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Copper(II)-Catalyzed Direct Sulfonylation of C(sp^2)−H Bonds with Sodium Sulfinates

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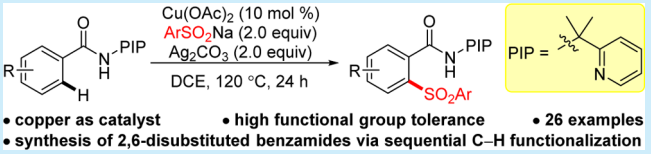
Supporting Information

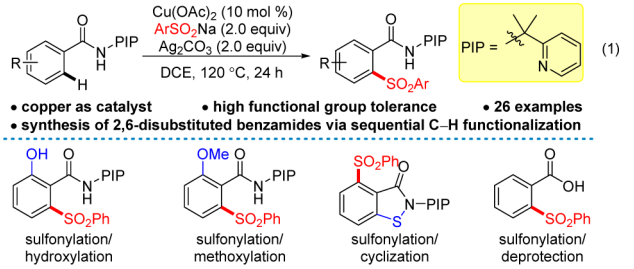
ABSTRACT: A copper-catalyzed direct sulfonylation of C(sp^2)−H bonds with sodium sulfinates using a removable directing group is described. This reaction tolerates a wide range of functional groups, providing an efficient protocol for the synthesis of diverse aryl sulfones. Moreover, a series of 2,6-disubstituted benzamides could be synthesized via sequential C−H functionalization.



Sulfones are an important class of structural moieties found in pharmaceuticals and advanced materials.[1] Moreover, sulfones could act as useful precursors for C−C bond formation via fragment coupling and Julia olefination in synthetic chemistry.[2] Consequently, the synthesis of sulfones has attracted more and more attention.[3] Recently, direct sulfonylation of C−H bonds cast a new vision for sulfone synthesis from the viewpoint of step- and atom-economy.[4−6] In this regard, the pioneering work from the Dong group described Pd-catalyzed C(sp^2)−H bond sulfonylation using pyridine as the auxiliary.[5a] Later, the first direct evidence of C(sp^2)−S reductive elimination from high-valent Pd(IV) intermediates was disclosed by the same group.[5b] However, these transformations relied on the use of expensive palladium catalysts and unremovable pyridine directing groups. Thus, it would be beneficial to replace the palladium catalyst with a low-cost metal for the direct C(sp^2)−H bond sulfonylation.

In recent years, significant advances in Cu-catalyzed/mediated C−H functionalization have been achieved.[7,8] In particular, bidentate directing groups, such as AQ (8-aminoquinolinyl),[9,10] PIP (2-pyridinyl isopropyl),[11] and an amide-tethered oxazoline,[12] have been widely used in copper-catalyzed direct C−H functionalization reactions. As part of our ongoing research in cheap-metal-catalyzed C−H functionalization reactions,[11,13] we envisioned that it would be possible to realize copper-catalyzed direct sulfonylation of C(sp^2)−H bonds with the assistance of a PIP group. Recently, Jiang reported an elegant example of Cu-catalyzed coupling of oxime acetates with sodium sulfonates to access sulfonylvinylamine and β-ketosulfones.[3b] To this end, sodium sulfinates were chosen as the benchmark sulfonylation reagents since sodium sulfinates are readily accessible and stable.[3b,h] Herein, we report a copper-catalyzed direct sulfonylation of C(sp^2)−H bonds with sodium sulfinates directed by a removable directing group.[14] This reaction tolerates a broad range of functional groups, providing an efficient protocol for the synthesis of aryl sulfones (Scheme 1). Moreover, a series of 2,6-disubstituted benzoic acids could be synthesized via sequential C−H functionalization.

Scheme 1. Copper(II)-Catalyzed Direct Sulfonylation of C(sp^2)−H Bonds with Sodium Sulfinates



We commenced our investigation by the reaction of benzamide derivative **1** with $PhSO_2Na$ as the model reaction (Table 1). After extensive screening of copper catalyst, we were pleased to find that the desired product **1a** was obtained in 15% yield when 10 mol % of $Cu(OAc)_2$ was used as catalyst and Ag_2CO_3 as oxidant (entry 1, see the Supporting Information for detailed optimization of copper catalyst). A thorough screening of solvents revealed that the reaction proceeded efficiently in DCE to afford the product **1a** in 72% isolated yield (entry 5). The use of other oxidants, such as AgOAc, $PhI(OAc)_2$, and NMO, did not give any desired product (entries 10−12).

