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Enantio- and diastereoselective addition of thioacetic acid to nitroalkenes via *N*-sulfinyl urea catalysis

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ABSTRACT

The enantioselective addition of thioacetic acid to nitroalkenes was achieved using *N*-sulfinyl urea catalysis. In this report, the scope of the reaction was extended to the enantio- and diastereoselective thioacetic acid addition to cyclic α,β-disubstituted nitroalkenes. Additionally, the role of the sulfinyl group was investigated by replacing it with a variety of aryl and sulfonyl groups. Of 15 urea catalysts synthesized and tested, none displayed comparable selectivity to the sulfinyl catalysts, highlighting the importance of the sulfinyl group in attaining high enantioselectivity in the thioacetic acid addition.

1. Introduction

Asymmetric hydrogen-bonding organocatalysis is a rapidly expanding field of organic chemistry, spanning a variety of catalytic systems, including chiral ureas and thioureas, cinchona alkaloids, squaramides, guanidines, diols, and phosphoric acids.[1] *N*-Sulfinyl ureas have recently emerged as a successful new class of hydrogen-bonding organocatalysts,[2] in which the sulfinyl group can serve as an easily tunable, chiral acidifying group.[3] 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 seminal report of *N*-sulfinyl urea catalysis was a highly enantio- and diastereoselective aza-Henry reaction, utilizing a *cis*-1,2-aminoindanol-derived *tert*-butanesulfinyl urea catalyst and achieving up to 96% ee and 97:3 diastereoselectivity.[2a] We then chose to use sulfinyl urea chemistry to explore asymmetric thioacetic acid additions to nitroalkenes, where the only previous report gave enantioselectivities ranging from 20 to 70% using Takemoto's thiourea organocatalyst **3**.[4–6] 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 penacillamine, penicillin, biotin, and sulconazole, a clinically used azole anti-fungal drug.[7]

Using a 1,2-cyclohexanediamine-derived triisopropylphenyl (trisyl) sulfinyl urea catalyst, we reported the first highly enantioselective addition of thioacetic acids to both aryl and alkyl nitroalkene substrates with up to 96% ee and 95% yield.[2b] Herein, we report the expansion of this work to cyclic nitroalkene substrates in which both an enantio- and diastereoselective process to set two stereocenters is achieved. Moreover, catalyst structure–activity relationships are defined to show that the sulfinyl moiety is an essential substituent for achieving a highly selective catalyst.

2. Results and discussion

Under optimized reaction conditions for the addition of thioacetic acid to *trans*-β-nitrostyrene, a variety of sulfinyl catalysts, as well as Takemoto's urea and thiourea catalysts, were evaluated for selectivity and catalytic activity (Table 1). In performing this catalyst screen, cyclopentyl methyl ether (CPME),[8] an increasingly popular industrial solvent, was employed because it provided the highest selectivity in an initial solvent screen.[2b] Takemoto's thiourea catalyst **3**, though highly active, gave low selectivity (32% ee), whereas the less acidic Takemoto urea catalyst **4** was less active and gave improved but still modest (68% ee) enantioselectivity. *tert*-Butanesulfinyl ureas **5** and **6** also were only moderately selective, but switching to the more sterically demanding trisyl sulfinyl ureas **7** and **8** brought the enantioselectivity up to 80 and 90% ee, respectively. Additionally, the more acidic and achiral trisyl *sulfonyl* group present in urea **9** gave diminished enantioselectivity as compared to the sulfinyl catalysts. Urea **8**, with a *syn* relationship between the sulfinyl and 1,2-diamine stereocenters, was identified as the optimal catalyst, affording the product in 90% ee and good conversion within 2 days at −78 °C.

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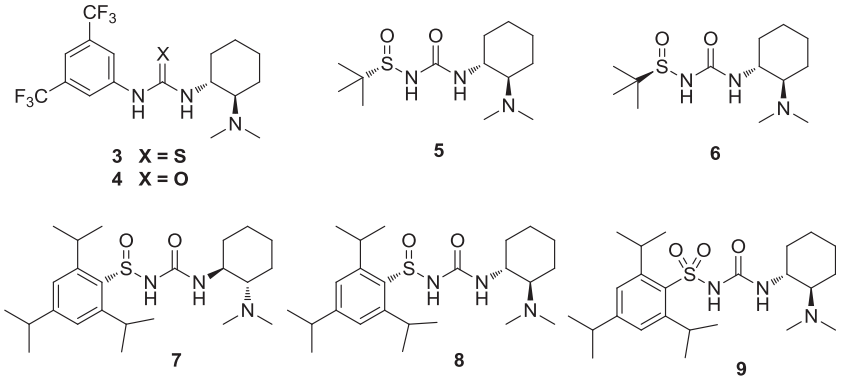
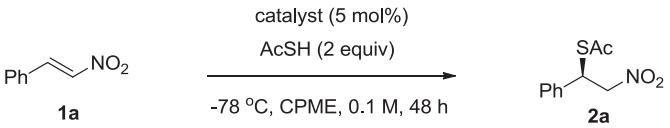


