JOC The Journal of Organic Chemistry

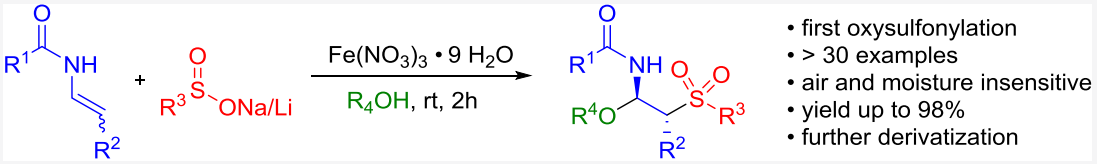
pubs.acs.org/joc Article

Iron(III)-Mediated Oxysulfonylation of Enamides with Sodium and Lithium Sulfinates

Philipp Kramer, Miro Halaczkiewicz, Yu Sun, Harald Kelm, and Georg Manolikakes*

Cite This: J. Org. Chem. 2020, 85, 3617−3637 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: An iron-mediated vicinal difunctionalization of enamides and enecarbamates with sulfinic acid salts and alcohols is described. This reaction proceeds under mild conditions and furnishes the oxysulfonylated products in moderate to excellent yields. Moreover, the direct incorporation of sulfur dioxide into the sulfonylated products via organolithium chemistry has been achieved. The formed *N*-*O*-acetals are competent acylimine precursors. Their utilization as building blocks for the synthesis of biologically relevant *β*-amidosulfones is described as well.

INTRODUCTION

Molecules bearing sulfonyl-derived functional groups, such as sulfones or sulfonamides, play an important role in organic chemistry and are widely used in various fields.[1,2] Among the different classes of sulfonyl-derived functional groups, sulfones are of particular interest. They display intriguing chemical and physical properties as well as interesting biological activities. Sulfones, which are often considered as chemical chameleons,[3] are versatile building blocks in organic synthesis. The sulfone motif can be found in various molecules with different applications ranging from agrochemicals and functional materials to active pharmaceutical ingredients.[2−4] Traditional approaches for the construction of sulfones include Friedel−Crafts-type reactions of arenes with sulfonyl chlorides,[5] the oxidation of sulfides and sulfoxides,[6] addition reactions of sulfonyl radicals to alkenes and alkynes,[7] or the electrophilic trapping of sulfinic acid salts.[8,9] In the last 10 years, novel approaches based on the direct incorporation of sulfur dioxide[10,11] or the functionalization of C−H bonds[12,13] have emerged as attractive and more sustainable alternatives.

Among the different types of sulfones, the *β*-amidosulfone motif represents an important scaffold. *β*-Amidosulfones are versatile building blocks for the synthesis of alkaloids,[14] carbohydrates,[15] or amino acids,[16] and this structural unit can be found in various pharmaceuticals. Selected examples are cystemustine,[17] a potential cure for glioma and melanoma, the MDM2 inhibitor AMG 232,[18] the benzodiazepine elfazepam,[19] or the PDE4 inhibitor apremilast,[20] which is used for the treatment of psoriasis (Figure 1).

In the last few years, several groups have reported different methods for the synthesis of *β*-amidovinylsulfones via a direct C−H sulfonylation of enamides (Scheme 1a).[21,22] These amidovinylsulfones are useful molecules for the construction of the *β*-amidosulfone structure. However, an additional step for the synthesis of the desired product is necessary.

Enamides are versatile building blocks, and the direct difunctionalization (Scheme 1b) of these electron-rich olefins gives rise to various highly functionalized scaffolds.[23,24] Although various methods for the amino- and halo-oxygenation[25] as well as the dioxygenation[26] of enamides and enecarbamates have been described, there is so far, to the best of our knowledge, no analogous oxysulfonylation. Such a process would provide an alternative, highly modular access to the *β*-amidosulfone unit.

Herein, we report an iron-mediated oxysulfonylation of enamides using sodium or lithium sulfinates and alcohols. This novel method gives access to a new class of *β*-amidosulfones. A further diversification of the obtained products is described as well.[27]

RESULTS AND DISCUSSION

During our investigations on the $Mn(OAc)_3$-promoted C−H sulfonylation of enamides,[22] we made an interesting observation (Scheme 2). Whereas the reaction of *p*-toluenesulfinate **2a** with the (*E*)-configured enamide **1a** in MeOH in the presence of $Mn(OAc)_3$ afforded the (*E*)-vinyl sulfone **3a** in 84% yield, the formation of the oxysulfonylation product **4a** with incorporation of MeOH was observed in the presence of $FeCl_3$.

Received: December 9, 2019
Published: February 4, 2020

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

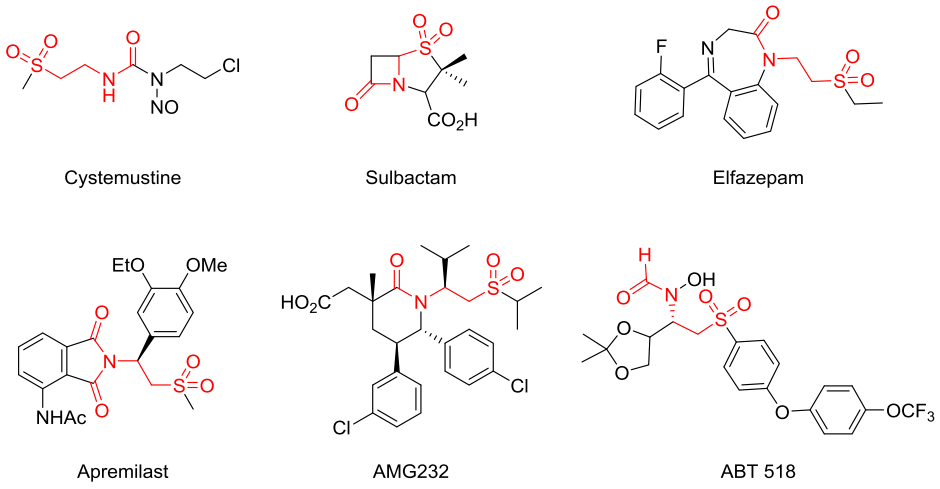
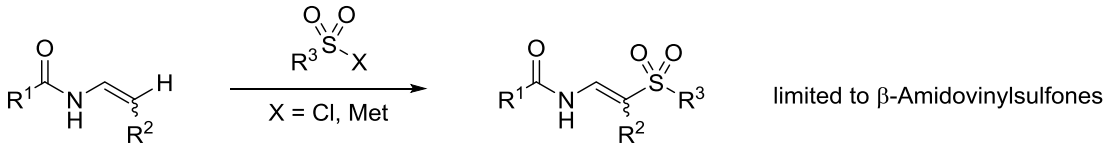


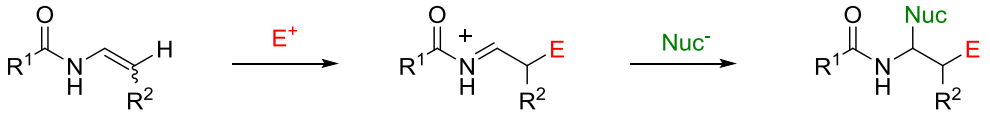
Figure 1. Biologically active *β*-amidosulfones.

Scheme 1. Previous and Typical Reactivity of Enamides[1]

(a.) Previous work



(b.) Typical reactivity of enamides



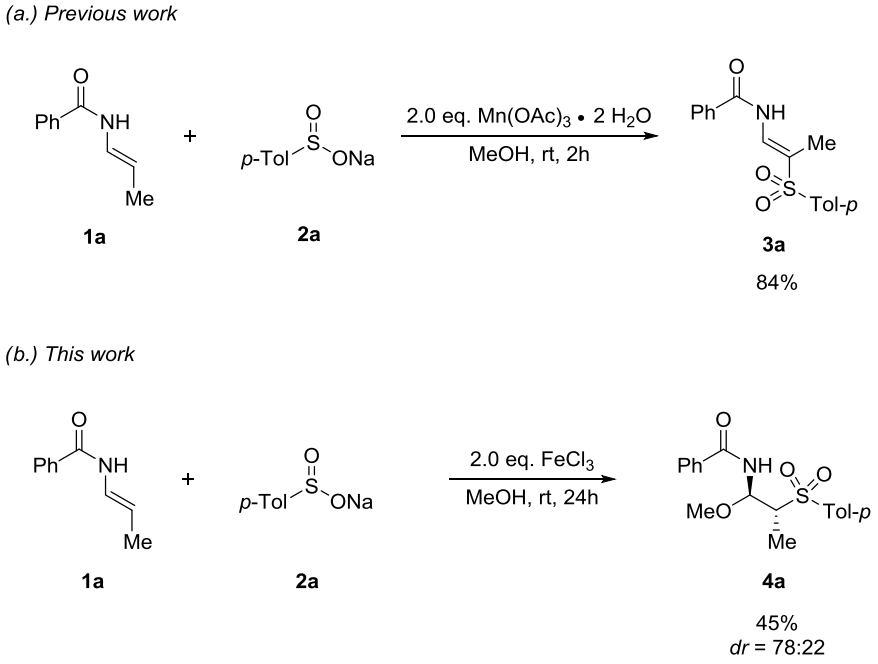
[1] E^+, electrophile; Nuc^-, nucleophile.

Since the direct oxysulfonylation of enamides has not been reported so far, we decided to further investigate this interesting transformation. As mentioned above, the reaction in the presence of anhydrous $FeCl_3$ afforded *β*-amidosulfone **4a** in 45% yield and a diastereomeric ratio of approx. 4:1 (see Table 1, entry 1). The structure of the major diastereomer could be unambiguously assigned by single X-ray crystallography.[28] The use of $FeCl_3 \cdot 6H_2O$ led to an improved yield of 64% (entry 2). No product formation was observed in the presence of iron(II) chloride (entry 3). In the presence of $Fe(ClO_4)_3$, only 24% of the desired product could be isolated (entry 4). Surprisingly, the use of $Fe(NO_3)_3 \cdot 9H_2O$ led to the rapid formation of amidosulfone **4a** in 91% yield within only 2 h at room temperature (entry 5). The use of iron salts bearing more strongly coordinating anions, such as $Fe(acac)_3$, has a detrimental effect on the reaction (entry 6). Two equivalents of the iron(III) salt are necessary for an efficient transformation. Decreasing the amount of $Fe(NO_3)_3 \cdot 9H_2O$ to only one equivalent led to an almost complete shutdown of the reaction (entry 7). All our attempts to substitute $Fe(NO_3)_3 \cdot 9H_2O$ at least partially with a cooxidant, such as $NaIO_4$ or IBX, did not afford the desired product in acceptable yields (entry 8). In contrast, lowering the amount of the sulfinate salt did only slightly affect the isolated yield (entries 9 and 10). Typically, all reactions were performed without any effort to exclude air or moisture. Interestingly, a control reaction performed under an atmosphere of nitrogen afforded the amidosulfone **4a** in only 66% yield, indicating a positive effect of oxygen on the reaction efficiency. MeOH is the solvent of choice for this transformation. The use of other solvents together with only 20 equiv of MeOH led to the formation of product **4a** in low to moderate yields (entry 11). Slightly acidic conditions seem to be optimal for this process. The addition of any buffering or basic additive, e.g., NaOAc, led to a sharp decrease in the isolated yield (entry 13).

In the next step, we investigated the reaction of the corresponding (*Z*)-configured enamide (*Z*)-**1a** under the optimized reaction conditions (Scheme 3). Interestingly, the desired *β*-amidosulfone **4a** could be obtained in 80% yield with a similar diastereomeric ratio of 4:1. A mixture of both configurational isomers of the enamide afforded amidosulfone **4a** in 85% yield with no changes in the observed diastereoselectivity. This reactivity allows for a considerable simplification of our method in terms of practicability. The nickel-catalyzed isomerization of allylamides **5a**, one of the most efficient approaches for the preparation of the required enamides, typically affords a difficult-to-separate mixture of the (*E*)- and the (*Z*)-enamide.[29] Since the configuration of the

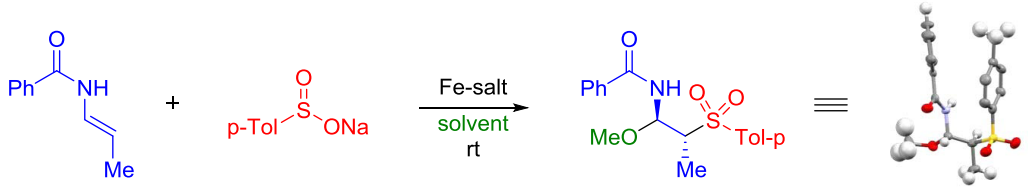
https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

Scheme 2. Previous Manganese-Mediated C-(sp^2) Functionalization and an Unprecedented Iron-Mediated Oxysulfonylation[2]



[2]The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

Table 1. Optimization of the Reaction Conditions[a]



entry	mediator (equiv)	additiv (equiv)	solvent	time (h)	yield (%)[b]	dr[c]
1	$FeCl_3$ (2.0)		MeOH	24	45	78:22
2	$FeCl_3{\cdot}6H_2O$ (2.0)		MeOH	24	64	76:24
3	$FeCl_2{\cdot}4H_2O$ (2.0)		MeOH	24		
4	$Fe(ClO_4)_3{\cdot}H_2O$ (2.0)		MeOH	24	32	42:58
5	$Fe(NO_3)_3{\cdot}9H_2O$ (2.0)		MeOH	2	91	80:20
6	$Fe(acac)_3$ (2.0)		MeOH	24		
7	$Fe(NO_3)_3{\cdot}9H_2O$ (1.0)		MeOH	24	7	80:20
8	$Fe(NO_3)_3{\cdot}9H_2O$ (1.0)	$NaIO_4$ (4.0), IBX (4.0)	MeOH	24	0–55	
9[d]	$Fe(NO_3)_3{\cdot}9H_2O$ (2.0)		MeOH	2	75	80:20
10[e]	$Fe(NO_3)_3{\cdot}9H_2O$ (2.0)		MeOH	2	71	80:20
11[f]	$Fe(NO_3)_3{\cdot}9H_2O$ (2.0)		MeOH	2	66	61:39
12	$Fe(NO_3)_3{\cdot}9H_2O$ (2.0)	MeOH (20)	DCM, EtOAc, Aceton, THF, MeCN	2	20–50	
13	$Fe(NO_3)_3{\cdot}9H_2O$ (2.0)	NaOAc (2.0)	MeOH	2	23	75:25

[a]Reaction conditions unless otherwise specified: oxidant (2.0 equiv), sulfinate salt (2.0 equiv), solvent (2 mL), 2 h, rt. [b]Overall isolated yield after column chromatography. [c]The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup. [d]1.5 equiv of the sulfinate salt was used. [e]1.1 equiv of the sulfinate salt was used. [f]Under a nitrogen atmosphere. X-ray crystal structure of **4a** (aromatic H atoms omitted for clarity).

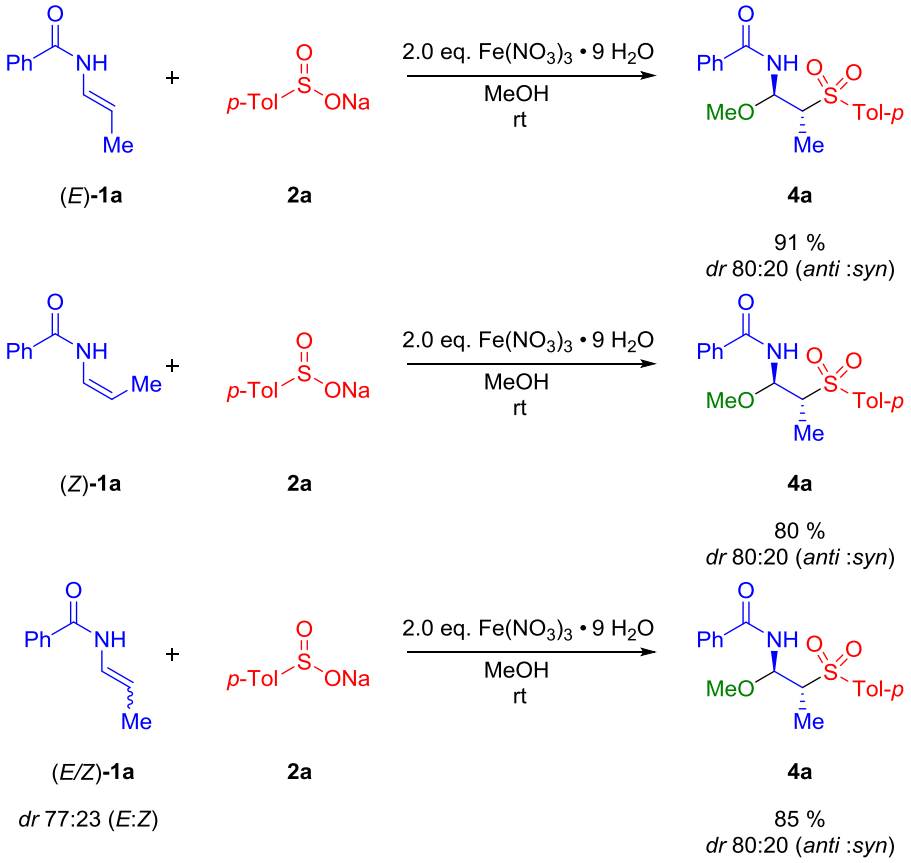
enamide double bond does not significantly affect the outcome of the oxysulfonylation reaction, these (*E*/*Z*)-mixtures could be used directly for all further investigations.

With the optimized reactions conditions at hand, we started to explore the substrate scope of this process.

At first, reactions with different alcohols were investigated. Replacement of MeOH as the solvent with other aliphatic alcohols, such as EtOH or *i*PrOH, delivered the expected *β*-amidosulfones **4b** and **4c** in slightly lower yields of 53 and 31%, respectively, and a comparable diastereomeric ratio of 4:1 (Scheme 4). Fluorinated alcohols such as trifluoroethanol or 1,1,1,3,3,3-hexafluoroisopropan-2-ol (HFIP), sterically more demanding alcohols (e.g., cyclohexanol), phenols, or water proved to be unsuitable for this reaction.

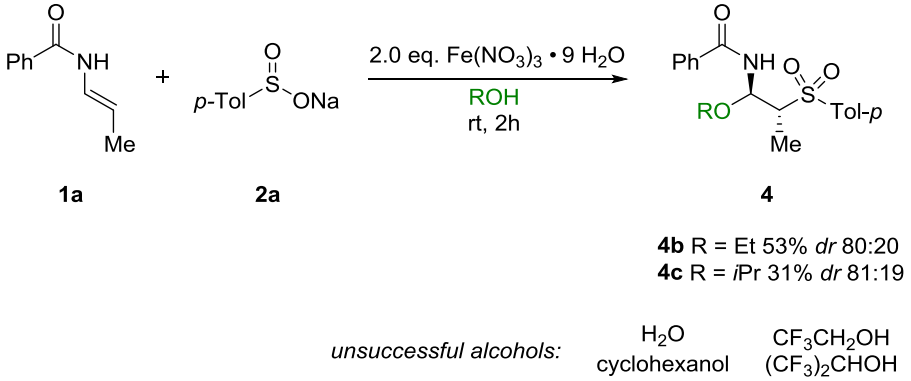
https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617–3637

Scheme 3. Reactivity of Different Geometrical Isomers in the Oxysulfonylation[3]



[3]Isolated yield after column chromatography. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

Scheme 4. Scope of Alcohols. Isolated Yield after Column Chromatography[4]



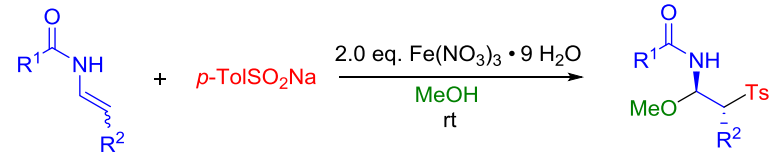
[4]The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

Subsequently, we studied the oxysulfonylation of different enamides (Scheme 5). Various benzamide-derived enamides bearing both electron-donating and electron-withdrawing groups provided the amidosulfones **4f–j** in 61–68% yield with similar diastereomeric ratios. Furthermore, reactions of heteroaryl- or alkylamide-derivatives afforded the compounds **4k–m** in 68–72% yield. Olefins or oxygen substituents in the enamide side chain were tolerated, and the corresponding products **4n** and **4o** could be isolated in 62 and 70% yields, respectively, with a decreased diastereoselectivity of 1.8:1.

