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Enantioselective Addition of Sodium Bisulfite to Nitroalkenes. A Convenient Approach to Chiral Sulfonic Acids

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An enantioselective organocatalytic addition of sodium bisulfite to (*E*)-nitroalkenes has been developed by using a chiral bifunctional organocatalyst. The present methodology provides a variety of chiral β-nitroethanesulfonic acid compounds (17 examples) with excellent results: up to 99% yield and excellent enantioselectivity (up to 96% ee). The reaction tolerates (hetero)aryl and alkyl substituents on the β-nitroalkenes, and β,β-disubstituted nitroalkenes.

Organosulfur compounds,[1] including optically active ones,[2] are of great importance in organic chemistry due to their occurrence in nature and their pharmaceutical applications. Among them, chiral sulfonic acids and their derivatives have shown remarkable significance and application in the areas of natural product and pharmaceutical chemistry. Examples include the antiulcer compound 6-gingesulfonic acid, isolated from *Zingiberis* rhizome,[3] the antibacterial α-sulfobenzylpenicillin,[4] or taurine,[5] a β-amino sulfonic acid precursor of the bile (Figure 1). Similarly, sulfonates and sulfamides have become important pharmacophores in medicinal molecules with a broad spectrum of biological activities, such as antiviral, antibacterial, antitumor and so forth. Among the pool of sulfonamides, sultams (cyclic sulfonamides) have emerged as privileged structures in drug discovery due to their diverse biological properties, even though they do not occur in nature. Chiral non benzo-fused sultams can be found, for instance in RORc inverse agonists as potential treatments of inflammatory diseases (Figure 1).[6]

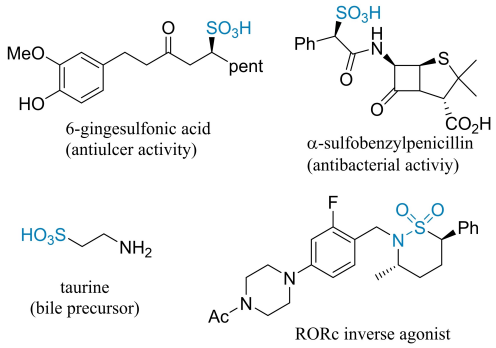

Figure 1. Examples of chiral sulfonic acid derivatives with biological and pharmacological activity.

As a result, the pursuit of new catalytic strategies that enable the effective synthesis of sulfur-containing organic molecules with the introduction of chiral information is an important goal in modern synthetic organic chemistry. Thus, the development of enantioselective carbon-sulfur (C–S) bond forming reactions constitute an important field in organic synthesis.[7]

In this context, the enantioselective addition of sulfur nucleophiles to carbon-carbon double bonds *via* sulfa-Michael reaction represent a powerful and straightforward strategy for the chiral synthesis of new C–S bonds. This strategy has been mainly approached via enantioselective organocatalysis,[8] providing access to valuable sulfur-containing compounds using thiols,[9] thioacids[10] as well as 1,4-dithiane-2,5-diol[11] as nucleophiles for the enantioselective sulfa-Michael addition.

On the other hand, nucleophilic addition of sodium bisulfite, a cheap and readily available chemical, has been used for the direct synthesis of sulfonic acids and their salts upon addition to electrophilic double bonds, including conjugated carbonyl compounds[12] and nitroalkenes.[13] Particularly, Adamo has reported the non-enantioselective amine-catalyzed addition of sodium bisulfite to nitrostyrene to give the corresponding nitrosulfonic acid under mild conditions.[12d] Despite this, the enantioselective versions of these or related reactions involving nucleophilic sodium bisulfite remain almost unexplored. In 2011, Adamo described the organocatalytic enantioselective addition of sodium bisulfite to chalcones catalyzed by an aminothiourea bifunctional catalyst to give β-carbonyl sulfonic acids in high yields and enantioselectivities (Scheme 1).[14] More recently, the enantioselective sulfa-Michael addition of sodium

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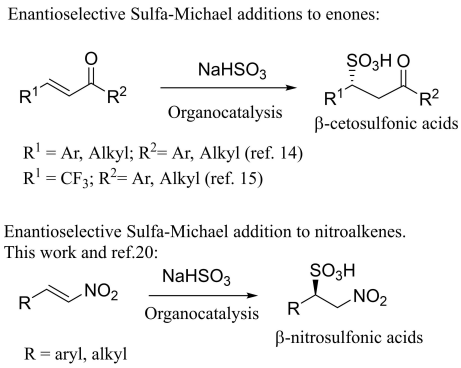


Scheme 1. Organocatalytic enantioselective addition of sodium bisulfite to electron-poor alkenes.

