Organocatalysis

DOI: 10.1002/anie.201406971

Catalytic Enantioselective Addition of Thioacids to Trisubstituted Nitroalkenes**

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Abstract: *The first example of a catalytic enantioselective addition to and nitronate protonation of trisubstituted nitroalkenes to produce highly enantioenriched products with a tetrasubstituted carbon is reported. Thioacids added in excellent yields and with high enantioselectivities to both activated and unactivated nitroalkenes. The 1,2-nitrothioacetate products can be readily converted in two steps to biomedically relevant 1,2-aminosulfonic acids without loss of enantiopurity.*

Catalytic enantioselective additions of numerous nucleophiles to nitroalkenes have been extensively studied and provide entry to many important enantioenriched compounds.[1] However, catalytic enantioselective additions to α-substituted nitroalkenes are much less common due to the difficulty in setting the α-stereocenter with high fidelity (Figure 1). These types of additions have primarily been investigated for α,β-disubstituted nitroalkenes in which the β-stereocenter has the potential to influence the stereochemistry of protonation at the α-site (Figure 1 a).[2] Recently, we reported the first and to date the only example of an enantioselective nitronate protonation with the catalytic enantioselective addition of Meldrum's acid to α-monosubstituted nitroalkenes (Figure 1 b).[3] Herein, we report the first example of a catalytic enantioselective addition and nitronate protonation for trisubstituted nitroalkenes to produce highly enantioenriched products with a tetrasubstituted carbon atom (Figure 1 c).[4] In particular, thioacids are added in high yields and with 86–96% *ee*, using 5 mol% of commercially available thiourea catalysts.[5] Moreover, the 1,2-nitrothioacetate products can readily be converted without any loss in stereochemical purity to enantioenriched 1,2-aminosulfonic acids, a structural motif found in natural products and drugs.[6]

We first evaluated conditions that we had previously developed for the addition of thioacetic acid to β-nitrostyrenes, namely, with *N*-trisylsulfinyl urea **4** (Figure 2) as the catalyst and cyclopentyl methyl ether (CPME) as the solvent.[7] Our study began with oxetane-containing nitroalkene **1a** because the oxetane ring is a motif utilized in medicinal chemistry to modulate drug properties.[8] Additionally, incorporating a strained ring facilitated the optimization process by increasing the reactivity of these fully substituted nitroalkenes. At −25 °C the reaction proceeded in high conversion but with poor enantioselectivity (Table 1, entry 1). By using catalyst **5**, which is the diastereomer of **4**,

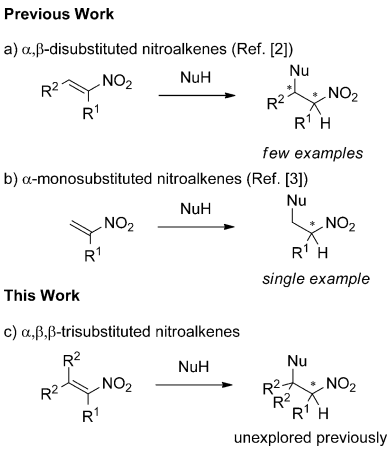
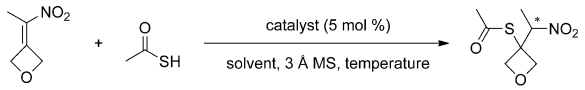


Figure 1. Enantioselective additions of α-substituted nitroalkenes.

Table 1: Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	*T* [°C]	Solvent	Catalyst	*ee* [%][b]
1	−25	CPME	**4**	18
2	−25	CPME	**5**	48
3	−78	CPME	**5**	52
4	−78	CPME	**7**	−44
5	−78	CPME	**6**	−90
6	−78	CPME	**8**	24
7	−78	CPME	**9**	72
8	−78	CPME	**10**	−90
9	−78	CPME	**11**	−90
10	−78	CPME	**12**	90
11[c]	−78	toluene	**6**	−88
12	−78	toluene	**12**	96
13	−78	toluene	**10**	−96
14[d]	−78	toluene	**12**	96
15[d,e]	−78	toluene	**12**	96

[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.10 mmol), 3 Å MS (20 mg) in 0.5 mL of solvent (0.1 M). Reactions run for 14–18 h and proceeded to >80% conversion. [b] Enantiomeric excess determined by HPLC of the crude reaction mixture on a chiral stationary phase. [c] 75% conversion. [d] Reaction conditions: **1a** (0.40 mmol), **2a** (0.80 mmol), 3 Å MS (250 mg) in 4 mL of solvent (0.1 M). [e] Run at 0.4 M.

