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Enantioselective Addition of Thioacetic Acid to Nitroalkenes via *N*-Sulfinyl Urea Organocatalysis

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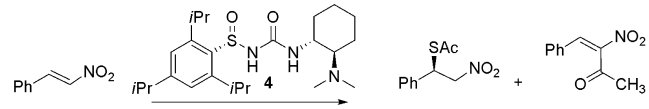
Asymmetric hydrogen-bonding organocatalysis is a burgeoning field of exploration in organic chemistry.[1] *N*-Sulfinyl ureas have recently emerged as a successful new class of hydrogen-bonding organocatalysts, in which the sulfinyl group can serve as an easily tunable, chiral acidifying group.[2] The sulfinyl moiety offers a potential advantage over other acidifying groups in achieving sufficient steric demand while simultaneously introducing chirality and good catalyst solubility in nonpolar solvents. The utility of *N*-sulfinyl urea catalysts has recently been demonstrated for the aza-Henry reaction with enantioselectivities of 93−96% for a variety of aryl and alkyl *N*-Boc imine substrates.[2a] To expand the scope of *N*-sulfinyl urea catalysis, we chose to explore thioacetic acid additions to nitroalkenes, where the only previous report[4a] gave enantioselectivities ranging from 20 to 70% using Takemoto's thiourea organocatalyst **9**.[3−5] Notably, nitroalkene thioacid addition products are versatile intermediates for the preparation of 1,2-aminothiol derivatives, which are prevalent in biologically active compounds such as penicillamine, penicillin, biotin, and sulconazole, a clinically used azole antifungal drug.[6] Herein we report that appropriately substituted *N*-sulfinyl ureas catalyze the enantioselective addition of thioacetic acid to a variety of nitroalkenes with selectivities up to 96% ee and further demonstrate application of the method to the first asymmetric synthesis of sulconazole.

In an initial catalyst screen, the *N*-trisylsulfinyl urea **4** was identified as the most selective catalyst, promoting the addition of thioacetic acid to *trans*-*β*-nitrostyrene (**1a**) with 87% ee in cyclopentyl methyl ether (CPME) at −78 °C (Table 1, entry 1). At this temperature no background reaction is observed; however, ∼30% of byproduct **3** is produced. To minimize the production of **3**, which could arise via a Baylis−Hilman type mechanism, the catalyst loading, substrate concentration, and equivalents of thioacetic acid were optimized (Table 1). As expected, byproduct formation was inhibited by lower reaction concentrations (entry 2), smaller excess of thioacetic acid (entries 3 and 4), and increased catalyst loading (entry 5). Under optimized conditions, the desired product was formed in 82% yield with 90% ee with only 6% of byproduct **3** being produced (entry 7).

The thioacetic acid addition reaction was evaluated with a range of urea catalysts (Table 2, Figure 1). The *N*-trisylsulfinyl urea diastereomer **5** (entry 2), the *N*-trisylsulfonyl urea **6**, and both diastereomers **7** and **8** of the corresponding *N*-*tert*-butanesulfinyl urea resulted in lower selectivities. Sulfinyl urea **4** was then compared with Takemoto's catalysts **9** and **10**, which contain the achiral *N*-3,5-bis(trifluoromethyl)phenyl group and have proven to be very effective catalysts for a number of transformations.[5,7] Thiourea **9** resulted in a dramatic decrease in selectivity, and urea **10** resulted in only moderate enantioselectivity and poor conversion. Sulfinyl catalyst **4** appears to possess the ideal steric demand, acidity, and stereochemistry, whereas all other catalysts surveyed lack at least one of these essential characteristics.

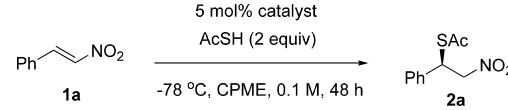
Table 1. Optimization of Thioacetic Acid Addition



entry	mol % catalyst	concn (M)	equiv of thioacid	ratio[a] **2a:1a:3**	ee[b] (%)
1	2.0	0.4	2.0	71:0:29	87
2	2.0	0.1	2.0	86:4:10	90
3	2.0	0.4	1.0	42:55:3	88
4	2.0	0.4	5.0	32:0:68	82
5	5.0	0.4	2.0	85:0:15	87
6	0.5	0.4	2.0	42:25:33	80
7	5.0	0.1	2.0	82:12:6	90

[a] Product ratios were determined by ^{1}H NMR analysis. [b] Enantiomeric excess was determined by chiral HPLC.

Table 2. Catalyst Screen Under Optimized Conditions



entry	catalyst	conv[a] (%)	ee[b] (%)
1	**4**	86	90
2	**5**	89	80[c]
3	**6**	99	53
4	**7**	99	46
5	**8**	99	50
6	**9**	99	32[c]
7	**10**	65	68

[a] Conversion was determined by ^{1}H NMR from the ratio of product to starting material. [b] Enantiomeric excess was determined by chiral HPLC. [c] Opposite enantiomer obtained as the major product.

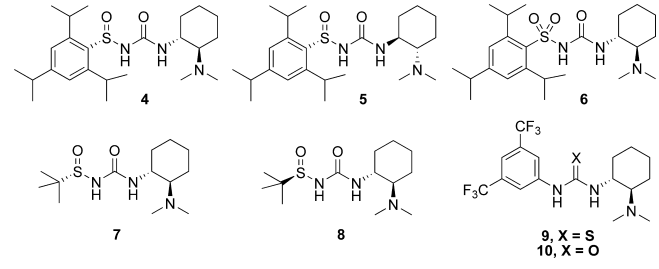


Figure 1. Catalysts tested in nitroalkene addition.