Table 1
Catalyst screen under optimized conditions



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

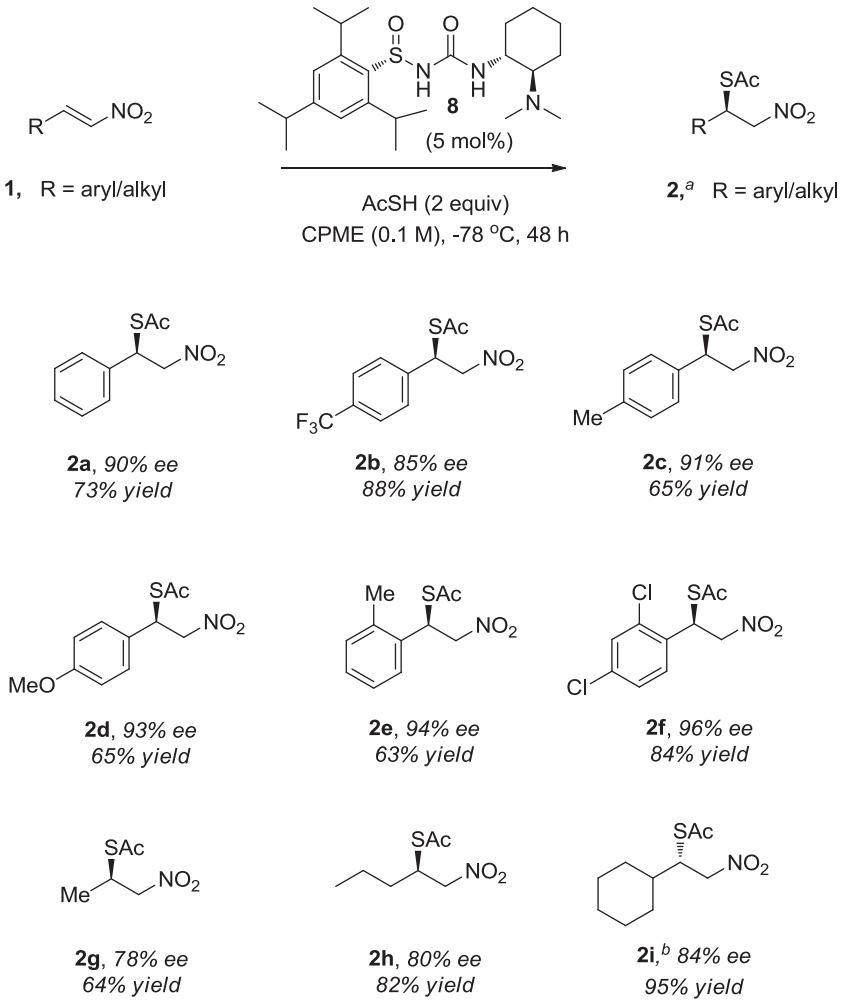
[a] Conversion was determined by ^{1}H NMR analysis based upon the ratio of product to starting material.
[b] Enantiomeric excess was determined by chiral HPLC analysis.
[c] Opposite enantiomer obtained as the major product.

Though seemingly simple, identifying conditions for the isolation of these compounds proved challenging. After aqueous extraction and purification by silica gel chromatography using hexanes/ethyl acetate as the eluent, the pure product was analyzed for enantiomeric excess. Much to our surprise, the observed enantiomeric purity after chromatography was <20% ee. Additionally, the isolated yield was very low (<30% yield). This raised the question of whether the enantiomeric purity determined on unpurified material was accurate or whether racemization and decomposition had in fact occurred during purification. We imagined that instability of the thioacid adducts could be causing the product to racemize during chromatographic purification. To probe the stability of the product toward various conditions, we devised an experiment wherein the crude product was partitioned and subjected to a 1% solution of mild base, mild acid, and strong acid, and then analyzed. Acetic acid exposure preserved the enantiomeric purity (90% ee), hydrochloric acid caused crystallization and enhanced enantiomeric purity (98% ee), and triethylamine caused complete racemization (0% ee) and partial decomposition to the starting nitroalkene. These results suggest that racemization and decomposition had occurred during chromatography through a process of base-promoted E_2 elimination of thioacetate, followed by partial nonselective re-addition. Due to the observed acid-stability of the products, chromatographic purification was modified through use of acetic acid buffered silica gel to enable straightforward and reliable isolation of pure product without racemization.

The scope of the reaction was then explored for both aromatic and aliphatic nitroalkenes (Scheme 1). The product of addition to *trans*-β-nitrostyrene was isolated in 90% ee and 73% yield. Electronic variation via *para* substitution shows that more electron-deficient nitroalkenes (products **2b** and **2f**) provide a higher yield, while electron-rich derivatives provide higher enantioselectivities (products **2c**–**e**).[9] *Ortho* substitution also results in an increase in enantioselectivity (product **2e**). Significantly, *o*,*p*-dichloro-*trans*-β-nitrostyrene, which can be converted to sulconazole (vide infra), provides both high yield and enantioselectivity (product **2f**). Aliphatic nitroalkenes also undergo the addition reaction in good yield for both linear (products **2g** and **2h**) and branched (product **2i**) 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 **7** provided the cyclohexyl product **2i** with higher selectivity (84% ee) than *N*-sulfinyl catalyst **8** (70% ee), which was the preferred catalyst for all other substrates (products **2a**–**h**).

In addition to the *trans*-β-substituted nitroalkenes discussed above, the enantioselective thioacetic acid addition can also be applied to the more complex α,β-disubstituted nitroalkenes (Scheme 2), in which two stereocenters are set in the addition reaction. Though the addition of thioacetic acid to nitrocyclohexene only proceeded in ~70% ee using sulfinyl catalyst **8**, diastereomeric sulfinyl catalyst **7** promoted the reaction in an impressive 94% ee (product **11a**). Additionally, the reaction was completely diastereoselective, affording exclusively the *trans*-addition product in 96% yield. Though variation of the substrate ring size tended to reduce the diastereoselectivity, both nitrocyclopentene (product **11b**) and nitrocycloheptene (product **11c**) underwent thioacetic acid addition with high enantioselectivities (93 and 86% ee, respectively) and good yields (80–82%). The thioacetic acid addition proceeds with high enantio- and diastereoselectivity for a variety of six-membered substrate analogs, including electron-deficient, electron-rich and sterically demanding 2-nitro-3,4-dihydronaphthalene substrates (85–90% ee, 95:5–97:3 dr, products **11d**–**g**). Additionally, the chemical yields are excellent for the entire range of substrates (96–98%). However, the acyclic substrate *trans*-β-methyl-β-nitrostyrene gave only modest (~2:1) diastereoselectivity, albeit with quite high enantioselectivity (94% ee, product **11h**).

