Organocatalytic enantioselective synthesis of β-amino sulfonic acid derivatives

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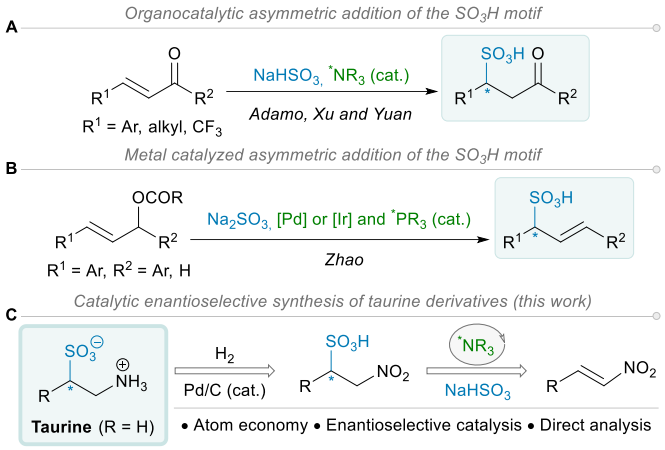
An unprecedented enantioselective conjugate addition reaction of sodium bisulfite to various nitrostyrenes occurred upon the influence of a bifunctional amino-thiourea organocatalyst; a strategy which opens a straightforward route to unprotected chiral taurines derivatives thanks to the reduction of the obtained β-nitroethanesulfonic acids into the corresponding amino derivatives.

Highly acidic chiral sulfonic acid derivatives (pK_a ~ 1 in DMSO), especially displaying an α-stereogenic center to SO_3H,[1] were successfully exploited in a variety of domains ranging from the elaboration of potent pharmaceutical ingredients[2] to the development of efficient resolution processes by crystallization.[3] From a historical point of view, the construction of α-chiral sulfonic acids were tackled by multistep asymmetric syntheses[4,5] and the separation of enantiomers from a racemic mixture.[3] In a perspective of modern sustainable methodologies, however, the enantioselective catalytic introduction of the SO_3H motif has only emerged recently.[6] By re-investigating the conjugate addition of bisulfite to electro-poor alkenes,[7] Adamo pioneered this sulfa-Michael onto chalcone derivatives in an enantioselective fashion by means of bifunctional thioureas-Cinchona alkaloid bases (Scheme 1A);[8] and extended this useful methodology to the synthesis of naturally occurring gingesulfonic acids.[8b] This straightforward catalytic strategy was recently extended to β-trifluoromethyl-α,β-unsaturated ketones by Xu and Yuan.[9] Alternatively, Zhao reported on the Pd and Ir-catalyzed asymmetric allylic sulfonation making use of sodium sulfite (Scheme 1B).[10] In spite of these promising early achievements in catalysis, the reaction scope, together with the structures of starting materials, and α-chiral sulfonic acid products obtained thereof, remain rather limited.



Scheme 1. Context of the investigation.

The naturally occurring taurine (R = H, Scheme 1C) and derivatives are fascinating β-aminoethanesulfonic acids, which have been successfully incorporated into various molecules such as bioactive and biosensor products with improved aqueous solubility in physiological medium, as well as dyes, polymers, etc.[11] Additionally, peptidosulfonamides provided novel peptides displaying specific electronic and conformational properties leading to unusual biological properties in peptidomimetics.[12] Notwithstanding the value of these chiral compounds,[13] few catalytic asymmetric methodologies tackled the construction of precursors of taurines. Upon Brønsted base catalysis, the (2+2) cycloaddition between sulfenes and aldehydes gave rise to the formation of β-sultams,[14] while the desymmetrization of *meso*-aziridines provided the corresponding cyclic β-aminothioethers.[15] Then, thanks to the transformation of the sulfur functionality to afford the corresponding SO_3H products (*via* oxidation or hydrolysis events), the authors succeeded in the syntheses of taurine derivatives in certain cases.[14,15] On the other hand, the asymmetric conjugate addition of thiol or thioacetic acid to