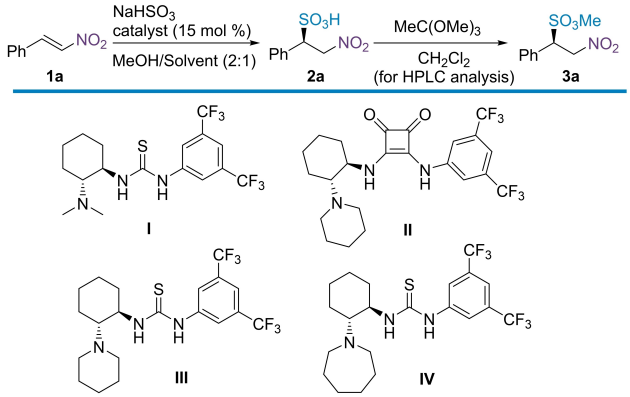
bisulfite to β-trifluoromethyl-α,β-unsaturated ketones catalyzed by a cinchona alkaloid-derived squaramide has been reported by Xu and Yuan.[15] Besides these two organocatalytic examples, Zhao has reported Ir- and Pd-catalyzed enantioselective sulfonations of allylic carbonates with sodium sulfite to afford allylic sulfonic acids.[16] In the view of these precedents, identification of new catalysts and new electrophiles to achieve enantioselective addition of bisulfite to obtain chiral functionalized sulfonic acids remains an important challenge.

The use of (*E*)-nitroalkenes as electrophiles in enantioselective Michael additions offers a powerful tool for the synthesis of valuable chiral amine derivative compounds.[17] Moreover, the nitro functional group is very versatile and can be converted into a variety of other useful functional groups.[18]

Inspired by the great potential of (*E*)-nitroalkenes and sulfonic acids, and considering the efficiency of bifunctional organocatalysts to promote the enantioselective conjugate addition of bisulfite to α,β-unsaturated carbonyls[14,15] as well as previous reports on amine-catalyzed sulfonation of nitroalkenes,[12d] we decided to study the catalytic enantioselective addition of sodium bisulfite to (*E*)-nitroalkenes catalyzed by a thiourea catalyst (Scheme 1). This methodology allows the preparation of chiral β-nitro sulfonic acids, which are precursors of taurine derivatives,[19] and potential building blocks for unnatural peptides. It must be noted that, while our work was ready to be submitted, a closely related work by Bischoff and Brière describing the same reaction was published.[20]

We started our investigation using (*E*)-(2-nitrovinyl)benzene (**1a**) as model substrate. Following initial conditions described by Adamo,[14] compound **1a** was treated with $NaHSO_3$ (0.1 M in aqueous solution) in a solvent mixture of MeOH/toluene (v/v, 2:1) at rt. To permit the determination of the enantiomeric excesses by chiral HPLC, the resulting nitrosulfonic acid **2a** was converted into the corresponding methyl ester **3a** upon treatment with trimethyl orthoacetate following a methylation procedure previously described by Xu and Yuan.[15,21] Under these conditions, a preliminary screening of different bifunctional organocatalysts was performed.[22] Takemoto's thiourea[23] catalyst **I** provided a promising result, giving the desire product **2a** with 30% *ee* (Table 1, entry 1). Importantly, when the

Table 1. Optimization of reaction conditions.[a]



