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ARTICLE

Manganese(III) Acetate-Mediated direct C(sp²)-H-Sulfonylation of Enamides with Sodium and Lithium Sulfinates

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A $Mn(OAc)_3$ mediated oxidative C(sp²)-H sulfonylation of enamides and encarbamates with sodium and lithium sulfinates is reported. This operationally simple transformation provides a straightforward and highly stereoselective access to (*E*)-*β*-amidovinyl sulfones in moderate to excellent yields. The reaction proceeds readily under mild conditions at room temperature and tolerates various sensitive functional groups. This process affords exclusively (*E*)-configurated *β*-amidovinyl sulfones independent of the staring material configuration. Moreover, a direct transformation of organolithium reagents and sulfur dioxide into *β*-amidovinyl sulfones is described.

Introduction

Sulfones have found widespread applications as versatile synthetic intermediates in organic chemistry and are frequently found in biologically active molecules.[1] Selected examples of active pharmaceutical ingredients containing a sulfone functional group include eletriptan, used for the treatment of migraine,[2] the antibiotic dapsone[3] or the anticancer agent bicalutamide[4] (Figure 1).

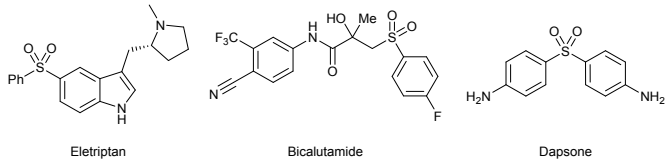

Figure 1 Biologically active sulfones

Commonly, sulfones are prepared from prefunctionalized molecules containing a sulfur functionality, for example by the oxidation of sulfides or Friedel-Crafts-type reactions with sulfonyl chlorides.[1,5] In the last ten years, the synthesis of sulfonyl-group containing molecules via the direct incorporation of sulfur dioxide has gained increasing attention.[6,7] . At the same time, the development of novel methods for the construction of sulfones via the direct functionalization of C-H-bonds has opened a new opportunity for a more sustainable synthesis of this important functional group.[8,9].

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Among the plethora of different sulfone-containing molecules, the *β*-amido sulfone motif represents a particularly interesting scaffold. *β*-Amido sulfones are useful building blocks for the synthesis of amino acids,[9] alkaloids[10] or carbohydrate derivatives.[11] The *β*-amido sulfone unit is present in molecules with attractive biological properties. Selected examples are depicted in Figure 2: the PDE4 inhibitor apremilast is used for the treatment of psoarisis;[12] LY404039, a glutamate receptor agonist, is under investigation as potential antipsychotic agent;[13] Sulbactam and Tazobactam are two synthetic *β*-lactam antibiotics.[14]

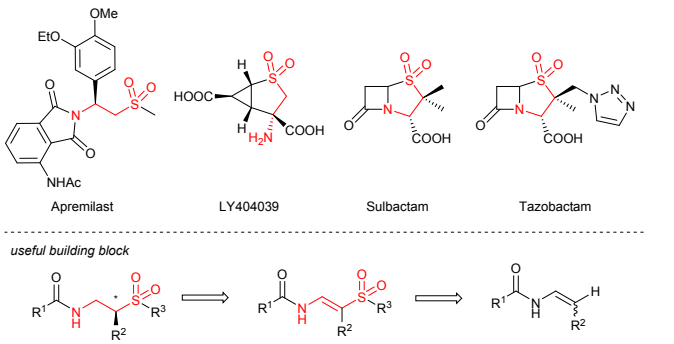
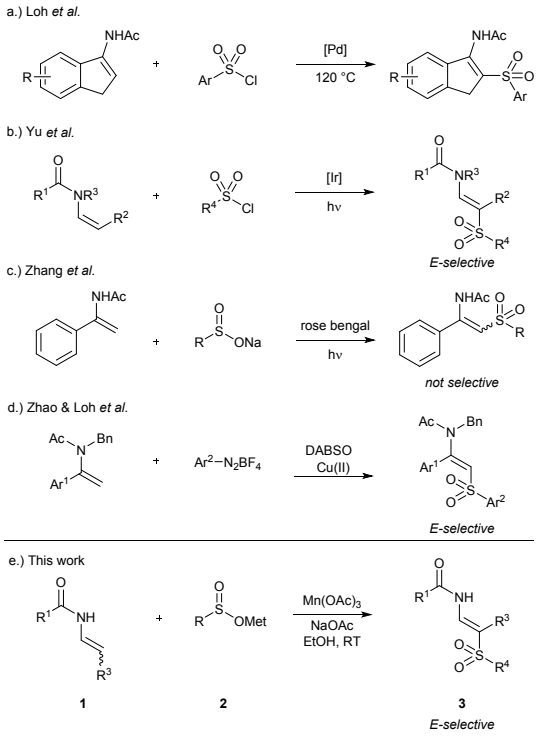


