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# Copper(II)-Catalyzed Alkene Aminosulfonylation with Sodium Sulfinates For the Synthesis of Sulfonylated Pyrrolidones

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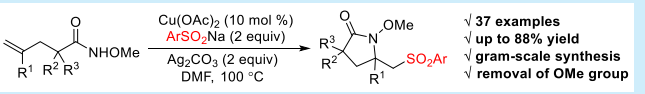
Supporting Information

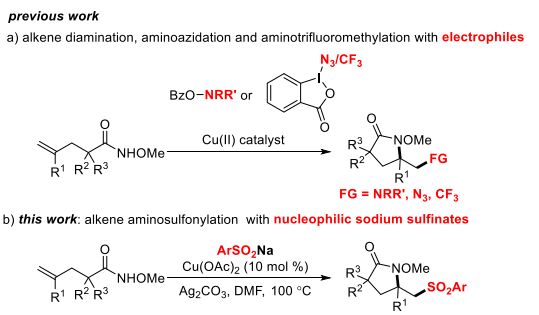
**ABSTRACT:** A copper-catalyzed direct aminosulfonylation of unactivated alkenes with sodium sulfinates for the efficient synthesis of sulfonylated pyrrolidones is described. This reaction features good functional group tolerance and wide substrate scope, providing an efficient and straightforward protocol to access this kind of pyrrolidones. Moreover, preliminary mechanistic investigations disclosed that a free-radical pathway might be invovled in the process.






In recent years, significant progress in copper-catalyzed alkene difunctionalizations has been gained,[1] and numerous functionalized heterocycles have been conveniently constructed based upon this strategy,[2] which not only allows direct cyclization of easily accessible unsaturated starting materials but also enables the simultaneous incorporation of a second useful functional group in the cyclization process. In this way, the molecular complexity can be rapidly and efficiently assembled. Although diversely functionalized heterocycles, such as cyclic amines,[3] lactones,[4] and cyclic ethers,[5] have been successfully constructed in this area, examples of the synthesis of functionalized pyrrolidones with this strategy remain rare. For instance, seminal works by the Wang group demonstrated the successful construction of amino-, azido-, and trifluoromethyl-containing pyrrolidones via copper-catalyzed alkene diamination,[6a] aminoazidation,[6b] and aminotrifluoromethylation[6c] (Scheme 1a), where highly active electrophiles are essential. However, these electrophiles require additional preparation. Given the significance of pyrrolidones in pharmaceutical and synthetic chemistry,[7] continuous efforts toward the exploration of alkene difunctionalizations to construct diversely functionalized pyrrolidones are highly desired, which would further enrich the chemistry of alkene difunctionalizations.

**Scheme 1. Copper-Catalyzed Alkene Aminofunctionalization For the Construction of Diversely Functionalized Pyrrolidones**




Sulfones are important structural motifs in pharmaceuticals and advanced materials[8] and function as useful precursors of C−C double bonds in synthetic chemistry.[9] Despite significant achievements gained in framing this skeleton,[10] applications of the powerful and straightforward strategy of copper-catalyzed alkene difunctionalizations toward the synthesis of functionalized sulfones are still underexplored. In this regard, the Buchwald group reported a copper-catalyzed oxysulfonylation of unsaturated carboxylic acids with aryl sulfonyl chloride.[11] Afterward, Zhang and et al. realized a copper-catalyzed alkene azidosulfonylation with sodium sulfinates.[12] Very recently, the Li group explored the aminosulfonylation of unsaturated aryl amides with sodium sulfinates,[13] which could potentially be beneficial to the synthesis of biologically active vicinal aminosulfones.[14] However, stoichiometric copper salts are required and the substrate scope was limited to styrene-type aryl amides. Herein, we report a copper-catalyzed version of unsaturated aliphatic amides with sodium sulfinates (Scheme 1b), which provides an efficient approach to access structurally novel sulfonylated pyrrolidones by merging pyrrolidone with sulfone.