While the sulfinyl stereochemistry is of critical importance for some transformations,[2c] for the enantioselective catalytic addition of thioacetic acid to nitroalkenes the impact of sulfinyl stereochemistry is clearly complex. Though catalysts **7** and **8** promote highly enantioselective additions for a broad variety of nitroalkene substrates, the role of sulfinyl stereochemistry is perplexing particularly because the preferred diastereomer of the catalyst seems to change somewhat randomly across substrates (see Scheme 1, products **2a**–**h** vs Scheme 1, product **2i** and Scheme 2, products **11**). Moreover, in some cases the sulfinyl stereochemistry of the catalyst seems to have a negligible effect (Table 1, entries 1 and 2). These

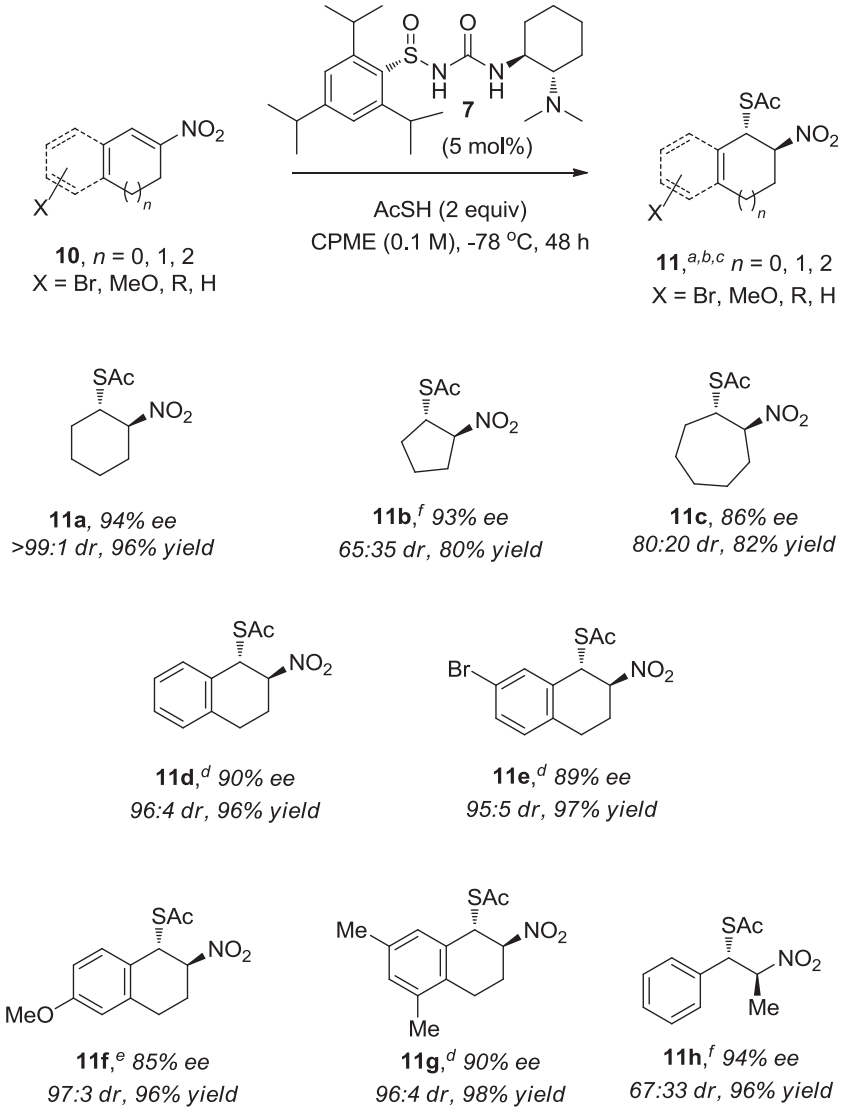


Scheme 1. Catalytic enantioselective addition of thioacetic acid to aromatic and aliphatic β-substituted nitroalkenes. [a]Isolated yield of analytically pure material after chromatography. [b]Catalyst **7** was used.

results prompted us to pose the question—does the catalyst require sulfinyl chirality at all or can the sulfinyl group be replaced with a simpler, more inexpensive *achiral* urea substituent with optimal steric and electronic properties?

