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Copper-Mediated Cross-Coupling of Diazo Compounds with Sulfinates

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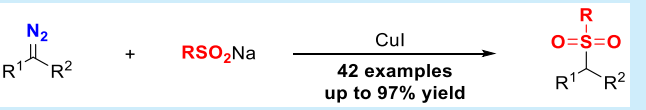
ABSTRACT: A copper-mediated cross-coupling reaction between a diazo compound and a sodium alkane(arene)sulfinate gives a sulfone as the product. This reaction proceeds under mild conditions and features excellent functional group compatibility. A wide range of sodium alkane(arene)sulfinates were successfully applied in this chemistry. Mechanistic studies revealed that the overall reaction efficiency of the sulfinates was in line with their nucleophilicity in this reaction.



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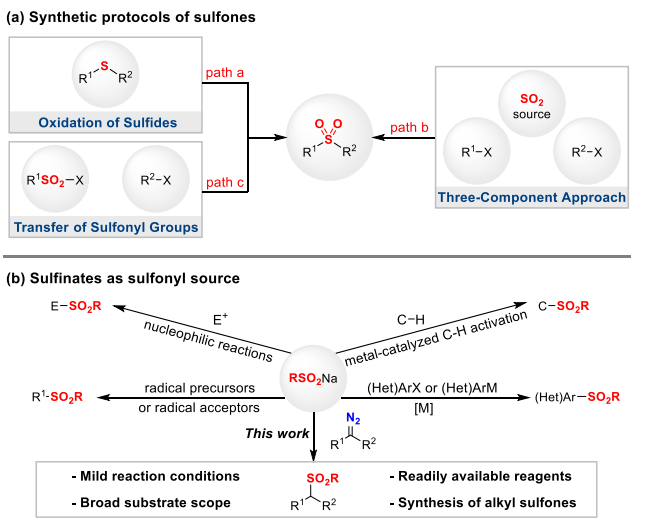
Sulfones are a ubiquitous class of organic molecules that have received much attention within the chemistry community.[1] They play a prominent role in a variety of chemical transformations, such as Julia olefination,[2] the Ramberg−Bäcklund reaction,[3] and cross-coupling reactions.[4] Furthermore, interest in the synthesis of sulfones has also been drawn by the widespread distribution of sulfone scaffolds in many biologically active compounds in pharmaceuticals and agrochemicals.[1b,5] Consequently, a number of methods for the synthesis of sulfones have been disclosed, which can be divided into three types (Scheme 1a): the oxidation of sulfides, three-component approaches, and the transfer of sulfonyl groups.[6] The sulfone unit has historically been accessed through the oxidation of the corresponding sulfides (path a).[1,6a] However, the strong oxidizing condition may lead to scope limitations and safety problems. Another strategy for the synthesis of sulfones involves three-component processes using two sulfur-free building blocks and sulfur dioxide or a suitable surrogate, yet the toxic and corrosive nature of sulfur dioxide largely limits the application of this protocol (path b).[6,7] Alternatively, those strategies involving the direct transfer of sulfonyl groups using sulfonyl sources, which are usually readily available, bench-stable, and nonodorous solids, are even more attractive (path c).[6]

Scheme 1. Strategies for the Synthesis of Sulfones



In this context, the transformation of sulfinates is currently one of the most valuable research topics. As easily prepared nucleophiles and radical precursors,[8,9] sulfinates are versatile reagents that can participate in various reactions, such as nucleophilic reactions,[6a,c,10] C−H bond functionalizations,[6d,11] radical processes,[6b,9,12] and transition-metal-catalyzed cross-coupling reactions.[6,13] Despite the elegance of the chemistry previously mentioned, to the best of our knowledge, the reaction of sulfinates with metal carbene remains elusive. In 2010, an elegant synthesis of sulfones from sulfonylhydrazones was demonstrated by Yu and coworkers.[14a] Nevertheless, the strategy is heavily based on prefunctionalized starting materials and displays a narrow substrate scope. More recently, Wan and coworkers reported a coupling reaction between sulfonyl radicals and silver carbenes.[14b] However, the reaction mainly focused on α-diazo carbonyl substrates. Therefore, the direct, efficient, and mild synthesis of sulfones from the reaction of sulfinates with metal carbene is still highly desirable.