We commenced our study by the reaction of *N*-methoxy unsaturated aliphatic amide **1** with $PhSO_2Na$ as the model reaction (Table 1). To our delight, the desired product **1a** was obtained in 15% yield by using $Cu(OAc)_2$ (10 mol %) as the catalyst and $Ag_2CO_3$ (2 equiv) as the oxidant in DCM (entry 1; see the Supporting Information for detailed optimization). Further evaluation of solvents (entries 2−9) revealed that the reaction proceeded efficiently in DMF to afford the product **1a**

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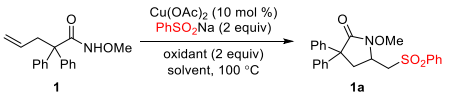
**Table 1. Optimization of the Reaction Conditions**[a]




| entry | oxidant (2.0 equiv) | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | $Ag_2CO_3$ | DCM | 15 |
| 2 | $Ag_2CO_3$ | DCE | 32 |
| 3 | $Ag_2CO_3$ | DMSO | 58 |
| 4 | $Ag_2CO_3$ | toluene | 12 |
| 5 | $Ag_2CO_3$ | MeCN | 0 |
| 6 | $Ag_2CO_3$ | 1,4-dioxane | 0 |
| 7 | **$Ag_2CO_3$** | **DMF** | **85** |
| 8 | $Ag_2CO_3$ | NMP | trace |
| 9 | $Ag_2CO_3$ | HFIP | trace |
| 10 | AgOAc | DMF | 76 |
| 11 | $Ag_2O$ | DMF | 71 |
| 12 | $K_2S_2O_8$ | DMF | trace |
| 13 | DTBP | DMF | 23 |
| 14 | TBHP | DMF | trace |
| 15 | $PhI(OAc)_2$ | DMF | 35 |
| 16[c] | – | DMF | trace |
| 17[d] | – | DMF | trace |
| 18[e] | $Ag_2CO_3$ | DMF | 0 |
| 19[f] | – | DMF | trace |

[a]Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), $PhSO_2Na$ (0.4 mmol, 2 equiv), and oxidant (2 equiv) in solvent (2 mL) at 100 °C for 24 h under $N_2$. [b]Isolated yields. [c]Under air. [d]Under $O_2$ atmosphere. [e]Without $Cu(OAc)_2$. [f]With $Cu(OAc)_2$ (2.0 equiv).

in 85% isolated yield (entry 7). Encouraged by the results, we next took a brief screening of several oxidants in order to further improve the yield. Silver salts, such as AgOAc and $Ag_2O$ (entries 10 and 11), as the oxidants could not give a higher yield than $Ag_2CO_3$. The use of other oxidants, including $K_2S_2O_8$, DTBP, TBHP, and $PhI(OAc)_2$, did not afford better results (entries 12−15). In virtue of the robust utilization of molecular oxygen as a green terminal oxidant in copper catalysis,[15] we subsequently examined air and molecular oxygen as the oxidants. Unfortunately, neither air nor molecular oxygen performed as expected (entries 16 and 17). A control experiment shows that copper was essential to the reaction since no product **1a** was detected under the same conditions in the absence of $Cu(OAc)_2$ (entry 18). Finally, a stoichiometric amount of $Cu(OAc)_2$ was used as the sole oxidant; only traces of **1a** were obtained (entry 19).

With the optimized conditions in hand, we next explored the scope of *N*-methoxy unsaturated amides (Figure 1). Generally, unsaturated quaternary amides underwent this transformation smoothly and afforded the corresponding aminosulfonylation products in good to high yields. It was also observed that the reaction overwhelmingly preferred the 5-*exo* cyclization process. Reaction of quaternary amides bearing $\alpha$-Me, -Et, and -Ph groups could proceed smoothly and generated the desired products **1a**−**5a** in good yields, albeit in poor *dr* ratios for products **2a** and **4a**. Notably, substrate derived from ibuprofen was compatible with this protocol and delivered the desired product **6a** in 73% yield, although with a poor *dr* ratio. Meanwhile, an ester group at the $\alpha$-site of substrate was well tolerated, and the desired product **7a** was obtained in 70% yield and with a 3.6:1 *dr* ratio. Interestingly, several $\alpha$-cyclic substrates could be subjected to the aminosulfonylation and provided $\alpha$-spiro pyrrolidones **8a**, **9a**, and **10a** in high yields.