Figure 2 Biologically active *β*-amido sulfones and a synthetic approach to this scaffold

The hydrogenation of the corresponding *β*-amidovinyl sulfones represents one of the most attractive approaches for the construction of the *β*-amido sulfone scaffold, especially for the asymmetric synthesis of chiral derivatives.[15] Therefore the development of novel methods for an efficient preparation of the required enamide-bearing starting materials is highly desirable. In principle, the direct C(sp²)-H sulfonylation of simple enamides as readily available building blocks[16] provides a very straightforward and flexible access to *β*-amidovinyl sulfones. Thus, several groups have established protocols for the C-H-sulfonylation of enamides (Scheme 1). The groups of Loh and Yu have reported Pd- and Ir-catalyzed reactions[18, 19]

for the direct C-H-functionalization of enamides with sulfonyl chlorides (Scheme 1a and 1b). Whereas method of Loh is solely limited to indenyl-derived enamides,[18] the reaction of Yu is compatible with various tertiary enamides and affords exclusively the corresponding (*E*)-configured *β*-amidovinyl sulfones.[19] Zhang and coworkers reported a metal-free, visible-light induced oxidative C-H-functionalization of secondary enamides with sodium sulfinates (Scheme 1c).[20] The authors did not observe any stereroselctivity in the case of acyclic products. More recently, Zhao and Loh described a $Cu(OTf)_2$-mediated C-H-sulfonylation of tertiary enamides with incorporation of sulfur dioxide, leading to the corresponding (*E*)-amidovinyl sulfones (Scheme 1d).[21] Despite these advances, novel synthetic procedures for the preparation of sulfonylated enamides with an expanded substrate scope avoiding the use of expensive catalysts would be highly desirable. Of particular interest are methods for the construction of geometrically well-defined acyclic *β*-amidovinyl sulfones as well as transformations with secondary enamides or encarbamates, which would allow a more facile subsequent modification of the amino-moiety.

Herein we want to report a novel procedure for the direct C-H-sulfonylation of secondary enamides and encarbamates with sodium and lithium sulfinates mediated by $Mn(OAc)_3$ as simple base metal promoter (Scheme 1e). This method affords synthetically valuable acyclic (*E*)-*β*-amidovinyl sulfones in good yields and excellent stereoselectivities.



Scheme 1 C-H-sulfonylation of enamides.

Results and Discussion

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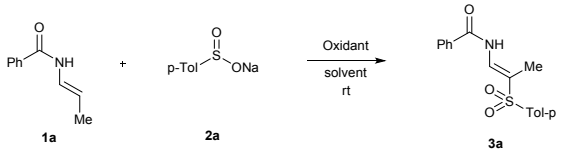
In the framework of our studies towards novel, highly modular procedures for the synthesis of sulfones[22] and sulfonamides[7c,], we were able to identify $Mn(OAc)_3$ in 1,1,1,3,3,3-hexafluoroisopropan-2-ol (HFIP) as an highly efficient promoter for the oxidative C-H-sulfonylation of 8-aminoquinolines,[9g] anilines,[23] or 1,4-dimethoxybenzenes[24] with sulfinic acid salts. We envisioned, that this system should be also capable of mediating an analogous cross-dehydrogenative coupling with enamides.

