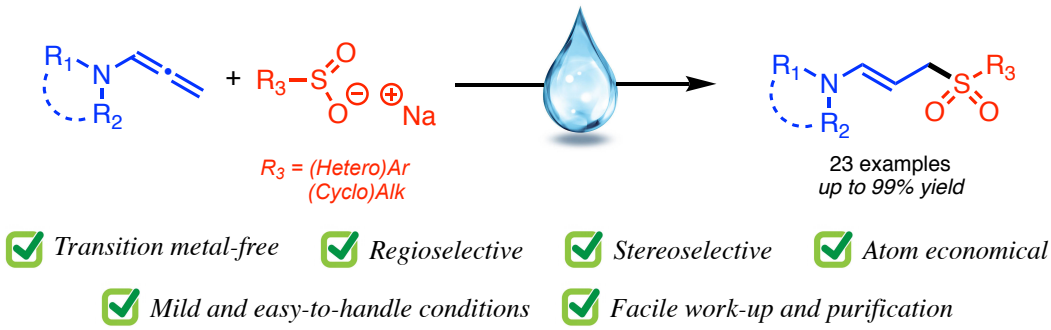
Easy Access To Allylic Sulfones Through Transition Metal-Free Hydrosulfonylation Of Allenes.

Lucas Pagès,[†] Sébastien Lemouzy,[†] Marc Taillefer,[†]* and Florian Monnier[†,‡]*

[†]Institut Charles Gerhardt Montpellier (ICGM), ENSCM, Université de Montpellier, CNRS, 240 Avenue du Professeur Emile JEANBRAU - 34296 Montpellier (France)

[‡]Institut Universitaire de France (IUF), 1 Rue DESCARTES, Paris 75231 Cedex 5, France.

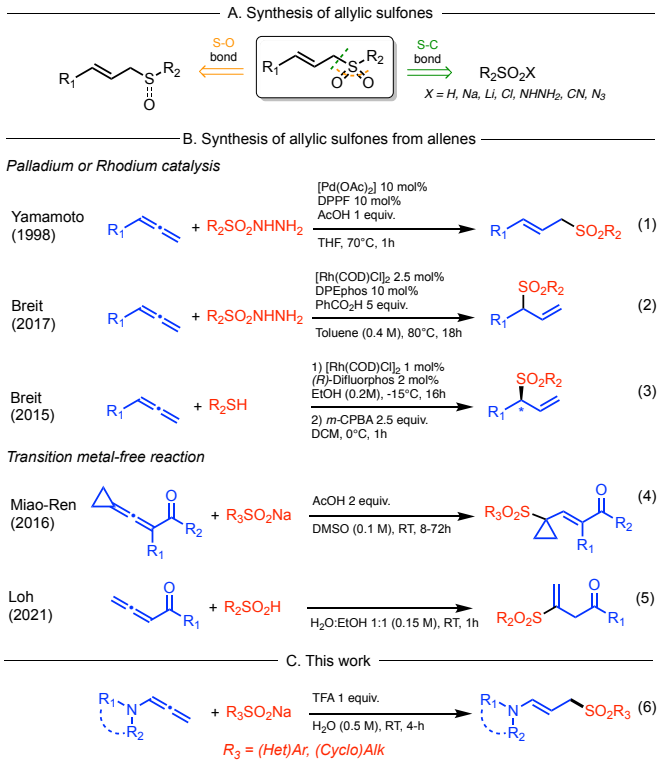


Abstract : A Brønsted acid-mediated addition of (hetero)aryl and (cyclo)alkyl sodium sulfinates to *N*-allenyl derivatives is described under very smooth conditions. This reaction provided a practical and efficient protocol for the synthesis of allylic sulfones in an atom- and step-economic fashion. In addition, an one-step double hydrosulfonylation has also been demonstrated, affording the corresponding 1,3-disulfone in to good yield.