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[**] NSF and Yale University are acknowledged for support of this work. We gratefully acknowledge Dr. Brandon Mercado for solving the crystal structures of **3i** and **3j**.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201406971.

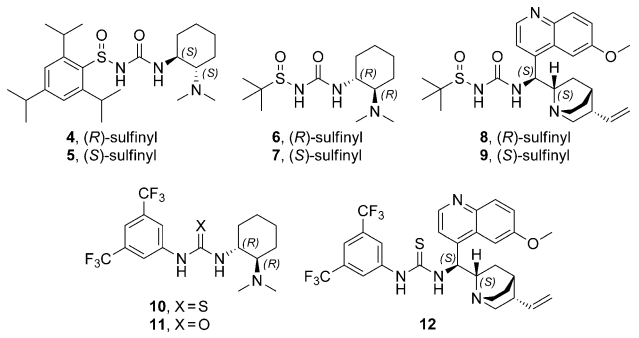


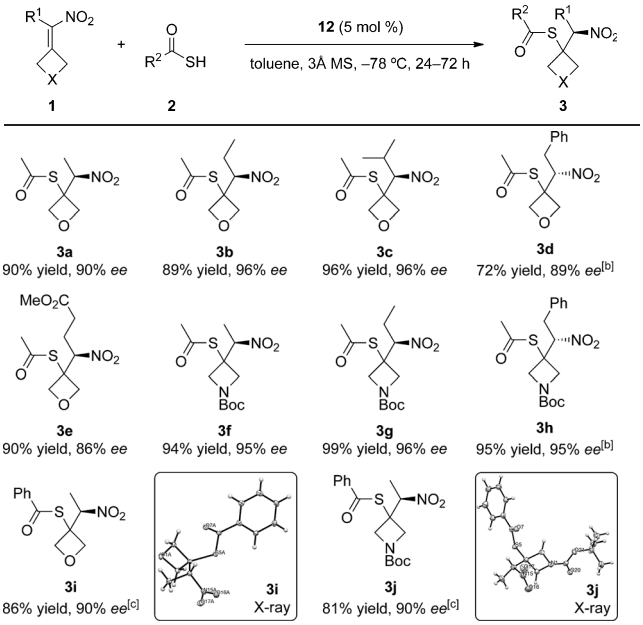
Figure 2. *N*-Sulfinyl and 3,5-bistrifluoromethylphenyl catalysts.

the enantioselectivity increased to 48% *ee* (entry 2). Lowering the temperature to −78 °C resulted in only a modest improvement of the enantioselectivity (entry 3). The corresponding *N*-*tert*-butanesulfinyl ureas **6** and **7** were tested (entries 4 and 5), with **6** providing a dramatic improvement in the enantioselectivity to 90% (entry 5). Attempts to further improve the selectivity by replacing the *N*,*N*-dimethylcyclohexane-1,2-diamine motif with 9-amino(9-deoxy)epiquinine were unsuccessful for both catalyst diastereomers (entries 6 and 7). However, these catalysts did support the hypothesis that the diamine is the overriding stereodetermining element. Achiral urea substituents were therefore explored in place of the chiral *N*-sulfinyl group. Catalysts incorporating the privileged 3,5-bistrifluoromethylphenyl motif were comparable to catalyst **6**, giving **3a** in 90% *ee* (entries 8–10).[9] However, upon switching from CPME to toluene we observed a further increase in enantioselectivity to 96% *ee* for 3,5-bistrifluoromethylphenyl catalysts **10** and **12** (entries 12 and 13) but a drop in selectivity for **6** (entry 11).[9a,10] Further solvent screening did not improve the selectivity of the transformation (see Table S1 in the Supporting Information). The investigation of the reaction concentration revealed that the reaction preceded equally well at 0.1 or 0.4 M (entries 14 and 15).