To our delight, a first test reaction of the (*E*)-configured secondary enamide **1a** with two equivalents of sodium p-toluenesulfinate **2a** and $Mn(OAc)_3{\cdot}2H_2O$ in HFIP afforded the desired β-amidovinyl sulfone **3a** in 78% yield within two hours at room temperature (Table 1, entry 1).

Table 1 Optimization of the reaction conditions.



Entry	Oxidant (equiv.)	Additiv (equiv.)	Solvent	Time (h)	Yield[a] (%)
1	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	HFIP	2	78
2	$Mn(OAc)_3{\cdot}2\ H_2O$ (3.0)	-	HFIP	2	44
3	$Mn(OAc)_3{\cdot}2\ H_2O$ (1.0)	-	HFIP	2	55
4	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	MeCN	24	43
5	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	acetone	24	47
6	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	THF	24	67
7	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	CH_2Cl_2	24	50
8	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	DMF	24	70
9	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	*i*PrOH	24	64
10	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	MeOH	2	84
11	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	EtOH	2	84
12	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	Water	24	-
13[b]	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	EtOH	2	72
14[c]	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	-	EtOH	2	71
15	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	NaOAc (2.0)	EtOH	2	**91**
16	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	NaOAc (1.0)	EtOH	2	**85**
17	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	Na_2CO_3 (2.0)	EtOH	2	63
18	$Mn(OAc)_2{\cdot}4\ H_2O$ (2.0)	-	EtOH	24	-
19	$Cu(OAc)_2{\cdot}$(2.0)	-	EtOH	24	10
20	$NaIO_4$ (2.0)	-	EtOH	24	-
21	$K_2S_2O_8$ (2.0)	-	EtOH	24	-
22	TBHP(2.0)	-	EtOH	24	-
23	PIDA (2.0)	-	EtOH	24	-
24[d]	$Mn(OAc)_3{\cdot}2\ H_2O$ (2.0)	NaOAc (2.0)	EtOH	2	87

Reaction conditions unless otherwise specified: Oxidant (2.0 equiv.), sulfinate salt (2.0 equiv.), solvent (2 mL), 2h, rt. [a] Overall isolated yield after column chromatography; In all cases, the (*E*)-configured *β*-amidovinyl sulfone **3a** could be isolated; [b] 1.5 equiv. of the sulfinate salt were used; [c] 1.1 equiv. of the sulfinate salt were used; [d] degassed, under nitrogen atmosphere.