To probe this question, a plethora of catalysts **12** that contain *achiral* replacements for the sulfinyl group, derived from readily available anilines or sulfonamides, were synthesized and tested in the enantioselective addition of thioacetic acid to *trans*-β-nitrostyrene (Table 2). These catalysts can be easily assembled using the standard carbonyldiimidazole-mediated coupling of the conserved 1,2-cyclohexanediamine component with a sulfinamide, sulfonamide or aniline input. Both aniline and sulfonamide-based catalysts were surveyed with a range of steric and electronic properties. It quickly became apparent that although catalytic efficiency was high for all catalysts surveyed, attaining high enantioselectivity was a more significant challenge. The benchmark for aniline-based catalysts, Takemoto's 3,4-bis(trifluoromethyl)phenyl urea **4** (Table 2, entry 1), afforded the product in 68% ee. The analogous 3,4-dinitrophenyl urea **12a** performed similarly, providing the adduct in 71% ee (entry 2). A variety of 2,4,6-trisubstituted aryl ureas **12b**–**e** were synthesized and surveyed and displayed overall mediocre selectivities (entries 3–6). Additionally, a few other types of highly activated scaffolds, such as the 2,6-dinitrophenyl urea **12f** (entry 7) and the pentafluorophenyl urea **12g** (entry 8), were also tested but displayed only moderate enantioselectivities. It should be noted that these catalysts span a broad range of urea acidities, from substantially less acidic than Takemoto's urea (entry 3) to more acidic (entry 7), but none outperformed Takemoto's catalyst. In addition, these catalysts span a range of steric properties, even up to the incredibly hindered 2,4,6-tri-*tert*-butylphenyl urea **12b**, but even this catalyst only provided 26% ee (entry 3).

Similarly to the aniline-based catalysts, sulfonamide-based catalysts spanning a range of acidities, steric profiles and substitution patterns were tested (Table 2). A range of substituted aryl sulfonamides with increasing acidity were surveyed, from the *p*-dimethylaminophenyl and *o*,*p*-dimethoxyphenyl sulfonyl ureas **12h** and **12i** with highly attenuated acidity (entries 9–10), to the *p*-methoxyphenyl sulfonyl urea **12j** (entry 11) of comparable acidity to a sulfinyl urea, to the more acidic sulfonyl ureas **12a**, and **12c**–**g** (entry 12). The electronic effect on catalyst selectivity adhered to a parabolic pattern rather than a linear trend, with the peak of selectivity corresponding to an intermediate acidity—that of the *p*-methoxyphenyl sulfonyl urea **12j** (68% ee, entry 11). Additionally, both 2,4,6-trisubstituted and 3,5-disubstituted aryl sulfonyl ureas of varying steric bulk were evaluated (entries 12–16). Among both the 2,4,6- and 3,5-substituted series, increasing the steric bulk of the sulfonamide increased the enantioselectivity, but only up to a maximum of 66% ee, with the original trisyl sulfonyl urea **9** as the best candidate (entry 14). Similarly, the *tert*-butylsulfonyl urea **12o**, with slightly attenuated acidity as compared to the aryl sulfonyl ureas but with similar steric bulk, did not surpass the benchmark



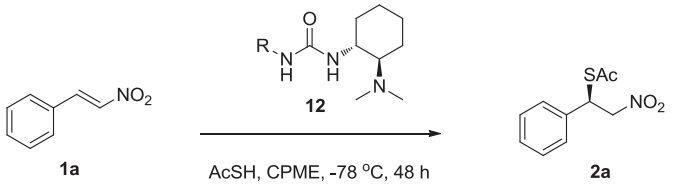
Scheme 2. Catalytic enantio- and diastereoselective addition of thioacetic acid to α,β-disubstituted nitroalkenes. [a]Isolated yield of analytically pure material after chromatography. [b]Diastereomeric ratios were determined by ^{1}H NMR and HPLC analysis. [c]Enantiomeric excess was determined by chiral HPLC analysis. [d]Reaction carried out at 0.4 M [**10**]. [e]Reaction performed using 5 equiv of thioacetic acid. [f]Reaction performed at 0.04 M [**10**] using 3 equiv of thioacetic acid.

68% ee of Takemoto's catalyst (entry 17). Despite several of these catalysts exhibiting similar steric bulk and acidity to trisyl *sulfinyl* urea **8**, none achieved selectivity even remotely close to the enantioselectivity of catalyst **8** (90% ee).

Our studies to date therefore 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.[4,5,10,11]

The utility of this process was also demonstrated for pharmaceutical applications. Upon examining the structures of a number of commercial drugs, it occurred to us that the backbone of the anti-fungal drug sulconazole[6] bears a striking resemblance to our thioacetic acid addition product. Conceptually, sulconazole appeared to be a derivative of our product in which the thioacid is converted into a benzyl thioester and the nitro group is converted into an imidazole moiety. Practically, these manipulations turned out to be quite feasible, enabling us to achieve the first asymmetric synthesis of sulconazole from addition product **2b** in only four steps (Scheme 3). 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 **13** in 74% yield. Additionally, it should be noted that the nitro reduction was accomplished with complete preservation of enantiomeric purity, a concern that had been raised during initial isolation issues (vide supra), but was expected to be mitigated by the acid-stability of the product. Acetyl protection of the amine, which occurred spontaneously upon reduction, was a convenient strategy to ensure complete chemoselectivity in the alkylation of the newly unmasked thiol. Alkylation with benzyl bromide **14** followed by quantitative amide hydrolysis gave free amine **15** in 71% overall yield. Final condensation of amine **15** with glyoxal and formaldehyde[12] afforded *R*-sulconazole in 74% yield. The drug was synthesized in 32% overall yield for the five steps and with 96% ee from β-nitrostyrene **1b**.