Allylic sulfones are highly valuable structures commonly found in bioactive molecules for pharmaceutical or agrochemical use.[1,2] They can also be useful intermediates to variously functionalized compounds, either through the C(sp_2)-C(sp_2) bond or the carbon atom adjacent to the sulfone group.[3] The SO_2 moiety is classically introduced either through *in situ* oxidation of sulfides (S^{II}) or sulfoxides (S^{IV}) or the use of pre-oxidized sulfur-based reagents (S^{VI}) *i.e.* sulfinic acid derivatives and their salts, in substitution or cross-coupling reactions.

Allenes are interesting precursors of allylic structures through hydrofunctionalization[4] with hydrothiolation followed by *in situ* oxidation or with direct hydrosulfonylation. The first allene hydrosulfonylation strategies were based on the use of sulfonylhydrazines as a source of sulfone. They can be catalyzed by a Palladium/diphosphine system (Yamamoto,[5] Scheme 1, eq 1) or by a Rhodium/DPEPhos system (Breit,[6] Scheme 1, eq 2), occurring respectively on the terminal and the proximal carbon of the allene. These two methods require the presence of a Brønsted acid in a at least stoichiometric quantity, the use of an organic solvent under a moderately high temperature (70°C-80°C). Breit's group also developed an asymmetric rhodium-catalyzed hydrothiolation of terminal allenes followed by oxidation to afford the chiral branched allylic sulfones in a two-step process (Scheme 1, eq 3).[7]

Over the last years, two transition metal-free allene hydrosulfonylation methods have been described. In 2016, Miao, Ren and coworkers reported a transition metal-free tunable hydrosulfonylation of 3-cyclopropylideneprop-2-en-1-ones using sodium sulfinates in the presence of acetic acid affording the corresponding allylic sulfone (γ-adduct) in DMSO[8] (Scheme 1, eq 4). Very recently, the group of Loh reported a transition-metal catalyst-free regioselective Michael addition of sulfinic acids to α-ketoallenes in a mixture of water and ethanol as a solvent, affording the corresponding vinylic sulfone[9] (Scheme 1, eq 5).[10] This method requires the synthesis of sulfinic acids in one to two steps, either from sodium sulfinate or sulfonyl chloride.



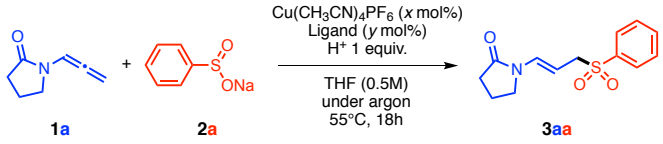
Scheme 1. Metal-catalyzed or metal-free hydrosulfonylation of allenes: known methods and novel pathway described herein with TFA.

In our course to build new original allylic structures, we started investigate the C-S bond formation *via* copper-catalyzed hydrofunctionalization of allenes. After starting with usual conditions described in our previous work for the C-C[11–13], C-N[14–17] and C-O[18] bonds formation, we quickly realized that the reaction could occur without a transition metal, in the

presence of a Brønsted acid and under very smooth and easy-to-handle conditions. We herein describe an efficient synthesis of allylic sulfones and 1,3-disulfones through regio- and stereoselective mono and double addition of various (hetero)aryl and (cyclo)alkyl sodium sulfinates to *N*-allenyl derivatives in aqueous conditions in presence of trifluoroacetic acid (TFA).

Based on our previous works on hydrofunctionalization of allenamides, we began to study the model reaction between *N*-allenyl-2-pyrrolidinone **1a** with benzene sulfinic acid sodium salt **2a** under various experimental conditions (Table 1). First we tested the influence of our classical copper-catalyzed system. With an acid source we showed that the presence of catalytic amount of copper allows the formation of 50% of **3aa** (entry 2, table1). Different ligands were associated to copper but no real improvement was detected (entries 3-5, table 1). The next set of experiments was based on the catalytic system of $Cu(CH_3CN)_4PF_6$/Bpy with different sources of acid (entries 6-8, table 1) and we defined trifluoroacetic acid (TFA) as the best one. However without copper system, we surprisingly showed that **3aa** could be obtained in total conversion with 90% yield (entry 9, table 1).