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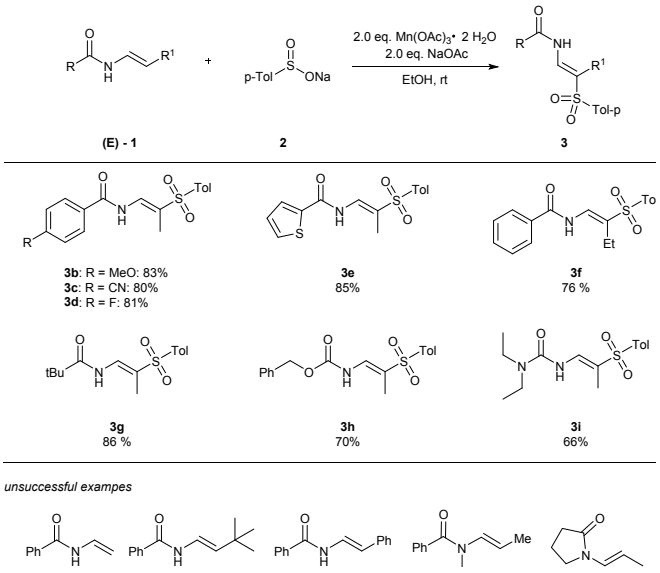
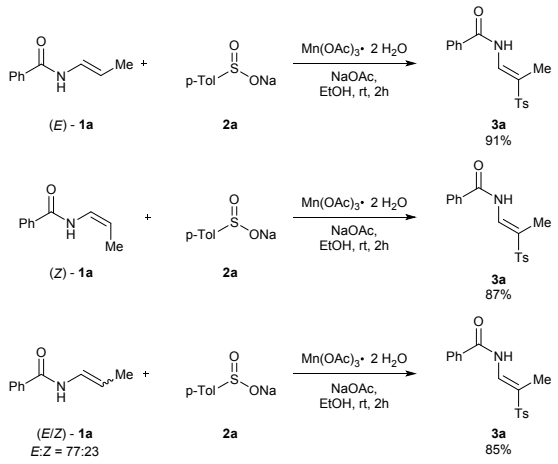
Interestingly, an exclusive formation of the (*E*)-configured product was observed.[25] Increasing or decreasing the amount of $Mn(OAc)_3{\cdot}2\ H_2O$ led to significantly lower yields (entries 2 and 3). Contrary to our pervious observations, the use of HFIP is not crucial for an efficient transformation. The *β*-amidovinyl sulfone **3a** was obtained in moderate to good yields in various solvents, such as acetonitrile, acetone, tetrahydrofuran (THF), CH_2Cl_2, dimethylformamide (DMF) or 2-propanol (entries 4-9). However, longer reaction times of 24 hours were needed in all cases. On the other hand, the use of methanol and ethanol afforded the desired product in 84% yield after only two hours reaction time (entries 10 and 11). Water proved to be not a suitable medium for this transformation (entry 12). For all further studies EtOH, a recommend solvent from the CHEM21 solvent selection guide,[26] was used. Lowering the amount of sulfinate **3a** to 1.5 or 1.1 equivalents afforded the product **3a** in slightly decreased yields of 71-72% (entries 13 and 14). The yield could be further increased to 91% by the addition of sodium acetate (entry 15). The weak base NaOAc might serve as a buffer, thereby suppressing a potential degradation of the acid-sensitive enamide. On the other hand, decreasing the amount of NaOAc or addition of stronger bases, such as Na_2CO_3, did afford the product **3a** in lower isolated yields (entry 16). No product formation was observed in the presence of manganese(II) acetate (entry 18). The reaction with $Cu(OAc)_2$ instead of $Mn(OAc)_3$ afforded the amidovinylsulfone **3a** in only 10% yield (entry 19). Other oxidants, such as $NaIO_4$, $K_2S_2O_8$ tert-butylhydroperoxide (TBHP) or (diacetoxyiodo)benzene (PIDA) did not furnish the product at all (entries 20-23). In general, the use of other oxidants did lead to a fast decomposition of the sulfinic acid salt. In our typical setup, the reaction is performed without any efforts to exclude air or moisture. However, performing the reaction under a nitrogen atmosphere did not affect the isolated yield (entry 24).

With the optimized conditions at hand, we started to investigate the substrate scope of this oxidative C-H-sulfonylation. First, reactions of geometrically defined (*E*)-enamides with sodium p-toluene sulfinate were investigated (Scheme 2). Different benzamide-derived enamides, bearing an electron-withdrawing or -donating group, afforded the desired amidovinyl sulfones **3b**-**d** in 80-81% yield. In a similar manner, reactions of a heterocyclic derivative or an enamide with an alkyl amide group afforded the expected products **3e** and **3g** in 85% and 86% yield. This process is not limited to C-H-sulfonylation of enamides. Using the standard reaction conditions the direct sulfonylation of the corresponding encarbamte or enurea derivatives afforded the aminovinyl sulfones **3h** and **3i** in 70 and 66% yield. The direct synthesis of products bearing different amino-protecting groups could be highly useful for subsequent transformations. In all cases, the exclusive formation of the (*E*)-configured products was observed. However, this process is sensitive towards structural modifications of the enamide. Whereas the reaction of an ethyl-substituted enamide furnished amidovinylsulfone **3f** in 76% yield, transformations with the parent, unsubstituted enamide **4** or enamides **5** and **6**, bearing a more bulky *tert*-butyl- or phenyl-substituent at the alpha carbon, were not successful. Tertiary enamides, such as **7** or **8**, lacking a free N-H, proved to be not suitable for our reaction.