The scope of the reaction was then explored for both aromatic and aliphatic nitroalkenes (Table 3). Electronic variation via *para* substitution shows that more electron-deficient nitroalkenes (entries 2 and 3) provide a higher yield, while electron-rich derivatives provide higher enantioselectivities (entries 4 and 5). *Ortho* substitu-

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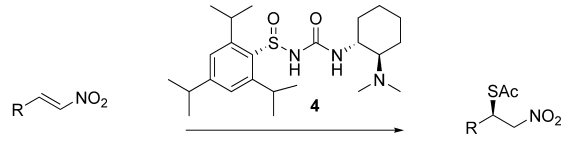
tion also results in an increase in enantioselectivity (entry 6). Significantly, *o*,*p*-dichloro-*trans*-β-nitrostyrene, which can be converted to sulconazole (vide infra), provides both high yield and enantioselectivity (entry 2). Aliphatic nitroalkenes also undergo the addition reaction in good yield for both linear (entries 7 and 8) and branched (entry 9) substrates, although with somewhat reduced enantioselectivity relative to the aryl substrates. The role of the configuration of the *N*-sulfinyl stereocenter in the urea catalyst is clearly complex because *N*-sulfinyl catalyst **5** provided the cyclohexyl product **2i** with higher selectivity (84% ee) than *N*-sulfinyl catalyst **4** (70% ee), which was the preferred catalyst for all other substrates (entries 1−8).

Table 3. Catalytic Enantioselective Addition of Thioacetic Acid to Aromatic and Aliphatic Nitroalkenes



1, R = aryl, alkyl — AcSH, CPME, -78 °C, 48 h[a] — **2**

entry	R	product	yield[b] (%)	ee[c] (%)
1	C_6H_5	**2a**	73	90
2	*o*,*p*-$Cl_2C_6H_3$	**2b**	84	96
3	*p*-$CF_3C_6H_4$	**2c**	88	85
4	*p*-MeC_6H_4	**2d**	65	91
5	*p*-$MeOC_6H_4$	**2e**	65	93
6	*o*-MeC_6H_4	**2f**	63	94
7	Me	**2g**	64	78
8	*n*-Pr	**2h**	82	80
9	*c*-Hex[d]	**2i**	95	84

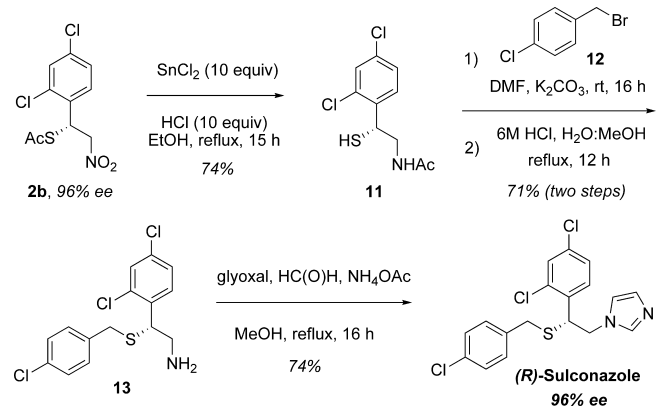
[a] Reactions were run with 5.0 mol % catalyst loading at 0.1 M concentration of substrate with 2.0 equiv of thioacetic acid. [b] Isolated yield of analytically pure material after chromatography. [c] Enantiomeric excess was determined by chiral HPLC. [d] Catalyst **5** was used and gave the enantiomer of **2**.

Our studies to date indicate that multiple factors contribute to asymmetric induction in sulfinyl urea catalysis, including the acidity, steric size, electronics, solubility, and stereochemistry of the catalyst. Based on mechanistic work by Takemoto and Jacobsen with similar organocatalytic systems, the reaction presumably proceeds with bifunctional organocatalysis, where the urea hydrogens activate the nitroalkene via hydrogen bonding while the pendant amine deprotonates thioacetic acid.[4a,5,7,8]

The utility of the method was next demonstrated by the first asymmetric synthesis of sulconazole from addition product **2b** in only four steps (Scheme 1). Reduction of the 1,2-nitrothiolate was unprecedented in the literature and is complicated by thiol poisoning of typical transition metal catalysts employed in nitro reduction. However, by using excess tin(II) chloride and anhydrous hydrochloric acid, reduction of **2b** was achieved with concomitant acyl transfer to the amine, providing thiol amide **11** in 74% yield. Alkylation of the unmasked thiol in **11** with benzyl bromide **12** followed by quantitative amide hydrolysis gave free amine **13** in 71% overall yield. Final condensation of amine **13** with glyoxal and formaldehyde[9] afforded *R*-sulconazole in 74% yield. The drug was synthesized in 96% ee and 32% overall yield for the five steps from β-nitrostyrene **1b**.

In conclusion, we have demonstrated that a sulfinyl urea organocatalyst promotes the first highly enantioselective addition of thioacetic acid to aromatic and aliphatic nitroalkenes. This reaction can serve as a general method for preparing chiral 1,2-aminothiols in compounds of pharmaceutical interest, as demonstrated by the expedient synthesis of *R*-sulconazole in 96% ee and good overall yield.

Scheme 1. Enantioselective Synthesis of (*R*)-Sulconazole



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Supporting Information Available: Complete experimental procedures, product characterization, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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