*Table 1. Copper-catalyzed hydrosulfonylation of **1a** with **2a** : selected data for reaction parametric study.*[a]



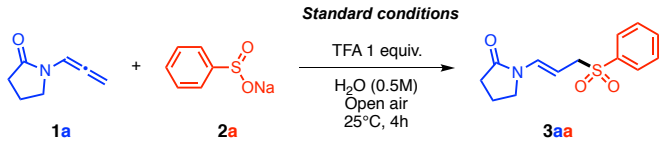
1a **2a** **3aa**

Entry	*x*	*y*	Ligand	H^+ source	Conversion (%)[b,c]	Yield (%)[c]
1	0	0	-	none	-	-
2	10	0	-	*p*-toluic acid	63%	50%
3	10	10	Bpy	*p*-toluic acid	86%	57%
4	10	10	Phen	*p*-toluic acid	74%	33%
5	10	10	TMEDA	*p*-toluic acid	95%	51%
6	10	10	Bpy	TMBA	79%	39%
7	10	10	Bpy	PTSA	76%	30%
8	10	10	Bpy	TFA	>99%	58%
9	**0**	**0**	**-**	**TFA**	**>99%**	**90%**

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2 equiv., 0.5 mmol), H^+ source (1 equiv.) catalyst and ligand were placed in a Schlenk tube under argon in 0.5 mL of THF (0.5M) for 18 hours at 55°C. [b] Based on recovered starting material. [c] Determined through ^1H NMR analysis using trichloroethylene (1 equiv., 0.25 mmol) as internal standard. TMBA = 2,4,6-trimethylbenzoic acid. PTSA = *p*-toluenesulfonic acid. Bpy = 2,2'-bipyridine. Phen = 1,10-phénantroline. TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

Based on observations of table 1, we performed variations of the reaction conditions (table 2). We rapidly found that the best conditions were based on 1 equivalent of TFA in H_2O at 25°C on open air in 4h (table 2, entry 6). Variations on the nature of solvent, on the atmosphere, on the reaction time and on the temperature did not improve the yield of **3aa** (entries 1-5, table 2).

*Table 2. Acid-mediated hydrosulfonylation of **1a** with **2a** : Selected data for reaction parametric study* [a].