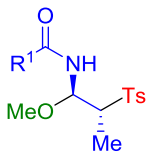
In contrast to the previous reports on the C–H sulfonylation of enamides, this transformation is less sensitive toward structural modifications on the enamide core. Our protocol is suitable for tertiary enamides without a free N–H-functionality, providing the sulfonylated *N,O*-acetals **4p** and **4q** in 40 and 60%, respectively. Modification of the olefin moiety is also possible, and the ethyl- as well as the un- or disubstituted products **4r–t** could be accessed in 43–77% yield. Moreover, encearbamates are suitable starting materials for this reaction. Although the desired *N*-protected *β*-aminosulfones **4u–w** were only formed in 40–44% yield with a diastereomeric ratio of roughly 1:1, the introduction of common Boc-, Cbz-, or Fmoc-protecting groups can be highly useful for subsequent

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617–3637

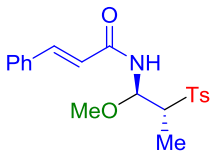
Scheme 5. Substrate Scope with an (*E*/*Z*)-Mixture of Enamide and Enecarbamates[5]



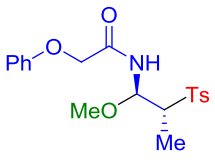
1 **2a** **4**



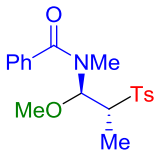
4f R^1 = *p*-Tol 64% *dr* 81:19
4g R^1 = Mesityl 63% *dr* 62:38
4h R^1 = 4-MeO-Ph 68% *dr* 80:20
4i R^1 = 4-F-Ph 62% *dr* 81:19
4j R^1 = 4-CF_3-Ph 61% *dr* 80:20
4k R^1 = 2-Thienyl 68% *dr* 83:17
4l R^1 = *t*Bu 72% *dr* 88:12
4m R^1 = $PhCH_2$ 70% *dr* 62:38



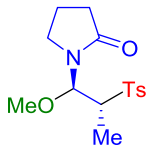
4n 62% *dr* 64:36



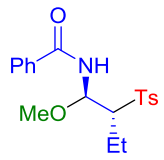
4o 70% *dr* 65:35



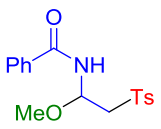
4p 40% *dr* >98:2



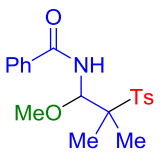
4q 60% *dr* 89:11



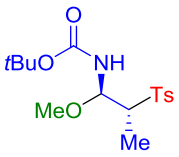
4r 77% *dr* 75:25



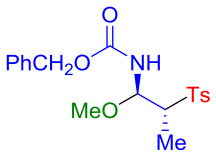
4s 67%



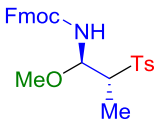
4t 43%



4u 40% *dr* 46:54

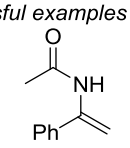


4v 44% *dr* 45:55

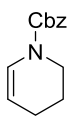


4w 43% *dr* 48:52

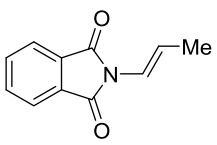
unsuccessful examples



1x



1y



1z

[5]Isolated yield after column chromatography. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

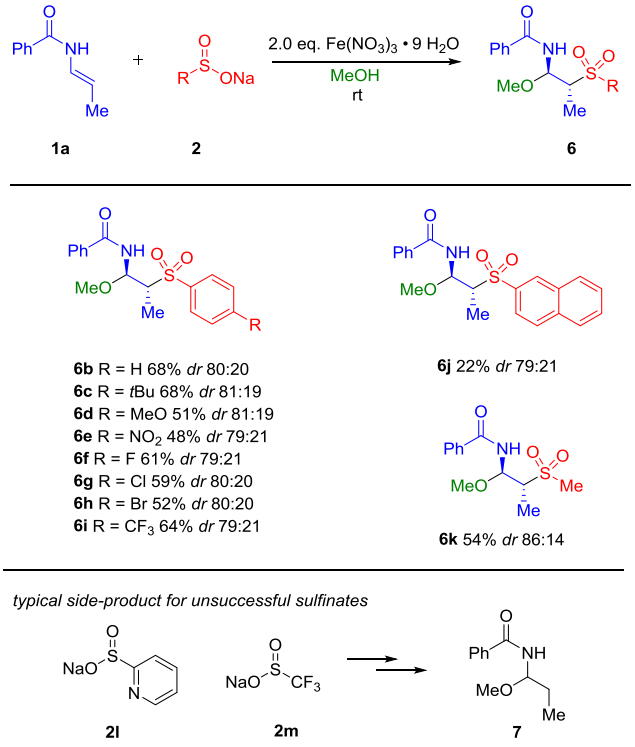
transformations. Reactions with cyclic enamides or encarbamates, such as **1y**, or the enimide **1z** were not successful.

Next, we investigated reactions of different sulfinic acid sodium salts (Scheme 6). Aromatic sulfinates bearing different functional groups performed satisfactorily under the standard reaction conditions, affording the *β*-amidosulfones **6b**−**i** in 48−68% yield. Both electron-withdrawing (**6e** and **6i**) and electron-donating (**6c** and **6d**) as well as halogen substituents **6g** and **6h** were well tolerated. Only in the case of the 2-naphthyl sulfinic acid sodium salt **2j**, the desired amidosulfone **6i** was obtained in only 22% yield. To our delight, the methylsulfone **6k** could be synthesized in 54% with a diastereoselectivity of 6:1 from the corresponding methyl sulfinate **2k**. Unfortunately, reactions with heteroaromatic sulfinates, e.g., pyridine sulfinate **2l**, or sodium trifluoromethane sulfinate **2m** did not afford the desired products. In these cases, only the MeOH-addition product **7** was obtained.

A common drawback of all methods based on sulfinic acid sodium salts is their limited commercial availability. One approach to circumvent this problem is the use of the

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

Scheme 6. Scope of Different Sodium Sulfinic Acids[6]

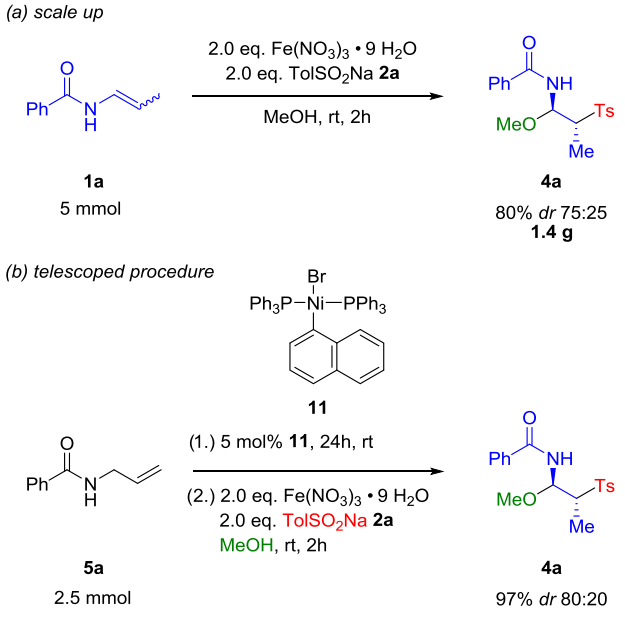


[6]Isolated yield after column chromatography. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

corresponding lithium salts. Lithium sulfinates can be easily accessed by the reaction of organolithium compounds with sulfur dioxide.[24,30] To explore their potential utilization, we synthesized several lithium sulfinates. Lithium *p*-toluenesulfinate **9a** was prepared in two steps from the 4-iodotoluene **8** via lithium-halide exchange and trapping with sulfur dioxide (Scheme 7a). The sulfinic acid salts **9b** and **9c** could be prepared from sulfur dioxide and the commercially available reagents phenyllithium **10a** and *n*-butyllithium **10b**. To our delight, all three crude lithium sulfinates **9a**–**c** are suitable starting materials for our oxysulfonylation process. The desired amidosulfones were obtained in 58–68% yield with a dr of 4:1 for the arylsulfones **4a** and **6b** and 2:1 for the alkylsulfone **6l**. These results exemplify that the *β*-amidosulfone scaffold can be accessed from simple building blocks and sulfur dioxide via classical organolithium chemistry.

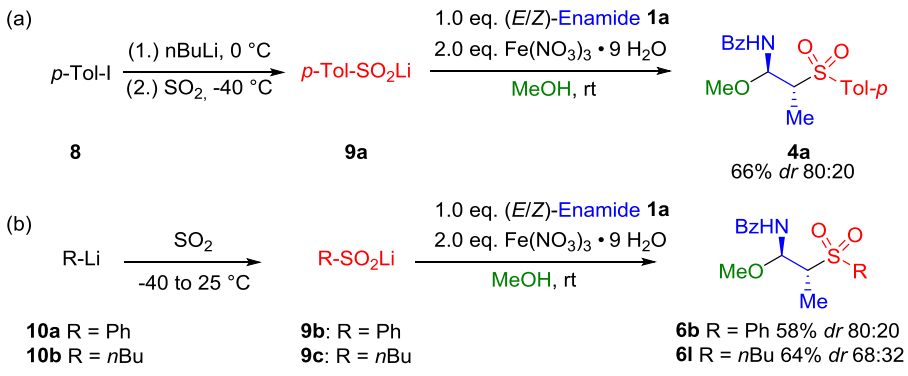
Since the formed *N*,*O*-acetals are stable acylimine precursors, we decided to investigate further transformations exploiting the labile hemiaminal functionality using **4a** as the model compound. To study this reactivity, we needed access to substantial amounts of **4a** (Scheme 8). Gratifyingly, the reaction of the (*E*/*Z*)-mixture of enamide (*E*/*Z*)-**1a** with *p*-toluenesulfinate **2a**, performed on a 5 mmol scale, afforded 1.4 g of the desired product **4a** (80% yield). To provide a more direct approach to the *N*,*O*-acetal **4a**, we studied a one-pot transformation of the parent allylamide **5a**. After the nickel-catalyzed isomerization of allylamide **5a**, the formed (*E*/*Z*)-mixture of enamide (*E*/*Z*)-**1a** was not isolated. Instead, sulfinate **2a** and $Fe(NO_3)_3{\cdot}9H_2O$ were directly added to the reaction mixture, affording the desired *N*,*O*-acetal **4a** in 97%

Scheme 8. Synthesis of *β*-Amidosulfones 4a on a Large Scale and via a One-Pot-Isomerization-Oxysulfonylation Process[8]



[8]Isolated yield after column chromatography. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

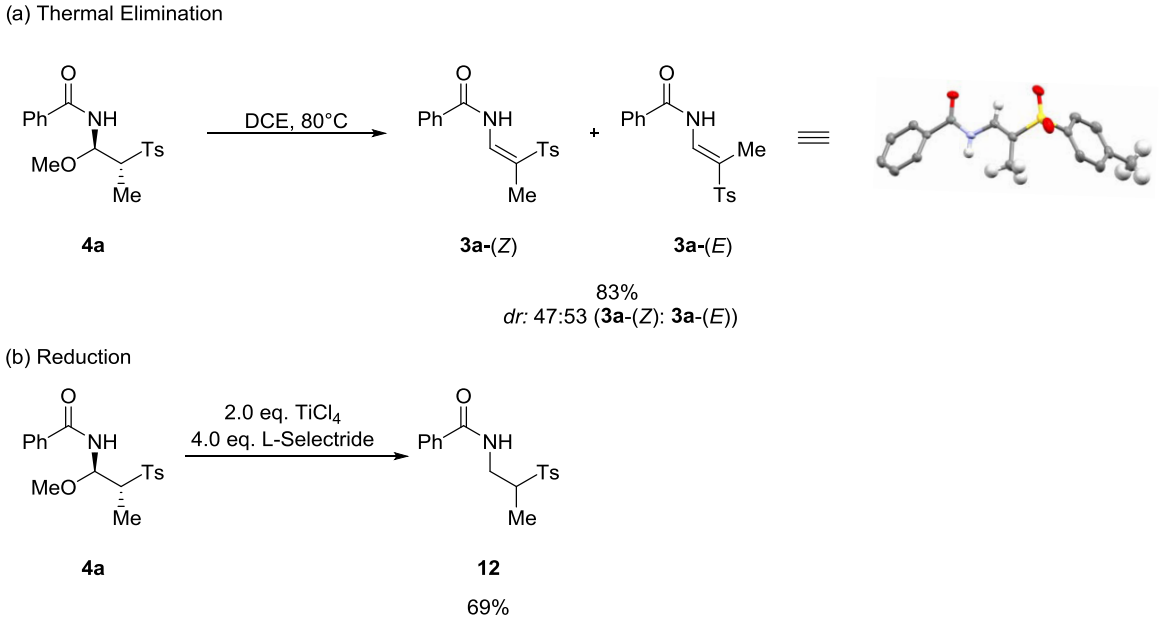
Scheme 7. Preparation of Lithium Sulfinates and the Addition to Enamides[7]



[7]Isolated yield after column chromatography. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup.

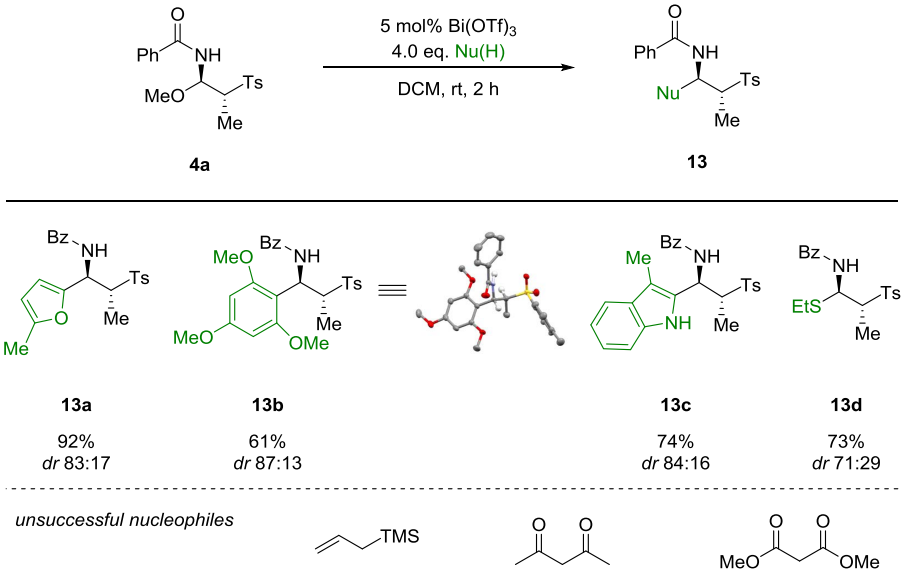
https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617–3637

Scheme 9. Thermal Elimination of 4a to (*E*/*Z*)-Amidovinylsulfones 3a and Reduction to the Amide 12[9]



[9]Isolated yield after column chromatography. X-ray crystal structure of (*E*)-**3a** (aromatic H atoms omitted for clarity).

Scheme 10. Reactivation of the Acylimine with Bi(OTf)$_3$[10]



[10]Isolated yield after column chromatography. The diastereomeric ratio (dr) was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture after aqueous workup. X-ray crystal structure of **13b** (aromatic and methyl H atoms omitted for clarity).

overall yield. This telescoped one-pot process offers a simple and fast access to various *β*-amidosulfones of type **4**.

With sufficient quantities of **4a** in hand, we started to investigate further transformations based on the labile hemiaminal functionality (Scheme 9). Although treatment of **4a** with a base did not lead to any reaction, simple heating in dichloroethylene (DCE) afforded a 1.1:1 mixture of the (*E*)- and the (*Z*)-amidovinylsulfone **3a** in 83% overall yield.[28] Reduction of **4a** with L-selectride in the presence of $TiCl_4$ afforded amide **12** in 69% yield.

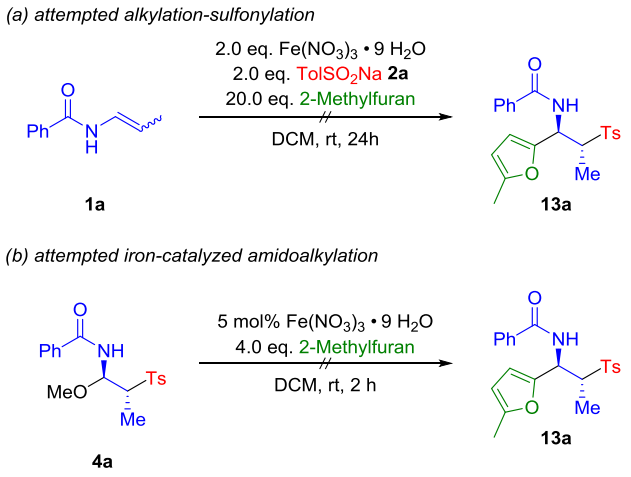
Interestingly, *N*,*O*-acetal **4a** underwent efficient reactions with different electron-rich (hetero)arenes in the presence of 5 mol % Bi(OTf)$_3$,[31,32] leading to the formation of the three amidoalkylation products **13a**−**c** in 61−92% yield (Scheme 10). In all cases, the shown anti-diastereomer was formed as a major isomer with a high degree of diastereoselectivity. The relative configuration of the major diastereomer of **13b** could be assigned unambiguously by single X-ray crystallography.[28] Reaction with ethanethiol afforded the *N*,*S*-acetal **13d** in 73% yield. Attempts to expand the Bi(OTf)$_3$-catalyzed acylimine activation to other nucleophiles, e.g., allylsilane, acetoacetone, or dimethylmalonate, were not successful.

Since a direct formation of a reactive imine species could also occur in the sulfonylation reaction (see also the mechanistic discussion below), we performed iron-mediated sulfonylation in the presence of 2-methylfuran. However, we

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

did not observe the formation of the expected trapping product **13a** (Scheme 11a). Instead, only decomposition of the starting

Scheme 11. Modified Alkylation Protocols for the Synthesis of 13a Based On (a) a One-Pot Alkylation-Sulfonylation and (b) an Iron-Catalyzed Reaction



materials was observed. An additional control experiment with the preformed *N,O*-acetal **4a** demonstrated that $Fe(NO_3)_3 \cdot 9H_2O$ is not capable of catalyzing the aminoalkylation of 2-methylfuran (Scheme 12b). The *N,O*-acetal proved to be stable in the presence of 5 mol % $Fe(NO_3)_3 \cdot 9H_2O$ for a prolonged time (up to 24 h).

The amidoalkylation products **13a−d** represent interesting molecular scaffolds and can be useful building blocks for the synthesis of biologically active targets. For instance, the oxidative cleavage of the furan residue in compound **13a** provided the α-amino-acid derivative **14** in 76% yield with retention of stereochemistry (Scheme 11).

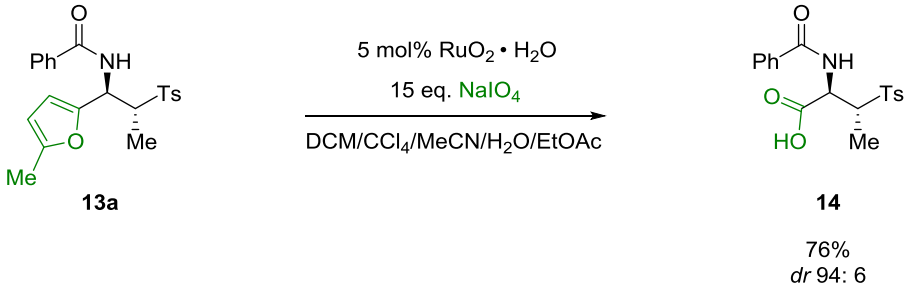
To gain some more insights into the reaction mechanism, a series of control experiments was performed (Scheme 13). The addition of radical inhibitors such as 1,1-diphenylethylene (DPE) or (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) led to significantly reduced yields or a complete shutdown of the reaction, indicating the involvement of radical processes. However, no trapping products such as **15**, a common product in reactions involving sulfonyl radicals, could be detected via ^{1}H NMR or MS. Interestingly, the reaction of sulfinate salt **2a** with $Fe(NO_3)_3 \cdot 9H_2O$ in MeOH in the absence of an enamide afforded the sulfonic acid ester **16** in 62% yield (Scheme 13b). Such products are typically formed from highly electrophilic, cationic sulfonyl species.[33] As the incorporation of MeOH into the final product of type **4** could also occur in a secondary acid-catalyzed addition to an initially formed amidovinylsulfone, we treated vinyl sulfone **3a** with MeOH in the presence of 2 equiv of $Fe(NO_3)_3 \cdot 9H_2O$. No product formation was observed in this case, and the enamide could be recovered almost quantitatively after 2 h.