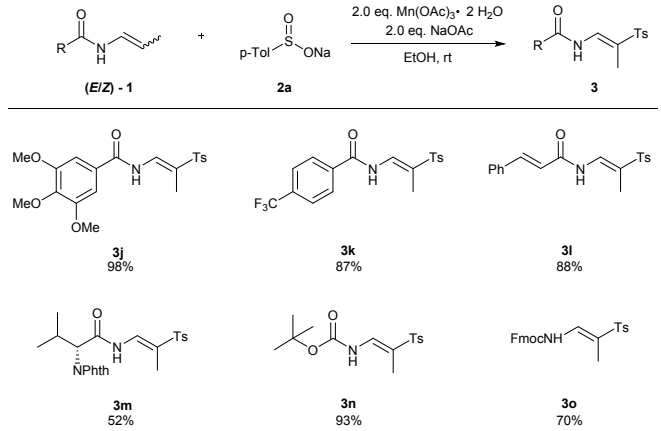
Scheme 2 Substrate scope with *E*-Enamides.

Next we studied the reaction of (*Z*)-configured enamide **1a** with p-toluene sulfinate **2a**. Interestingly, a selective formation of the (*E*)-configured amidovinyl sulfone **3a** in a comparable yield of 87% was observed (Scheme 3). The formation of the same product from both geometrical isomers of an enamide implies the formation of a common intermediate during the reaction. Since our preferred method for the synthesis of the required enamide starting materials, a nickel-catalyzed isomerization of the corresponding allylamides,[27] usually affords a mixture of the (*E*)- and the (*Z*)-enamide, we investigated the direct transformation of such a mixture using our standard conditions. To our delight, an exclusive formation of the (*E*)-configured amidovinyl sulfone **3a** in 85% yield took place.



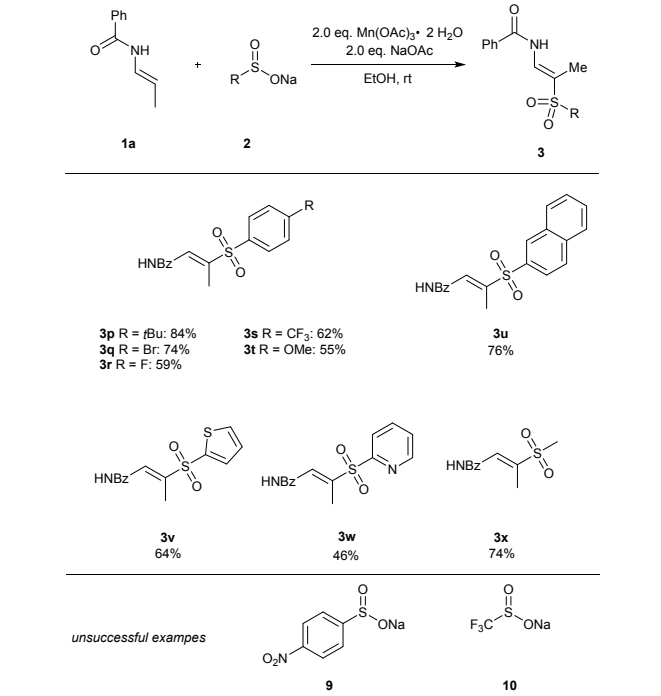
Scheme 3 Sulfonylation of configurational isomers of **1a**. Ts = Tosyl.

As the separation of both isomers of an given enamide can be quite cumbersome, we decided to perform a further set of reactions directly with the (*E*/*Z*)-mixtures obtained after the Ni-catalyzed isomerization (Scheme 4). Also in these cases, the



Scheme 4 Substrate Scope with (*E*/*Z*)-mixtures of enamides. Ts = Tosyl, Phth = Phth.

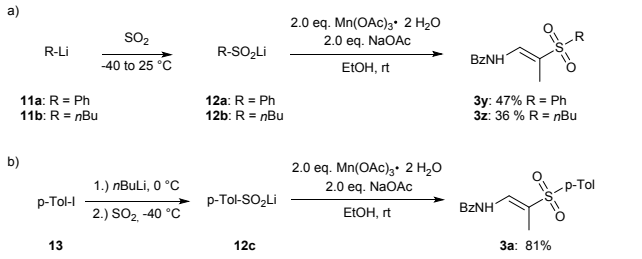
desired sulfonylated enamides **3j**-**o** were formed exclusively as the (*E*)-isomer. Again electron-rich or electron-poor benzamide derived enamides were efficiently sulfonylated. A chemoselective sulfonylation of the more-electron-rich enamide moiety was observed for substrate **3l**. The reaction of a structurally more complex valine-derived enamide afforded the amidovinyl sulfone **3m** in 52% yield. Interestingly, the transformations of Boc- and Fmoc-derived encarbamates **1n** and **1o** proceeded with similar efficiency, furnishing the *N*-protected aminovinyl sulfones **3n** and **3o** in 95% and 70% yield.