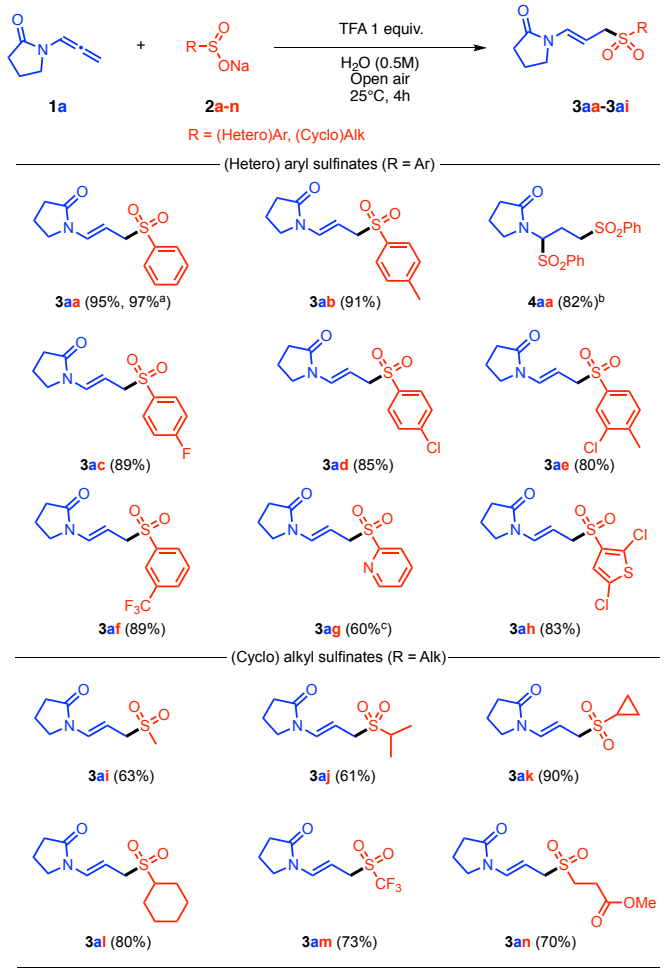
1a **2a** **3aa**

Entry	Variations from the standard conditions	Conversion (%)[b,c]	Yield (%)[c]
1	THF, instead of H_2O	>99%	80%
2	under Argon, instead of open air	>99%	90%
3	18h, instead of 4h	>99%	>99%
4	55°C, instead of 25°C	>99%	96%
5	no TFA	66%	0
6	**none**	**>99%**	**>99%**

[a] Reaction conditions : **1a** (0.25 mmol), **2a** (2 equiv., 0.5 mmol) and TFA (1 equiv., 0.25 mmol) were placed in a tube under open air in 0.5 mL of solvent (0.5M) for 4 hours at 25°C. [b] Based on recovered starting material. [c] Determined through ^1H NMR analysis using trichloroethylene (1 equiv., 0.25 mmol) as internal standard.

With these optimized conditions in hand, we first explored the scope and limitations of the method for the hydrosulfonylation of *N*-allenyl-2-pyrrolidinone **1a** with various readily available (hetero)aryl and (cyclo)alkyl sodium sulfinates compounds **2a-o** (Scheme 2). Different *para*-substituted benzene sodium sulfinates were tested, such as sodium p-toluenesulfinate **2b**, 4-fluoro and 4-chlorobenzenesulfinic acid **2c** and **2d**, and afforded the corresponding products **3ab** to **3ad** in high yields (85-91%). *Meta* substituted aryl sulfinates partners, 3-chloro 4-methyl benzenesulfinic acid sodium salt **2e** and 3-(trifluoromethyl)benzenesulfinic acid sodium salt **2f** were also successfully engaged in the reaction (80-89%). Finally, N- (pyridine-2-sulfinic acid sodium salt **2g** and S-(2,5-dichlorothiophene-3-sulfinic acid sodium salt **2h** containing heteroaromatic compounds provided the desired products **3ag** and **3ah** in good-to-high yields (60-83%). Alkyl sulfinates were then investigated, and both linear (**2i**, **2j**) and cyclic (**2k**, **2l**) derivatives yielded the hydrosulfonylation products, but with lower yields (61-75%) in comparison with aryl sulfinates. Functionalized sulfinates such as sodium triflinate **2m** and sodium 1-methyl 3-sulfinopropanoate **2n** were also able to provide the allylic sulfones in good yields (70-73%), showing the high tolerance of the process. To prove the robustness of the reaction, we were interested in performing it on a larger scale. The reaction between our model substrates **1a** and **2a** was then conducted on a 2 mmol scale, *i.e.* on a scale eight times larger than usual, and afforded the corresponding hydrosulfonylation product **3aa** with a 97% isolated yield.