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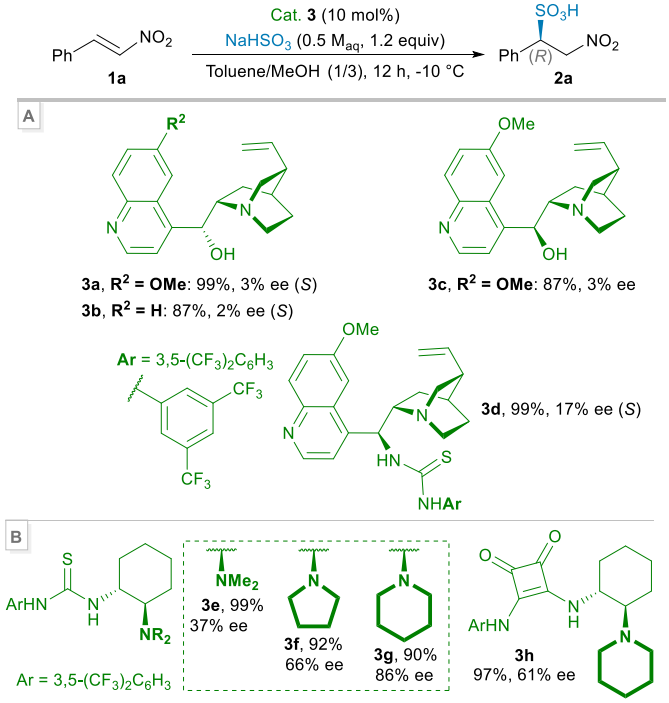
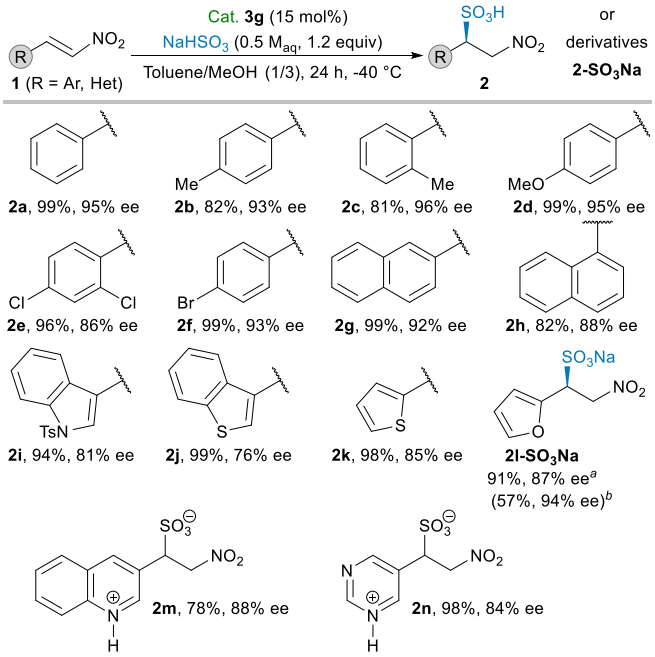
nitrostyrenes has met some success in recent years.[16,17] Nevertheless, the subsequent oxidation/reduction sequences, required for the formation of β-aminoethanesulfonic acids, were achieved only from a limited number of aliphatic or disubstituted precursors.[16d,16e] In this field of research, the direct asymmetric catalytic addition of $NaHSO_3$ to nitrostyrenes is unprecedented, although this sequence would afford a step and atom economy entry to chiral taurine derivatives (Scheme 1C), after a simple reduction procedure of β-nitroethanesulfonic acid intermediates.[7] However, this valuable asymmetric strategy should address several challenges such as (1) the design of a suited organocatalyst capable to orchestrate a catalytic process under significantly acidic conditions, (2) to deal with the competitive complexation between the sulfite and nitro functionalities of both the nucleophilic and electrophilic species, and (3) to manage the purification and analysis of the highly polar obtained products (without difficult derivatization events as commonly used procedures thus far in these series). We are pleased to report hereby on the unprecedented enantioselective addition of $NaHSO_3$ to nitrostyrenes under organocatalytic conditions affording an entry to taurine derivatives after a simple hydrogenation of the nitro-sulfonic acid intermediates.



Scheme 2. Reaction optimization. Isolated yields after purification on Dowex 50WX8. Ees of product **2a** were determined by chiral HPLC. The absolute configuration of **2a** was determined by comparison with known compounds by means of $[\alpha]^D$ and chemical transformations (see SI).