Table 2
Catalyst structure–activity relationship study



Entry	Catalyst	R	Conv[a,b] (%)	ee[c] (%)
1	**4**	3,5-$(CF_3)_2$Ph	65	68
2	**12a**	3,5-$(NO_2)_2$Ph	54	71
3	**12b**	2,4,6-*t*-Bu_3Ph	88	26
4	**12c**	4-NO_2–2,6-Cl_2Ph	34	53
5	**12d**	4-NO_2–2,6-Br_2Ph	92	52
6	**12e**	4-CF_3–2,6-Br_2Ph	97	46
7	**12f**	2,6-$(NO_2)_2$Ph	71	12
8	**12g**	C_6F_5	49	54
9	**12h**	SO_2(4-NMe_2Ph)	93	59
10	**12i**	SO_2(2,4-MeO_2Ph)	82	44
11	**12j**	SO_2(4-MeOPh)	88	68
12	**12k**	Ts	73	48
13	**12l**	SO_2Mes	98	62
14	**9**	SO_2Trisyl	97	66
15	**12m**	SO_2(3,5-Me_2Ph)	86	44
16	**12n**	SO_2(3,5-*t*-Bu_2Ph)	99	60
17	**12o**	SO_2*t*Bu	94	66

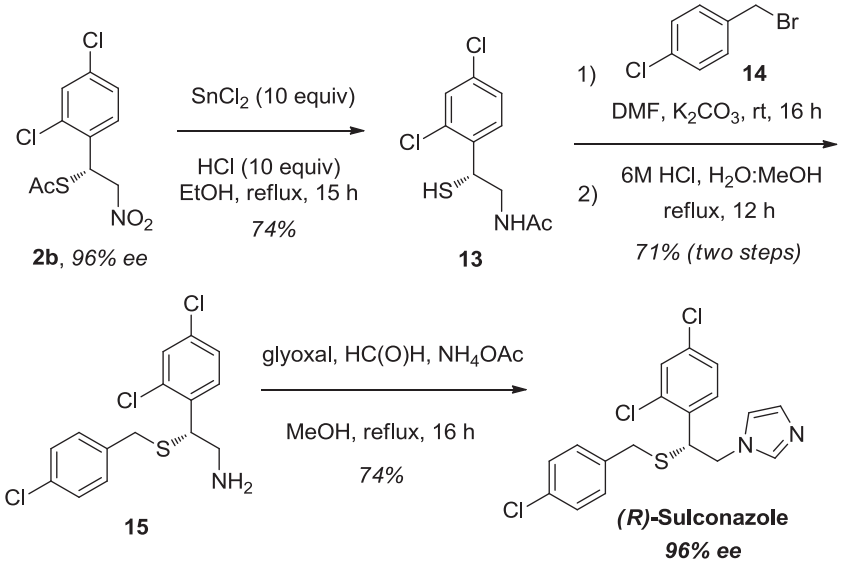
[a] Reactions were performed with 5.0 mol % of catalyst loading at 0.1 M concentration of substrate with 2.0 equiv of thioacetic acid.
[b] Conversion was determined by ^{1}H NMR analysis.
[c] Enantiomeric excess was determined by chiral HPLC analysis.

expansive structure–activity relationship study of urea catalysts, we have shown that a sulfinyl group is a key component in the catalyst that enables high enantioselectivities. Current work is devoted to the further development of hydrogen-bonding catalysts that rely on the N-sulfinyl urea motif to attain the optimal electronic, steric and stereochemical profile for efficient and selective catalysis.

4. Experimental section

4.1. General experimental

Unless otherwise noted, all reactions were carried out in flame dried glassware under inert nitrogen atmosphere. All reagents were obtained from commercial suppliers and used without further purification unless otherwise noted. Tetrahydrofuran (THF), ether, methylene chloride (CH_2Cl_2) and dioxane were passed though columns of activated alumina under nitrogen pressure immediately prior to use. Cyclopentyl methyl ether (CPME) was distilled over finely cut elemental sodium, re-distilled under inert atmosphere over benzophenone ketyl into an oven-dried Schlenk tube, then freeze-pump-thawed and stored in the glove box. All urea catalysts were dried under high vacuum over fresh P_2O_5 overnight prior to use. Thioacetic acid was distilled under inert atmosphere. Dry potassium hydride was stored and weighed under inert atmosphere in the glove box. Takemoto catalysts **3** and **4**,[11] diamine ***S*-1**,[13] triisopropylbenzene sulfonamide,[14] and triisopropylbenzene sulfinamide[2b,15,16] were prepared according to literature procedure.

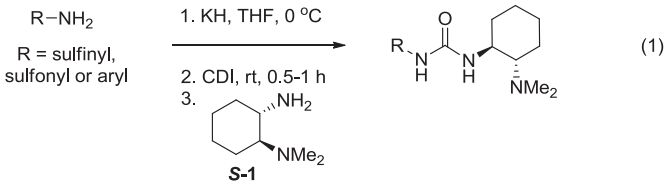


Scheme 3. Enantioselective synthesis of (*R*)-sulconazole.

3. Conclusion

In conclusion, we have demonstrated that a sulfinyl urea organocatalyst promotes the first highly enantioselective addition of thioacetic acid to aromatic and aliphatic β-substituted nitroalkenes as well as a range of cyclic nitroalkenes to introduce two stereocenters. 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. Furthermore, through an

Experimental procedures and full analytical data for compounds **2**, **5**–**9**, and **13**–**15** have been previously reported.[2b] Reactions were monitored by thin layer chomatography (TLC) and visualized with ultraviolet light and ninhydrin or potassium permanganate stains. Unless otherwise noted, ^{1}H and ^{13}C{^{1}H} NMR chemical shifts are reported in parts per million relative to either the residual solvent peak (^{1}H, ^{13}C) or TMS (^{1}H) as an internal standard. IR spectra were recorded on an FTIR spectrometer equipped with an attenuated total reflectance accessory as thin films on a KBr beamsplitter, and only partial data are listed.