Good substrate scope was observed for the addition of thioacetic acid to oxetane nitroalkenes (Table 2). High yields and enantioselectivities were achieved for methyl, ethyl, and isopropyl substrates (**3a**–**c**). Interestingly, when R^1 is a benzyl group, catalyst **12** furnishes **3d** in 62% *ee*, whereas catalyst **10** provides **3d** in 89% *ee*. Perhaps this difference in enantioselectivity is due to a deleterious aryl–aryl interaction between the quinolone motif of **12** and the benzyl side chain of **1d**. The reaction also proceeded well in the presence of a pendant methyl ester (**3e**). The catalytic enantioselective addition of thioacetic acid to *N*-Boc-azetidine nitroalkenes also proceeds in high yields and with excellent enantioselectivities (**3f**–**h**). As observed for the corresponding oxetane derivative, when R^1 is a benzyl group the enantioselectivity provided by catalyst **10** proved superior to that provided by catalyst **12** (**3h**).

This transformation is not limited to alkyl thioacids; thiobenzoic acid also adds in high yield and enantioselectivity to both oxetane and *N*-Boc-azetidine nitroalkenes (**3i** and **3j**). However, these reactions were conducted at 0.1 rather than 0.4 M due to the poor solubility of thiobenzoic acid in

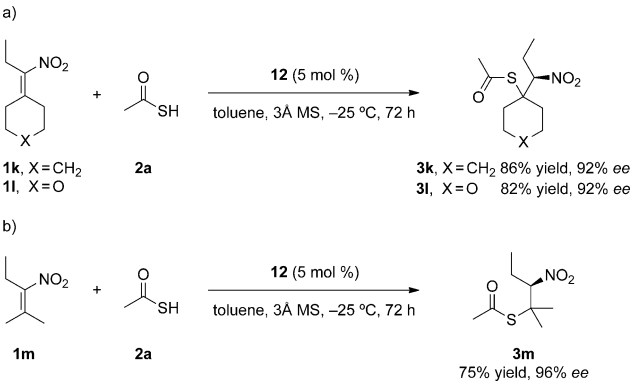
Table 2: The substrate scope for oxetane and azetidine nitroalkenes.[a]



[a] Reaction conditions: **1** (1 equiv), **2** (2 equiv), **12** (5 mol%), 3 Å MS (250 mg mmol^{-1}) in toluene (0.4 M). Yields are of isolated product after chromatography. Enantiomeric excess of isolated products was determined using HPLC analysis on a chiral stationary phase. [b] Reaction conducted using catalyst **10** (5 mol%). [c] Reaction run at 0.1 M.

toluene at −78 °C. The sense of induction for these addition reactions was rigorously established by X-ray structural characterization of crystalline **3i** and **3j**.[11] The reaction likely proceeds through *syn* thioacid addition and protonation through either urea hydrogen bonding of the nitroalkene or formation of a chiral thioacetate–catalyst salt (see the Supporting Information for additional details).

Oxetane and *N*-Boc-azetidine nitroalkenes **1** are activated for nucleophilic addition by the release of ring strain. We therefore also evaluated catalytic enantioselective thioacid additions to trisubstituted nitroalkenes lacking any ring strain (Scheme 1). Thioacetic acid did not add to cyclohexyl and pyranyl substrates **1k** and **1l**, respectively, at −78 °C, but good yields and high enantioselectivities were observed at −25 °C (Scheme 1a). Acyclic nitroalkene **1m** displayed a similar

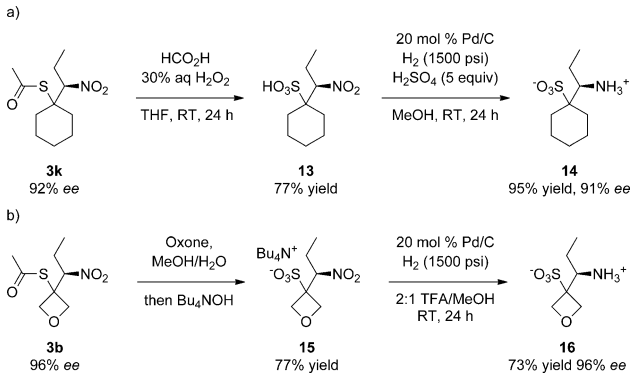


Scheme 1. Thioacetic acid additions to unstrained nitroalkenes.

reactivity to **1k** and **1l**, reacting smoothly with thioacetic acid at −25 °C to give **3m** with high enantioselectivity (Scheme 1b).