On the other hand, the recent decades have witnessed rapid and significant advances in the alliance of diazo chemistry and organofluorine chemistry.[15,16] Since our pioneering develop-

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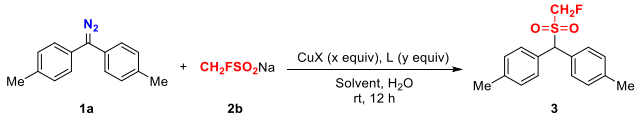
ment of the trifluoromethylation of diazo compounds,[17] diazo chemistry has been widely applied to versatile transformations in organofluorine chemistry.[18] As part of our ongoing investigations dedicated to diazo chemistry, we explored the reaction of sulfinates with diazo compounds, thus synthesizing alkyl sulfones, which are usually difficult to access. Here we present a direct copper-mediated cross-coupling of diazo compounds with sulfinates, providing easy access to structurally diverse sulfones in good yields under very mild reaction conditions.

To test our hypothesis, we investigated the reaction between bis(4-methylphenyl)diazomethane (**1a**) and CH_2FSO_2Na (**2b**) as a model reaction (Table 1). Considering the poor solubility

Table 1. Optimization of the Reaction Conditions[a]



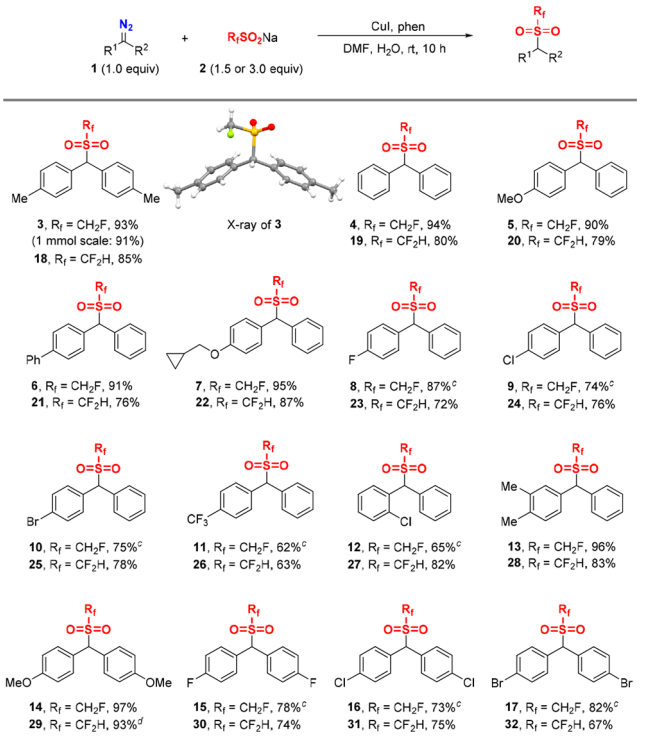
entry	CuX (x)	L (y)	solvent	yield (%)[b]
1	CuI (1.0)		CH_3CN	46
2	CuI (1.0)		NMP	77
3	CuI (1.0)		dioxane	65
4	CuI (1.0)		DMF	84
5[c]	CuI (1.0)		DMF	55
6	CuCl (1.0)		DMF	64
7	CuBr (1.0)		DMF	69
8	CuTc (1.0)		DMF	54
9	CuI (0.2)		DMF	20
10	CuI (0.6)		DMF	57
11	CuI (1.0)	phen (0.2)	DMF	>99 (93[d])
12	CuI (1.0)	phen (0.5)	DMF	97
13	CuI (1.0)	phen (1.0)	DMF	87

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), **2b** (0.3 mmol, 1.5 equiv), CuX, L, solvent (2.0 mL), H_2O (0.2 mL), room temperature for 12 h. [b]Yields were determined by ^{19}F NMR using $PhOCF_3$ as an internal standard. [c]In the absence of H_2O. [d]Isolated yield.