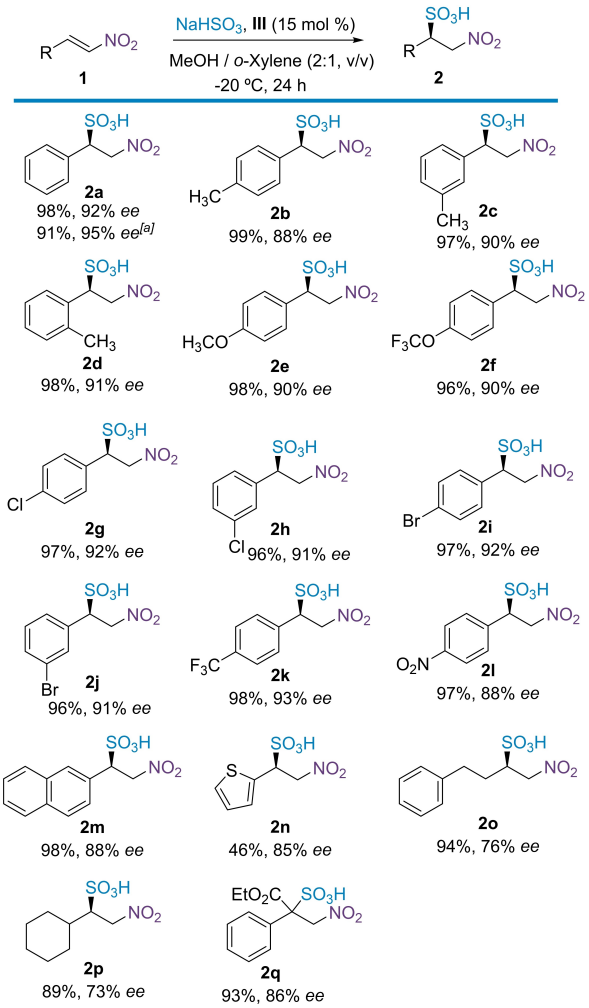
Entry	Cat.	T [°C]	co-solvent (2:1, v/v)	Conv. [%][b]	ee [%][c]
1	**I**	25	toluene	Full	30
2	**I**	−20	toluene	Full	58
3	**I**	−40	toluene	Full	48
4	**II**	−20	toluene	Full	84
5	**III**	−20	toluene	Full	88
6	**IV**	−20	toluene	Full	78
7	**III**	−20	*p*-xylene	Full	78
8	**III**	−20	chlorobenzene	Full	91
8	**III**	−20	*o*-xylene	Full (98%[d])	92

[a] Reaction Conditions:1) **1a** (0.2 mmol), cat. (15 mol%), $NaHSO_3$ (50 mg, 0.48 mmol, in 0.5 mL of H_2O), (2:1, v/v) MeOH/co-solvent (2 mL); 2) MeC$(OMe)_3$ (excess), CH_2Cl_2 (for HPLC analysis) [b] Conversion for the formation of **2a**. Determined by ^1H NMR. [c] Determined for compound **3a** by HPLC using a chiralpak AY–H column from Daicel. [d] Isolated yield.

reaction was performed at −20 °C, β-nitro sulfonic acid **2a** was afforded with full conversion increasing the enantioselectivity up to 58% (entry 2). However, at lower temperature the enantioselectivity of **2a** was compromised (entry 3). Inspired by Rawal catalyst,[24] we prepared and tested organocatalysts **II**–**IV** bearing a cyclic tertiary amine. Remarkably, higher enantioselectivities were obtained when these catalysts were tested (entries 4–6). The best result was afforded using thiourea **III** as organocatalyst giving **2a** with 88% enantiomeric excess (entry 5). Further, other co-solvents were examined employing organocatalyst **III** in MeOH (entries 7–9). The product was obtained in excellent yield (98%) and enantioselectivity (92% *ee* for **3a**) when the reaction was performed in MeOH/*o*-xylene (entry 9).

Thus, the reaction of **1a** with $NaHSO_3$ (1 M in aqueous solution) in a solvent mixture of MeOH/*o*-xylene (v/v, 2:1) at −20 °C catalyzed by thiourea **III** was chosen as optimal conditions. Under these conditions, we studied the substrate scope of the enantioselective addition of sodium bisulfite to (*E*)-nitroalkenes (Scheme 2).

First, a number of β-arylnitroalkenes **1b**–**1f** bearing electron-donating groups (Me, MeO and CF_3O) in *ortho*, *meta* and *para* position of the aromatic ring were evaluated obtaining in all cases excellent yields and high enantioselectivities (88–92% ee). *Trans*-β-nitrostyrenes **1g**–**1l** bearing electron withdrawing substituents (Cl, Br, CF_3 and NO_2) in different positions of the aromatic ring were well tolerated. The reaction provided the desired β-nitro sulfonic acids **2g**–**2l** in excellent yields and



Scheme 2. Scope of organocatalytic enantioselective addition of sodium bisulfite to (*E*)-nitroalkenes. Enantiomeric excesses were determined by HPLC under chiral stationary phases after conversion of the sulfonic acids into the corresponding methyl esters. [a] Reaction carried out at 1 mmol scale.