Based on these results and previous studies on the radical C−H sulfonylation of enamides, two reaction pathways seem to be possible. In analogy to previously proposed mechanisms for the sulfonylation of enamides,[22] SET oxidation of the sulfinate affords a sulfonyl radical **A** (Scheme 14a). Direct addition of this radical to the enamide leads to the intermediate **B**. Oxidation of **B** with a second equivalent $Fe(NO_3)_3 \cdot 9H_2O$ furnishes the acliminiumion **C**. Trapping of this reactive species with MeOH yields the final product **4a**. Although this scenario seems plausible, one should also consider an ionic reaction pathway as shown in Scheme 14b. In this mechanism, the sulfinate is first oxidized to the cationic sulfur species **D** with 2 equiv of $Fe(NO_3)_3 \cdot 9H_2O$. This highly electrophilic species adds to the nucleophilic enamide, furnishing the acyliminium ion **C**. This reactive intermediate is immediately trapped by MeOH. In the absence of the enamide, a direct reaction of **D** with MeOH leads to the formation of the sulfonate **16**. The second pathway can offer an explanation for the lack of any sulfonyl radical trapping products. In general, sulfonyl radicals are quite long-lived radical species and have been trapped successfully in previous studies. In addition, one has to consider that in the presence of $Fe(NO_3)_3 \cdot 9H_2O$, the oxysulfonylated enamide is formed, whereas in all previously reported cases, a C−H sulfonylation took place. It seems very unlikely that the same pathway should lead to two different products. Therefore, we assume that the ionic pathway seems to be more likely in this case.

CONCLUSIONS

In summary, we have developed the first vicinal oxysulfonylation of enamides and enecarbamates with sulfinic acid salts and alcohols. This highly modular three-component transformation enables the facile preparation of β-amidosulfones, an important scaffold in pharmacologically relevant structures. The reaction proceeds readily at room temperature and tolerates a variety of functional groups, including carbamate-protecting groups on the nitrogen. This process is amendable to the gram-scale synthesis of the amidosulfone products. A telescoped isomerization-oxysulfonylation process starting from the corresponding allylamides provides a fast access to the β-amidosulfone unit from simple starting materials. The use of readily available organolithium reagents

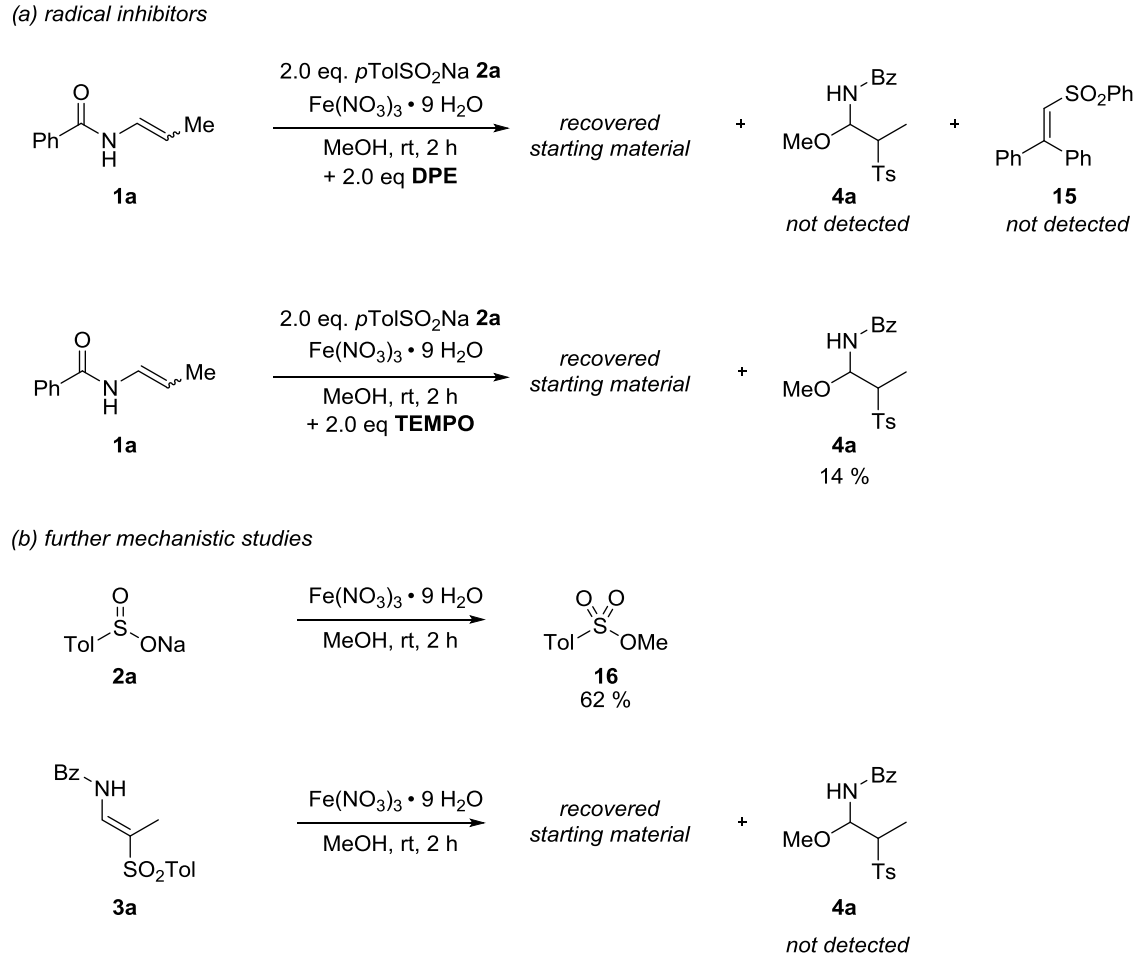
Scheme 12. Preparation of Sulfonated α-Amino-Acid Derivative 14[11]



[11]Isolated yield after column chromatography.

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

Scheme 13. Mechanistic Experiments



enables construction of the sulfonyl moiety in the amidosulfone products directly from sulfur dioxide. The resulting *N,O*-acetals are competent acylimine precursors, and their reactivity can be exploited for the synthesis of different amidosulfone scaffolds. Mechanistic studies indicate an ionic reaction pathway.

EXPERIMENTAL SECTION

Reactions. All yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR.

Chromatography. Column chromatography was performed with Silica 60 (0.04−0.063 mm, 230−400 mesh) and the specified solvent mixture. Thin-layer chromatography was performed on aluminum sheets coated with SiO_2 (TLC silica gel 60 F_{254}). The spots were visualized by ultraviolet light, iodine, cerium ammonium molybdate (CAM), or vanillin.

Solvents. Solvents for reactions and column chromatography were obtained from different commercial suppliers in >97% purity and used as received. Solvents for column chromatography were technical standard.

Materials. All starting materials obtained from commercial sources were used without further purification.

SO_2 (sulfur dioxide, purity 3.8) was used directly without further purification. *Caution*: SO_2 is a toxic and corrosive gas! It should be handled with care only in a well-ventilated fume-hood with the necessary precaution! All reactions were performed with a defined amount of liquid SO_2. Therefore, SO_2 was condensed into a dry and Ar-filled Schlenk flask, cooled to −78 °C. Because of its high heat of evaporation, liquid and cooled SO_2 can be easily handled, measured, and transferred with syringes. For small-scale reactions, we recommend this procedure.

Enamides **1a−n** and **1q−s** were synthesized from the corresponding *N*-allylamides via the isomerization protocol of Halli et al.[29]

All sulfinic acid sodium salts were either obtained from different providers or prepared from the corresponding sulfonyl chlorides using reported procedures.[34]

Anhydrous $Bi(OTf)_3$ was obtained from different providers and used directly. No special precautions were taken to avoid exposure of $Bi(OTf)_3$ to moisture. Therefore, we cannot rule out the formation of $Bi(OTf)_3{\cdot}xH_2O$ during storage. However, no changes in catalytic activity and yield even upon prolonged storage (>1 year) were observed. Therefore, the amount of $Bi(OTf)_3$ used is always calculated on anhydrous $Bi(OTf)_3$. The actual catalyst loading for particular reactions might be slightly lower, depending on the batch quality and storage time.

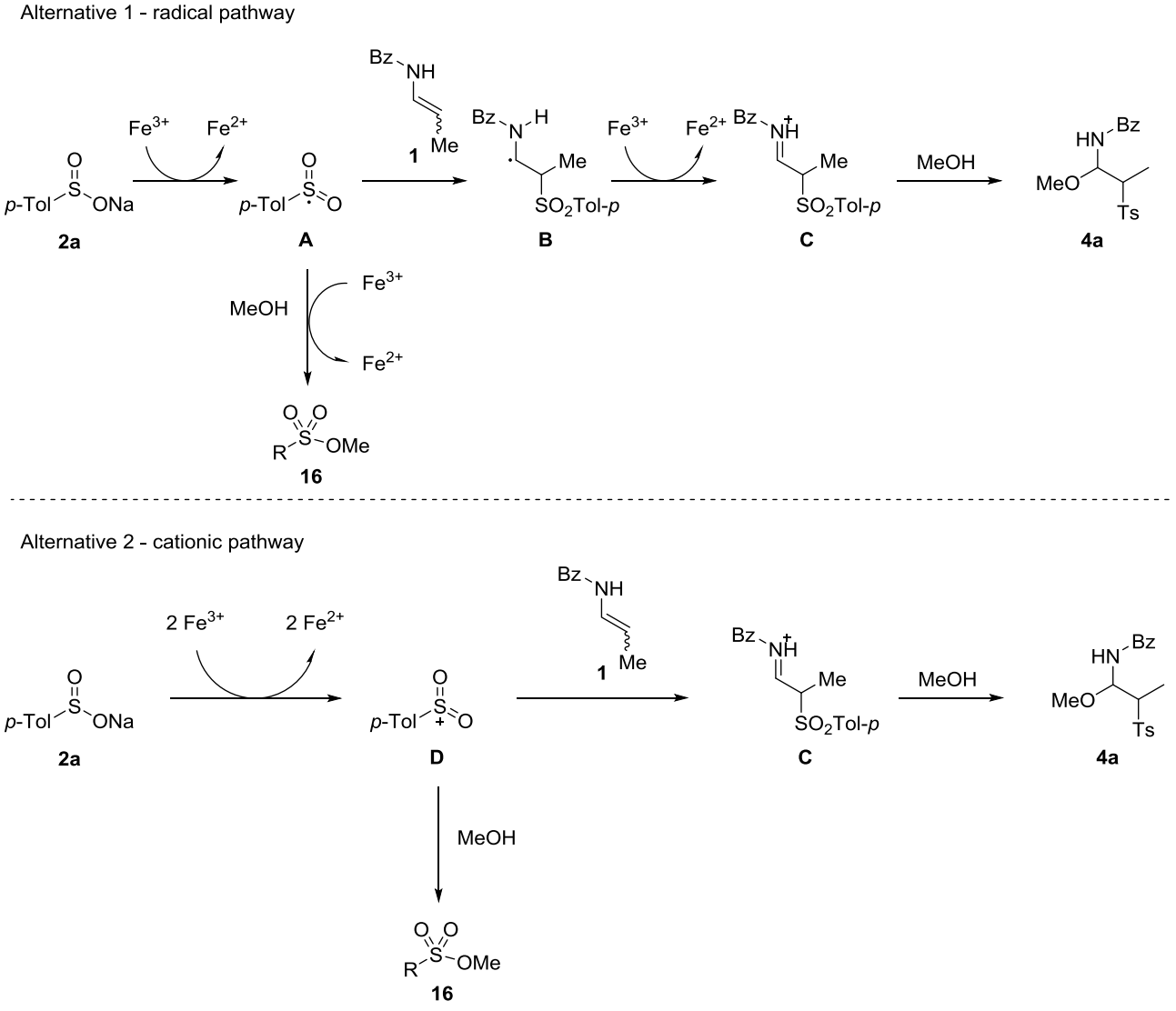
Analytical Data and Instrumentation. *NMR Spectroscopy.* Proton nuclear magnetic resonance spectra (^{1}H NMR) and carbon spectra (^{13}C NMR) were recorded at 400 MHz (^{1}H), 101 MHz (^{13}C), and 376 MHz (^{19}F), respectively. Chemical shifts are reported as δ values relative to the residual $CDCl_3$ (δ = 7.26 ppm for ^{1}H and δ = 77.16 ppm for ^{13}C). Coupling constants (J) are given in hertz, and multiplicities of the signals are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; sp, septet; m, multiplet; dd, doublet of doublets; dt, doublet of triplets; dqd, doublet of quartets of doublets.

Melting Points. Melting points are reported uncorrected.

Mass Spectrometry. Mass spectra (MS) were measured using electrospray ionization (ESI) techniques. High-resolution mass spectra (HRMS) were measured using electron ionization mass spectroscopy (EI-MS-TOF). Since the prepared *N,O*-acetals are

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

Scheme 14. Proposed Reaction Mechanism



inherently unstable, the elimination of the alcohol moiety was observed in HRMS measurements.

Infrared Spectroscopy. Infrared spectra (IR) of neat substances were recorded on an Fourier transform infrared spectroscopy (FT-IR) spectrometer equipped with a diamond universal attenuated total reflectance (ATR) sampling technique. The absorption bands are reported in wavenumbers (cm^{-1}).

Diastereomeric Ratio. The diastereomeric ratio (dr) was determined by ^1H NMR analysis of the unpurified product after aqueous workup and after isolation via column chromatography.

A diastereomeric ratio of dr > 98:2 indicates that no other isomer was observed by ^1H NMR. Minor diastereomers were, in most cases, not fully characterized. In some cases, no minor isomers could be isolated after column chromatography, although their formation was observed via NMR analysis of the crude reaction mixture. Presumably, small amounts of the side products were lost during column chromatography.

Preparation and Analytical Data. *Synthesis of N,O-Acetals 4 from Sodium Sulfinates. Typical Procedure 1.* An oven-dried, 10 mL tube was charged with a magnetic stirring bar, enamide (1.0 equiv, 0.2 mmol), sulfinate salt (2.0 equiv, 0.4 mmol), and the alcohol (2 mL). $Fe(NO_3)_3 \cdot 9\ H_2O$ (162 mg, 2.0 equiv, 0.4 mmol) was added, and the tube was closed with a rubber septum. The resulting mixture was stirred at room temperature for 2 h. Upon completion of the reaction (as judged by thin-layer chromatography), saturated aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.

Synthesis of N-(1-Methoxy-2-tosylpropyl)benzamide ***4a.*** It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) and recrystallization from toluene/cyclohexane (1:8) afforded the analytically pure sulfone **4a** as colorless crystals (63 mg, 0.18 mmol, 91%, isolated dr 98:2; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 53−67 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97−7.87 (m, 2H), 7.85−7.74 (m, 3H), 7.55 (d, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.66−5.46 (m, 1H), 3.62 (qd, *J* = 7.2, 4.0 Hz, 1H), 3.24 (s, 3H), 2.44 (s, 3H), 1.43 (d, *J* = 7.3 Hz, 3H). (Peaks only for the major diastereomer.) $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 144.9, 137.1, 133.3, 132.4, 129.6, 128.9, 127.4, 81.3, 62.6, 55.9, 21.8, 10.9. (Peaks only for the major diastereomer.) HRMS (EI) *m*/*z* calcd for $C_{17}H_{17}NO_3S$ 315.0929 $[M - MeOH]^+$, found 315.0924 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 2937 (w), 1652 (m),

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

1598 (w), 1517 (m), 1487 (m), 1350 (w), 1286 (m), 1192 (w), 1135 (s), 1073 (s), 910 (m), 844 (w), 814 (m), 802 (m), 725 (m).

5 mmol Reaction. An oven-dried, 100 mL round-bottom flask was charged with a magnetic stirring bar, (*E*/*Z*)-enamide derivative **1a** (806 mg, 1.0 equiv, 5.0 mmol, *E*/*Z* = 76:24), and sulfinate salt **2a** (1.78 g, 2.0 equiv, 10.0 mmol) in methanol (50 mL). $Fe(NO_3)_3 \cdot 9H_2O$ (4.04 g, 2.0 equiv, 10.0 mmol) was added, and the flask was closed with a rubber septum. The resulting mixture was stirred at room temperature for 3 h. Upon completion of the reaction (as judged by thin-layer chromatography), saturated aqueous NH_4Cl (50 mL) was added. (*Note:* on bigger scales, an additional washing step with saturated aqueous NH_4Cl is recommended to avoid the accumulation of inorganic salts in the organic phase.) The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4a** as a colorless foam (1.40 g, 4.02 mmol, 80%, isolated dr 75:25; dr of the crude mixture 76:24 as determined by ^1H NMR analysis of the unpurified product after aqueous workup).

*Analytical Data Match Those of **4a**. Synthesis of N-(1-Ethoxy-2-tosylpropyl)benzamide **4b**.* It was prepared according to TP1 from the (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in ethanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4b** as a colorless oil (38 mg, 0.105 mmol, 53%, isolated dr 79:21; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.26. ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.7 Hz, 1H; minor diastereomer), 7.88 (dd, *J* = 5.5, 3.1 Hz, 3H), 7.80 (t, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.62 (ddd, *J* = 9.3, 5.9, 3.3 Hz, 1H), 3.73−3.31 (m, 3H), 2.43 (s, 3H), 1.47 (d, *J* = 7.3 Hz, 3H; major diastereomer), 1.42 (d, *J* = 7.1 Hz, 3H; minor diastereomer), 1.05 (t, *J* = 7.0 Hz, 3H; minor diastereomer), 0.88 (t, *J* = 7.0 Hz, 3H; major diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.6, 144.7, 137.5, 133.3, 132.3, 129.4, 129.0, 128.9, 127.3, 79.8, 64.1, 62.7, 21.7, 14.7, 10.6. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.1, 145.0, 135.2, 133.5, 132.3, 130.0, 129.3, 128.8, 127.4, 79.5, 64.8, 64.6, 21.8, 14.8, 13.1. MS (ESI): *m*/*z* calcd for $C_{19}H_{22}NO_4S^-$ 360.1 $[M - H]^-$, found 360.0 $[M - H]^-$. HRMS (EI) *m*/*z* calcd for $C_{17}H_{17}NO_3S$ 315.0929 $[M - EtOH]^+$, found 315.0937 $[M - EtOH]^+$. IR (ν in cm^{-1}): 3335 (w), 2978 (w), 1650, 1598 (w), 1581 (w), 1517 (m), 1487 (m), 1453 (m), 1286 (s), 1138 (s), 1068 (s), 845 (m), 801 (m), 713 (m), 693 (m), 663 (m).

*Synthesis of N-(1-Isopropoxy-2-tosylpropyl)benzamide **4c**.* It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in isopropanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4c** as a colorless oil (23 mg, 0.062 mmol, 31%, isolated dr 79:21; dr of the crude mixture 81:19 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.44. ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 9.6 Hz, 1H; minor diastereomer), 7.93−7.69 (m, 5H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.72 (dd, *J* = 9.6, 4.0 Hz, 1H; major diastereomer), 5.68 (dd, *J* = 9.8, 2.1 Hz, 1H; minor diastereomer), 3.89−3.71 (m, 1H), 3.60 (qd, *J* = 7.2, 4.1 Hz, 1H; major diastereomer), 3.42 (qd, *J* = 7.0, 2.1 Hz, 1H; minor diastereomer), 2.44 (s, 3H; minor diastereomer), 2.43 (s, 3H; major diastereomer), 1.47 (d, *J* = 7.3 Hz, 3H; major diastereomer), 1.38 (d, *J* = 7.1 Hz, 3H; minor diastereomer), 1.05 (dd, *J* = 6.0, 4.4 Hz, 1H; minor diastereomer), 0.96 (d, *J* = 6.0 Hz, 3H; major diastereomer), 0.89 (d, *J* = 6.2 Hz, 3H; major diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.4, 144.5, 137.9, 133.5, 132.3, 129.4, 128.9, 128.9, 127.3, 77.8, 69.8, 63.2, 23.0, 21.7, 21.2, 10.7. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.0, 144.9, 135.1, 133.6, 132.2, 130.3, 129.2, 128.9, 127.4, 77.6, 70.0, 65.3, 23.2, 21.8, 21.1, 13.4. MS (ESI): *m*/*z* calcd for $C_{20}H_{24}NO_4S^-$ 374.2 $[M - H]^-$, found 374.1 $[M - H]^-$. HRMS (EI) *m*/*z* calcd for $C_{17}H_{17}NO_3S$ 315.0929 $[M - C_3H_7OH]^+$, found 315.0948 $[M - C_3H_7OH]^+$. IR (ATR, ν in cm^{-1}): 3359 (w), 2975 (w), 1647, 1598 (w), 1581 (w), 1518 (m), 1486 (m), 1451 (m), 1380 (w), 1286 (s), 1136 (s), 1079(s), 1048 (s), 929 (w), 814 (m), 713 (m), 669 (m).