of sulfinates in most organic solvents, we chose H_2O as a cosolvent, which also served as a proton source. CuI was selected as the copper reagent for the initial screening of solvents. Gratifyingly, the use of MeCN as the solvent formed the desired product **3** in a moderate ^{19}F NMR yield (entry 1). Our further screening of solvents (entries 2−4) demonstrated that dimethylformamide (DMF) was the best choice, providing **3** in 84% ^{19}F NMR yield (entry 4). Notably, in the absence of H_2O, the yield decreased to 55%, implying that H_2O played a critical role in the reaction (entry 5). Using other copper reagents, such as CuCl, CuBr, and CuTc, provided **3** in lower yields (entries 6−8). Decreasing the loading amount of CuI (entries 9 and 10) led to significant decreases in yields (20% for 0.2 equiv of CuI; 57% for 0.6 equiv of CuI). These results indicate that the copper species is presumably transformed to unreactive Cu_2O, making it unavailable for catalysis, which is consistent with our previous findings.[17] Finally, we were pleased to find that the use of 1,10-phenanthroline (0.2 equiv) delivered **3** in a nearly quantitative ^{19}F NMR yield and a 93% isolated yield (entry 11).

With the optimized conditions in hand, we explored the generality of the reaction by first varying the scope of diazo compounds using CH_2FSO_2Na (**2b**) as the coupling reagent (Scheme 2). A range of diazo compounds bearing different substituents on the aromatic ring, such as alkyls (**3**, **13**), ethers

Scheme 2. Scope of Diazo Compounds[a,b]



[a]Reaction was performed on a 0.4 mmol scale with **2**, CuI (0.4 mmol, 1.0 equiv), phen (0.08 mmol, 0.2 equiv), DMF (4.0 mL), H_2O (0.4 mL), room temperature, 10 h. [b]Isolated yields. [c]phen (1.0 equiv) was used. [d]Yields were determined by ^{19}F NMR with $PhOCF_3$ as an internal standard.

(**5**, **7**, **14**), halogens (**8**−**10**, **12**, **15**−**17**), and trifluoromethyl groups (**11**), were well accommodated, giving the desired products in moderate to high isolated yields (62−97%). The ortho-substituted diaryl diazomethane also worked well, as shown in the case of **12** and **27**. Of note, the C(sp^2)−Br bonds remained unreacted under our cross-coupling conditions (**10**, **17**), providing a platform for further elaborations via traditional cross-coupling strategies. Lower yields were observed in the case of a strong electron-deficient substrate (**11**), probably due to its lower reactivity with copper species. Next, we were interested in extending this chemistry toward the synthesis of difluoromethyl sulfones, which have led to the development of various transformations.[2b,c,4c,g] Gratifyingly, CF_2HSO_2Na (**2c**) could also react smoothly with all of the previously mentioned diazo compounds, and the corresponding products (**18**−**32**) were successfully obtained. It is worth mentioning that compared with CH_2FSO_2Na (**2b**), lower yields were obtained in most cases, which will be discussed in detail in the mechanistic studies.

Subsequently, the sulfinate component was further varied using **1a** or **1c** as the coupling partner (Scheme 3). Not surprisingly, an array of commercially available alkyl sulfinates (**33**−**35**) could be smoothly converted to target sulfones in high yields (92−97%). The aryl sulfinates were also competent coupling partners, and halogen atoms (F, Cl) or a trifluoromethoxy group (OCF_3) on the phenyl moiety of sulfinates were well tolerated in the reaction, yielding the

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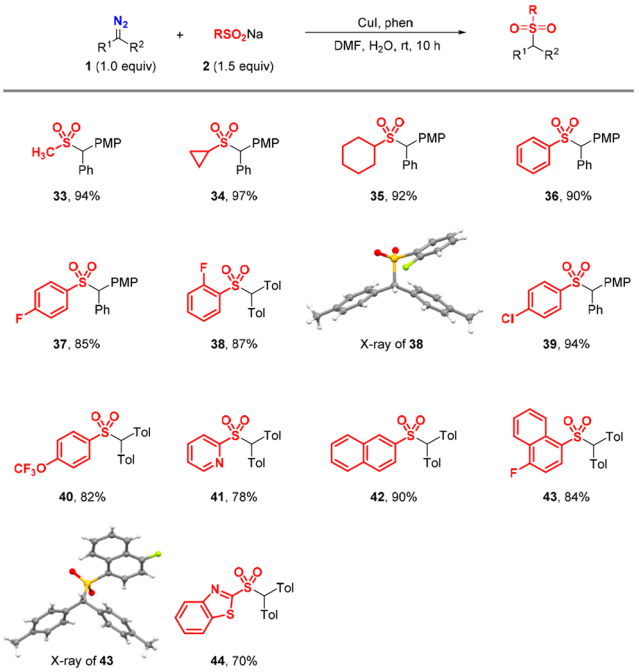
Scheme 3. Scope of Sulfinate Salts[a,b]