With the optimized conditions in hand, we next explored the scope of benzamides. Generally, both electron-rich and electron-deficient benzamides reacted smoothly with $PhSO_2Na$ to afford the corresponding products in moderate to high yields (Figure 1). Fluoro (**3a** and **6a**), chloro (**7a** and **14a**), bromo (**8a**), and trifluoromethyl (**10a**) groups were well tolerated (Figure 1). Reactions with substrates bearing a methyl or fluoro group in the *ortho* position gave the desired products in lower

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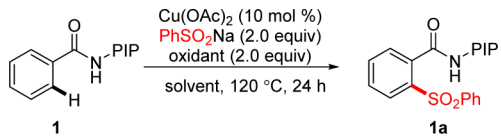
Table 1. Optimization of the Reaction Conditions[a]



1 1a

entry	oxidant (2.0 equiv)	solvent	yield[b] (%)
1	Ag_2CO_3	DMF	15
2	Ag_2CO_3	NMP	trace
3	Ag_2CO_3	DMSO	trace
4	Ag_2CO_3	toluene	12
5	**Ag_2CO_3**	**DCE**	**73 (72)**[c]
6	Ag_2CO_3	1,4-dioxane	0
7	Ag_2CO_3	DME	0
8	Ag_2CO_3	*t*-AmyOH	0
9	Ag_2CO_3	*t*-BuOH	0
10	AgOAc	DCE	0
11	$PhI(OAc)_2$	DCE	0
12	NMO	DCE	0

[a]Reaction conditions: **1a** (0.1 mmol), $Cu(OAc)_2$ (10 mol %), $PhSO_2Na$ (2.0 equiv), and oxidant (2.0 equiv) in solvent (1.0 mL) at 120 °C for 24 h. [b]^1H NMR yields using CH_2Br_2 as the internal standard. [c]Isolated yield in parentheses.

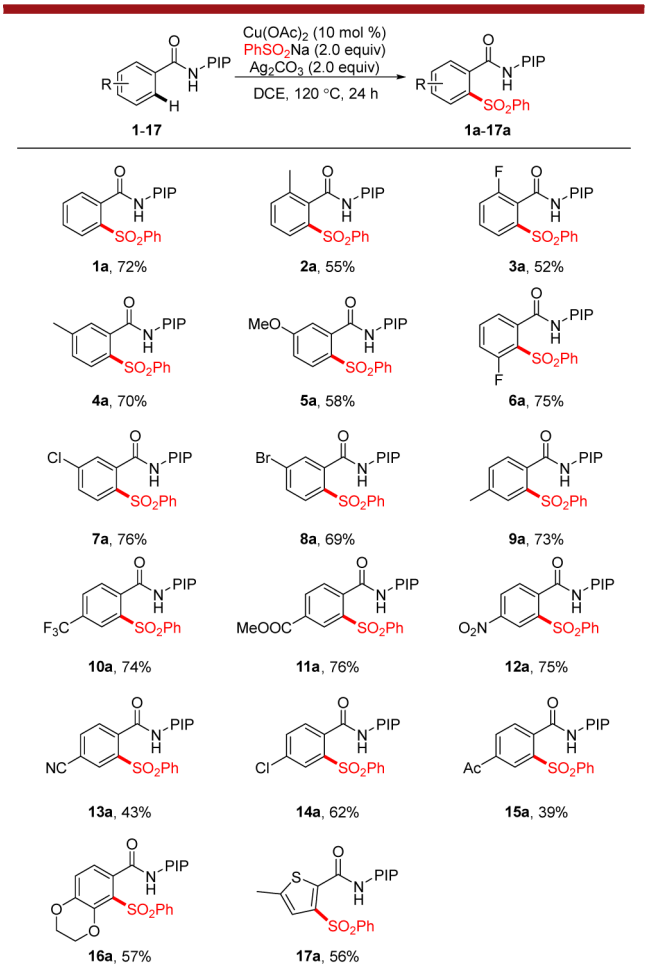


Figure 1. Scope of benzamides. Reaction conditions: **1**–**17** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), $PhSO_2Na$ (0.4 mmol), and Ag_2CO_3 (0.4 mmol) in DCE (2.0 mL) at 120 °C for 24 h under N_2. Isolated yields.