(1)

4.2. General procedure for the preparation of ureas from sulfinamides, sulfonamides or anilines (Eq. 1)

A suspension of potassium hydride (3 equiv) in THF (0.6 M) was cooled in an ice-water bath. A solution of sulfonamide, sulfonamide or aniline (1.0 equiv) in THF (0.20 M) was added dropwise, and the suspension was stirred for 15 min. 1,1′-Carbonyldiimidazole (1.0 equiv) was dissolved in 1:1 THF/dioxane (0.20 M) and added dropwise to the reaction mixture, resulting in the formation of a white precipitate. The ice-water bath was removed, and the reaction mixture was allowed to warm to ambient temperature and was stirred for 2 h. A solution of diamine ***S*-1** (1.0 equiv) in THF (1.0 M) was added dropwise, and the suspension was stirred at room temperature for 20 h. The reaction was quenched with a solution of acetic acid (3 equiv) in THF (1.0 M). The crude product was concentrated in vacuo and purified by silica gel chromatography.

*4.2.1. Urea **12a** (Table 2).* The general procedure (B) was followed using 3,5-dinitroaniline (183 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*S*,*S*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12a** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12a** was isolated as a yellow powder (265 mg, 75% yield), mp 109 °C. IR: 2936, 2863, 1674, 1532, 1472, 1335, 1260, 1207, 1067, 892, 726 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 8.70 (d, J=2.0 Hz, 2H), 8.53 (t, J=2.0 Hz, 1H), 3.61 (td, J=10.7, 4.0 Hz, 1H), 2.53–2.40 (m, 1H), 2.34 (s, 6H), 2.26 (m, 1H), 1.96 (m, 1H), 1.87 (m, 1H), 1.79–1.71 (m, 1H), 1.41–1.24 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.2, 150.6, 144.6, 118.7, 111.9, 68.2, 52.7, 40.9, 35.2, 26.6, 26.4, 23.7. HRMS (ESI) calcd for $C_{15}H_{21}N_5O_5$ $[MH]^+$ 352.16155; found 352.16150.

*4.2.2. Urea **12b** (Table 2).* The general procedure (B) was followed using 2,4,6-tri-*tert*-butylaniline (120 mg, 0.460 mmol), potassium hydride (56 mg, 1.4 mmol), 1,1′-carbonyldiimidazole (74 mg, 0.46 mmol), and (*R*,*R*)-diamine ***S*-1** (65 mg, 0.46 mmol). Urea **12b** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12b** was isolated as a white powder (47 mg, 24% yield), mp 190 °C. IR: 3178, 2930, 2863, 2781, 1661, 1510, 1477, 1362, 1341, 1267, 1241, 811, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 2H), 5.60 (br s, 1H), 4.67 (br s, 1H), 3.19 (m, 1H), 2.71 (m, 1H), 2.05–1.79 (s, 6H), 1.78–1.65 (m, 2H), 1.59 (m, 1H), 1.44 (s, 9H), 1.43 (s, 9H), 1.34 (s, 9H), 1.25 (m, 2H), 1.16–1.03 (m, 2H), 0.94 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 149.5, 131.0, 123.3, 122.9, 66.7, 51.3, 40.1, 36.8, 36.6, 35.0, 32.7, 32.2, 32.0, 31.9, 31.5, 25.4, 24.4, 21.3. HRMS (ESI) calcd for $C_{27}H_{47}N_3O$ $[MH]^+$ 430.37919; found 430.37780.

*4.2.3. Urea **12c** (Table 2).* The general procedure (B) was followed using 2,6-dichloro-4-nitroaniline (140 mg, 0.676 mmol), potassium hydride (79 mg, 2.0 mmol), 1,1′-carbonyldiimidazole (110 mg, 0.679 mmol), and (*R*,*R*)-diamine ***S*-1** (96 mg, 0.676 mmol). Urea **12c** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12c** was isolated as a yellow powder (180 mg, 73% yield), mp 160 °C. IR: 2932, 2859, 2784, 1651, 1530, 1456, 1386, 1340, 1253, 1232, 811, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 5.66 (s, 1H), 3.49–3.25 (m, 1H), 2.32–2.12 (m, 2H), 2.22 (s, 6H), 1.89–1.78 (m, 1H), 1.78–1.69 (m, 1H), 1.64 (m, 1H), 1.27–1.01 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.0, 146.8, 142.0, 135.0, 125.1, 68.1, 53.2, 41.1, 35.4, 26.7, 26.4, 24.6. HRMS (ESI) calcd for $C_{15}H_{20}Cl_2N_4O_3$ $[MH]^+$ 375.09852; found 375.09817.

*4.2.4. Urea **12d** (Table 2).* The general procedure (B) was followed using 2,6-dibromo-4-nitroaniline (296 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12d** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12d** was isolated as a yellow powder (373 mg, 80% yield), mp 104 °C. IR: 2931, 2858, 2783, 1650, 1523, 1449, 1376, 1340, 1233, 738 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 8.49 (s, 2H), 3.70–3.48 (m, 1H), 2.43 (m, 1H), 2.38 (s, 6H), 2.23 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 1.38–1.22 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.0, 147.4, 144.5, 128.8, 125.1, 68.0, 53.2, 41.2, 35.5, 26.7, 26.4, 24.9. HRMS (ESI) calcd for $C_{15}H_{20}Br_2N_4O_3$ $[MH]^+$ 464.99553; found 464.99497.