*Synthesis of N-(1-Methoxy-2-tosylpropyl)-4-methylbenzamide **4f**.* It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1b** (35 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 76:24) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4f** as a colorless solid (46 mg, 0.128 mmol, 64%, isolated dr 81:19; dr of the crude mixture 81:19 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 57−92 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.21. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 9.8 Hz, 1H; minor diastereomer), 7.82−7.73 (m, 5H), 7.36−7.27 (m, 4H), 5.60−5.53 (m, 1H), 3.61 (qd, *J* = 7.2, 4.0 Hz, 1H; major diastereomer), 3.43−3.39 (m, 1H; minor diastereomer), 3.33 (s, 3H; minor diastereomer), 3.23 (s, 3H; major diastereomer), 2.43 (d, *J* = 6.5 Hz, 6H), 1.42 (d, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.6, 144.8, 143.0, 137.2, 130.4, 129.6, 129.6, 128.9, 127.4, 81.3, 62.6, 55.9, 21.8, 21.7, 10.9. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.2, 145.0, 142.9, 135.5, 130.5, 129.7, 129.5, 129.0, 127.4, 81.3, 64.5, 56.4, 21.8, 21.7, 12.9. MS (ESI): *m*/*z* calcd for $C_{19}H_{23}NaNO_4S^+$ 384.1 $[M + Na]^+$, found 384.0 $[M + Na]^+$. HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}NO_3S$ 329.1086 $[M - MeOH]^+$, found 329.1100 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3345 (w), 2931 (w), 1649 (m), 1612 (m), 1524 (m), 1494 (m), 1453 (m), 1349 (w), 1286 (s), 1187 (m), 1133 (s), 1072 (s), 1018 (m), 952 (m), 815 (m), 748 (m), 664 (m).

*Synthesis of N-(1-Methoxy-2-tosylpropyl)-2,4,6-trimethylbenzamide **4g**.* It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1c** (41 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 17:83) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4g** as a colorless solid (49 mg, 0.125 mmol, 63%, isolated dr 62:38; dr of the crude mixture 62:38 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 181−203 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.24. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 3.1 Hz, 3H), 5.74−5.66 (m, 1H major diastereomer), 5.60−5.54 (m, 1H minor diastereomer), 3.57 (qd, *J* = 7.2, 3.2 Hz, 1H), 3.43 (s, 3H), 3.34 (s, 3H), 2.45 (s, 3H), 2.37 (s, 2H), 2.34 (s, 4H), 2.28 (s, 3H), 1.42 (d, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 170.9, 145.0, 144.8, 139.0, 139.0, 137.0, 135.7, 134.3, 134.3, 134.1, 134.1, 129.6, 129.0, 128.6, 81.1, 80.8, 64.5, 62.8, 56.9, 56.5, 21.8, 21.2, 19.7, 19.6, 12.9, 10.3. MS (ESI): *m*/*z* calcd for $C_{21}H_{27}NO_4SNa^+$ 412.2 $[M + Na]^+$, found 412.1 $[M + Na]^+$. HRMS (EI) *m*/*z* calcd for $C_{20}H_{23}NO_3S$ 357.1399 $[M - MeOH]^+$, found 357.1417 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 2922 (w), 1636 (m), 1611 (m), 1522 (m), 1454 (m), 1376 (w), 1287 (s), 1183 (m), 1130 (s), 1026 (s), 1075 (s), 1054 (s), 949 (w), 815 (m), 726 (s), 665 (m).

*Synthesis of 4-Methoxy-N-(1-methoxy-2-tosylpropyl)benzamide **4h**.* It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1d** (38 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 74:26) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4h** as a colorless foam (51 mg, 0.136 mmol, 68%, isolated dr 79:21; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 51−78 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.12. ^1H NMR (400

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

MHz, $CDCl_3$) δ 8.12 (d, J = 9.8 Hz, 1H; minor diastereomer), 7.89−7.84 (m, 2H), 7.78 (dd, J = 8.4, 2.1 Hz, 2H), 7.74 (d, J = 9.6 Hz, 1H; major diastereomer), 7.33 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.8 Hz, 2H), 5.60−5.51 (m, 1H), 3.87 (s, 3H), 3.62 (qd, J = 7.2, 4.0 Hz, 1H; major diastereomer), 3.43−3.37 (m, 1H; minor diastereomer), 3.33 (s, 3H; minor diastereomer), 3.23 (s, 3H; major diastereomer), 2.44 (s, 3H), 1.42 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.2, 163.0, 144.8, 137.2, 129.6, 129.3, 128.9, 125.5, 114.1, 81.3, 62.6, 55.9, 55.6, 21.8, 11.0. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 166.8, 162.9, 145.1, 135.5, 129.7, 129.6, 129.3, 128.9, 125.6, 114.1, 81.3, 64.6, 56.4, 55.6, 13.0, 8.5. MS (ESI): m/z calcd for $C_{19}H_{23}NO_5SNa^+$ 400.1 $[M + Na]^+$, found 400.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{18}H_{19}NO_4S$ 345.1035 $[M - MeOH]^+$, found 345.1035 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 2931 (w), 1650 (m), 1605 (m), 1527 (m), 1493 (m), 1351 (w), 1288 (m), 1251 (s), 1177 (m), 1135 (s), 1073 (s), 1025 (m), 952 (m), 843 (m), 814 (m), 767 (m), 733 (m), 666 (w).

Synthesis of 4-Fluoro-N-(1-methoxy-2-tosylpropyl)benzamide ***4i.*** It was prepared according to TP1 from (E/Z)-enamide derivative **1e** (36 mg, 1.0 equiv, 0.2 mmol, E/Z = 75:25) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4i** as a colorless foam (45 mg, 0.123 mmol, 62%, isolated dr 80:20; dr of the crude mixture 81:19 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 109−127 °C. R_f (n-hexane/EtOAc = 7:3) 0.19. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 9.8 Hz, 1H), 7.90 (ddd, J = 5.2, 4.2, 2.7 Hz, 2H), 7.81 (d, J = 9.7 Hz, 1H), 7.79−7.73 (m, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.15 (t, J = 8.6 Hz, 2H), 5.58−5.48 (m, 1H), 3.61 (qd, J = 7.2, 4.1 Hz, 1H), 3.44−3.37 (m, 1H), 3.33 (s, 3H), 3.23 (s, 3H), 2.43 (s, 3H), 1.41 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.6, 165.3 (d, J = 253.1 Hz), 144.9, 137.0, 129.80 (d, J = 9.1 Hz), 129.6, 129.6, 128.9, 116.0 (d, J = 21.9 Hz), 81.4, 62.5, 56.0, 21.8, 11.0. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 166.2, 165.3 (d, J = 253.0 Hz), 145.1, 135.3, 129.7, 129.6, 129.5 (d, J = 3.1 Hz), 128.9, 116.0 (d, J = 21.7 Hz), 81.3, 64.4, 56.5, 21.8, 12.9. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −106.90 (tt, J = 8.4, 5.3 Hz; major diastereomer), −107.00 (tt, J = 8.4, 5.2 Hz; minor diastereomer). MS (ESI): m/z calcd for $C_{18}H_{20}NO_4SFNa^+$ 388.1 $[M + Na]^+$, found 388.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{17}H_{16}NO_3SF$ 333.0835 $[M - MeOH]^+$, found 333.0849 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 2939 (w), 1650 (m), 1602 (m), 1526 (m), 1493 (s), 1350 (m), 1286 (m), 1229 (m), 1133 (s), 1073 (s), 1014 (m), 962 (m), 851 (m), 815 (m), 764 (m), 732 (m), 665 (m).

Synthesis of N-(1-Methoxy-2-tosylpropyl)-4-(trifluoromethyl)-benzamide ***4j.*** It was prepared according to TP1 from (E/Z)-enamide derivative **1f** (50 mg, 1.0 equiv, 0.2 mmol, E/Z = 55:45) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4j** as a colorless foam (51 mg, 0.123 mmol, 61%, isolated dr 80:20; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 129−141 °C. R_f (n-hexane/EtOAc = 7:3) 0.24. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 9.8 Hz, 1H), 8.01 (d, J = 8.2 Hz, 2H), 7.94 (d, J = 9.5 Hz, 1H), 7.77 (t, J = 8.3 Hz, 4H), 7.34 (d, J = 8.1 Hz, 2H), 5.56 (dt, J = 9.7, 3.4 Hz, 1H), 3.63 (qd, J = 7.2, 4.1 Hz, 1H), 3.42 (td, J = 6.8, 4.5 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 2H), 2.45 (s, 3H), 1.43 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.5, 166.0, 145.3, 145.0, 137.0, 136.7, 136.6, 136.6, 135.2, 134.2, 134.1 (q, J = 32.8 Hz), 133.8, 129.7, 129.7, 129.6, 128.9, 127.9, 127.8, 126.0 (dd, J = 7.4, 3.6 Hz), 123.7 (d, J = 272.6 Hz), 81.6, 81.4, 64.4, 62.4, 56.7, 56.1, 21.8, 13.0, 11.2. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −63.0 (s; minor diastereomer), −63.0 (s; major diastereomer). MS (ESI): m/z calcd for $C_{19}H_{20}NO_4SF_3Na^+$ 438.1 $[M + Na]^+$, found 338.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{18}H_{16}NO_3S$ $F_3$383.0803 $[M - MeOH]^+$, found 383.0820 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3323 (w), 2933 (w), 1659 (m), 1533 (m), 1510 (m), 1451 (m), 1364 (w), 1325 (m), 1298 (s), 1140 (m), 1111 (s), 1064 (s), 1014 (m), 966 (m), 860 (m), 850 (m), 816 (m), 774 (m), 738 (m), 682 (m), 665 (m).

Synthesis of N-(1-Methoxy-2-tosylpropyl)thiophene-2-carboxamide ***4k.*** It was prepared according to TP1 from (E/Z)-enamide derivative **1g** (33 mg, 1.0 equiv, 0.2 mmol, E/Z = 69:31) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4k** as a colorless foam (48 mg, 0.136 mmol, 68%, isolated dr 83:17; dr of the crude mixture 83:17 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 145−148 °C. R_f (n-hexane/EtOAc = 7:3) 0.19. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 9.8 Hz, 1H; minor diastereomer), 7.81−7.74 (m, 2H), 7.66 (d, J = 9.6 Hz, 1H; major diastereomer), 7.61 (dd, J = 4.7, 1.9 Hz, 1H), 7.55 (dd, J = 4.9, 0.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.11 (dd, J = 4.9, 3.8 Hz, 1H), 5.56−5.45 (m, 1H), 3.59 (qd, J = 7.2, 4.1 Hz, 1H; major diastereomer), 3.39 (dd, J = 7.2, 2.6 Hz, 1H; minor diastereomer), 3.33 (s, 3H; major diastereomer), 3.24 (s, 3H; major diastereomer), 2.43 (s, 3H), 1.41 (dd, J = 7.2, 3.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 162.3, 144.9, 138.1, 137.0, 131.4, 129.6, 128.9, 128.0, 81.2, 62.5, 56.0, 21.8, 10.8. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 161.9, 145.1, 138.3, 135.4, 131.4, 129.5, 128.9, 128.0, 81.2, 64.4, 56.5, 21.8, 12.9. MS (ESI): m/z calcd for $C_{16}H_{19}NO_4S_2Na^+$ 376.1 $[M + Na]^+$, found 376.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{15}H_{15}NO_3S_2$ 321.0493 $[M - MeOH]^+$, found 321.0512 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3228 (w), 3091 (w), 2931 (w), 2836 (w), 1616 (m), 1532 (m), 1509 (m), 1451 (m), 1420 (m), 1361 (m), 1285 (s),1251 (m), 1197 (w), 1119 (s), 1131 (s), 1074 (s), 1038 (m), 945 (m), 863 (w), 801 (m), 729 (s), 665 (m).

Synthesis of N-(1-Methoxy-2-tosylpropyl)pivalamide ***4l.*** It was prepared according to TP1 from (E/Z)-enamide derivative **1h** (28 mg, 1.0 equiv, 0.2 mmol, E/Z = 91:9) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4l** as a colorless oil (47 mg, 0.144 mmol, 72%, isolated dr 89:11; dr of the crude mixture 88:12 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (n-hexane/EtOAc = 7:3) 0.25. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (t, J = 16.0 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 7.4 Hz, 1H), 5.37 (dd, J = 9.7, 3.9 Hz, 1H; major diastereomer), 5.33 (dd, J = 9.8, 2.7 Hz, 1H; minor diastereomer), 3.52 (qd, J = 7.2, 3.9 Hz, 1H; major diastereomer), 3.33−3.25 (m, 1H; minor diastereomer), 3.24 (s, 3H; minor diastereomer), 3.14 (s, 3H; major diastereomer), 2.44 (s, 3H; minor diastereomer), 1.33 (dd, J = 7.3, Hz, 3H), 1.29−1.24 (m, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 179.6, 144.8, 137.2, 129.6, 128.9, 80.8, 62.4, 55.6, 39.3, 27.6, 21.8, 10.8. MS (ESI): m/z calcd for $C_{16}H_{25}NO_4SNa^+$ 350.1 $[M + Na]^+$, found 350.1 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{15}H_{21}NO_3S$ 295.1242 $[M - MeOH]^+$, found 295.1234 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3364 (w), 2957 (w), 1658 (m), 1598 (w), 1502 (m), 1454 (m), 1366 (w), 1302 (m), 1287 (m), 1239 (m), 1183 (m), 1136 (s),1074 (s), 955 (w), 879 (m), 814 (m), 744 (m), 714 (m), 680 (w), 665 (w).

Synthesis of N-(1-Methoxy-2-tosylpropyl)-2-phenylacetamide ***4m.*** It was prepared according to TP1 from (E/Z)-enamide derivative **1i** (35 mg, 1.0 equiv, 0.2 mmol, E/Z = 60:40) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4m** as a colorless oil (51 mg, 0.141 mmol, 70%, isolated dr 63:37; dr of the crude mixture 62:38 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (n-hexane/EtOAc = 7:3) 0.1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 8.3, 2.2 Hz, 2H), 7.43−7.28 (m, 7H), 7.00 (d, J = 9.8 Hz, 1H; minor diastereomer), 6.70 (d, J = 9.4 Hz, 1H; major diastereomer), 5.35 (dd, J = 9.7, 4.0 Hz, 1H; major diastereomer), 5.31 (dd, J = 10.0, 3.0 Hz, 1H; minor diastereomer), 3.64 (s, 2H), 3.40 (qd, J = 7.2, 4.0 Hz, 1H; major diastereomer), 3.23−3.16 (m, 4H; minor diaster-

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

eomer), 3.11 (s, 3H; major diastereomer), 2.43 (d, J = 3.1 Hz, 3H), 1.28 (d, J = 7.2 Hz, 3H; minor diastereomer), 1.21 (d, J = 7.2 Hz, 3H; major diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ major diastereomer) δ 171.9, 144.8, 136.7, 134.4, 129.6, 129.5, 129.3, 129.0, 127.7, 80.6, 62.5, 55.8, 44.2, 21.8, 10.3. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 171.5, 144.9, 136.7, 134.4, 129.6, 129.5, 129.4, 129.3, 127.7, 80.6, 64.0, 56.3, 44.2, 21.8, 11.9. MS (ESI): m/z calcd for $C_{19}H_{23}NO_4SNa^+$ 384.1 $[M + Na]^+$, found 384.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{18}H_{19}NO_3S$ 329.1086 $[M - MeOH]^+$, found 329.1090 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3312 (w), 2938 (w), 1658 (m), 1597 (w), 1516 (m), 1495 (m), 1454 (m), 1357 (w), 1299 (m), 1287 (m), 1138 (s), 1073 (s), 931 (w), 814 (m), 728 (m).

Synthesis of N-(1-Methoxy-2-tosylpropyl)cinnamamide ***4n***. It was prepared according to TP1 from (E/Z)-enamide derivative **1j** (37 mg, 1.0 equiv, 0.2 mmol, E/Z = 48:52) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4n** as a colorless solid (46 mg, 0.124 mmol, 62%, isolated dr 64:36; dr of the crude mixture 64:36 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 70−78 °C. R_f (n-hexane/EtOAc = 7:3) 0.14. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.2, 3.1 Hz, 2H), 7.72−7.65 (m, 1H), 7.54 (dd, J = 6.1, 3.3 Hz, 2H), 7.45 (d, J = 10.0 Hz, 1H), 7.40 (d, J = 4.7 Hz, 3H), 7.34 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 9.7 Hz, 1H), 6.48 (dd, J = 15.7, 3.7 Hz, 1H), 5.53 (dd, J = 9.8, 4.0 Hz, 1H; major diastereomer), 5.49 (dd, J = 10.0, 2.5 Hz, 1H; minor diastereomer), 3.56 (qd, J = 7.2, 4.0 Hz, 1H; major diastereomer), 3.37 (dd, J = 7.1, 2.6 Hz, 1H; minor diastereomer), 3.32 (s, 3H; minor diastereomer), 3.22 (s, 3H; major diastereomer), 2.44 (s, 3H), 1.41 (dd, J = 7.2, 1.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.5, 166.1, 145.1, 144.8, 143.0, 142.9, 137.1, 135.5, 134.6, 134.6, 130.3, 130.3, 129.7, 129.6, 129.6, 129.1, 129.0, 128.2, 120.2, 120.0, 80.9, 80.9, 64.5, 62.6, 56.4, 55.9, 21.8, 12.9, 10.7. MS (ESI): m/z calcd for $C_{20}H_{23}NO_4SNa^+$ 396.1 $[M + Na]^+$, found 396.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{19}H_{19}NO_3S$ 341.1086 $[M - MeOH]^+$, found 341.1100 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3305 (w), 2933 (w), 1661 (m), 1626 (m), 1599 (m), 1517 (m), 1450 (m), 1353 (m), 1287 (m), 1207 (m), 1185 (m), 1139 (s), 1072 (s), 977 (m), 814 (m), 747 (m), 665 (w).

Synthesis of N-(1-Methoxy-2-tosylpropyl)-2-phenoxyacetamide ***4o***. It was prepared according to TP1 from (E/Z)-enamide derivative **1k** (38 mg, 1.0 equiv, 0.2 mmol, E/Z = 55:45) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4o** as a low melting solid (53 mg, 0.141 mmol, 70%, isolated dr 65:35; dr of the crude mixture 65:35 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (n-hexane/EtOAc = 7:3) 0.12. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 10.6 Hz, 1H; minor diastereomer), 7.77 (d, J = 9.8 Hz, 1H; major diastereomer), 7.70 (dd, J = 17.2, 8.2 Hz, 2H), 7.37−7.27 (m, 4H), 7.08−7.01 (m, 1H), 7.00−6.94 (m, 2H), 5.48 (dd, J = 9.8, 4.0 Hz, 1H; major diastereomer), 5.41 (dd, J = 10.2, 3.2 Hz, 1H; minor diastereomer), 4.58−4.49 (m, 2H), 3.47 (qd, J = 7.2, 4.0 Hz, 1H; major diastereomer), 3.31 (d, J = 19.6 Hz, 1H; minor diastereomer), 3.25 (s, J = 4.3 Hz, 3H; minor diastereomer), 3.18 (s, 3H; major diastereomer), 2.40 (s, 3H), 1.37 (d, J = 7.2 Hz, 3H; minor diastereomer), 1.30 (d, J = 7.2 Hz, 3H; major diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.2, 169.0, 157.2, 157.1, 144.9, 144.8, 136.7, 135.7, 129.9, 129.5, 129.5, 129.4, 128.9, 122.4, 122.3, 114.8, 114.8, 80.2, 80.0, 67.0, 63.9, 62.5, 58.7, 56.4, 56.0, 21.7, 11.9, 10.0, 8.4. MS (ESI): m/z calcd for $C_{19}H_{22}NO_5S^-$ 376.1 $[M - H]^-$, found 376.2 $[M - H]^-$. HRMS (EI) m/z calcd for $C_{18}H_{19}NO_4S$ 345.1035 $[M - MeOH]^+$, found 345.1039 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3350 (w), 2932 (w), 1682 (m), 1598 (m), 1512 (m), 1493 (m), 1288 (m), 1236 (m), 1139 (s), 1078 (s), 816 (m), 751 (m), 690 (m).