*Scheme 2. TFA-mediated hydrosulfonylation of allene **1a** with various sodium sulfinates **2a-n**.*

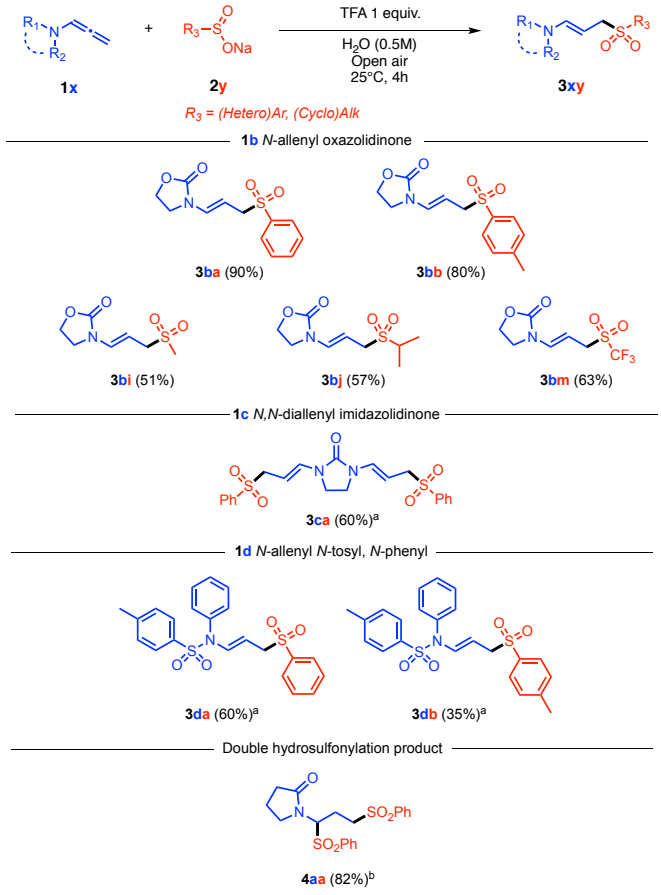


*Reaction conditions: **1a** (0.25 mmol), **2a-n** (2 equiv., 0.5 mmol), TFA (1 equiv., 0.25 mmol), H_2O (0.5M, 0.5 mL), open air, 25°C, 4h. Isolated yields.* [a] *The reaction was performed on a 2 mmol scale.* [b] *The reaction was performed at 40°C over two days under open air with 4 equiv. of TFA, 4 equiv. of $PhSO_2Na$ and H_2O/THF 1:1 (0.25M) as the solvent.* [c] *The reaction was performed with 2 equiv. of TFA.*

We then investigated the reactivity of different *N*-allenyl derivatives with several (hetero)aryl and (cyclo)alkyl sodium sulfinates (Scheme 3). The *N*-allenyl-2-oxazolidinone **1b** was successfully involved in the reaction, affording both aryl and alkyl allylic sulfones in medium to good yields (51-90%). The symmetrical diallene *N,N*-diallenyl-2-imidazolidinone **1c** afforded the corresponding double hydrosulfonylation product **3ca** in 60% yield when a mixture 1:1 of water and THF was used as solvent. We then investigated the reactivity of *N*-sulfonyl allenamides, and quickly observed that either these substrates and their corresponding hydrofunctionalization products are sensitive under our acidic conditions. Nevertheless, the sulfones **3da** and **3db** were obtained in moderate to good yields (35-60%).

Interestingly, we were able to perform a one step double hydrosulfonylation of **1a** with **2a** to obtain the corresponding 1,3-disulfone **4aa** in high yield. It is noteworthy to mention that the same 1,3-disulfone **4aa** can also be obtained through the hydrosulfonylation of **3aa**, demonstrating that our reaction can be applied both to *N*-allenyl and *N*-alkenyl derivatives.

