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# Preparation of Functionalized α,β-Unsaturated Sulfonamides via Olefin Cross-Metathesis

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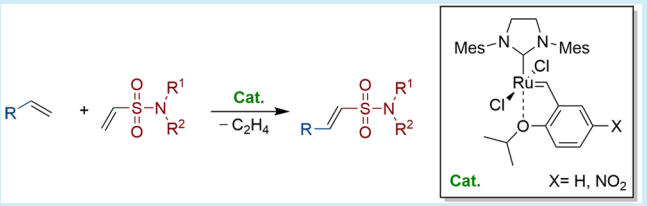
**ABSTRACT:** The synthesis of functionalized α,β-unsaturated sulfonamides by means of cross-metathesis of vinyl sulfonamides and olefins has been developed. The reaction proceeds smoothly in the presence of Hoveyda−Grubbs catalyst and its nitro analogue, providing a wide range of substituted products. The usefulness of this methodology has been proven in the preparation of new derivatives of biologically active ingredients, moxifloxacin and naratriptan.



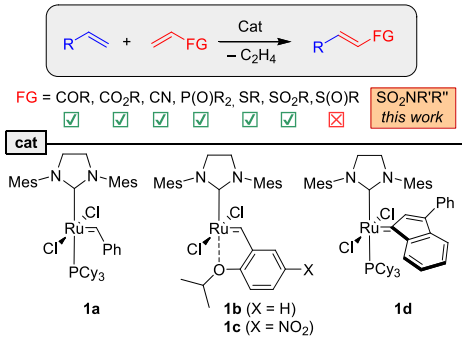



Functionalized α,β-unsaturated compounds are highly useful substrates in organic synthesis. Because of their inherent advantages, such as mild reaction conditions and availability of the olefinic substrates, the catalytic olefin cross-metathesis (CM) reaction appears to be potentially a very useful method for synthesis of these building blocks (Scheme 1).[1] However, it should be noted that not all functionalities at the reacting C−C double bond (functional groups, FG, in Scheme 1) are easily tolerated in CM.[1] For example, while acrylic acid esters and amides or α,β-unsaturated aldehydes and ketones are usually well tolerated, acrylonitrile got reputation of a rather problematic substrate.[2] The same is true for vinyl phosphine oxides which require extensive optimization to react in CM.[3]

Similarly, a number of challenges were noted in the cross-metathesis reaction of α,β-unsaturated partners containing sulfur at various oxidation states.[4] In contrast to allyl sulfides (type I olefins), vinyl sulfides (type III olefins) are much less reactive, which is generally assumed with their ability to arrest the propagating Ru species into stable Fisher carbenes during the reaction course.[5] While this problem can be at least partially overcome by using higher loading of the catalyst and microwave irradiation, vinyl sulfides are not easy partners in Ru-catalyzed CM.[6]

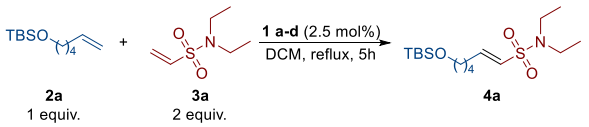
Another important building blocks are sulfone- and sulfoxide-containing alkenes. Vinyl sulfoxides were reported as completely inert in the CM reaction with olefins,[7] and according to our knowledge, only one example of a partially successful allylsulfoxide CM was reported.[4] The latter was, however, not seamless, and despite the high catalyst loading and forcing conditions used only 31% of the product was

**Scheme 1. Synthesis of Functionalized α,β-Unsaturated Compounds by Cross-Metathesis[a]**




[a]Selected Ru catalysts used in this transformation.

**Table 1. Optimizations of the CM Reaction of Sulfonamide 3a and Alkene 2a**




| entry | solvent | catalyst | GC conversion[a] (%) |
|---|---|---|---|
| 1 | DCM | **1a** | 76 |
| 2 | DCM | **1b** | 92 |
| 3 | DCM | **1c** | 89 |
| 4 | toluene | **1c** | 81 |
| 5 | diethyl ether | **1c** | 87 |
| 6 | DCM | **1d** | 57 |

[a]Tetradecane was used as an internal standard.