Synthesis of N-(1-Methoxy-2-tosylpropyl)-N-methylbenzamide ***4p***. It was prepared according to TP1 from (E/Z)-enamide derivative **1l** (35 mg, 1.0 equiv, 0.2 mmol, E/Z = 60:40) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4p** as a colorless oil (29 mg, 0.080 mmol, 40%, isolated dr > 98:2; dr of the crude mixture >98:2 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (n-hexane/EtOAc = 7:3) 0.18. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89−7.28 (m, 9H), 5.81 (d, J = 8.6 Hz, 1H), 3.55−3.48 (m, 1H), 3.33−3.10 (m, 3H), 2.89 (s, 3H), 2.43 (s, 3H), 1.35 (d, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 173.1, 145.1, 136.3, 133.7, 130.1, 129.9, 129.8, 128.6, 127.3, 82.1, 60.7, 55.9, 31.1, 21.8, 12.6. MS (ESI): m/z calcd for $C_{19}H_{26}NO_4SNa^+$ 384.1 $[M + Na]^+$, found 384.1 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{18}H_{19}NO_3S$ 329.1086 $[M - MeOH]^+$, found 329.1080 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 2939 (w), 1641 (s), 1597 (m), 1446 (m), 1395 (m), 1344 (m), 1303 (s), 1290 (s), 1189 (m), 1138 (s), 1073 (s), 1049 (s), 1023 (s), 952 (m), 815 (m), 723 (m), 699 (s), 659 (m).

Synthesis of 1-(1-Methoxy-2-tosylpropyl)pyrrolidin-2-one ***4q***. It was prepared according to TP1 from (E/Z)-enamide derivative **1m** (25 mg, 1.0 equiv, 0.2 mmol, E/Z = 100:0) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4q** as a colorless oil (37 mg, 0.120 mmol, 60%, isolated dr 90:10; dr of the crude mixture 89:11 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (n-hexane/EtOAc = 7:3) 0.14. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 5.30 (d, J = 7.5 Hz, 1H; minor diastereomer), 5.22 (d, J = 8.5 Hz, 1H; major diastereomer), 3.45−3.26 (m, 3H), 3.17 (s, 3H; major diastereomer), 3.05 (s, 3H; minor diastereomer), 2.47−2.35 (m, 5H), 1.99−1.84 (m, 2H), 1.36 (d, J = 7.0 Hz, 3H; major diastereomer), 1.27 (d, J = 7.3 Hz, 3H; minor diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 176.5, 145.1, 134.2, 129.8, 129.5, 80.8, 60.7, 55.8, 42.0, 31.5, 21.8, 18.3, 11.9. MS (ESI): m/z calcd for $C_{15}H_{21}NO_4SNa^+$ 334.1 $[M + Na]^+$, found 334.2 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{15}H_{21}NO_4S$ 311.1191 $[M]^+$, found 311.1208 $[M]^+$. IR (ATR, ν in cm^{-1}): 2935 (w), 1692 (s), 1596 (w), 1494 (w), 1454 (w), 1406 (m), 1285 (m), 1259 (m), 1202 (m), 1138 (s), 1076 (s), 958 (m), 911 (w), 818 (m), 801 (m), 741 (m).

Synthesis of N-(1-Methoxy-2-tosylbutyl)benzamide ***4r***. It was prepared according to TP1 from (E/Z)-enamide derivative **1n** (35 mg, 1.0 equiv, 0.2 mmol, E/Z = 89:11) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (n-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4r** as a colorless foam (56 mg, 0.155 mmol, 77%, isolated dr 75:25; dr of the crude mixture 75:25 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 97−108°C. R_f (n-hexane/EtOAc = 7:3) 0.28. ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 9.8 Hz, 1H; minor diastereomer), 8.18 (d, J = 9.9 Hz, 1H; major diastereomer), 7.95−7.87 (m, 2H), 7.83−7.75 (m, 2H), 7.55 (d, J = 7.1 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.84−5.58 (m, 1H), 3.45 (dd, J = 8.7, 4.4 Hz, 1H; major diastereomer), 3.34 (s, 3H; minor diastereomer), 3.22−3.18 (m, 1H; minor diastereomer), 3.17 (s, 3H; major diastereomer), 2.43 (s, 3H), 2.25−2.15 (m, 1H; major diastereomer), 1.93−1.86 (m, 1H; minor diastereomer), 1.80−1.65 (m, 1H), 1.08 (dd, J = 13.1, 5.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.6, 144.6, 138.4, 133.2, 132.4, 129.4, 128.9, 128.7, 127.3, 79.7, 68.5, 55.5, 21.7, 18.9, 12.2. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.2, 145.0, 135.8, 133.3, 133.2, 132.3, 129.7, 129.4, 128.8, 78.7, 70.9, 56.4, 20.9, 11.7, 8.3. MS (ESI): m/z calcd for $C_{19}H_{22}NO_4S^-$ 360.1 $[M - H]^-$, found 360.2 $[M - H]^-$. HRMS (EI) m/z calcd for $C_{18}H_{19}NO_3S$ 329.1086 $[M - MeOH]^+$, found 329.1094 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3366 (w), 2942 (w), 1667 (m), 1600 (w), 1518 (m), 1489 (m), 1358 (w), 1280 (s), 1187 (w), 1137 (s), 1100 (m), 1065 (s), 1036 (m), 974 (m), 813 (m), 714 (m), 681 (m), 665 (w).

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

Synthesis of N-(1-Methoxy-2-tosylethyl)benzamide ***4s***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1o** (32 mg, 1.0 equiv, 0.2 mmol) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4s** as a colorless foam (45 mg, 0.135 mmol, 67%). Mp 139−142 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.14. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 11.7, 7.9 Hz, 4H), 7.62 (d, *J* = 9.5 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.70 (dt, *J* = 9.3, 4.5 Hz, 1H), 3.68 (dd, *J* = 14.7, 5.1 Hz, 1H), 3.52 (dd, *J* = 14.7, 3.9 Hz, 1H), 3.29 (s, 3H), 2.43 (s, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3, 145.2, 137.5, 133.3, 132.4, 129.9, 128.9, 128.4, 127.4, 60.0, 56.1, 21.8. HRMS (EI) *m*/*z* calcd for $C_{16}H_{15}NO_3S$ 301.0773 [M − MeOH]$^+$, found 301.0787 [M − MeOH]$^+$. IR (ATR, ν in cm^{-1}): 3267 (m), 2934 (m), 1641 (s), 1601 (m), 1581 (m), 1529 (s), 1490 (w), 1404 (w), 1362 (w), 1300 (s), 1179 (w), 1101 (s), 1082 (s), 1034 (m), 959 (m), 871 (w), 852 (w), 804 (m), 781 (m).

Synthesis of N-(1-Methoxy-2-methyl-2-tosylpropyl)benzamide ***4t***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1p** (35 mg, 1.0 equiv, 0.2 mmol) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4t** as a colorless foam (31 mg, 0.086 mmol, 43%). Mp 55−68°C. R_f (*n*-hexane/EtOAc = 7:3) 0.32. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 9.9 Hz, 1H), 7.97−7.90 (m, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.61−7.53 (m, 1H), 7.53−7.46 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.36 (d, *J* = 10.0 Hz, 1H), 3.27 (s, 3H), 2.44 (s, 3H), 1.44 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.7, 144.8, 135.3, 133.4, 132.3, 130.7, 129.1, 128.9, 127.4, 85.4, 66.3, 56.2, 21.8, 21.8, 19.7. HRMS (EI) *m*/*z* calcd for $C_{19}H_{23}NO_4S$ 361.1348 [M]$^+$, found 361.1369 [MH]$^+$. IR (ATR, ν in cm^{-1}): 3329 (w), 2941 (w), 1659 (m), 1598 (w), 1513 (m), 1485 (m), 1460 (m), 1344 (m), 1283 (s), 1124 (s), 1094 (s), 1073 (s), 1051 (s), 814 (m), 714 (m), 690 (m).

Synthesis of tert-Butyl (1-Methoxy-2-tosylpropyl)carbamate ***4u***. It was prepared according to TP1 from (*E*/*Z*)-enecarbamate derivative **1q** (31 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 42:58) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4u** as a colorless oil (27 mg, 0.079 mmol, 40%, isolated dr 57:43; dr of the crude mixture 44:56 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.1, 4.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 10.2 Hz, 1H; major diastereomer), 5.72 (d, *J* = 9.9 Hz, 1H; minor diastereomer), 5.12 (dd, *J* = 10.2, 3.8 Hz, 1H; minor diastereomer), 5.02 (dd, *J* = 10.5, 3.1 Hz, 1H; major diastereomer), 3.47−3.38 (m, 1H; minor diastereomer), 3.37−3.30 (m, 1H; minor diastereomer), 3.24 (s, 3H; minor diastereomer), 3.18 (s, 3H; minor diastereomer), 2.43 (s, 3H), 1.46 (d, *J* = 2.7 Hz, 9H), 1.36 (dd, *J* = 7.0, 3.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 155.4, 155.4, 144.8, 144.6, 136.8, 135.7, 129.5, 129.5, 129.1, 82.5, 82.2, 80.4, 80.4, 64.3, 63.1, 55.7, 55.4, 28.4, 28.8, 21.8, 11.9, 10.2. MS (ESI): *m*/*z* calcd for $C_{16}H_{25}NO_5SNa^+$ 366.1 [M + Na]$^+$, found 366.1 [M + Na]$^+$. HRMS (EI) *m*/*z* calcd for $C_{15}H_{21}NO_4S$ 311.1191 [M − MeOH]$^+$, found 311.1173 [M − MeOH]$^+$. IR (ATR, ν in cm^{-1}): 3350 (w), 2980 (w), 1705 (m), 1597 (w), 1495 (m), 1455 (m), 1366 (m), 1300 (m), 1286 (m), 1247 (m),1140 (s), 1074 (s), 1008 (m), 916 (m), 853 (w), 815 (m), 728 (m), 664 (m).

Synthesis of Benzyl (1-Methoxy-2-tosylpropyl)carbamate ***4v***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1r** (38 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 42:58) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4v** as a colorless oil (33 mg, 0.087 mmol, 44%, isolated dr 55:45; dr of the crude mixture 45:55 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.26. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.42−7.34 (m, 5H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.27 (d, *J* = 10.2 Hz, 1H), 5.99 (d, *J* = 9.9 Hz, 1H), 5.24−5.07 (m, 3H), 3.43 (dd, *J* = 6.8, 4.0 Hz, 1H), 3.35 (dd, *J* = 7.1, 3.1 Hz, 1H), 3.27 (s, 1H), 3.20 (s, 2H), 2.43 (s, 3H), 1.35 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.1, 144.9, 144.7, 136.6, 136.2, 136.1, 135.6, 129.5, 129.5, 129.0, 128.7, 128.4, 128.3, 128.2, 83.0, 82.7, 67.3, 67.2, 64.2, 63.0, 55.9, 55.6, 21.8, 11.7, 10.1. MS (ESI): *m*/*z* calcd for $C_{19}H_{23}NO_5SNa^+$ 400.1 [M + Na]$^+$, found 400.0 [M + Na]$^+$. HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}NO_4S$ 345.1035 [M − MeOH]$^+$, found 345.1050 [M − MeOH]$^+$. IR (ATR, ν in cm^{-1}): 3335 (w), 2945 (w), 1722 (s), 1708 (s), 1597 (w), 1514 (m), 1454 (m), 1303 (m), 1287 (m), 1229 (m), 1140 (s), 1075 (s), 1016 (m), 964 (m), 915 (m), 817 (m), 732 (m), 698 (m), 665 (w).

Synthesis of (9H-Fluoren-9-yl)methyl (1-methoxy-2-tosylpropyl)-carbamate ***4w***. It was prepared according to TP1 from (*E*/*Z*)-enecarbamate derivative **1s** (56 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 54:46) and sulfinate salt **2a** (71 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4w** as a colorless foam (40 mg, 0.086 mmol, 43%, isolated dr 52:48; dr of the crude mixture 48:52 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Mp 66−82 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.28. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 4H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.41 (s, 2H), 7.33 (t, *J* = 6.8 Hz, 5H), 6.27 (d, *J* = 10.5 Hz, 1H), 6.00 (d, *J* = 10.0 Hz, 1H), 5.15 (ddd, *J* = 24.0, 10.2, 3.3 Hz, 1H), 4.52−4.37 (m, 2H), 4.24 (dt, *J* = 10.1, 5.1 Hz, 1H), 3.50−3.40 (m, 1H), 3.39−3.33 (m, 1H), 3.24 (s, 1H), 3.17 (s, 2H), 2.43 (s, 4H), 1.36 (dd, *J* = 6.9, 4.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.1, 144.8, 143.7, 141.5, 129.6, 129.5, 129.1, 127.9, 127.3, 125.2, 120.2, 83.2, 82.9, 67.2, 64.3, 63.0, 55.9, 55.6, 47.3, 21.8, 11.9, 10.4. MS (ESI): *m*/*z* calcd for $C_{26}H_{27}NO_5SNa^+$ 488.2 [M + Na]$^+$, found 487.8 [M + Na]$^+$. HRMS (EI) *m*/*z* calcd for $C_{26}H_{27}NO_5S^+$ 465.1610 [M]$^+$, found 465.1620 [M]$^+$. IR (ATR, ν in cm^{-1}): 3329 (w), 2946 (w), 1724 (m), 1597 (w), 1511 (m), 1449 (m), 1287 (m), 1226 (m), 1194 (m), 1140 (s), 1075 (s), 1017 (m), 958 (m), 815 (m), 758 (m), 738 (s), 658 (w).

Synthesis of N-(1-Methoxy-2-(phenylsulfonyl)propyl)benzamide ***6b***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2b** (66 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6b** as a colorless oil (46 mg, 0.136 mmol, 68%, isolated dr 80:20; dr of the crude mixture 80:20 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.16. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.9 Hz, 1H; minor diastereomer), 7.97−7.87 (m, 4H), 7.83 (d, *J* = 9.6 Hz, 1H; major diastereomer), 7.68−7.61 (m, 1H), 7.60−7.46 (m, 5H), 5.66−5.52 (m, 1H), 3.67 (qd, *J* = 7.3, 3.9 Hz, 1H; major diastereomer), 3.44 (tt, *J* = 7.0, 3.6 Hz, 1H; minor diastereomer), 3.34 (s, 3H; minor diastereomer), 3.21 (s, 3H; major diastereomer), 1.45 (dd, *J* = 7.2, 2.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.7, 140.3, 133.8, 133.2, 132.4, 129.0, 129.0, 128.8, 127.4, 81.3, 62.5, 55.9, 10.8 ppm. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, minor diastereomer): δ 167.3, 138.4, 134.0, 133.4, 132.4, 129.7, 129.7,128.9, 127.4, 81.3, 64.6, 56.5, 13.0 ppm. MS (ESI): *m*/*z* calcd for $C_{17}H_{18}NO_4S^-$ 332.4 [M − H]$^-$, found 332.0 [M − H]$^-$. HRMS (EI) *m*/*z* calcd for $C_{16}H_{15}NO_3S$ 301.0773 [M − MeOH]$^+$, found 301.0790 [M − MeOH]$^+$. IR (ATR, ν in cm^{-1}): 3335 (w), 2936 (w), 1649 (m), 1603 (w), 1581 (w), 1515 (m), 1486 (m), 1446 (m), 1351 (w), 1288 (m), 1196 (w), 1136 (s), 1070 (s), 999 (m), 956 (m), 844 (m), 802 (w), 768 (w), 736 (m), 715 (m), 688 (m).

Synthesis of N-(2-((4-(tert-Butyl)phenyl)sulfonyl)-1-methoxypropyl)benzamide ***6c***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2c** (88 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6c** as a colorless foam (53 mg, 0.136 mmol, 68%, isolated dr 83:17; dr of the crude mixture 81:19 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 144−154 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.29. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 9.8 Hz, 1H; minor diastereomer), 7.90 (d, J = 7.3 Hz, 2H), 7.82 (d, J = 8.5 Hz, 3H), 7.62−7.44 (m, 5H), 5.60 (dt, J = 9.7, 3.7 Hz, 1H), 3.64 (qd, J = 7.2, 4.0 Hz, 1H; major diastereomer), 3.47−3.39 (m, 1H; minor diastereomer), 3.36 (s, 3H; minor diastereomer), 3.24 (s, 3H; major diastereomer), 1.45 (d, J = 7.0 Hz, 3H), 1.44 (d, J = 7.2 Hz, 3H), 1.34 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.7, 157.8, 137.1, 133.3, 132.4, 129.0, 129.0, 128.7, 127.4, 126.0, 81.4, 62.5, 56.0, 31.2, 11.0. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.3, 158.0, 135.4, 133.4, 132.4, 129.5, 129.0, 128.9, 127.4, 126.0, 81.3, 64.5, 56.5, 35.4, 13.0. MS (ESI): m/z calcd for $C_{21}H_{27}NO_4SNa^+$ 412.2 $[M + Na]^+$, found 412.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{20}H_{23}NO_3S$ 357.1399 $[M - MeOH]^+$, found 357.1417 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3337 (w), 2938 (w), 1648 (s), 1593 (w), 1524 (s), 1491 (m), 1450 (m), 1364 (m), 1303 (s), 1291 (s), 1265 (m), 1143 (s), 1096 (m), 1071 (s), 965 (m), 842 (m), 831 (m), 804 (w), 761 (m), 701 (s), 667 (m).

Synthesis of N-(1-Methoxy-2-((4-methoxyphenyl)sulfonyl)-propyl)benzamide ***6d***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2d** (78 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6d** as a colorless foam (37 mg, 0.102 mmol, 51%, isolated dr 81:19; dr of the crude mixture 81:19 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 56−58 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.8 Hz, 1H; minor diastereomer), 7.89 (d, J = 7.4 Hz, 2H), 7.82 (d, J = 8.9 Hz, 3H), 7.55 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 6.98 (d, J = 8.9 Hz, 2H), 5.64−5.50 (m, 1H), 3.86 (s, 3H), 3.59 (qd, J = 7.2, 4.2 Hz, 1H; major diastereomer), 3.40 (dd, J = 7.1, 2.5 Hz, 1H; minor diastereomer), 3.33 (s, 3H; minor diastereomer), 3.25 (s, 3H; major diastereomer), 1.42 (d, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.7, 163.9, 133.3, 132.4, 131.9, 131.1, 128.9, 127.3, 114.1, 81.3, 62.7, 56.0, 55.8, 11.0. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.3, 164.0, 133.4, 132.3, 132.1, 131.4, 128.8, 127.2, 114.1, 81.2, 64.5, 56.5, 55.8, 12.9. MS (ESI): m/z calcd for $C_{18}H_{20}NO_5S^-$ 362.1 $[M - H]^-$, found 362.2 $[M - H]^-$. HRMS (EI) m/z calcd for $C_{17}H_{17}NO_4S$ 331.0878 $[M - MeOH]^+$, found 331.0886 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3335 (w), 2940 (w),1652 (m), 1595 (m), 1518 (m),1488 (m), 1292 (m), 1260 (s), 1183 (w), 1135 (s), 1073 (s), 1024 (m), 835 (m), 804 (m), 733 (m).

Synthesis of N-(1-Methoxy-2-((4-nitrophenyl)sulfonyl)propyl)-benzamide ***6e***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2e** (84 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6e** as a light-yellow foam (36 mg, 0.095 mmol, 48%, isolated dr 79:21; dr of the crude mixture 79:21 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 150−165 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.13. ^1H NMR (400 MHz, $CDCl_3$) δ 8.41−8.32 (m, 2H), 8.16−8.05 (m, 2H), 7.99 (d, J = 10.1 Hz, 1H; minor diastereomer), 7.89 (d, J = 7.3 Hz, 2H), 7.76 (d, J = 9.7 Hz, 1H; major diastereomer), 7.63−7.54 (m, 1H), 7.51 (t, J = 7.5 Hz, 2H), 5.65 (dd, J = 9.9, 3.7 Hz, 1H; major diastereomer), 5.58 (dd, J = 10.0, 2.7 Hz, 1H; minor diastereomer), 3.74 (qd, J = 7.3, 3.8 Hz, 1H; major diastereomer), 3.54 (qd, J = 7.2, 2.8 Hz, 1H; minor diastereomer), 3.30 (s, 3H; minor diastereomer), 3.17 (s, 3H; major diastereomer), 1.53 (d, J = 7.3 Hz, 2H; major diastereomer), 1.48 (d, J = 7.2 Hz, 3H; minor diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.8, 150.8, 146.6, 133.0, 132.7, 130.3, 129.1, 127.3, 124.0, 80.9, 63.0, 55.8, 10.0. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.3, 151.0, 146.6, 133.1, 132.6, 131.4, 129.0, 127.4, 123.9, 81.0, 65.4, 56.4, 13.1. MS (ESI): m/z calcd for $C_{17}H_{18}N_2O_6SNa^+$ 401.1 $[M + Na]^+$, found 401.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{16}H_{14}N_2O_5S$ 346.0623 $[M - MeOH]^+$, found 346.0642 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3331 (m), 2932 (w), 1651 (m), 1603 (w), 1580 (w), 1520 (s), 1489 (m), 1348 (m), 1297 (s), 1265 (m), 1190 (w), 1133 (m), 1098 (m), 1070 (s), 967 (m), 854 (m), 802 (w), 758 (m), 742 (m), 720 (m), 701 (m).