*4.2.5. Urea **12e** (Table 2).* The general procedure (B) was followed using 2,6-dibromo-4-(trifluoromethyl)aniline (319 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*S*,*S*)-diamine ***S*-1** (156 mg, 1.10 mmol). Urea **12e** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12e** was isolated as a white powder (360 mg, 74% yield), mp 180 °C. IR: 2933, 2859, 1645, 1538, 1392, 1312, 1267, 1234, 1163, 1127, 1096, 880, 738 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.94 (s, 2H), 3.57 (td, J=10.3, 3.8 Hz, 1H), 2.45–2.37 (m, 1H), 2.34 (s, 6H), 2.27–2.18 (m, 1H), 1.89 (m, 1H), 1.82 (m, 1H), 1.69 (m, 1H), 1.35–1.20 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 157.5, 142.1, 131.8 (q, J=135 Hz), 130.7 (q, J=15 Hz), 126.4, 124.3 (q, J=1085 Hz), 68.02, 53.13, 41.21, 35.60, 26.76, 26.42, 25.12. HRMS (ESI) calcd for $C_{16}H_{20}Br_2F_3N_3O$ $[MH]^+$ 487.99783; found 487.99633.

*4.2.6. Urea **12f** (Table 2).* The general procedure (B) was followed using 2,6-dinitroaniline (183 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12f** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12f** was isolated as an orange powder (257 mg, 81% yield), mp 110 °C. IR: 2934, 2860, 2787, 1668, 1532, 1478, 1344, 1298, 1236, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J=8.2 Hz, 2H), 7.10 (t, J=8.3 Hz, 1H), 6.08 (br s, 1H), 3.25 (td, J=10.5, 3.0 Hz, 1H), 2.33–2.17 (m, 2H), 2.14 (s, 6H), 1.78–1.61 (m, 2H), 1.51 (m, 1H), 1.07 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 156.0, 145.6, 131.4, 130.1, 124.3, 68.1, 52.9, 41.1, 35.6, 26.6, 26.5, 24.4. HRMS (ESI) calcd for $C_{15}H_{21}N_5O_5$ $[MH]^+$ 352.16155; found 352.16147.2

*4.2.7. Urea **12g** (Table 2).* The general procedure (B) was followed using pentafluoroaniline (147 mg, 0.803 mmol), potassium hydride (97 mg, 2.4 mmol), 1,1′-carbonyldiimidazole (131 mg, 0.808 mmol), and (*R*,*R*)-diamine ***S*-1** (115 mg, 0.810 mmol). Urea **12g** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12g** was isolated as a yellow powder (229 mg, 65% yield), mp 147 °C. IR: 2935, 2862, 1648, 1551, 1518, 1267, 1233, 1003, 975, 874, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (br s, 1H), 3.43 (m, 1H), 2.39 (td, J=10.9, 3.3 Hz, 1H), 2.28 (s, 6H), 2.18–2.16 (m, 1H), 1.84 (m, 1H), 1.81–1.70 (m, 1H), 1.65 (m, 1H), 1.27–1.03 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 162.9 (m), 157.8, 145.3 (dm, J=1000 Hz), 141.1 (dm, J=1000 Hz), 139.5 (dm, J=1000 Hz), 117.3 (m), 115.3 (m), 69.9, 51.4, 43.1, 38.1, 34.5, 25.9, 25.5, 24.6. HRMS (ESI) calcd for $C_{15}H_{18}F_5N_3O$ $[MH]^+$ 352.14428; found 352.14410.

*4.2.8. Urea **12h** (Table 2).* The general procedure (B) was followed using 4-(*N*,*N*-dimethyl)benzenesulfonamide (46 mg, 0.23 mmol),

potassium hydride (28 mg, 0.69 mmol), 1,1′-carbonyldiimidazole (37 mg, 0.23 mmol), and (*S*,*S*)-diamine ***S*-1** (33 mg, 0.23 mmol). Urea **12h** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12h** was isolated as a white powder (22 mg, 26% yield), mp 134 °C. IR: 2936, 2860, 1596, 1512, 1446, 1319, 1235, 1115, 1086, 867, 652 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.63 (d, J=8.8 Hz, 2H), 6.63 (d, J=9.0 Hz, 2H), 3.53 (m, 1H), 2.90 (s, 6H), 2.89 (m, 1H), 2.61 (s, 6H), 1.92 (m, 1H), 1.81 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H), 1.33 (m, 1H), 1.20 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 152.7, 130.7, 128.3, 128.3, 110.7, 69.3, 39.3, 33.0, 29.7, 29.6, 24.5, 24.2, 22.9. HRMS (ESI) calcd for $C_{17}H_{28}N_4O_3S$ $[MH]^+$ 369.19549; found 369.19533.

*4.2.9. Urea **12i** (Table 2).* The general procedure (B) was followed using 2,4-dimethoxybenzenesulfonamide (217 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*S*,*S*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12i** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12i** was isolated as a white solid (165 mg, 43% yield), mp 113 °C. IR: 3053, 2939, 2861, 1702, 1593, 1578, 1466, 1314, 1254, 1212, 1163, 1076, 1026, 732 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 7.86 (d, J=8.7 Hz, 1H), 6.65 (d, J=2.1 Hz, 1H), 6.61 (dd, J=8.8, 2.2 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.73 (s, 1H), 3.11 (td, J=11.8, 3.5 Hz, 1H), 2.78 (s, 6H), 2.06 (m, 1H), 1.90 (m, 2H), 1.74 (m, 1H), 1.46 (m, 1H), 1.35 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 165.8, 160.1, 159.7, 132.8, 124.0, 105.4, 100.2, 69.9, 56.7, 56.2, 54.8, 40.3, 34.1, 25.5, 25.2, 24.0. HRMS (ESI) calcd for $C_{17}H_{27}N_3O_5S$ $[MH]^+$ 386.17442; found 386.17427.