enantioselectivities (ee > 90%) showing the robustness of this method. Moreover, other substituents such as 2-naphthyl group or 2-thienyl substituent provided the products **2m** and **2n** in high enantioselectivities (88% ee and 85% ee, respectively), although the yield of **2n** was moderate. Remarkably, this method was also applied to β-alkyl substituted nitroalkenes giving the β-nitro sulfonic acids **2o** and **2p** in good yields and moderate enantioselectivities (ee > 70%). Remarkably, a β,β-disubstituted nitroalkene **1q** was also reactive under these conditions to give compound **2q** bearing a quaternary stereogenic center in 93% yield and 86% ee.[25]

The reaction with **1a** was also performed at 1 mmol scale to give the corresponding product **2a** even with better enantiomeric excess (95%) in 91% yield, showing the robustness of the method.

The methyl ester **3e**, prepared from nitrosulfonic acid **2e**, could be crystallized and subjected to single crystal X-ray diffraction analysis,[26] which allowed to establish the *R* configuration of the stereogenic center of **3e** and **2e** (Figure 2). The

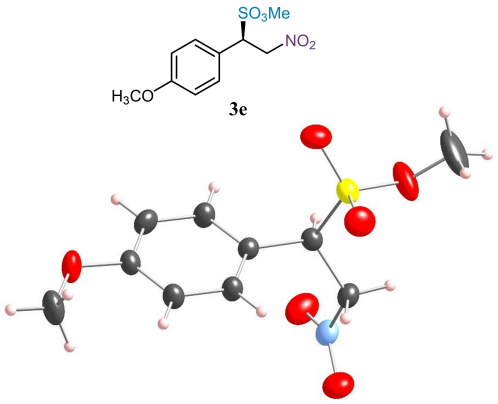


Figure 2. Otrep plot for the X-ray structure of compound **3e**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter 0.09(3).

absolute stereochemistry of all compounds **2** was assigned by analogy upon the assumption of a uniform stereochemical pathway.

In conclusion, we have established an organocatalytic enantioselective addition of sodium bisulfite to β-nitroalkenes using a thiourea organocatalyst (15 mol%), obtaining the corresponding chiral β-nitro sulfonic acids with high yields (up to 99%) and enantioselectivities (up to 93% *ee*), under mild reaction conditions. The reaction showed a wide substrate scope for a variety of β-nitroalkenes bearing aryl and alkyl groups. Moreover, β,β-disubstituted nitroalkenes are suitable substrates. We have determined the absolute stereochemistry of the β-nitroalkenes by X-ray analysis. Studies to further extend the scope of this reaction are currently underway in our laboratory.

General procedure for the enantioselective synthesis of β-nitro sulfonic acids 2. The nitroalkene **1** (0.2 mmol) and catalyst **III** (14 mg, 0.03 mmol, 15 mol%) were dissolved in 2 mL of MeOH:*o*-xylene (2:1), and the mixture was stirred for 10 min at −20 °C. Then, a freshly made solution of sodium bisulfite (50 mg, 0.48 mmol)) in water (0.5 mL) was added and the reaction was vigorously stirred at −20 °C. The reaction was monitored by TLC until complete consumption of the starting material. The mixture was filtered off over a short Celite pad eluting with H_2O (10 mL) and the solvent was evaporated under reduced pressure. Then, the crude product was dissolved in 3 mL of THF:H_2O (2:1), and the solution was passed through a plug of freshly activated acidic ion-exchange resin (Amberlyst@15) and washed with deionized water three consecutive times (3×3 mL). Then, the aqueous solution was concentrated under reduced pressure and the product dried in high vacuum in the presence of P_2O_5. When necessary, product **2** could be purified by flash chromatography, eluting with CH_2Cl_2:MeOH mixtures.

General procedure for the synthesis of β-nitro sulfonic esters 3. Sulfonic acid **2** (0.1 mmol) obtained after filtration through amberlyst was dissolved in dichloromethane (1 mL) and $CH_3C(OCH_3)_3$ (0.5 mL) was added. The mixture was stirred for 2 h, concentrated under reduced pressure and solvent traces

were removed in high vacuum to give almost pure ester **3**. Compound **3** decomposed under column chromatography to give the starting nitroalkene.

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Conflict of Interest

The authors declare no conflict of interest.

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[26] Deposition Number 2098671 (for **3e**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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