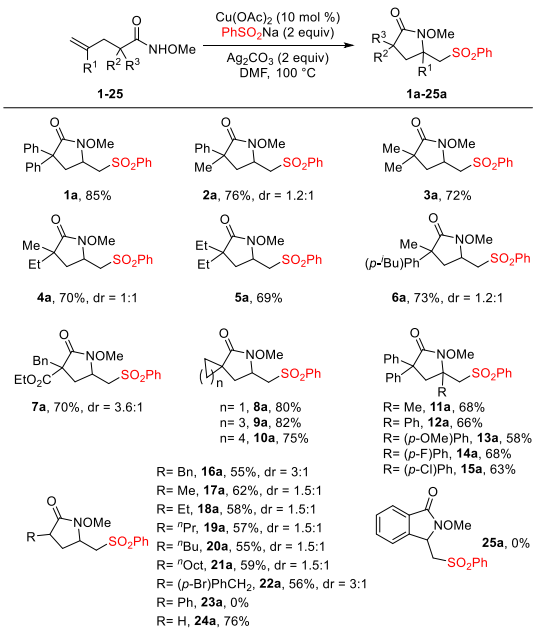



**Figure 1.** Scope of alkenes. Reaction conditions: **1**−**25** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), $PhSO_2Na$ (1 mmol, 2 equiv), and $Ag_2CO_3$ (1 mmol, 2 equiv) in DMF (5 mL) at 100 °C for 24 h under $N_2$. Isolated yields. The dr ratios were determined by $^1H$ NMR.

Besides monosubstituted alkenes, 1,1-disubstituted alkenes were acceptable substrates in the aminosulfonylation transformation, as evidenced by the successful formation of **11a**−**15a** in good yields. $\alpha$-Monosubstituted usaturated tertiary amides also reacted well to produce the desired products **16a**−**22a** in moderate yields, albeit in poor *dr* ratios. Incredibly, when the benzyl group was replaced with a phenyl group, the aminosulfonylation did not occur and the desired product **23a** was not obtained. Gratifyingly, an unsaturated secondary amide was a suitable substrate, as manifested by the formation of **24a** in 76% yield. Unfortunately, with an unsaturated aromatic amide substrate, the reaction did not occur and the desired product **25a** was not produced.

Subsequently, we examined the scope of sodium sulfinates (Figure 2). A variety of sodium arylsulfinates bearing substituents on the aryl ring were suitable for this transformation and provided the desired product **1b**−**1m** in moderate to high yields, regardless of their electronic properties. With sodium 4-toluenesulfinte, several unsaturated quaternary amides could be subjected to this protocol to yield the desired products **1b**−**1e** in high yields. Notably, halides, such as fluoride, chloride, and bromide, exhibited tolerance under the standard reaction conditions (**1i**−**1l**), which provided the opportunity for further derivation. Furthermore, the useful trifluoromethyl group was compatible with this protocol (**1m**).

As shown in Scheme 2, the structure of the aminosulfonylation product **11a** was characterized by single crystal X-ray diffraction (CCDC 1875942).

To prove the practicability of this transformation, a gram-scale synthesis and removal of the OMe group were performed. As shown in Scheme 3, the aminosulfonylation product **1a** was obtained in 81% yield under the standard conditions on a gram scale. Next, treatment of **1a** with $SmI_2$ in THF at room temperature for 10 min could readily remove the OMe group and afforded the desired product **1n** in 87% yield.[16]



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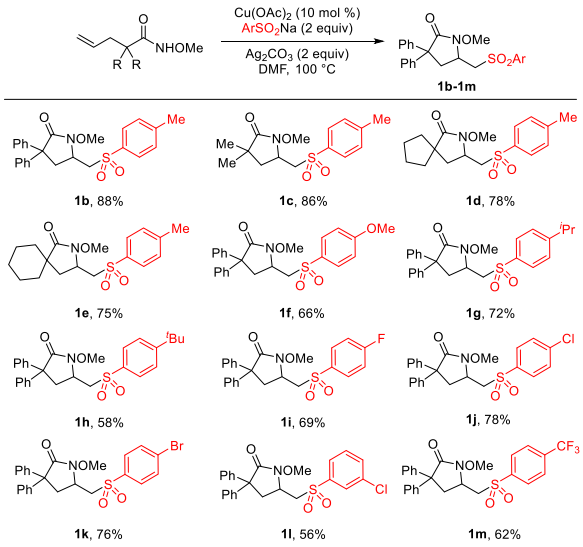
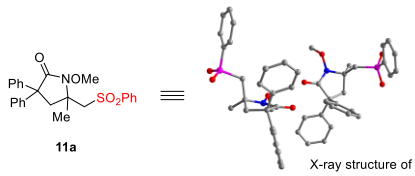
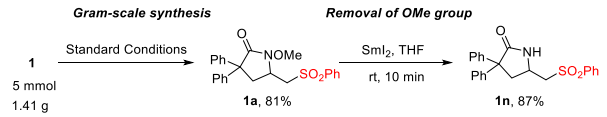