The enantiomerically enriched 1,2-nitrothioacetates serve as direct intermediates to the biomedically relevant class of 1,2-aminosulfonic acids, an important structural motif found in natural products and pharmaceuticals.[6] Although precedent exists for the conversion of 1,2-nitrothioacetates to 1,2-aminosulfonic acids, this transformation had not been previously conducted on sterically congested systems or in the presence of acid-sensitive functionalities as represented by the oxetane ring.[12]

We first explored the transformation of cyclohexyl nitrothioacetate **3k** to the corresponding 1,2-aminosulfonic acid **14** (Scheme 2a). Using performic acid generated in situ, **3k** was



Scheme 2. The transformation of 1,2-nitrothioacetates into 1,2-aminosulfonates.

effectively oxidized to nitrosulfonic acid **13** in 77% yield. Likely due to the sterically congested nature of the substrate, high pressure and acidic conditions were necessary to achieve the complete reduction to aminosulfonate **14**, which was isolated in 95% yield and with almost complete retention of enantiopurity.

The conversion of the more challenging oxetane nitrothioacetate **3b** to 1,2-aminosulfonic acid **16** required additional optimization (Scheme 2b). Whereas performic acid did oxidize the thioacetate in **3b** to the sulfonic acid, the acid-labile oxetane ring was unstable to the reaction conditions. Multiple alternative oxidants were examined with oxone cleanly oxidizing **3b** to the nitrosulfonic acid. Unfortunately, the strong inherent acidity of the product resulted in oxetane degradation upon attempted isolation. Salt metathesis was therefore performed to enable the isolation of the stable tetrabutylammonium salt **15**. Reduction of **15** to 1,2-aminosulfonic acid **16** was complicated by the presence of the tetrabutylammonium cation, but a 2:1 solvent mixture of trifluoroacetic acid and methanol enabled clean conversion to **16** in 73% yield without any loss of stereochemical purity.

In conclusion, we have developed a catalytic enantioselective addition of thioacids to trisubstituted nitroalkenes. This transformation constitutes the first example of a nucleophilic addition to a trisubstituted nitroalkene followed by enantioselective protonation. The methodology furnishes 1,2-nitrothioacetates in good yields and with high enantioselectivity for both activated and unactivated substrates. We have also demonstrated the utility of the addition products for the synthesis of highly substituted enantioenriched 1,2-aminosulfonic acids, an important class of bioactive compounds. The enantioselective catalytic addition of other nucleophiles to trisubstituted nitroalkenes will be reported in due course.

Experimental Section

Representative procedure: A flame dried 4 mL vial equipped with a stir bar and open top screw cap with a pierceable PTFE/silicone rubber septum was charged with nitroalkene (0.4 mmol, 1 equiv), catalyst **12** (12 mg, 0.020 mmol, 5 mol%), and 3 Å molecular sieves (100 mg). Under a static positive pressure of N_2, dry toluene (1.0 mL, [nitroalkene] = 0.40 M) was added to the vial and it was then placed in a prechilled cryo-cool bath. After equilibration of the mixture to −78 °C, neat thioacetic acid (60 μL, 0.85 mmol, 2 equiv) was injected all at once. The mixture was stirred for 24–72 h. Upon completion, the reaction was quenched at −78 °C by addition of 1 mL of 1% (v/v) trifluoroacetic acid in toluene. The crude reaction mixture was immediately eluted through a silica plug with ethyl acetate and the resulting solution was concentrated in vacuo. The crude product was purified by column chromatography and the enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Received: July 7, 2014
Published online: September 2, 2014

Keywords: asymmetric catalysis · michael addition · nitroalkene · organocatalysis

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