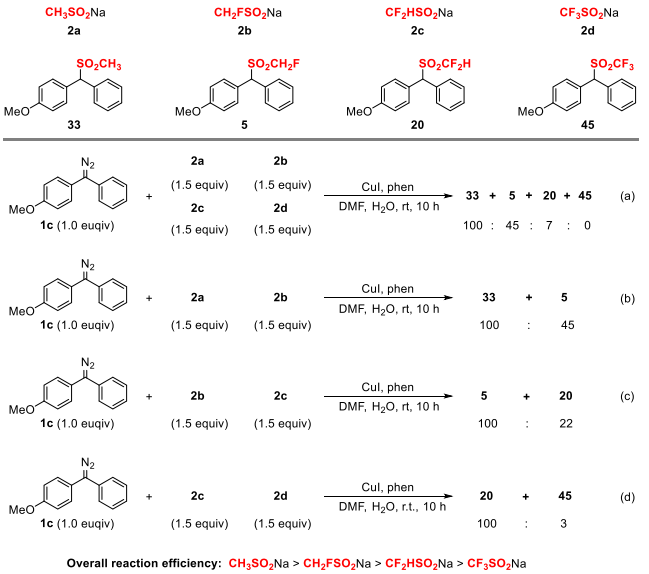
[a]Unless otherwise mentioned, the reaction was performed on a 0.4 mmol scale with **2** (0.6 mmol, 1.5 equiv), CuI (0.4 mmol, 1.0 equiv), phen (0.4 mmol, 1.0 equiv), DMF (4.0 mL), H_2O (0.4 mL), room temperature, 10 h. [b]Isolated yields. Tol = *p*-tolyl, PMP = 4-methoxyphenyl.

corresponding products with high efficiency (**36**−**40**). In addition, substrates containing medicinally relevant heterocycles, including pyridine (**41**), naphthalene (**42**, **43**), and benzothiazole (**44**), all proved to be effective coupling partners.

To gain more insights into the mechanism, we carried out some additional experiments. With our continuous interest in probing the unique fluorine effects,[9c,19,20] we started off with a comparison of the overall reaction efficiencies of different sodium sulfinates (Scheme 4). First, an intermolecular competition experiment using equimolar amounts of CH_3SO_2Na (**2a**), CH_2FSO_2Na (**2b**), CF_2HSO_2Na (**2c**), and CF_3SO_2Na (**2d**) under the standard reaction conditions with **1c** was carried out (Scheme 4a). The ratio of the corresponding products was 100:45:7:0, which was in line with the order of the nucleophilicity of sulfinates (**2a**−**2d**). The following competition experiments were also consistent with this result, giving ratios of 100:45, 100:22, and 100:3 for **2a**/**2b**, **2b**/**2c**, and **2c**/**2d**, respectively (Scheme 4b−d). The significant electronic preference found in these experiments suggests that the overall efficiencies of these sodium sulfinates in the reaction decrease with their decreasing nucleophilicity in the following order: **2a** > **2b** > **2c**> **2d**.

Subsequently, a parallel experiment was carried out to study the kinetics of the reaction. Two separate reactions of CH_2FSO_2Na (**2b**) and CF_2HSO_2Na (**2c**) under the standard reaction conditions with phenyl (4-fluorophenyl)-diazomethane (**1f**) were conducted, and the rate constants of two reactions (k_1 and k_2) were measured independently (see details in the Supporting Information (SI)). Interestingly, it was found that the reaction of the more nucleophilic **2b** had a lower reaction rate constant (k_1). In contrast, the reaction of **2c**