**Figure 2.** Scope of sodium sulfinates. Reaction conditions: unsaturated amides (0.5 mmol), $Cu(OAc)_2$ (10 mol %), $ArSO_2Na$ (1 mmol, 2 equiv), and $Ag_2CO_3$ (1 mmol, 2 equiv) in DMF (5 mL) at 100 °C for 24 h under $N_2$. Isolated yields.

**Scheme 2. X-ray Structure of Compound 11a**

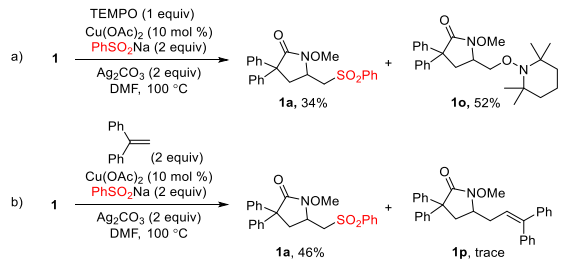



**Scheme 3. Gram-Scale Synthesis and Removal of OMe Group**[a]




To gain mechanistic insights into the aminosulfonylation reaction, some control experiments were conducted (Scheme 4). With addition of TEMPO (1.0 equiv) as a radical

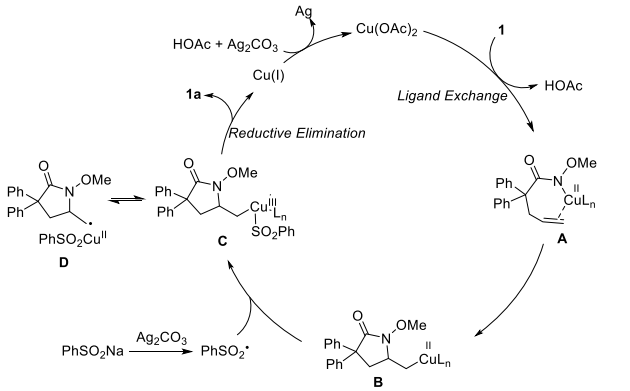
**Scheme 4. Mechanistic Experiments**




scavenger, the aminosulfonylation reaction was remarkably suppressed and the yield of **1a** was decreased to 34%, and the TEMPO-trapped product **1o** was isolated in 52% yield. Moreover, 1,1-diphenyethylene as a radical scavenger also suppressed the reaction and led to a lower yield of **1a**, and a trace amount of **1p** was detected by HPLC-MS (see the Supporting Information). These results clarify that a radical pathway with a carbon-centered radical species is likely involved in the aminosulfonylation process.

Based on our observations above and literature reports,[6,10c,11] a plausible catalytic cycle is proposed to elucidate the aminosulfonylation reaction as depicted in Scheme 5.

**Scheme 5. Proposed Mechanism**




Initially, ligand exchange of copper acetate with alkene **1** affords intermediate **A**. Then, **A** likely undergoes the intramolecular aminocupration to furnish intermediate **B** in an *exo* cyclization manner. Reaction of $PhSO_2Na$ and $Ag_2CO_3$ generates a phenylsulfonyl radical which would couple with **B** to afford complex alkyl−Cu(III)−$SO_2Ph$ (**C**). An equilibrium between complex **C** and the radical **D** possibly exists. Subsequent reductive elimination of complex **C** would furnish the aminosulfonylation **1a** along with Cu(I) species. Finally, oxidation of Cu(I) species with $Ag_2CO_3$ leads to the regeneration of the Cu(II) catalyst.

In conclusion, we have developed a copper-catalyzed direct aminosulfonylation of unactivated alkenes with sodium sulfinates for the synthesis of sulfonylated pyrrolidones. Good functional group tolerance and a wide substrate scope are observed with this protocol. Moreover, preliminary mechanistic investigations suggest that a free-radical pathway might be invovled in the process.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00907.

Experimental details and spectral data for all new compounds (PDF)

### Accession Codes

CCDC 1875942 contains 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.

## ■ ACKNOWLEDGMENTS

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