Synthesis of N-(2-((4-Fluorophenyl)sulfonyl)-1-methoxypropyl)-benzamide ***6f***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2f** (73 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6f** as a colorless oil (43 mg, 0.122 mmol, 61%, isolated dr 80:20; dr of the crude mixture 79:21 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.18. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 9.7 Hz, 1H; minor diastereomer), 7.98−7.85 (m, 4H), 7.80 (d, J = 9.5 Hz, 1H; major diastereomer), 7.56 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.20 (dd, J = 12.0, 5.0 Hz, 2H), 5.60 (dd, J = 9.7, 3.8 Hz, 1H; major diastereomer), 5.55 (dd, J = 9.9, 2.6 Hz, 1H; minor diastereomer), 3.64 (qd, J = 7.2, 3.9 Hz, 1H; major diastereomer), 3.44 (qd, J = 7.1, 2.6 Hz, 1H; minor diastereomer), 3.31 (s, 3H; minor diastereomer), 3.21 (s, 3H; major diastereomer), 1.51−1.41 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.7, 165.9 (d, J = 256.3 Hz), 136.3 (d, J = 3.2 Hz), 133.2, 132.5, 131.8 (d, J = 9.6 Hz), 128.9, 127.3, 116.2 (d, J = 22.7 Hz), 81.2, 62.8, 55.9 (s), 10.6 (s). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.3, 166.1 (d, J = 256.8 Hz), 134.3 (d, J = 3.2 Hz), 133.3, 132.7 (d, J = 9.6 Hz), 132.4, 128.9, 127.3, 116.1 (d, J = 22.6 Hz), 81.2, 64.8, 56.4, 13.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −103.1 to −103.2 (m, minor diastereomer), −103.4 to −103.6 (m; major diastereomer). MS (ESI): m/z calcd for $C_{17}H_{18}NO_4SFNa^+$ 374.1 $[M + Na]^+$, found 374.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{16}H_{14}NO_3SF$ 319.0678 $[M - MeOH]^+$, found 319.0688 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3336 (w), 2937 (w), 1649 (m), 1590 (m), 1517 (m), 1489 (m), 1350 (w), 1311 (m), 1287 (s), 1230 (m), 1198 (w), 1134 (s), 1071 (s), 961 (w), 837 (m), 819 (m), 691 (m), 671 (m), 709 (m).

Synthesis of N-(2-((4-Chlorophenyl)sulfonyl)-1-methoxypropyl)-benzamide ***6g***. It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2g** (79 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6g** as a colorless foam (43 mg, 0.117 mmol, 59%, isolated dr 80:20; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 109−137 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.26. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 9.7 Hz, 1H; minor diastereomer), 7.96−7.82 (m, 4H), 7.78 (d, J = 9.7 Hz, 1H; major diastereomer), 7.58 (t, J = 7.4 Hz, 1H), 7.54−7.47 (m, 4H), 5.61 (dd, J = 9.8, 3.8 Hz, 1H; major diastereomer), 5.56 (dd, J = 9.9, 2.5 Hz, 1H; minor diastereomer), 3.65 (qd, J = 7.3, 3.9 Hz, 1H; major diastereomer), 3.45 (ddd, J = 16.4, 9.5, 6.7 Hz, 1H; minor diastereomer), 3.33 (s, 3H, minor diastereomer), 3.22 (s, 3H; major diastereomer), 1.47 (d, J = 7.3 Hz, 3H; major diastereomer), 1.44 (d, J = 7.2 Hz, 3H; minor diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.7, 140.6, 139.0, 133.1, 132.5, 130.4, 129.2, 129.0, 127.3, 81.2, 62.8, 55.9, 10.5. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.3, 140.9, 136.8, 133.3, 132.5, 131.4, 129.2, 129.0, 127.4, 81.2, 64.9, 56.5, 13.1. MS (ESI): m/z calcd for $C_{17}H_{18}NO_4SNaCl^+$ 390.83 $[M + Na]^+$, found 390.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{16}H_{14}NO_3SCl$ 335.0383 $[M - MeOH]^+$, found 335.0398 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3325 (w), 2925 (w), 1649 (s), 1603 (w), 1580 (m), 1522 (s), 1491 (m), 1474 (m), 1450 (m), 1366 (m), 1353 (m), 1308 (s), 1280 (m), 1262 (m), 1189 (w), 1137 (m), 1069 (s), 1011 (m), 964

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

(m), 932 (m), 834 (m), 817 (m), 801 (m), 765 (m), 694 (m), 672 (w), 665 (w).

Synthesis of N-(2-((4-Bromophenyl)sulfonyl)-1-methoxypropyl)-benzamide ***6h.*** It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2h** (97 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6h** as a colorless foam (43 mg, 0.102 mmol, 52%, isolated dr 79:21; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 57−65 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.27. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 10.0 Hz, 1H minor diastereomer), 7.88 (dd, J = 5.4, 3.2 Hz, 2H), 7.77 (dt, J = 9.0, 2.1 Hz, 3H), 7.71−7.64 (m, 2H), 7.58 (dd, J = 10.5, 4.2 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 5.61 (dd, J = 9.8, 3.8 Hz, 1H major diastereomer), 5.59 (ddd, J = 12.5, 9.9, 3.2 Hz, 1H minor diastereomer), 5.56 (dd, J = 9.9, 2.5 Hz, 1H major diastereomer), 3.65 (qd, J = 7.3, 3.8 Hz, 1H major diastereomer), 3.52−3.35 (m, 1H minor diastereomer), 3.32 (s, 3H minor diastereomer), 3.22 (s, 3H major diastereomer), 1.47 (d, J = 7.3 Hz, 3H major diastereomer), 1.44 (d, J = 7.2 Hz, 3H minor diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ major diastereomer) δ 167.7, 139.5, 133.1, 132.5, 132.2, 130.5, 129.2, 129.0, 127.3, 81.2, 62.8, 55.9, 10.5. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$ minor diastereomer) δ 167.3, 137.4, 133.3, 132.5, 132.2, 131.4, 129.5, 129.0, 127.4, 81.2, 64.9, 56.5, 13.1. MS (ESI): m/z calcd for $C_{17}H_{17}NO_4SBr^-$ 411.3 $[M - H]^-$, found 409.9 $[M - H]^-$. HRMS (EI) m/z calcd for $C_{16}H_{14}NO_3SBr$ 380.9857 $[M - MeOH]^+$, found 380.9879 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3275, 2925 (w), 1646, 1604, 1574, 1523, 1489, 1389, 1363, 1311, 1274, 1190, 1139, 1103, 1065, 1036, 1009, 961, 926, 844, 825, 800, 754, 724, 692, 668.

Synthesis of N-(1-Methoxy-2-((4-(trifluoromethyl)phenyl)-sulfonyl)propyl)benzamide ***6i.*** It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2i** (93 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6i** as a colorless foam (51 mg, 0.127 mmol, 64%, isolated dr 79:21; dr of the crude mixture 79:21 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 109−127 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.28. ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 7.3 Hz, 2H), 7.83−7.74 (m, 3H), 7.59 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.5 Hz, 2H), 5.64 (dd, J = 9.8, 3.8 Hz, 1H; major diastereomer), 5.58 (dd, J = 10.0, 2.6 Hz, 1H; minor diastereomer), 3.71 (qd, J = 7.3, 3.8 Hz, 1H; major diastereomer), 3.50 (ddd, J = 14.5, 7.4, 2.9 Hz, 1H; minor diastereomer), 3.32 (s, 3H; minor diastereomer), 3.19 (s, 3H; major diastereomer), 1.50 (d, J = 7.3 Hz, 3H; major diastereomer), 1.46 (d, J = 7.2 Hz, 3H; minor diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.8, 144.3, 133.1, 132.6, 130.6, 129.5, 129.0, 128.9, 127.3, 126.0 (dd, J = 7.2, 3.5 Hz), 81.1, 62.8, 55.8, 10.3 (no peaks for the minor diastereomer could be observed in the ^{13}C NMR in this case). $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −63.1 (s, major diastereomer), −63.2 (s, minor diastereomer). MS (ESI): m/z calcd for $C_{18}H_{18}NO_4SF_3Na^+$ 424.1 $[M + Na]^+$, found 424.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{17}H_{14}NO_3SF_3$ 369.0646 $[M - MeOH]^+$, found 369.0634 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3334 (w), 2936 (w), 1648 (m), 1603 (w), 1581 (w), 1523 (m), 1491 (m), 1455 (w), 1404 (w), 1355 (w), 1318 (s), 1293 (s), 1126 (s), 1102 (m), 1074 (m), 1059 (s), 1017 (m), 969 (m), 843 (m), 787 (m), 748 (m), 721 (m), 699 (s), 666 (m).

Synthesis of N-(1-Methoxy-2-(naphthalen-2-ylsulfonyl)propyl)-benzamide ***6j.*** It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2j** (86 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **6j** as a colorless foam (17 mg, 0.044 mmol, 22%, isolated dr 79:21; dr of the crude mixture 80:20 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). Mp 80−86 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.22. ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.23 (d, J = 9.9 Hz, 1H; minor diastereomer), 8.02−7.95 (m, 2H), 7.94−7.82 (m, 5H), 7.72−7.54 (m, 3H), 7.49 (t, J = 7.5 Hz, 2H), 5.62 (td, J = 9.8, 3.2 Hz, 1H), 3.75 (qd, J = 7.2, 4.0 Hz, 1H; major diastereomer), 3.53 (qd, J = 7.1, 2.5 Hz, 1H; minor diastereomer), 3.34 (s, 1H; minor diastereomer), 3.20 (s, 3H; major diastereomer), 1.48 (t, J = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 137.2, 135.4, 133.2, 132.4, 132.2, 130.7, 129.6, 129.4, 129.0, 128.9, 128.1, 127.7, 127.4, 123.6, 81.3, 62.7, 55.9, 10.9. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.3, 135.5, 135.3, 133.4, 132.4, 132.1, 131.7, 129.7, 129.4, 129.0, 128.9, 128.1, 127.8, 127.4, 124.2, 81.3, 64.7, 56.5, 13.0. MS (ESI): m/z calcd for $C_{21}H_{21}NO_4SNa^+$ 406.1 $[M + Na]^+$, found 406.0 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{20}H_{17}NO_3S$ 351.0929 $[M - MeOH]^+$, found 351.0947 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3332 (w), 2936 (w), 1648 (m), 1517 (m), 1486 (m), 1454 (m), 1347 (m), 1299 (s), 1196 (w), 1140 (s), 1122 (s), 1068 (s), 947 (m), 855 (m), 815 (m), 752 (m), 690 (m), 659 (m).

Synthesis of N-(1-Methoxy-2-(methylsulfonyl)propyl)benzamide ***6k.*** It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **2k** (41 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) and recrystallization from toluene/cyclohexane afforded the analytically pure sulfone **6k** as a low melting solid (29 mg, 0.11 mmol, 54%, isolated dr >98:2; dr of the crude mixture 86:14 as determined by ^1H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 9.7 Hz, 1H), 7.86 (d, J = 7.3 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 5.70 (dd, J = 10.0, 3.4 Hz, 1H), 3.54 (qd, J = 7.3, 3.4 Hz, 1H), 3.45 (s, 3H), 3.16 (s, 3H), 1.42 (d, J = 7.3 Hz, 3H) (peaks listed only for the major diastereomer). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.9, 133.0, 132.5, 128.9, 127.3, 80.8, 60.8, 56.3, 44.4, 9.1 (peaks listed only for the major diastereomer). MS (ESI): m/z calcd for $C_{12}H_{17}NO_4SNa^+$ 294.1 $[M + Na]^+$, found 293.9 $[M + Na]^+$. HRMS (EI) m/z calcd for $C_{11}H_{13}NO_3S$ 239.0616 $[M - MeOH]^+$, found 239.0621 $[M - MeOH]^+$. IR (ATR, ν in cm^{-1}): 3349 (w), 2934 (w), 1648 (m), 1580 (w), 1518 (m), 1486 (m), 1349 (w), 1288 (s), 1196 (w), 1120 (m), 1073 (s), 959 (m), 847 (m), 801 (w), 764 (m), 712 (m), 691 (m).

Synthesis of N-(1-Methoxypropyl)benzamide ***7.*** It was prepared according to TP1 from (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23) and sulfinate salt **1m** (88 mg, 2.0 equiv, 0.4 mmol) in methanol (2 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure *N*,*O*-acetal **7** as a colorless solid (30 mg, 0.157 mmol, 79%). Mp 61−65 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.38. ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dt, J = 3.5, 2.4 Hz, 2H), 7.57−7.51 (m, 1H), 7.50−7.43 (m, 2H), 6.23 (d, J = 7.9 Hz, 1H), 5.33−5.24 (m, 1H), 3.42 (s, 3H), 1.92−1.61 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.7, 134.2, 132.0, 128.9, 127.1, 83.0, 56.2, 29.0, 9.3. MS (ESI): m/z calcd for $C_{11}H_{15}NO_2Na^+$ 216.1 $[M + Na]^+$, found 216.1 $[M + Na]^+$. IR (ATR, ν in cm^{-1}): 3227 (w), 2935 (w), 1635 (s), 1605 (m), 1579 (m), 1540 (s), 1489 (m), 1470 (m), 1445 (m), 1364 (w), 1320 (m), 1298 (m), 1260 (m), 1198 (m), 1143 (m), 1096 (s), 1047 (m), 1027 (m), 1014 (m), 939 (m), 920 (m), 842 (m), 808 (m), 765 (w), 707 (s), 693 (s), 666 (m). Analytical data match those reported in the literature.[35]

Synthesis of N-(1-Methoxy-2-tosylpropyl)benzamide ***4a*** *from Lithium Sulfinate* ***9a.*** A solution of 1-iodo-4-methylbenzene **8a** (1.6 g, 7.5 mmol, 1.0 equiv) in Et_2O (15 mL) was treated with *n*BuLi (2.9 mL, 2.58 M in hexane, 7.5 mmol, 1.0 equiv) dropwise at 0 °C (ice bath cooling). The mixture was allowed to stir at 0 °C for 30 min. After cooling to −40 °C, liquid SO_2 (0.5 mL, 25 mmol, 3.3 equiv) was added and the reaction mixture was allowed to warm to 25 °C for 90 min. The resulting suspension was filtered. The obtained solid was washed with EtOAc (3 × 30 mL) and DCM (3 × 30 mL) to give

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

sulfinate **9a** as a colorless solid (870 mg, 72%). The crude sulfinate was used without further purification in the next step.

An oven-dried, 10 mL tube was charged with a magnetic stirring bar, lithium sulfinate **9a** (65 mg, 2.0 equiv, 0.4 mmol), (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*:*Z* = 77:23), and methanol (2 mL). $Fe(NO_3)_3{\cdot}9H_2O$ (162 mg, 2.0 equiv, 0.4 mmol) was added, and the tube was closed with a rubber septum. The resulting mixture was stirred at room temperature for 2 h. Upon completion of the reaction (as judged by thin-layer chromatography), saturated aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product as a colorless foam (46 mg, 0.132 mmol, 66% isolated dr 80:20; dr of the crude mixture 80:20 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Analytical data match those of **4a** prepared from the corresponding sodium sulfinate.

*Synthesis of N-(1-Methoxy-2-(phenylsulfonyl)propyl)benzamide **6b** from Lithium Sulfinate **9b**.* A dry, N_2-flushed Schlenk flask equipped with a magnetic stirrer and a rubber septum was charged with phenyllithium (14.6 mL, 23 mmol, 1.55 M solution in Et_2O, 1.0 equiv) and cooled to −40 °C. At this temperature, liquid SO_2 (0.5 mL, 25 mmol, 1.1 equiv) was added and the reaction mixture was allowed to warm to 25 °C within 90 min. It was then concentrated under reduced pressure and coevaporated two times with DCM (150 mL) to afford the solid benzenesulfinic lithium salt **9b** (4.3 g). This procedure affords sulfinate **9b** sufficiently pure for the following transformation.

An oven-dried, 10 mL tube was charged with a magnetic stirring bar, lithium sulfinate **9b** (65 mg, 2.0 equiv, 0.4 mmol), (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*:*Z* = 77:23), and methanol (2 mL). $Fe(NO_3)_3{\cdot}9H_2O$ (162 mg, 2.0 equiv, 0.4 mmol) was added, and the tube was closed with a rubber septum. The resulting mixture was stirred at room temperature for 2 h. Upon completion of the reaction (as judged by thin-layer chromatography), saturated aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product as a colorless oil (39 mg, 0.117 mmol, 58%, isolated dr 80:20; dr of the crude mixture 80:20 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Analytical data match those of **6b** prepared from the corresponding sodium sulfinate.

*Synthesis of N-(2-(Butylsulfonyl)-1-methoxypropyl)benzamide **6l** from Lithium Sulfinate **9c**.* A dry, N_2-flushed Schlenk flask equipped with a magnetic stirrer and a rubber septum was charged with *n*BuLi (1.63 mL, 3.8 mmol, 2.34 M) and tetrahydrofuran (THF; 5 mL) and then cooled to −40 °C. At this temperature, liquid SO_2 (0.5 mL, 25 mmol) was added and the reaction mixture was allowed to warm to 25 °C within 90 min. It was then concentrated under reduced pressure and coevaporated two times with CH_2Cl_2 (150 mL) to afford the solid lithium salt **9c** (500 mg), which can be used directly for the next step.

An oven-dried, 10 mL tube was charged with a magnetic stirring bar, the obtained lithium sulfinate **9c** (65 mg, 2.0 equiv, 0.4 mmol), (*E*/*Z*)-enamide derivative **1a** (32 mg, 1.0 equiv, 0.2 mmol, *E*/*Z* = 77:23), and methanol (2 mL). $Fe(NO_3)_3{\cdot}9H_2O$ (162 mg, 2.0 equiv, 0.4 mmol) was added, and the tube was closed with a rubber septum. The resulting mixture was stirred at room temperature for 2 h. Upon completion of the reaction (as judged by thin-layer chromatography—TLC), saturated aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product as a colorless oil (40 mg, 0.128 mmol, 64% isolated dr 71:29; dr of the crude mixture 68:32 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). R_f (*n*-hexane/EtOAc = 7:3) 0.22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 9.8 Hz, 1H; minor diastereomer), 8.16 (d, J = 9.8 Hz, 1H; major diastereomer), 7.91−7.82 (m, 2H), 7.53 (ddd, J = 7.3, 6.1, 4.4 Hz, 1H), 7.49−7.42 (m, 2H), 5.66 (dd, J = 10.0, 3.3 Hz, 1H; major diastereomer), 5.58 (dd, J = 9.8, 2.7 Hz, 1H; minor diastereomer), 3.55 (qd, J = 7.3, 3.3 Hz, 1H; major diastereomer), 3.44 (s, 3H; minor diastereomer), 3.42 (s, 3H; major diastereomer), 3.33−3.16 (m, 2H), 3.13−3.05 (m, 1H; minor diastereomer), 1.95−1.76 (m, 2H), 1.60 (d, J = 7.3 Hz, 3H; minor diastereomer), 1.54−1.44 (m, 2H), 1.40 (d, J = 7.3 Hz, 3H; major diastereomer), 0.96 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$; major diastereomer) δ 167.9, 133.0, 132.4, 128.9, 127.3, 81.0, 58.5, 56.2, 56.1, 23.9, 21.9, 13.7, 9.1. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$; minor diastereomer) δ 167.2, 133.2, 132.3, 128.8, 127.3, 80.8, 63.5, 56.8, 52.0, 22.4, 22.0, 13.8, 13.0. MS (ESI): *m*/*z* calcd for $C_{15}H_{22}NO_4S^-$ 312.1 $[M - H]^-$, found 312.1 $[M - H]^-$. HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}NO_3S^+$ 282.1158 $[M - MeO]^+$, found 282.11640 $[M - MeO]^+$. IR (ATR, ν in cm^{-1}): 3348 (w), 2959 (w), 1661 (m), 1582 (w), 1516 (m), 1488 (m), 1463 (m), 1352 (m), 1285 (m), 1264 (s), 1194 (m), 1117 (s), 1094 (s), 1071 (s), 949 (w), 845 (m), 801 (w), 706 (m), 687 (m).