yields (**2a** and **3a**), largely due to the steric congestion caused by the amide. When *meta*-fluorobenzamide **6** was employed as substrate, sulfonylated product **6a** was obtained exclusively, largely due to enhanced kinetic acidity of the corresponding C–H bond. In addition, 2,3-dihydrobenzo[*b*][1,4]dioxine-6-carboxamide **16** also reacted predominantly adjacent to the dioxine, indicating that the coordination of the dioxine could potentially stabilize the arylcopper intermediates. Moreover, the thiophene substrate could also be subjected to the sulfonylation reaction to give the desired product **17a** in 56% yield.

Subsequently, the scope of sodium sulfinates was examined. As shown in Figure 2, a variety of sodium arylsulfinates bearing

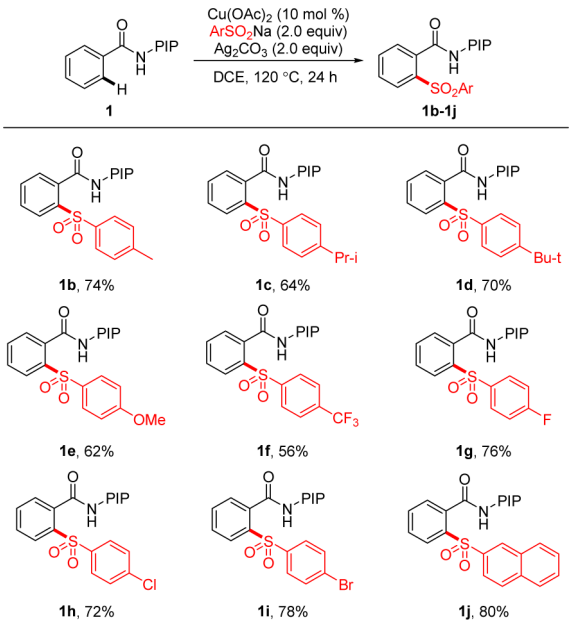


Figure 2. Scope of sodium sulfinates. Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), $ArSO_2Na$ (0.4 mmol) and Ag_2CO_3 (0.4 mmol) in DCE (2 mL) at 120 °C for 24 h under N_2. Isolated yields.

both electron-donating groups (**1b**–**e**, R = Me, OMe, ^{i}Pr, and ^{t}Bu) and electron-withdrawing groups (**1f**–**i**, R = F, Cl, Br, and CF_3) were tolerated and gave the desired sulfonylated products in moderate to high yields. It was noteworthy that halides such as fluoride, chloride, and bromide could survive under the standard reaction conditions (**1g**–**i**), which could be used for further elaboration. Moreover, a sterically bulky sodium 2-naphthylsulfinate also reacted smoothly with **1** to give the desired product **1j** in 80% yield. Unfortunately, no desired sulfonylation products were obtained when sodium alkyl sulfinates were employed.

Diverse transformations of sulfonylated product **1a** were performed as shown in Figure 3. Treatment of **1a** with $Cu(OAc)_2$, TBAI, and Ag_2CO_3 in DMF afforded the *ortho*-hydroxylated product **18** in 81% yield.[11e] Pd-catalyzed methoxylation of **1a** with $PhI(OAc)_2$ as the oxidant and MeOH/*m*-xylene as the solvent gave **19** in 85% yield.[15] Notably, **1a** could be subjected to copper-mediated C–S/N–S bond formation to afford the benzoisothiazolone **20** in 76% yield.[11d] Finally, the PIP auxiliary was efficiently removed via a mild *N*-nitrosylation/hydrolysis sequence to afford the corresponding carboxylic acid **21** in 83% yield.[15]