Scheme 5 Substrate scope with different sodium sulfinates. Bz = Benzoyl.

In parallel with studied the reaction of enamide **1a** with different sulfinic acid sodium salts (Scheme 5). In general arene sulfinates bearing different functional groups, proved to be suitable substrates for our transformation, affording the amidovinyl sulfones **3p**-**3x** in 55-84% yield. Halogen-substituents, such as a bromo- or fluoro-functionality, were well tolerated, thereby providing a handle for further manipulations. Only in the case of the very electron-poor p-nitrobenzene sulfinate **9** no product formation was observed. Reactions with heterocyclic sulfinic acid salts provided the sulfonylated enamide **3v** and **3w** in 46% and 64% yield. Using sodium methane sulfinate the methylsulfone derivative **3x** was synthesized in 74% yield. Unfortunately, no reaction was observed with the corresponding trifluoromethyl derivative **10**.

In order to expand the scope of our method, we studied the C-H-sulfonylation with different lithium sulfinates, which can be easily synthesized from the corresponding organolithium reagent and sulfur dioxide.[28] Thus, two sulfinic acid salts **12a** and **12b** were prepared from sulfur dioxide and phenyllithium **11a** or n-butyllithium **11b** in quantitative yields (Scheme 6). Gratifyingly, the crude lithium sulfinates are suitable substrates for our direct C-H-sulfonylation, furnishing the amidovinyl sulfones **3y** and **3z** in 36% and 47% yield. In a similar manner, reaction of lithium p-toluene sulfinate **12c**, prepared in two steps from 4-iodotoluene via lithium-halide exchange and trapping with sulfur dioxide, afforded the sulfonylated enamide **3a** in 81% yield. Although the isolated yields are not as high as for the corresponding sodium sulfinates, these results demonstrate, that *β*-amidovinyl sulfones can be directly accessed from simple building blocks by merging classical organolithium chemistry with our oxidative coupling procedure.



Scheme 6 Synthesis of *β*-amidovinyl sulfones using organolithium chemistry.

Since the preparation of the starting enamides as well as the oxidative C-H-sulfonylation can be performed in the same solvent (EtOH), we investigated a merger of both reactions into a one-pot procedure (Scheme 7). Therefore, allylamide **14** was isomerized using an air-stable nickel-precatalyst.[27] After completion of the isomerization, the formed (*E*/*Z*)-mixture of enamide **1a** was not isolated. Instead, sulfinate **2a**, NaOAc and $Mn(OAc)_3$ were directly added to the reaction mixture. To our delight, the nickel-catalyst does not interfere with the oxidative C-H-sulfonylation and the desired *β*-amidovinyl sulfone **3a** could be obtained in 87% overall yield. This

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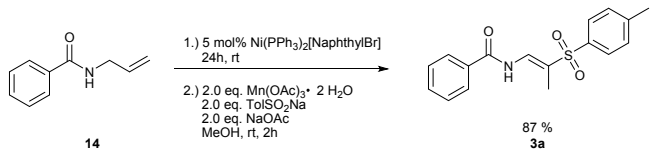
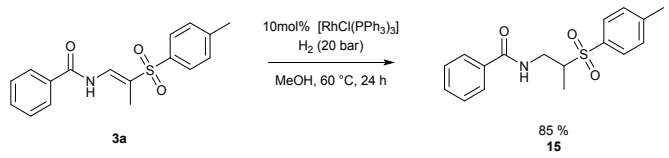
operationally simple one-pot procedure offers a very attractive avenue for the preparation of different amidovinyl sulfones.

Finally, we briefly studied the hydrogenation of amidovinyl sulfone **3a** as model substrate (scheme 8). In the presence of 10 mol% of Wilkionson's catalyst a smooth hydrogenation takes place, furnishing the *β*-amido sulfone **15** in 85% yield.