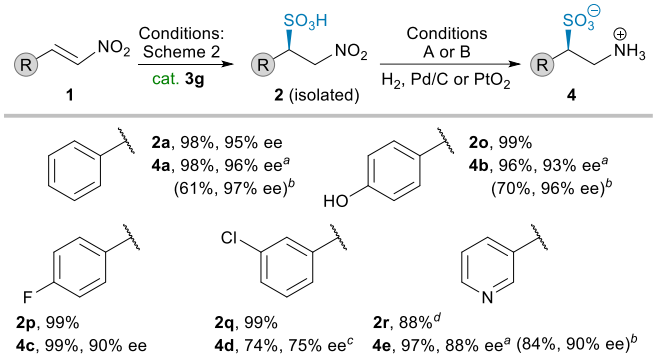
The identification of a suited organocatalyst (10 mol%) commenced by carrying out the sulfa-Michael reaction in toluene/MeOH at -10 °C (Scheme 2A).[18] The cinchona-derived Brønsted bases **3a**-**3d** turned out to be inefficient in our hand, giving the corresponding nitro sulfonic acid product **2a** in 2-17% enantiomeric excess (ee) after purification on a ion exchange sulfonic acid-based resin and a direct HPLC analysis (Scheme 2A).[19,20] Nonetheless, the bifunctional Takemoto catalyst **3e**, with a cyclohexane diamine backbone, furnished promising 37% ee in 99% yield (Scheme 2B).[21] The modification of the tertiary amine NR_2 allowed to improve the ee from 66% with a pyrrolidinyl moiety (**3f**, 92%) to 86% ee with the piperidyl-derived catalyst **3g** with an excellent 90% yield. Obviously, the thiourea part of catalyst **3g** was a more adapted hydrogen-bonding donor function than the analogous squaramide on **3h** (86% *versus* 61 % ee),[22] showing the subtle topology requirement of the employed catalyst for this sulfa-Michael reaction of bisulfite. With the catalyst **3g** in hands (Scheme 2C), the variation of conditions revealed that toluene/MeOH (Tol/MeOH: 1/3) was the most suited mixture of solvent, both for ee and solubility issues, and a decrease in temperature from -10 °C to -40 °C secured 95% ee with 99% yield albeit in a longer 36 hours of reaction (instead of 12h).[18] Eventually, a compromise was found with a catalyst **3g** loading of 15 mol% which furnished the nitro sulfonic acid product **2a** in 95% ee and 99% yield in a reasonable time of 15 hours.



Scheme 3. Scope and limitation in nitro sulfonic acid derivatives. Reaction conditions: nitrostyrene (0.25-0.5 mmol) in toluene/MeOH (1/3, 0.1 M) – Isolated yields after purification on Dowex 50WX8 and ee determined by HPLC. [a]Isolated after partitioning between water and CH_2Cl_2 layers and evaporation of the aqueous phase. [b]Precipitation from a MeOH/acetone/Et_2O solution.

We subsequently probed the scope and limitation of these novel enantioselective reaction conditions (24 hours, -40 °C) toward the synthesis of nitro sulfonic acid products **2** (Scheme 3). Pleasingly, the sulfa-Michael process took place efficiently (82-99% yields) on an array of aryl-substituted nitroalkenes **1a**-**1h** to afford the corresponding products **2a**-**h** with ees of 86-96% regardless the *ortho*-substitution (**2c**, 81%, 96% ee) or the

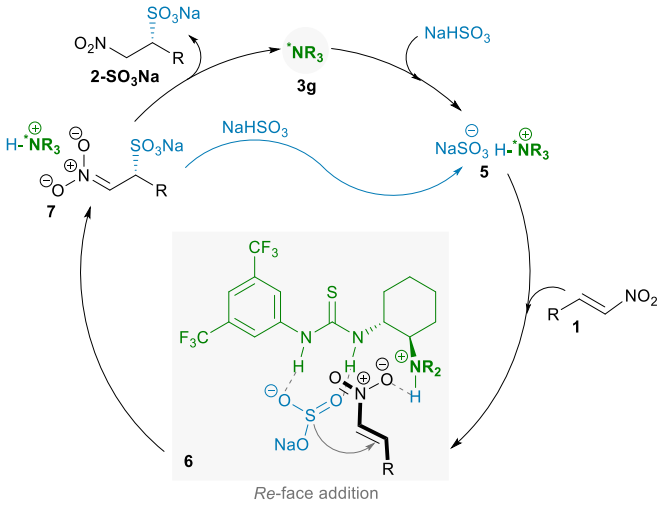
para-substitution by a methyl group (**2b**, 82%, 93% ee), an electron-rich OMe (**2d**, 99%, 95% ee) and even with electron-poor groups (**2e-2f**, 96%-99% and 86-93% ee respectively). The sterically more hindered naphtyl derivatives **2g**-**2h** (82-99%) were also successfully synthesized in 88-92% ee. The nitroalkenes flanked by a heterocycle moiety were transformed into the corresponding sulfonic derivatives **2i**-**2n** but with different outcomes. For instance, *N*-protected indole **2i** (94%, 81% ee), benzothiophene **2j** (99%, 76% ee) and thiophene **2k** (98%, 85% ee) derivatives were obtained with a slight decrease in ee (76-85%), but the furan product **2l** readily decomposed during purification on the acid resin Dowex 50WX8. However, by partitioning the reaction mixture between aqueous and organic layers, the furan-product **2l** was isolated as a sodium sulfonate salt with 91% yield and 87% ee. The enantiomeric excess of **2l** was improved to 94% ee after reprecipitation from a ternary MeOH/acetone/Et_2O solution with an overall 57% yield. The quinoline **2m** and pyrimidine **2n** adducts were synthesized with 88% ee (78% yield) and 84% ee (98% yield) respectively albeit these products were isolated as zwitterionic species, subsequent to the elution through the acid resin.