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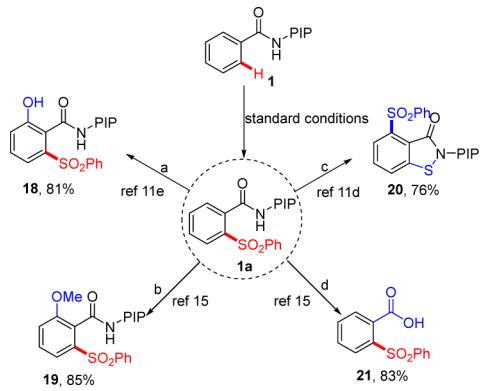
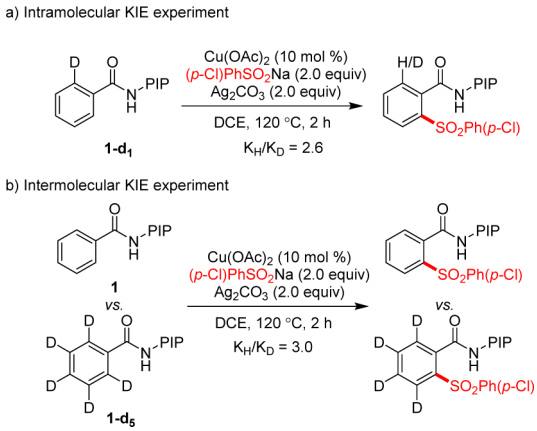


Figure 3. Diverse transformations of **1**. Reaction conditions: (a) $Cu(OAc)_2$, TBAI, Ag_2CO_3 and DMF, 100 °C, 12 h. (b) $Pd(OAc)_2$, $PhI(OAc)_2$ and MeOH/*m*-xylene, 90 °C, 24 h. (c) $Cu(OAc)_2{\cdot}H_2O$, S_8, TBAI, Ag_2O and DCM, 90 °C, 18 h. (d) $NaNO_2$, $HOAc/Ac_2O$, −15 °C; LiOH, 30% H_2O_2, THF/H_2O, −15 °C.

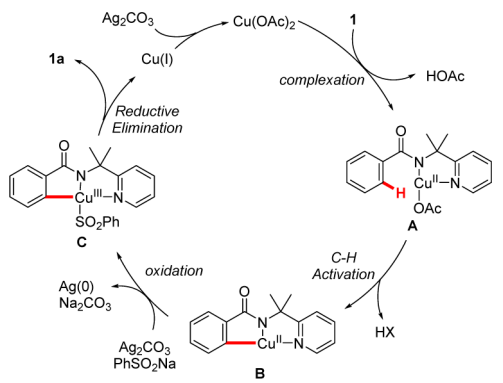
To gain further insight into the mechanism of the sulfonylation reaction, intra- and intermolecular KIE experiments were conducted (Scheme 2). The intramolecular and intermolecular KIE were determined to be 2.6 and 3.0, respectively, indicating that C−H cleavage could potentially be involved in the rate-limiting step.

Scheme 2. Intra- and Intermolecular KIE Experiments



On the basis of the observations above and related precedents,[10−12,16] a plausible mechanism was proposed (Scheme 3). Complexation of benzamide **1** with copper acetate

Scheme 3. Proposed Mechanism



followed by cyclometalation via C−H cleavage affords Cu(II) intermediate **B**. The putative C,N,N-pincer type Cu(III) species **C** was formed by oxidation with Ag_2CO_3 and coordination with $PhSO_2Na$. Subsequent $C-SO_2Ph$ reductive elimination of **C** leads to the formation of sulfonylation product **1a** together with Cu(I) species. Finally, the catalytic cycle is closed by the oxidation of Cu(I) species with Ag_2CO_3.

In conclusion, we have developed a copper-catalyzed direct sulfonylation of $C(sp^2)-H$ bonds with sodium sulfinates with the assistance of a PIP group. The reaction demonstrates excellent regioselectivity with good functional group tolerance. Moreover, the procedure can occur in the presence of a catalytic amount of $Cu(OAc)_2$, providing a useful tool for the synthesis of sulfones.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01198.

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Notes

The authors declare no competing financial interest.

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