*Telescoped Process for the Synthesis of **4a**.* An oven-dried, 25 mL round-bottom flask was charged with a magnetic stirring bar, $Ni(PPh_3)_2$[NaphthylBr] **11** (100 mg, 5 mol %, 0.5 mmol), and MeOH (10 mL) and capped with a rubber septum. The resulting suspension was degassed by slowly bubbling nitrogen through the mixture for 15 min with simultaneous sonication in an ultrasound bath. Then, *N*-allylamide **5a** (400 mg, 1.0 equiv, 2.5 mmol) was added at room temperature under vigorous stirring. The reaction mixture was stirred for 24 h. After complete conversion of the allylamide (as judged by thin-layer chromatography), sulfinate salt **2a** (890 mg, 2.0 equiv, 5.0 mmol) and $Fe(NO_3)_3{\cdot}9H_2O$ (2.02 g, 2.0 equiv, 5.0 mmol) were added to the reaction mixture. The resulting mixture was stirred at room temperature for 2 h. Upon completion of the reaction (as judged by thin-layer chromatography), saturated aqueous NH_4Cl (20 mL) was added. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **4a** as a colorless foam (843 mg, 2.4 mmol, 97%, isolated dr 80:20; dr of the crude mixture 80:20 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Analytical data match those of **4a**.

*Synthesis of N-(2-Tosylprop-1-en-1-yl)benzamide **3** via Thermal Elimination of **4a**.* An oven-dried, 10 mL screw cap glass tube with a PP cap was charged with a magnetic stirring bar, sulfone **4a** (35 mg, 1.0 equiv, 0.1 mmol), and dichloroethane (1 mL). The reaction mixture was stirred at 80 °C for 20 h. After cooling to room temperature, saturated aqueous $NaHCO_3$ (3 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Purification by flash column chromatography (*n*-hexane/EtOAc) afforded the (*E*)- and (*Z*)-β-amidovinylsulfones **3** as a colorless solid (26 mg, 0.083 mmol, 83%, isolated dr 53:47; (**3**-(E):**3**-(Z)) dr of the crude mixture 53:47 (**3**-(*E*):**3**-(Z)); as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Separation of both isomers by column chromatography was possible.

3-(*E*): R_f (*n*-hexane/EtOAc = 7:3) 0.22. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 11.7 Hz, 1H), 7.85−7.72 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 2.42 (s, 1H), 1.89 (d, J = 0.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.1, 137.0, 133.2, 132.5, 131.4, 129.9, 129.2, 128.1, 127.5, 118.5, 21.7, 10.7. Analytical data match those reported in the literature.

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

Crystals of (*E*)-**3** suitable for X-ray could be obtained by slow evaporation from ethylacetate.

3-(*Z*): Mp 159−164 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.53. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (d, J = 11.4 Hz, 1H), 8.02−7.93 (m, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.58−7.48 (m, 3H), 7.35 (d, J = 8.1 Hz, 2H), 2.45 (s, 3H), 1.87 (d, J = 1.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.1, 145.0, 136.6, 133.1, 132.2, 130.8, 130.1, 129.2, 127.8, 127.6, 113.2, 21.8, 16.1. MS (ESI): m/z calcd for $C_{17}H_{17}NO_3SNa^+$ 338.1 [M + Na]$^+$, found 338.2 [M + Na]$^+$. HRMS (EI) m/z calcd for $C_{17}H_{17}NO_3S$ 315.0929 [M]$^+$, found 315.0940 [M]$^+$. IR (ATR, ν in cm^{-1}): 3350 (m), 2924 (w), 1688 (m), 1641 (s), 1476 (m), 1287 (s), 1128 (s), 1073 (m), 944 (m), 875 (m), 806 (m), 711 (s), 688 (s), 668 (m).

Synthesis of N-(2-Tosylpropyl)benzamide ***12***. A flame-dried and argon-flushed Schlenk tube, equipped with a septum and a magnetic stirrer, was charged with *N,O*-acetal **4a** (87 mg, 0.25 mmol, 1.0 equiv) and 2.5 mL of DCM and cooled to −50 °C. $TiCl_4$ (55 μL, 0.5 mmol 2.0 equiv) was added, and the reaction was stirred for 15 min. Then, L-selectride (1 mL, 1 mmol, 4.0 equiv; 1 M in THF) was added dropwise. The reaction was allowed to warm to rt overnight. After TLC showed complete consumption of the starting material, saturated aqueous $NaHCO_3$ (5 mL) was added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure. Column chromatography (*n*-hexane/EtOAc = 9:1 → 4:1 → 7:3 → 1:1) afforded the desired amide **12** as a colorless solid (55 mg, 0.17 mmol, 69%). R_f (*n*-hexane/EtOAc = 7:3) 0.12. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.74 (m, 4H), 7.52 (d, J = 7.2 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.20 (s, 1H), 3.94 (ddd, J = 14.9, 6.5, 3.2 Hz, 1H), 3.85−3.67 (m, 1H), 3.36 (pd, J = 7.1, 3.2 Hz, 1H), 2.45 (s, 3H), 1.29 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 145.5, 133.9, 133.9, 131.9, 130.2, 128.9, 128.8, 127.1, 59.7, 39.4, 21.8, 12.7. Analytical data match those reported in the literature.[19]

Nucleophilic Trapping of N,O-Acetyl ***4a***. *Typical Procedure 2*. An oven-dried, 10 mL screw cap glass tube with a PP cap was charged with a magnetic stirring bar, *N,O*-acetal **4a** (1.0 equiv), $Bi(OTf)_3$ (5 mol %), and 1 mL of dichloromethane. Then, the nucleophile (4.0 equiv) was added, and the resulting mixture was stirred at room temperature for 2 h. Upon completion of the reaction (as judged by thin-layer chromatography), the reaction mixture was diluted with EtOAc and filtered through a short plug of celite and silica gel. The plug was rinsed with additional EtOAc, and the solvent was evaporated under reduced pressure. Purification of the crude residue by flash column chromatography afforded the analytically pure product.

Synthesis of N-(1-(5-Methylfuran-2-yl)-2-tosylpropyl)benzamide ***13a***. It was prepared according to TP2 from sulfone **4a** (35 mg, 1.0 equiv, 0.1 mmol), $Bi(OTf)_3$ (7 mg, 5 mol %, 0.01 mmol), and 2-methylfuran (72 μL, 1.0 equiv, 0.4 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc) afforded the analytically pure sulfone **13a** as a colorless oil (74 mg, 0.185 mmol, 92%, isolated dr 83:17; dr of the crude mixture 83:17 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Mp 142−147 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.32. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.83 (m, 2H), 7.77−7.66 (m, 1H), 7.61−7.44 (m, 5H), 7.29 (d, J = 8.2 Hz, 1H, minor diastereomer), 7.23 (d, J = 8.2 Hz, 2H, major diastereomer), 6.15 (d, J = 3.0 Hz, 1H, minor diastereomer), 6.06 (d, J = 3.0 Hz, 1H major diastereomer), 5.87 (d, J = 3.0 Hz, 1H, minor diastereomer), 5.73 (d, J = 2.3 Hz, 1H major diastereomer), 5.63 (dd, J = 8.4, 3.2 Hz, 1H, minor diastereomer), 5.49 (dd, J = 8.4, 5.7 Hz, 1H major diastereomer), 4.04−3.92 (m, 1H major diastereomer), 3.66 (dd, J = 7.3, 3.5 Hz, 1H, minor diastereomer), 2.40 (s, 3H), 2.16 (s, 1H, minor diastereomer), 1.97 (s, 3H, major diastereomer), 1.49 (t, J = 6.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9, 151.9, 148.6, 144.6, 135.4, 133.8, 132.1, 129.7, 128.9, 128.5, 127.4, 108.8, 106.5, 61.2, 49.5, 21.7, 13.3, 12.4. MS (ESI): m/z calcd for $C_{22}H_{22}NO_4S^-$ 396.1 [M − H]$^-$, found 396.1 [M − H]$^-$. HRMS (EI) m/z calcd for $C_{17}H_{17}NO_3S$ 315.0929 [M − C_5H_6OH]$^+$, found 315.0925 [M + H]$^+$. IR (ATR, ν in cm^{-1}): 3284 (m), 2936 (m), 1636 (m), 1542 (m), 1492 (m), 1447 (m), 1307 (s), 1291 (s), 1216 (m), 1184 (m), 1135 (s), 1083 (m), 1023 (m), 852 (w), 802 (m), 785 (m), 719 (m), 696 (m).

Synthesis of N-(2-Tosyl-1-(2,4,6-trimethoxyphenyl)propyl)-benzamide ***13b***. It was prepared according to TP2 from sulfone **4a** (35 mg, 1.0 equiv, 0.1 mmol), $Bi(OTf)_3$ (3.3 mg, 5 mol %, 5.0 μmol), and 2,4,6-trimethoxybenzene (38 mg, 4.0 equiv, 0.4 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) afforded the analytically pure sulfone **13b** as a colorless solid (30 mg, 0.061 mmol, 61%, isolated dr 87:13; dr of the crude mixture 87:13 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Crystals of **13b** suitable for X-ray could be obtained by slow evaporation from toluene/*c*-Hex (1:8). Mp 76−83 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.08. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.74−7.70 (m, J = 7.1 Hz, 2H), 7.47−7.35 (m, 4H), 7.30−7.24 (m, 2H), 6.07 (s, 2H), 5.94 (t, J = 9.8 Hz, 1H), 3.92−3.85 (m, 1H), 3.79 (s, 6H), 3.75 (s, 3H), 2.34 (s, 3H), 1.11 (d, J = 7.1 Hz, 3H). (Peaks only for the major diastereomer) ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6, 161.1, 158.8, 144.5, 135.0, 134.6, 131.2, 129.7, 129.3, 128.5, 127.2, 108.5, 91.3, 62.6, 56.2, 55.4, 45.4, 21.7, 13.4. (Peaks only for the major diastereomer) MS (ESI): m/z calcd for $C_{26}H_{28}NO_6S^-$ 482.2 [M − H]$^-$, found 482.4 [M − H]$^-$. HRMS (EI) m/z calcd for $C_{26}H_{29}NO_6S$ 483.1716 [M]$^+$, found 483.1699 [M]$^+$. IR (ATR, ν in cm^{-1}): 3393 (w), 2931 (m), 1653 (m), 1592 (m), 1526 (m), 1489 (m), 1455 (m), 1418 (m), 1287 (m), 1204 (m), 1115 (s), 953 (m), 856 (w), 801 (m), 724 (m), 694 (m).

Synthesis of N-(1-(3-Methyl-1H-indol-2-yl)-2-tosylpropyl)-benzamide ***13c***. It was prepared according to TP2 from sulfone **4a** (35 mg, 1.0 equiv, 0.1 mmol), $Bi(OTf)_3$ (3.3 mg, 0.05 equiv, 5.0 μmol), and 3-methylindole (53 mg, 4.0 equiv, 0.4 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) and recrystallization from toluene/cyclohexane afforded the analytically pure sulfone **13c** as colorless needles (33 mg, 0.074 mmol, 74%, isolated dr > 98:2 dr of the crude mixture 84:16 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Mp 109−116 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.23. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.75 (d, J = 7.3 Hz, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.45 (dt, J = 31.4, 7.1 Hz, 5H), 7.30 (d, J = 8.1 Hz, 1H), 7.21−7.13 (m, J = 12.5, 8.1 Hz, 3H), 7.07 (t, J = 7.4 Hz, 1H), 5.35 (t, J = 8.0 Hz, 1H), 4.50 (dq, J = 14.4, 7.1 Hz, 1H), 2.30 (d, J = 4.5 Hz, 6H), 1.12 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.9, 145.1, 135.6, 135.3, 133.8, 132.1, 131.2, 129.9, 128.7, 128.3, 128.3, 127.3, 122.6, 119.4, 119.0, 111.4, 109.6, 60.4, 49.2, 21.7, 13.4, 9.0. MS (ESI): m/z calcd for $C_{26}H_{25}N_2O_3S^-$ 445.2 [M − H]$^-$, found 445.3 [M − H]$^-$. HRMS (EI) m/z calcd for $C_{26}H_{26}N_2O_3S$ 446.1664 [M]$^+$, found 446.1670 [M]$^+$.IR (ATR, ν in cm^{-1}): 3347 (w), 2921 (w), 1634 (m), 1525 (m), 1488 (m), 1458 (m), 1286 (s), 1137 (s), 1082 (m), 906 (m), 813 (m), 731 (m).

Synthesis of N-(1-(Ethylthio)-2-tosylpropyl)benzamide ***13d***. It was prepared according to TP2 from sulfone **4a** (35 mg, 1.0 equiv, 0.1 mmol), $Bi(OTf)_3$ (3.3 mg, 0.05 equiv, 5.0 μmol), and ethanethiol (29 μL, 4.0 equiv, 0.4 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 2 h. Purification by flash column chromatography (*n*-hexane/EtOAc + 0.2 vol % NEt_3) and recrystallization from toluene/cyclohexane afforded the analytically pure sulfone **13d** as a colorless foam (28 mg, 0.073 mmol, 73%, isolated dr 98:2; dr of the crude mixture 71:29 as determined by ^{1}H NMR analysis of the unpurified product after aqueous workup). Mp 53−57 °C. R_f (*n*-hexane/EtOAc = 7:3) 0.30. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.77 (m, 4H), 7.55 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.40−7.30 (m, 3H), 5.66 (dd, J = 9.5, 4.7 Hz, 1H), 3.66 (qd, J = 7.1, 4.8 Hz, 1H), 2.75−2.55 (m, 2H), 2.45 (s, 3H), 1.45 (d, J = 7.1 Hz, 3H), 1.25 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.8, 145.5, 135.5, 133.4, 132.3, 130.1, 129.0, 128.9, 127.3, 63.8, 55.4, 26.4, 21.9, 14.7, 13.9. MS (ESI): m/z calcd for $C_{19}H_{22}NO_3S_2^-$376.1 [M −

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

H]$^-$, found 376.3 [M − H]$^-$. HRMS (EI) m/z calcd for $C_{17}H_{17}NO_3S$ 315.0929 [M − C_2H_5SH]$^+$, found 315.0937 [M − C_2H_5SH]$^+$. IR (ATR, ν in cm^{-1}): 3349 (w), 2934 (w), 1648 (m), 1580 (w), 1518 (m), 1486 (m), 1349 (w), 1288 (s), 1196 (w), 1120 (m), 1073 (s), 959 (m), 847 (m), 801 (w), 764 (m), 712 (m), 691 (m).

Synthesis of 2-Benzamido-3-tosylbutanoic Acid **14**. A 25 mL round-bottom flask was charged with a magnetic stirring bar, $NaIO_4$ (802 mg, 15.0 equiv, 3.75 mmol), CCl_4 (1.3 mL), MeCN (1.3 mL), H_2O (2.0 mL), and EtOAc (0.8 mL). $RuO_2{\cdot}H_2O$ (1.4 mg, 5 mol %, 12.5 μmol) was added, and the resulting suspension was stirred for 1 h. Then, sulfone **13a** (99.4 mg, 1.0 equiv, 0.25 mmol) in DCM (1.5 mL) was added, and the resulting mixture was stirred at room temperature for 24 h. Upon completion of the reaction (as judged by thin-layer chromatography), the reaction mixture was acidified with 1 N $NaHSO_4$ (pH = 1) and filtered through a short plug of celite. The plug was rinsed with additional DCM, and the solvent was washed with brine and three times with an aqueous $NaHCO_3$ (50 mL). The aqueous phase was again carefully acidified with 1 N $NaHSO_4$ to pH = 1 and then extracted three times with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were evaporated under reduced pressure to afford the analytically pure product as a colorless foam (69 mg, 0.19 mmol, 76%, isolated dr 94:6). Mp 67−75 °C. R_f (DCM/MeOH = 9:1) 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.86 (d, J = 7.4 Hz, 2H), 7.75 (d, J = 8.1 Hz, 2H), 7.54 (dd, J = 24.1, 8.1 Hz, 2H), 7.44 (t, J = 7.5 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.21 (dd, J = 8.8, 3.5 Hz, 1H), 4.12−4.00 (m, 1H), 2.39 (s, 3H), 1.40 (d, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.9, 168.3, 145.7, 134.6, 133.0, 132.4, 130.1, 128.8, 128.8, 127.5, 60.7, 53.5, 21.7, 13.1. MS (ESI): m/z calcd for $C_{18}H_{19}NO_5S$ 360.4 [M − H]$^+$, found 360.3 [M − H]$^+$. HRMS (EI) m/z calcd for $C_{18}H_{19}NO_5S$ 361.0984 [M]$^+$, found 361.0996 [M]$^+$. IR (ATR, ν in cm^{-1}): 3341 (w), 3062 (w), 2928 (w), 1735 (m), 1640 (m), 1600 (w), 1579 (m), 1526 (w), 1489 (m), 1452 (w), 1286 (s), 1139 (s), 1084 (m), 816 (w), 710 (m).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03299.

NMR spectra and X-ray crystal structures (PDF)
X-ray data for compound **3-(*E*)** (CIF)
X-ray data for compound **4a** (CIF)
X-ray data for compounds **13b** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Georg Manolikakes − *Institute for Organic Chemistry, Technical University Kaiserslautern 67663 Kaiserslautern, Germany*; orcid.org/0000-0002-4013-5757; Email: manolikakes@chemie.uni-kl.de

Authors

Philipp Kramer − *Institute for Organic Chemistry, Technical University Kaiserslautern 67663 Kaiserslautern, Germany*

Miro Halaczkiewicz − *Institute for Organic Chemistry, Technical University Kaiserslautern 67663 Kaiserslautern, Germany*

Yu Sun − *Institute for Organic Chemistry, Technical University Kaiserslautern 67663 Kaiserslautern, Germany*

Harald Kelm − *Institute for Organic Chemistry, Technical University Kaiserslautern 67663 Kaiserslautern, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.9b03299

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to thank the Polytechnische Gesellschaft Frankfurt am Main (Ph.D. Fellowship to P.K.), the DFG, and NanoKat for financial support, Albemarle (Frankfurt) for the generous donation of chemicals, and Prof. Michael Göbel (Goethe-University Frankfurt) for his support.

■ REFERENCES

(1) (a) Whitham, G. H. *Organosulfur Chemistry*; Oxford University Press: Oxford, 1995. (b) Engberts, J. B. F. N. *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C., Eds.; John Wiley & Sons: Chichester, 1988. (c) Simpkins, N. S. *Sulphones in Organic Synthesis*, 1st ed.; Pergamon: Oxford, England, New York, 1993. (d) Liu, N.-W.; Liang, S.; Manolikakes, G. Recent Advances in the Synthesis of Sulfones. *Synthesis* **2016**, *48*, 1939−1973.

(2) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, *16*, 1200−1216.

(3) Trost, B. M.; Kalnmals, C. A. Sulfones as Chemical Chameleons: Versatile Synthetic Equivalents of Small-Molecule Synthons. *Chemistry* **2019**, *25*, 11193−11213.

(4) (a) Devendar, P.; Yang, G.-F. Sulfur-containing agrochemicals. *Top. Curr. Chem.* **2017**, *375*, No. 82. (b) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-approved drugs containing sulfur atoms. *Top. Curr. Chem.* **2018**, *376*, No. 5.

(5) (a) de Noronha, R. G.; Fernandes, A. C.; Romão, C. C. MoO_2Cl_2 as a novel catalyst for Friedel−Crafts acylation and sulfonylation. *Tetrahedron Lett.* **2009**, *50*, 1407−1410. (b) Marquié, J.; Laporterie, A.; Dubac, J.; Roques, N.; Desmurs, J. R. Acylation and related reactions under microwaves. 4. Sulfonylation reactions of aromatics. *J. Org. Chem.* **2001**, *66*, 421−425. (c) Borujeni, K. P.; Tamami, B. Polystyrene and silica gel supported $AlCl_3$ as highly chemoselective heterogeneous Lewis acid catalysts for Friedel−Crafts sulfonylation of aromatic compounds. *Catal.* **2007**, *8*, 1191−1196.