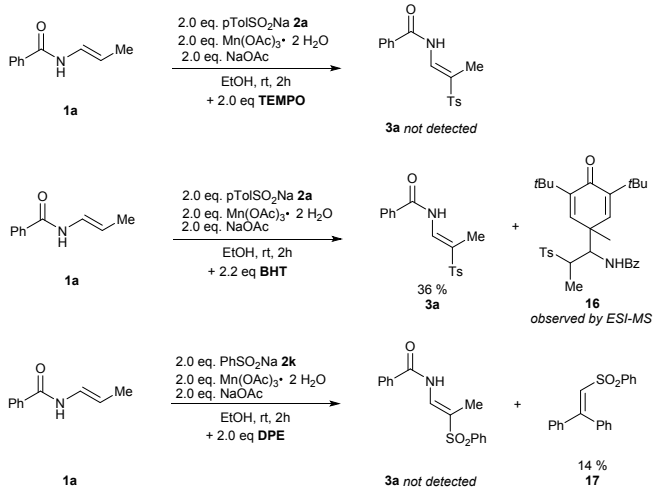
Scheme 7 Telescoped process for the direct synthesis of amidovinylsulfone **3a** from allylamide **14**.

Since the synthesis of molecules bearing a stereogenic carbon center directly attached to a sulfonyl group is scarcely studied, the herein obtained amidovinyl sulfones can provide a new opportunity for the enantioselective synthesis of such structural motifs.



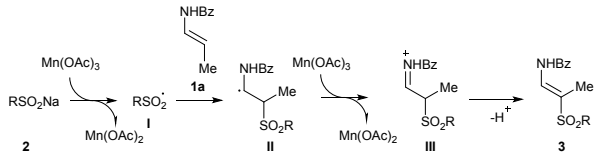
Scheme 8 Hydrogenation of **3a** with Wilkinson's catalyst.

In order to gain more insight into the reaction mechanism, a series of control experiments were performed. In the presence of radical inhibitors a marked decrease of the reaction rate was observed (Scheme 9). Whereas the addition of TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) or DPE (1,1-Diphenylethylene) led to a complete shutdown of the reaction, amidovinyl sulfone **3a** was isolated in 36% yield in the presence of BHT (2,6-Di-*tert*-butyl-4-methylphenol).



Scheme 9. Mechanistic studies. Ts = Tosyl, Bz = Benzoyl.

In this case compound **16**, presumably formed via trapping of a radical reaction intermediate with BHT, could be observed by ESI-MS. In the presence of DPE, vinyl sulfone **17** could be obtained in 14% yield, indicating the formation of sulfonyl radicals. Based on these results and previous studies we propose the following reaction mechanism. Single-electron oxidation of the sulfinate salt **2** with $Mn(OAc)_3$ affords a sulfonyl radical **I**. Addition of this electrophilic radical to the nucleophilic alpha-carbon of the enamide **1a** leads to the formation of a radical intermediate **I**. Single-electron-oxidation of **II** with a second equivalent of $Mn(OAc)_3$ furnishes the *N*-Acyliminium intermediate **III**. Finally loss of a proton leads to the formation of the amidovinyl sulfone product **3**.



Scheme 10. Proposed reaction mechanism.

Conclusions and Outlook

In summary, we have reported a $Mn(OAc)_3$-promoted $C(sp^2)$-H-sulfonylation of enamides and encarbamtes with sulfinic acid salts. This novel method allows a facile preparation of *β*-amidovinyl sulfones, important building blocks for pharmacologically relevant scaffolds, in high yields. The reaction proceeds at room temperature under mild conditions and tolerates various functional groups as well as common carbamte protecting groups on the nitrogen. This process is highly stereoselective, affording exclusively *E*-configured sulfonylated enamides, independent of the configuration of the starting material. In combination with organolithium chemistry, amidovinyl sulfones can be accessed in a very modular manner. Further, we could demonstrate a telescoped transformation of a readily available allylamide into the corresponding sulfonylated enamide. Mechanistic studies support a radical reaction pathway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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