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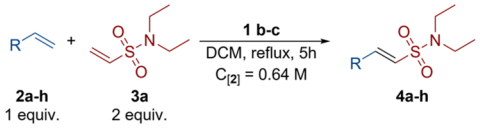
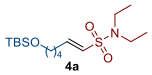
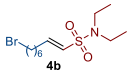
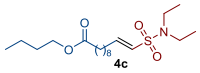
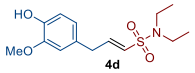
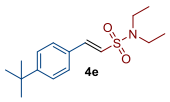
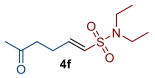
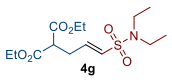
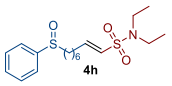
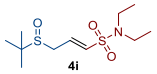
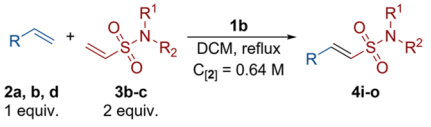
**Table 2. Cross-Metathesis between Sulfonamide 3a and Alkenes 2a−i**

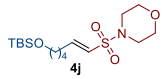
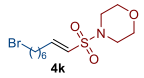
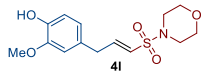
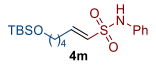
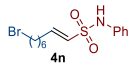
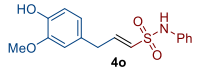



| Entry | Cat (mol %) | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | **1b** (2.5) |  | 5 | 92 |
| 2 | **1b** (2.5)<br>**1c** (2.5) |  | 22<br>3 | 65<br>95 |
| 3 | **1b** (3.5) |  | 22 | 75 |
| 4 | **1b** (2.5) |  | 5 | 95 |
| 5 | **1b** (5.0) |  | 22 | 62 |
| 6 | **1b** (5.0)<br>**1c** (5.0) |  | 5<br>5 | 30[a]<br>29 |
| 7 | **1c** (5.0) |  | 5 | 32 |
| 8 | **1b** (2.5) |  | 22 | 70 |
| 9 | **1b** (2.5) |  | 28 | 0 |

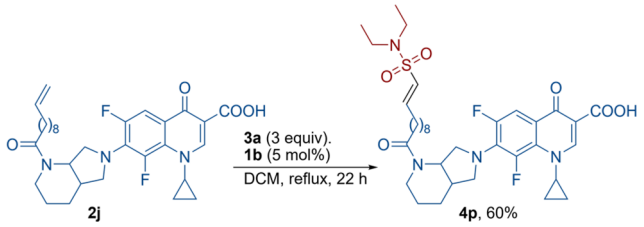
[a]Reaction performed in the presence of 10 mol % of $Ti(OiPr)_4$; the dimer of **2f** was obtained with 62% yield.

**Table 3. Cross-Metathesis between Sulfonamides 3b,c and Alkenes 2a-b,d**




| Entry | Cat (mol %) | Product | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | **1b** (2.5) |  | 5 | 86 |
| 2 | **1b** (2.5) |  | 5 | 88 |
| 3 | **1b** (2.5) |  | 5 | 81 |
| 4 | **1b** (2.5)<br>**1b** (5.0) |  | 5<br>5 | 44<br>70 |
| 5 | **1b** (2.5)<br>**1b** (5.0) |  | 5<br>5 | 50<br>76 |
| 6 | **1b** (2.5)<br>**1b** (5.0) |  | 24<br>24 | 22<br>37 |

**Scheme 2. Cross-Metathesis between Vinyl Sulfonamide 3a and Moxifloxacin Derivative 2j**




formed in this transformation. In contrary, allyl sulfones very easily undergo cross-metathesis reactions even in the presence of the first generation Grubbs catalyst under mild conditions.[8] The analogous CM reaction of vinyl sulfones is far more demanding and requires the use of a second-generation catalyst.[9] Nevertheless, under optimized conditions the desired CM products can be obtained in high yield and with complete (*E*)-selectivity.[7] In addition, the reactivity of divinyl sulfone was investigated,[10] and the selective formation of monosubstituted derivatives exclusively as (*E*)-isomer was observed. Therefore, this transformation found applications in total synthesis, providing easy access to variously functionalized $\alpha,\beta$-unsaturated sulfone building blocks.[11] Importantly, the CM reaction of vinyl sulfones has become useful also in a medicinal chemistry context, as this function can increase the biological activity of a drug.[12]

It is striking that despite so many functional groups (Scheme 1) having already been tested in CM, the applicability of vinyl sulfonamides as partners in this transformation is barely known[13] (although there are single examples of use in RCM - ring-closing metathesis),[14] and only one report describing CM of allyl sulfonamides[15] is available.

On the basis of our previous investigations, we assumed that vinyl sulfonamides can act as suitable partners in CM, leading to synthetically useful products, and herein, we present a detailed report on this transformation.