(6) (a) Jereb, M. Highly atom-economic, catalyst- and solvent-free oxidation of sulfides into sulfones using 30% aqueous H_2O_2. *Green Chem.* **2012**, *14*, 3047−3052. (b) Lutz, M.; Wenzler, M.; Likhotvorik, I. An efficient oxidation of sulfides to sulfones with urea−hydrogen peroxide in the presence of phthalic anhydride in ethyl acetate. *Synthesis* **2018**, *50*, 2231−2234.

(7) (a) Quebatte, L.; Thommes, K.; Severin, K. Highly efficient atom transfer radical addition reactions with a RuIII complex as a catalyst precursor. *J. Am. Chem. Soc.* **2006**, *128*, 7440−7441. (b) Meyer, A. U.; Jäger, S.; Prasad Hari, D.; König, B. Visible light-mediated metal-free synthesis of vinyl sulfones from aryl sulfinates. *Adv. Synth. Catal.* **2015**, *357*, 2050−2054. (c) Pan, X.-Q.; Zou, J.-P.; Yi, W.-B.; Zhang, W. Recent advances in sulfur- and phosphorous-centered radical reactions for the formation of S−C and P−C bonds. *Tetrahedron* **2015**, *71*, 7481−7529. (d) Zeng, X.; Ilies, L.; Nakamura, E. Iron-catalyzed regio- and stereoselective chlorosulfonylation of terminal alkynes with aromatic sulfonyl chlorides. *Org. Lett.* **2012**, *14*, 954−956.

(8) (a) Umierski, N.; Manolikakes, G. Metal-free synthesis of diaryl sulfones from arylsulfinic acid salts and diaryliodonium salts. *Org. Lett.* **2013**, *15*, 188−191. (b) Chawla, R.; Kapoor, R.; Singh, A. K.; Yadav, L. D. S. A one-pot regioselective synthetic route to vinyl sulfones from terminal epoxides in aqueous media. *Green Chem.* **2012**, *14*, 1308−1313. (c) Pandya, V. G.; Mhaske, S. B. Transition-metal-free C-S bond formation: a facile access to aryl sulfones from sodium sulfinates via arynes. *Org. Lett.* **2014**, *16*, 3836−3839. (d) Liang, S.; Zhang, R.-Y.; Xi, L.-Y.; Chen, S.-Y.; Yu, X.-Q. Sulfonylation of five-membered heterocycles via an S(N)Ar reaction. *J. Org. Chem.* **2013**, *78*, 11874−11880. (e) Maloney, K. M.; Kuethe, J. T.; Linn, K. A practical, one-pot synthesis of sulfonylated pyridines. *Org. Lett.* **2011**, *13*, 102−105.

(9) (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. Unsymmetrical diaryl sulfones through palladium-catalyzed coupling of aryl iodides and arenesulfinates. *Org. Lett.* **2002**, *4*, 4719−4721. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R.

Unsymmetrical diaryl sulfones and aryl vinyl sulfones through palladium-catalyzed coupling of aryl and vinyl halides or triflates with sulfinic acid salts. *J. Org. Chem.* **2004**, *69*, 5608−5614. (c) Baskin, J. M.; Wang, Z. An efficient copper catalyst for the formation of sulfones from sulfinic acid salts and aryl iodides. *Org. Lett.* **2002**, *4*, 4423−4425. (d) Cabrera-Afonso, M. J.; Lu, Z.-P.; Kelly, C. B.; Lang, S. B.; Dykstra, R.; Gutierrez, O.; Molander, G. A. Engaging sulfinate salts via Ni/photoredox dual catalysis enables facile Csp^2-SO_2R coupling. *Chem. Sci.* **2018**, *9*, 3186−3191. (e) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. K. A general copper-catalyzed sulfonylation of arylboronic acids. *Org. Lett.* **2007**, *9*, 3405−3408. (f) Liu, N.-W.; Hofman, K.; Herbert, A.; Manolikakes, G. Visible-light photoredox/nickel dual catalysis for the cross-coupling of sulfinic acid salts with aryl iodides. *Org. Lett.* **2018**, *20*, 760−763. (g) Reeves, D. C.; Rodriguez, S.; Lee, H.; Haddad, N.; Krishnamurthy, D.; Senanayake, C. H. Palladium-catalyzed coupling of vinyl tosylates with arylsulfinate salts. *Tetrahedron Lett.* **2009**, *50*, 2870−2873. (h) Yue, H.; Zhu, C.; Rueping, M. Cross-coupling of sodium sulfinates with aryl, heteroaryl, and vinyl halides by nickel/photoredox dual catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 1371−1375. (i) Zhu, W.; Ma, D. Synthesis of aryl sulfones via L-proline-promoted CuI-catalyzed coupling reaction of aryl halides with sulfinic acid salts. *J. Org. Chem.* **2005**, *70*, 2696−2700.

(10) (a) Bisseret, P.; Blanchard, N. Taming sulfur dioxide: a breakthrough for its wide utilization in chemistry and biology. *Org. Biomol. Chem.* **2013**, *11*, 5393−5398. (b) Qiu, G.; Zhou, K.; Gao, L.; Wu, J. Insertion of sulfur dioxide via a radical process: an efficient route to sulfonyl compounds. *Org. Chem. Front.* **2018**, *5*, 691−705. (c) Liu, G.; Fan, C.; Wu, J. Fixation of sulfur dioxide into small molecules. *Org. Biomol. Chem.* **2015**, *13*, 1592−1599. (d) Zheng, D.; Wu, J. *Sulfur Dioxide Insertion Reactions for Organic Synthesis*; Springer Singapore: Singapore, 2017. (e) Deeming, A.; Emmett, E.; Richards-Taylor, C.; Willis, M. Rediscovering the chemistry of sulfur dioxide: new developments in synthesis and catalysis. *Synthesis* **2014**, *46*, 2701−2710. (f) Emmett, E. J.; Willis, M. C. The development and application of sulfur dioxide surrogates in synthetic organic chemistry. *Asian J. Org. Chem.* **2015**, *4*, 602−611. (g) Hofman, K.; Liu, N.-W.; Manolikakes, G. Radicals and sulfur dioxide: A versatile combination for the construction of sulfonyl-containing molecules. *Chemistry* **2018**, *24*, 11852−11863.

(11) (a) Chen, Y.; Murray, P. R. D.; Davies, A. T.; Willis, M. C. Direct copper-catalyzed three-component synthesis of sulfonamides. *J. Am. Chem. Soc.* **2018**, *140*, 8781−8787. (b) Chen, Z.; Liu, N.-W.; Bolte, M.; Ren, H.; Manolikakes, G. Visible-light mediated 3-component synthesis of sulfonylated coumarins from sulfur dioxide. *Green Chem.* **2018**, *20*, 3059−3070. (c) Zheng, D.; Chen, M.; Yao, L.; Wu, J. A general route to sulfones via insertion of sulfur dioxide promoted by cobalt oxide. *Org. Chem. Front.* **2016**, *3*, 985−988.

(12) (a) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. Recent advances in C-S bond formation via C-H bond functionalization and decarboxylation. *Chem. Soc. Rev.* **2015**, *44*, 291−314. (b) Shaaban, S.; Liang, S.; Liu, N.-W.; Manolikakes, G. Synthesis of sulfones via selective C-H-functionalization. *Org. Biomol. Chem.* **2017**, *15*, 1947−1955.

(13) (a) Ramesh, B.; Jeganmohan, M. Ruthenium-Catalyzed Remote C-H Sulfonylation of N-Aryl-2-aminopyridines with aromatic sulfonyl chlorides. *Org. Lett.* **2017**, *19*, 6000−6003. (b) Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Zhu, W.; Dong, Y.; Wu, Y.; Kong, X.; Jiang, L.; Wu, Y. Copper(I)-Catalyzed Sulfonylation of 8-aminoquinoline amides with sulfonyl chlorides in air. *Org. Lett.* **2015**, *17*, 6086−6089. (c) Zhao, X.; Dimitrijević, E.; Dong, V. M. Palladium-catalyzed C-H bond functionalization with arylsulfonyl chlorides. *J. Am. Chem. Soc.* **2009**, *131*, 3466−3467 and references cited therein.

(14) Carretero, J. C.; Arrayás, R. G.; de Gracia, I. S. A stereoselective approach to polyhydroxylated quinolizidine alkaloids. *Tetrahedron Lett.* **1997**, *38*, 8537−8540.

(15) Ermolenko, L.; Sasaki, N. A.; Potier, P. Asymmetric synthesis of amino sugars. Part 2. A novel versatile approach to the chiral non-racemic synthesis of 2-amino-2-deoxy sugars. Preparation of L-glucosamine, L-mannosamine and L-talosamine derivatives. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2465−2473.

(16) Wang, Q.; Tran Huu Dau, M.-E.; André Sasaki, N.; Potier, P. Facile synthesis of N-Boc-(2S,5R)-5-(1′-hydroxy-1′-methylethyl)-proline. *Tetrahedron* **2001**, *57*, 6455−6462.

(17) (a) Cellarier, E.; Terret, C.; Labarre, P.; Ouabdesselam, R.; Curé, H.; Marchenay, C.; Maurizis, J. C.; Madelmont, J. C.; Cholle, P.; Armand, J. P. Pharmacokinetic study of cystemustine, administered on a weekly schedule in cancer patients. *Ann. Oncol.* **2002**, *13*, 760−769. (b) Durando, X.; Thivat, E.; Roché, H.; Bay, J. O.; Lemaire, J.-J.; Verrelle, P.; Lentz, M.-A.; Chazal, J.; Curé, H.; Chollet, P. Cystemustine in recurrent high grade glioma. *J. Neurooncol.* **2006**, *79*, 33−37.

(18) Sun, D.; Li, Z.; Rew, Y.; Gribble, M.; Bartberger, M. D.; Beck, H. P.; Canon, J.; Chen, A.; Chen, X.; Chow, D.; Deignan, J.; Duquette, J.; Eksterowicz, J.; Fisher, B.; Fox, B. M.; Fu, J.; Gonzalez, A. Z.; Gonzalez-Lopez De Turiso, F.; Houze, J. B.; Huang, X.; Jiang, M.; Jin, L.; Kayser, F.; Liu, J. J.; Lo, M.-C.; Long, A. M.; Lucas, B.; McGee, L. R.; McIntosh, J.; Mihalic, J.; Oliner, J. D.; Osgood, T.; Peterson, M. L.; Roveto, P.; Saiki, A. Y.; Shaffer, P.; Toteva, M.; Wang, Y.; Wang, Y. C.; Wortman, S.; Yakowec, P.; Yan, X.; Ye, Q.; Yu, D.; Yu, M.; Zhao, X.; Zhou, J.; Zhu, J.; Olson, S. H.; Medina, J. C. Discovery of AMG 232, a potent, selective, and orally bioavailable MDM2-p53 inhibitor in clinical development. *J. Med. Chem.* **2014**, *57*, 1454−1472.

(19) Baile, C. A.; McLaughlin, C. L. A review of the behavioral and physiological responses to elfazepam, a chemical feed intake stimulant. *J. Anim. Sci.* **1979**, *49*, 1371−1395.

(20) (a) Schafer, P. H.; Parton, A.; Gandhi, A. K.; Capone, L.; Adams, M.; Wu, L.; Bartlett, J. B.; Loveland, M. A.; Gilhar, A.; Cheung, Y.-F.; Baillie, G. S.; Houslay, M. D.; Man, H.-W.; Muller, G. W.; Stirling, D. I. Apremilast, a cAMP phosphodiesterase-4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br. J. Pharmacol.* **2010**, *159*, 842−855. (b) Man, H.-W.; Schafer, P.; Wong, L. M.; Patterson, R. T.; Corral, L. G.; Raymon, H.; Blease, K.; Leisten, J.; Shirley, M. A.; Tang, Y.; Babusis, D. M.; Chen, R.; Stirling, D.; Muller, G. W. Discovery of (S)-N-2-1-(3-ethoxy-4-methoxyphenyl)-2-methanesulfonylethyl-1,3-dioxo-2,3-dihydro-1H-isoindol-4-yl acetamide (apremilast), a potent and orally active phosphodiesterase 4 and tumor necrosis factor-alpha inhibitor. *J. Med. Chem.* **2009**, *52*, 1522−1524.

(21) (a) Jiang, H.; Chen, X.; Zhang, Y.; Yu, S. C-H Functionalization of Enamides: Synthesis of β-Amidovinyl Sulfones via Visible-Light Photoredox Catalysis. *Adv. Synth. Catal.* **2013**, *355*, 809−813. (b) Sun, D.; Zhang, R. Transition-metal-free, visible-light-induced oxidative cross-coupling for constructing β-acetylamino acrylosulfones from sodium sulfinates and enamides. *Org. Chem. Front.* **2018**, *5*, 92−97. (c) Xu, Y.-H.; Wang, M.; Lu, P.; Loh, T.-P. Palladium-catalyzed alkenyl C−H bond sulfonylation reaction using organosulfonyl chlorides. *Tetrahedron* **2013**, *69*, 4403−4407.

(22) Kramer, P.; Krieg, S.-C.; Kelm, H.; Manolikakes, G. Manganese(iii) acetate-mediated direct $C(sp^2)$-H-sulfonylation of enamides with sodium and lithium sulfinates. *Org. Biomol. Chem.* **2019**, *17*, 5538−5544.

(23) (a) Kramer, P.; Grimmer, J.; Bolte, M.; Manolikakes, G. An enamide-based domino reaction for a highly stereoselective synthesis of tetrahydropyrans. *Angew. Chem., Int. Ed.* **2019**, *58*, 13056−13059. (b) Halli, J.; Bolte, M.; Bats, J.; Manolikakes, G. Modular two-step approach for the stereodivergent synthesis of 1,3-diamines with three continuous stereocenters. *Org. Lett.* **2017**, *19*, 674−677. (c) Bernadat, G.; Masson, G. Enamide derivatives: versatile building blocks for highly functionalized α,β-substituted amines. *Synlett* **2014**, *25*, 2842−2867. (d) Carbery, D. R. Enamides: valuable organic substrates. *Org. Biomol. Chem.* **2008**, *6*, 3455−3460. (e) Gigant, N.; Chausset-Boissarie, L.; Gillaizeau, I. Direct metal-catalyzed regioselective functionalization of enamides. *Chemistry* **2014**, *20*, 7548−7564.

(24) Matsubara, R.; Kobayashi, S. Enamides and enecarbamates as nucleophiles in stereoselective C-C and C-N bond-forming reactions. *Acc. Chem. Res.* **2008**, *41*, 292−301.

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637

(25) (a) Dumoulin, A.; Lalli, C.; Retailleau, P.; Masson, G. Catalytic, highly enantioselective, direct amination of enecarbamates. *Chem. Commun.* **2015**, *51*, 5383−5386. (b) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. Photoredox-induced three-component oxy-, amino-, and carbotrifluoromethylation of enecarbamates. *Org. Lett.* **2014**, *16*, 1240−1243. (c) Nakanishi, M.; Minard, C.; Retailleau, P.; Cariou, K.; Dodd, R. H. Copper(I) catalyzed regioselective asymmetric alkoxyamination of aryl enamide derivatives. *Org. Lett.* **2011**, *13*, 5792−5795. (d) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. Highly enantioselective electrophilic α-bromination of enecarbamates: chiral phosphoric acid and calcium phosphate salt catalysts. *J. Am. Chem. Soc.* **2012**, *134*, 10389−10392.

(26) (a) Drouet, F.; Zhu, J.; Masson, G. Iron Chloride-Catalyzed Three-Component Domino Sequences: Syntheses of Functionalized α-Oxy-N-acylhemiaminals and α-Oxyimides. *Adv. Synth. Catal.* **2013**, *355*, 3563−3569. (b) Bekkaye, M.; Su, Y.; Masson, G. Metal-free dioxygenation of enecarbamates mediated by a hypervalent iodine reagent. *Eur. J. Org. Chem.* **2013**, *2013*, 3978−3982. (c) Adam, W.; Bosio, S. G.; Wolff, B. T. Chiral-auxiliary-controlled diastereoselectivity in the epoxidation of enecarbamates with DMD and *m*CPBA. *Org. Lett.* **2003**, *5*, 819−822. (d) Xiong, H.; Hsung, R. P.; Shen, L.; Hahn, J. M. Chiral enamide. Part 1: Epoxidations of chiral enamides. A viable approach to chiral nitrogen stabilized oxyallyl cations in [4+3] cycloadditions. *Tetrahedron Lett.* **2002**, *43*, 4449−4453.

(27) An Initial Version of this Work was Deposited in ChemRxiv on 28.11.2019, Reference. Kramer, P.; Halaczkiewicz, M.; Sun, Y.; Kelm, H.; Manolikakes, G. Iron(III)-Mediated Oxy-Sulfonylation of Enamides with Sodium and Lithium Sulfinates, 2019. DOI: 10.26434/chemrxiv.11294543.v1.ChemRxiv.

(28) Relative configurations of **3**-(*E*), **4a** and **13b** were unambiguously assigned by single-crystal X-ray diffraction. CCDC 1961011, 19610124 and 1967186 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre. The relative configurations of all other amidosulfones were assigned in analogy from the ^3J coupling constants.

(29) Halli, J.; Kramer, P.; Bechthold, M.; Manolikakes, G. Nickel-Catalyzed Synthesis of enamides and enecarbamates via Isomerization of allylamides and allylcarbamates. *Adv. Synth. Catal.* **2015**, *357*, 3321−3324.

(30) (a) Emmett, E. J.; Hayter, B. R.; Willis, M. C. Palladium-catalyzed three-component diaryl sulfone synthesis exploiting the sulfur dioxide surrogate DABSO. *Angew. Chem., Int. Ed.* **2013**, *52*, 12679−12683. (b) Umierski, N.; Manolikakes, G. Arylation of lithium sulfinates with diaryliodonium salts: a direct and versatile access to arylsulfones. *Org. Lett.* **2013**, *15*, 4972−4975.

(31) (a) Gaspard-Iloughmane, H.; Le Roux, C. Bismuth(III) triflate in organic synthesis. *Eur. J. Org. Chem.* **2004**, *2004*, 2517−2532. (b) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S. Applications of bismuth(III) compounds in organic synthesis. *Chem. Soc. Rev.* **2011**, *40*, 4649−4707.

(32) (a) Halli, J.; Kramer, P.; Grimmer, J.; Bolte, M.; Manolikakes, G. $Bi(OTf)_3$-Catalyzed Diastereoselective One-pot synthesis of 1,3-diamines with three continuous stereogenic centers. *J. Org. Chem.* **2018**, *83*, 12007−12022. (b) Aliyenne, A.; Pin, F.; Nimbarte, V. D.; Lawson, A. M.; Comesse, S.; Sanselme, M.; Tognetti, V.; Joubert, L.; Daïch, A. $Bi(OTf)_3$ -catalysed access to 2,3-substituted isoindolinones and tricyclic N,O-acetals by trapping of bis- N -acyliminium species in a tandem process. *Eur. J. Org. Chem.* **2016**, *2016*, 3592−3602. (c) Pin, F.; Comesse, S.; Garrigues, B.; Marchalín, S.; Daïch, A. Intermolecular and intramolecular alpha-amidoalkylation reactions using bismuth triflate as the catalyst. *J. Org. Chem.* **2007**, *72*, 1181−1191. (d) Kadam, S. T.; Thirupathi, P.; Kim, S. S. Synthetic application of in situ generation of N-acyliminium ions from α-amido p-tolylsulfones for the synthesis of α-amino nitriles. *Tetrahedron* **2010**, *66*, 1684−1688.

(33) Deruer, E.; Hamel, V.; Blais, S.; Canesi, S. Rapid transformation of sulfinate salts into sulfonates promoted by a hypervalent iodine(III) reagent. *Beilstein J. Org. Chem.* **2018**, *14*, 1203−1207.

(34) (a) Meyer, A. U.; Berger, A. L.; König, B. Metal-free C-H sulfonamidation of pyrroles by visible light photoredox catalysis. *Chem. Commun.* **2016**, *52*, 10918−10921. (b) Liu, J.; Zhou, X.; Rao, H.; Xiao, F.; Li, C.-J.; Deng, G.-J. Direct synthesis of aryl ketones by palladium-catalyzed desulfinative addition of sodium sulfinates to nitriles. *Chemistry* **2011**, *17*, 7996−7999.

(35) Yi, Y.; Gholami, H.; Morrow, M. G.; Borhan, B. XtalFluor-E mediated proto-functionalization of N -vinyl amides: access to N-acetyl N, O -acetals. *Org. Biomol. Chem.* **2017**, *15*, 9570−9574.

https://dx.doi.org/10.1021/acs.joc.9b03299
J. Org. Chem. 2020, 85, 3617−3637