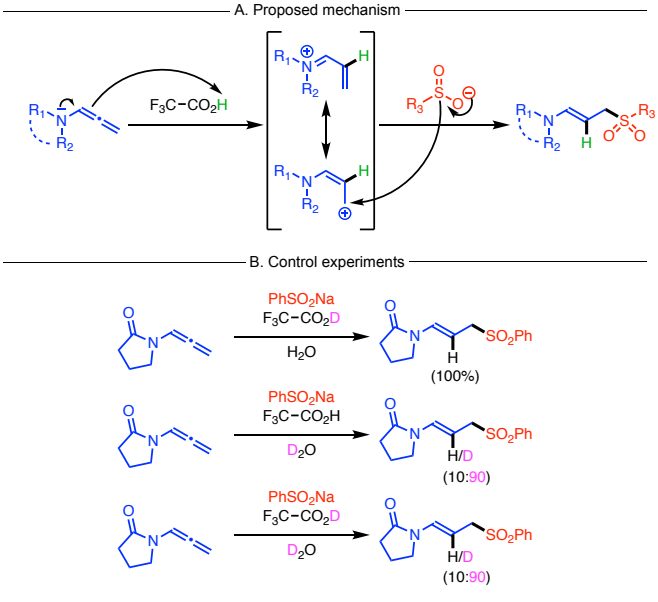
Scheme 3. TFA-mediated hydrosulfonylation of various allenyl derivatives with different sodium sulfinates.



*Reaction conditions (unless otherwise mentionned): **1** (0.25 mmol), **2** (2 equiv., 0.5 mmol), TFA (1 equiv., 0.25 mmol), H_2O (0.5M, 0.5 mL), open air, 25°C, 4h. Isolated yields.* [a] *H_2O/THF 1:1 (0.5M) was used as the solvent.*

The mechanism of the reaction could take place in two stages: the formation of a carbocation following by the addition of a proton to the allene. The second step consists of the addition of sulfinate to the terminal position of the allene, which finally leads to the formation of the allylic sulfone (Scheme 4, A.). When the reaction was performed using D_2O as a solvent, while in the presence of TFA or deuterated TFA, 90% deuterium incorporation was observed at the central position of the allene, which is consistent with the mechanism proposed above (Scheme 5, A). By using benzenesulfinic acid ($PhSO_2H$) instead of the corresponding sodium salt **2a** ($PhSO_2Na$), no product was formed, suggesting either that there is no protonation of the sulfinate by TFA during the reaction or there is decomposition of this reagent.

Scheme 4. Proposed mechanism and control experiments.



*Reaction conditions : **1** (0.25 mmol), **2** (2 equiv., 0.5 mmol), TFA or d-TFA (1 equiv., 0.25 mmol), H_2O or D_2O (0.5M, 0.5 mL), open air, 25°C, 4h. Isolated yields.*

Conclusion

To conclude, we developed a Brønsted acid-mediated allylation of S(VI)-containing nucleophiles. This transition metal-free methodology occurs in mild conditions and allows the hydrosulfonylation of a wide range of *N*-allenyl derivatives substrates with total regio- and stereoselectivity. Highly valuable and unprecedented *(E)*-allylic sulfones and a 1,3-disulfone were obtained with moderate to excellent yields in a total atom economical fashion. Further investigations fon hydrofunctionalization of allenes will be reported in due course.

Experimental Section

Detailed experimental procedures and characterization data (NMR ^{1}H, ^{13}C, ^{19}F, ESI-HRMS and m.p., if solid) for all new compounds are provided in the supporting information (PDF).

General procedure for the hydrosulfonylation of allenes

In a tube of appropriate size was added under open air sodium sulfinate **2** (2 equiv., 0.5 mmol), solvent (0.5M, 0.5 mL), allene **1** (1 equiv., 0.25 mmol) and trifluoroacetic acid (TFA) (1 equiv., 0.25 mmol). The mixture was stirred at 25°C during 4 hours under open air unless otherwise mentionned. After an aqueous work-up, the organic phase was separated. The remaining aqueous layer was further extracted with DCM. The gathered organic layers were then dried over anhydrous magnesium sulfate and concentrated under vacuum. Then, trichloroethylene (1 eq, 0.25 mmol) was added as the internal standard to estimate the NMR yield. In most cases analytically pure hydrosulfonylation product can be obtained directly without further purification, however if necessary purification by triethylamine (NEt_3) treated silica gel column chromatography was used.

Acknowledgments

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