Vinyl sulfonamides **3a−c**, needed as CM partners, were conveniently obtained in the reaction between 2-chloroethanesulfonyl chloride and the corresponding amine in the presence of $Et_3N$ (see the SI).[16]

First, a model cross-metathesis between *N*,*N*-diethylethenesulfonamide (**3a**) and *tert*-butyl(hex-5-en-1-yloxy)-dimethylsilane (**2a**) was carried out in order to find the optimal reaction conditions (Table 1). The CM reaction was performed in the presence of 2.5 mol % of selected second-generation ruthenium catalysts, with tetradecane as an internal standard. As the result, we found that Hoveyda−Grubbs-type catalysts **1b** and **1c** give the best yields and DCM is the solvent of choice. In all cases, the expected product **4a** was formed exclusively as (*E*)-isomer. Importantly, as olefin **2a** is a Type I CM partner in Grubbs classification,[5] in order to avoid a concomitant formation of the undesired homodimer (TBSO-$(CH_2)_4$CH = CH$(CH_2)_4$OTBS), 2 equiv of vinyl sulfonamide **3a** was used. The self-CM of **3a** was not observed during the process, which renders this substrate as a type III CM partner (not undergoing "homodimerization").[17]

With the optimized conditions in hand, the scope of the CM reaction between sulfonamide **3a** and selected alkenes was examined. A wide range of CM partners underwent these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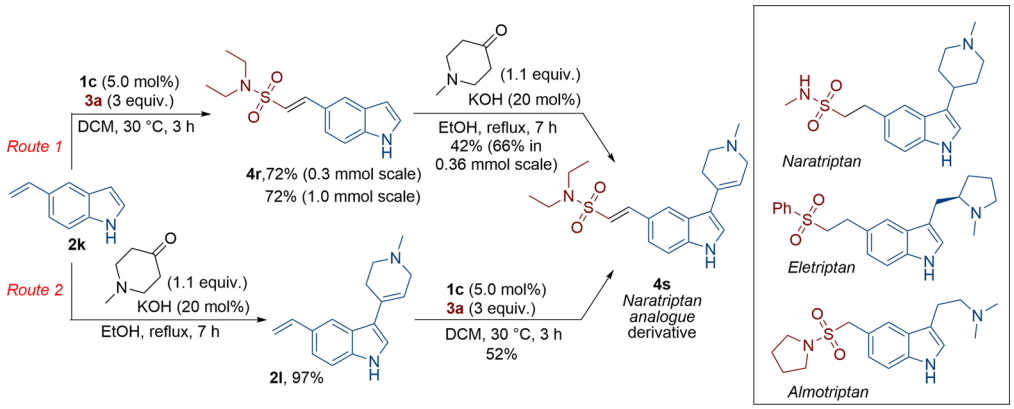
**Scheme 3. Synthesis of Naratriptan Analogue 4s and Structures of Selected Marketed Triptan Drugs**




reactions leading to diversely substituted sulfonamide derivatives, as shown in Table 2. For example, when simple terminal olefins (**2a**–**d**) were reacted with **3a** in the presence of Hoveyda–Grubbs-type catalyst, the desired products **4a**–**d** were obtained in good or very good yields (entries 1–4). The situation was slightly different when the styrene derivative **2e** was used (entry 5). Under standard conditions (2.5 mol % of **1b**, 5 h) the only product was a stilbene, resulting from self-CM of styrene **2e**. However, increasing the catalyst loading to 5 mol % and extending the reaction time to 22 h allowed the isolation of sulfonamide **4e** in a satisfactory yield of 62%. Sulfonamide **3a** also worked with ketone **2f** and sterically demanding allylmalonate derivative **2g**, although in these cases lower yields were obtained, 30 and 32%, respectively, even with increased catalysts loading (entries 7 and 8). As mentioned before, sulfoxides are considered as very demanding partners in CM, and achieving the expected sulfoxide-containing product requires forcing conditions.[4] Thus, we were pleased to find that sulfoxide–sulfonamide **4h**, bearing two sulfur atoms exhibiting different oxidation states, was produced in 70% isolated yield. Encouraged by this result, we decided to perform the CM reaction between **3a** and allyl *tert*-butyl sulfoxide (**2i**). Unfortunately, but according to the literature warnings about inactivity of **2i** in CM,[4] this reaction was completely ineffective as even traces of the expected product **4i** were not observed. Such results might suggest that poisoning of the catalyst by ligation of a sulfoxide function happens mainly when sulfoxide is located close to the reacting C–C double bond.[18]

The scope and limitation study was next extended to other vinyl sulfonamides (Table 3). Morpholine-based sulfonamide **3b** exhibited slightly lower reactivity than **3a**, although yields remained high (entries 1–3). A cross-metathesis reaction of *N*-monosubstituted sulfonamide **3c** performed under standard conditions led to the desired products in moderate yields, but increasing the catalyst loading to 5 mol % in all cases practically doubled the yield (entries 4–6).