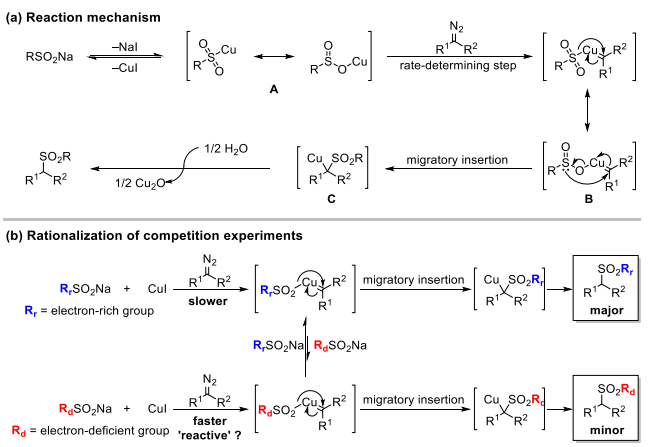
Scheme 4. Competition Experiments



showed a higher reaction rate constant (k_2) at inception (k_2/k_1 = 1.50). It should be emphasized that **2c** seems to be more "reactive" in the parallel experiments, which seemingly contradicts the result of the previously described competition experiments (Scheme 4c).

Therefore, to excavate more details, we carried out the N_2 evolution experiments to investigate the formation rate of the copper carbene species. (See Part 4.3 in the SI.) The volumes of released N_2 gas were measured in the reaction of CH_2FSO_2Na (**2b**) and CF_2HSO_2Na (**2c**) under the standard reaction conditions with **1f**, respectively. As we can see from Figure S3 (in the SI), the diazo compound **1f** decomposed more quickly during the reaction of **2c**. Specifically, 10.7 mL of N_2 gas was generated within just 148 min during the reaction of **2c**, whereas 9.4 mL of N_2 gas was generated within 660 min during the reaction of **2b**. (Theoretically, 11.2 mL of N_2 gas should be produced after the complete decomposition of the diazo compound at standard temperature and pressure.) These significant differences indicate that the sulfinate-coordinated copper A (see Scheme 5a) was an active species to react with the diazo compounds, and the electron-deficient species (**2c**) was more "reactive" owing to its high electrophilicity toward

Scheme 5. Proposed Mechanism



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diazo compounds. This is also consistent with the results from parallel experiments. Furthermore, ^{19}F NMR analysis of these reactions revealed that both products were formed just after the N_2 evolution (85% for reaction of **2b** at 660 min; 61% for reaction of **2c** at 148 min). We can thus conclude that the generation of final products after the N_2 evolution is relatively faster, and the formation of a copper-carbene species is likely the rate-determining step.

Another particularly noteworthy result is that the more "reactive" CF_2HSO_2Na (**2c**) provided lower yields compared with CH_2FSO_2Na (**2b**), which was also observed during our survey of the substrate scope (Scheme 2). We believe that the main reason lies in the stronger binding forces between the more electron-rich **2b** and the copper-carbene species.

On the basis of the aforementioned mechanistic studies, a possible mechanism is proposed in Scheme 5a. Rapid cation exchange between sodium sulfinate and CuI forms the sulfinate-coordinated copper species A.[14,21,22] Subsequently, A reacts with the diazo substrate to form the copper-carbene species B, and this process is presumably the rate-determining step. The migration insertion of B generates intermediate C. Finally, the protonation of C delivers the final product and CuOH, which is unstable and further decomposes into Cu_2O and H_2O.[17,23] On the basis of the above analysis, the competition experiments can be well explained (Scheme 5b). In the presence of different sulfinates, the more electron-deficient sulfinate reacts faster with the diazo compound and is therefore called the more "reactive" species; however, the electron-rich sulfinate dominants the subsequent steps because sulfinates are in rapid equilibrium via ligand exchange on copper-carbene species.[24]

In conclusion, we have developed an effective protocol for the synthesis of sulfones through the copper-mediated cross-coupling of diazo compounds with sulfinates. Various readily available sulfinates are directly utilized as sulfonyl group sources through the migration insertion of copper carbene species, enabling rapid access to an array of structurally diverse sulfones. The reaction is also an interesting case where a more "reactive" species does not necessarily result in higher reaction efficiency. Further efforts in the efficient synthesis and new applications of sulfones are currently underway in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02481.

Detailed experimental procedures and spectra data for all new compounds (PDF)

Accession Codes

CCDC 2076580−2076582 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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