was closed with a teflon-lined screw cap and the resulting reaction mixture was stirred at 80 °C for 20 h. After cooling down to room temperature, ammonium hydroxide (1 M, 10 mL) was added. The aqueous layer was extracted with EtOAc (2×15 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the crude residue by column chromatography (Hexane/EtOAc) afforded the analytically pure product.

Acknowledgements

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