Scheme 4. Scope and limitation in taurine derivatives. Reaction conditions: nitrostyrene (0.5-1.5 mmol) in toluene/MeOH (1/3, 0.1 M). Isolated yields after purification on Dowex 50WX8 and ee measured by chiral HPLC. [a]**Conditions A** for reduction: H_2 (24 bar), Pd/C (10 mol%, 20% w/w), MeOH, 60 °C, 24 h. [b]Precipitation in MeOH allowing the isolation of the product in a solid form. [c]**Conditions B** for reduction: H_2 (35 bar), 5% PtO_2 (5 mol%), MeOH, 70 °C, 72 h. [d] Isolated after column on resin as a zwitterionic species.

At that stage, we faced two issues such as (1) the analysis of several nitro sulfonic acid products **2** proved to be challenging as long as no separation by chiral HPLC was obtained (compounds **2o**-**2r** in Scheme 4), and (2) the reduction of the NO_2 into NH_2 functional group had to be validated on enantiopure nitro-precursors **2** in order to open a route to non-racemic taurine derivatives. Pleasingly, the model nitro sulfonic acid **2a** with a phenyl pendant was reduced (H_2, 24 bars) in the presence of palladium on charcoal into the corresponding amino sulfonic acid **4a** in 98% yield and a preservation of the ee to 96% ee (Scheme 4). In that vein, the enantioselective sulfa-Michael and reduction sequence was applied to furnish the products flanked by a *para*-phenol (**4b**, 96%, 93% ee) or *para*-fluorophenyl moiety (**4c**, 99%, 90% ee) with successful measurement of ee by chiral HPLC. In similar sequence, but carrying out the reduction in the presence of PtO_2 instead of Pd/C, the construction of the *meta*-chlorophenyl derivative **4d** was allowed in 74% and 75% ee without any extensive cleavage of C-Cl bond. Additionally, the amino sulfonic acid **4e**, having a 2-pyridyl moiety, was obtained in 97% yield and good 86% ee. Interestingly, the compound **4a**, **4b** and **4e** could be obtained in a solid form after trituration in methanol solution with a slight decrease in yields but rather similar ee.

Based on recent mechanistic investigations,[23] we propose the Pápai's model to rationalize the asymmetric induction obtained with Takemoto type catalyst **3g** along the catalytic cycle depicted in Scheme 5.[23b] After the deprotonation event with the Brønsted base pendant of **3g**, giving the ion pair **5**, the sulfite anion is complexed by the thiourea moiety of the bifunctional catalyst.[24] Then, the tertiary ammonium part of the protonated catalyst **3g** assists (through hydrogen-bonding in the ternary complex **6**) the positioning of the *Re*-face of the nitroalkene electrophile **1** towards the incoming sulfite nucleophile. Finally, the protonation of the transient (*R*)-nitronate **7** would occur either by the tertiary ammonium salt in order to afford product **2-SO_3Na** while regenerate the catalyst **3g**, or by a molecule of bisulfite en route to another catalytic cycle though ion pair **5**.



Scheme 5. Proposed model of induction and catalytic cycle.

In conclusion, a straightforward two steps synthesis of valuable, enantioenriched and unprotected taurines -namely β-aminoethanesulfonic acid derivatives- was developed based on an efficient and unprecedented enantioselective organocatalytic sulfa-Michael of bisulfite to nitrostyrenes, followed by the direct hydrogenation of the nitro functional group. The exploitation of the newly accessible derivatives is currently under investigation in synthesis and catalysis.

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Conflicts of interest

There are no conflict to declare.

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18. See Supporting Information (SI) for further information.
19. The determination of the enantiomeric excess by HPLC or GC of chiral sulfonic acids is usually carried out after a required methylation reaction (see references 8-10 for instance). These methylation procedures were not satisfying in our hand on the nitro-derived sulfonic acid products and adapted while challenging chiral reversed-phase HPLC conditions were developed for the direct analysis of the obtained products.
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24. For an insightful discussion on the reactive monomeric *versus* the less-reactive dimeric form of bisulfite, and how both the dilution and an external base can influence these equilibriums in favor of the monomeric species, see reference 7b.