Having successfully demonstrated the practicality of the CM reaction between vinyl sulfonamides and olefins bearing carbonyl, ester, and sulfoxide groups or halogens, this methodology was applied to more sophisticated substrates of potential medicinal interest. To do so, we attempted the CM reaction between *N*,*N*-diethylethenesulfonamide (**3a**) and a relative of the fluoroquinolone antibacterial agent moxifloxacin (Scheme 2). In order to prevent dimerization of the moxifloxacin derivative **2j** (which can be classified as type I olefin), the cross-metathesis partner **3a** was used in excess. As a result, we were pleased to see that with help of catalyst **1b** (5 mol %) the corresponding heavily functionalized product **4p** was obtained in a good yield of 60% as the exclusive (*E*)-isomer.

Another example of a polyfunctional molecule of pharmaceutical interest is naratriptan, one of the potent triptan drugs marketed by GlaxoSmithKline used for the treatment of acute migraine attacks and severe headaches.[19] This drug can be produced by Heck cross-coupling between vinyl sulfonamide and the appropriate brominated indole and subsequent hydrogenation of the product.[20] In an alternative approach envisioned by us, the cross-metathesis reaction between 5-vinyl-1*H*-indole derivative and vinyl sulfonamide may be considered (Scheme 3). Indeed, when indole **2l** was subjected to CM with *N*,*N*-diethylethenesulfonamide (**3a**) in the presence of 5 mol % of the nitro analogue of Hoveyda–Grubbs catalyst **1c**, the precursor **4s** of the naratriptan analogue was obtained with a satisfactory yield of 52%.

In summary, we have developed a simple but effective methodology leading to functionalized $\alpha,\beta$-unsaturated sulfonamides by means of olefin cross-metathesis utilizing a wide range of alkene partners. The title CM reactions can be simply carried out in the presence of commercially available Hoveyda-Grubbs-type catalysts **1b** and **1c** and the expected products were formed in moderate to good yields exclusively as (*E*)-isomers. Notably, a range of functionality is tolerated within this reaction, including not only carbonyl functions, esters, and sulfoxides, but also carboxylic acids and basic nitrogen groups. Because of their wide compatibility, this transformation can be successfully used in the synthesis of polyfunctional biologically active molecules as one of the alternatives in the formation of aliphatic sulfonamides.[21]

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01471.

Experimental details and $^{1}H$ and $^{13}C$ NMR spectra (PDF)

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## Author Contributions

[§]Ł.W. and A.A.R. contributed equally.

## Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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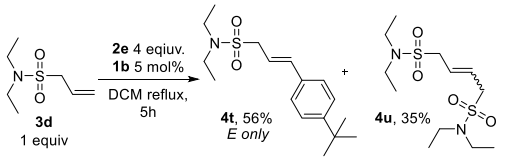
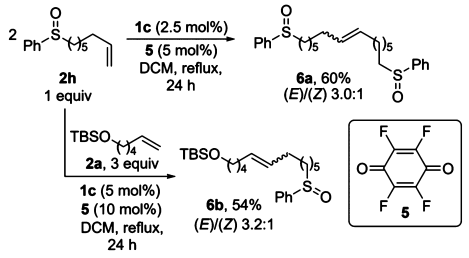
(17) As the reactivity of allyl sulfonamides in CM is only little explored (cf. ref 15), in order to compare them with vinyl sulfonamides we conducted a model CM reaction of **3d** to find that unlike the latter (Type III partners) these substrates undergo homodimerization and so are type I CM partners according to Grubbs classification.




(18) Due to the ambiguities of sulfoxide-containing alkenes reactivity in CM (cf. Table 2, entry 9), we applied **2h** in homodimerization and in CM reaction with Type I olefin **2a**. In both cases, good activity was observed, rendering sulfoxide **2h** as a regular Type I partner according to Grubbs classification. On the contrary, allyl and vinyl sulfoxides are classified as Type IV (nonreactive; ref 4). while homoallyl and higher sulfoxides are reactive (for more discussion, see the SI).

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