*4.2.10. Urea **12j** (Table 2).* The general procedure (B) was followed using 4-methoxybenzenesulfonamide (207 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12j** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12j** was isolated as a white solid (220 mg, 58% yield), mp 114 °C. IR: 2941, 2863, 1595, 1497, 1383, 1242, 1123, 1082, 1025, 729, 666 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.82 (d, J=8.7 Hz, 2H), 6.95 (d, J=8.8 Hz, 2H), 3.80 (s, 3H), 3.63 (m, 1H), 3.12 (td, J=11.9, 3.4 Hz, 1H), 2.72 (s, 6H), 1.99 (m, 1H), 1.81 (m, 2H), 1.65 (m, 1H), 1.45–1.21 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 163.2, 138.2, 129.8, 129.7, 114.5, 69.8, 56.1, 50.8, 40.3, 34.1, 25.6, 25.2, 24.1. HRMS (ESI) calcd for $C_{16}H_{25}N_3O_4S$ $[MH]^+$ 356.16385; found 356.16400.

*4.2.11. Urea **12k** (Table 2).* The general procedure (B) was followed using *p*-toluenesulfonamide (187 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12k** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12k** was isolated as a white solid (107 mg, 30% yield), mp 81 °C. IR: 2939, 2864, 1597, 1437, 1249, 1119, 1070, 869, 813, 729 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.89 (d, J=8.3 Hz, 2H), 7.42 (d, J=8.0 Hz, 2H), 3.81 (td, J=11.1, 4.3 Hz, 1H), 3.29–3.23 (m, 1H), 2.88 (s, 3H), 2.78 (s, 3H), 2.46 (s, 3H), 2.11 (m, 1H), 1.91 (m, 1H), 1.85–1.78 (m, 1H), 1.75 (m, 1H), 1.56–1.47 (m, 1H), 1.37 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 154.5, 146.4, 139.0, 131.1, 129.2, 69.7, 50.9, 43.3, 38.2, 34.3, 25.8, 25.4, 24.4, 21.9. HRMS (ESI) calcd for $C_{16}H_{25}N_3O_3S$ $[MH]^+$ 340.16894; found 340.16900.

*4.2.12. Urea **12l** (Table 2).* The general procedure (B) was followed using mesitylenesulfonamide (199 mg, 1.00 mmol), potassium hydride (120 mg, 3.00 mmol), 1,1′-carbonyldiimidazole (162 mg, 1.00 mmol), and (*R*,*R*)-diamine ***S*-1** (142 mg, 1.00 mmol). Urea **12l** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12l** was isolated as a white solid (92 mg, 25% yield), mp 108 °C. IR: 2936, 2861, 1702, 1601, 1450, 1379, 1339, 1236, 1112, 851, 658 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 6.92 (s, 2H), 3.62 (m, 1H), 3.00 (td, J=11.7, 2.8 Hz, 1H), 2.78 (s, 6H), 2.69 (s, 6H), 2.27 (s, 3H), 2.05 (m, 1H), 1.90 (m, 2H), 1.73 (m, 1H), 1.49–1.25 (m, 4H). ^{13}C NMR (101 MHz, MeOD) δ 162.9, 141.6, 141.6, 139.8, 132.2, 71.6, 70.5, 50.9, 40.4, 34.1, 25.6, 25.2, 24.0, 23.3, 20.9. HRMS (ESI) calcd for $C_{18}H_{29}N_3O_3S$ $[MH]^+$ 368.20024; found 368.20020.

*4.2.13. Urea **12m** (Table 2).* The general procedure (B) was followed using 3,5-dimethylbenzenesulfonamide (93 mg, 0.50 mmol), potassium hydride (60 mg, 1.5 mmol), 1,1′-carbonyldiimidazole (81 mg, 0.50 mmol), and (*S*,*S*)-diamine ***S*-1** (85 mg, 0.60 mmol). Urea **12m** was purified by reverse phase chromatography using a 43 g C18 column (95:5 H_2O/MeCN to 100% MeCN, 40 mL/min, λ=254, 210 nm). Product **12m** was isolated as a white powder (144 mg, 81% yield), mp 114–115 °C. IR: 3047, 2937, 2862, 1602, 1513, 1468, 1450, 1381, 1321, 1274, 1243, 1126, 1096, 886, 786 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ 7.54 (s, 2H), 7.14 (s, 1H), 3.67 (m, 1H), 3.19 (td, J=12.0, 3.5 Hz, 1H), 2.78 (s, 6H), 2.36 (s, 6H), 2.09–2.01 (m, 1H), 1.88 (m, 2H), 1.72 (m, 1H), 1.54–1.26 (m, 4H). ^{13}C NMR (126 MHz, MeOD) δ 163.7, 146.6, 139.7, 133.8, 125.8, 70.3, 51.2, 40.7, 34.6, 26.1, 25.6, 24.5, 21.8. HRMS (ESI) calcd for $C_{17}H_{27}O_3N_3S$ $[MH]^+$ 354.18459; found 354.18397.

*4.2.14. Urea **12n** (Table 2).* The general procedure (B) was followed using 3,5-di(*tert*-butyl)benzenesulfonamide (135 mg, 0.500 mmol), potassium hydride (60 mg, 1.5 mmol), 1,1′-carbonyldiimidazole (81 mg, 0.50 mmol), and (*S*,*S*)-diamine ***S*-1** (78 mg, 0.55 mmol). Urea **12n** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12n** was isolated as a white solid (106 mg, 48% yield), mp 132 °C. IR: 2955, 2865, 1702, 1595, 1517, 1476, 1394, 1364, 1322, 1245, 1097, 882, 734 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 2H), 7.60 (s, 1H), 3.71 (m, 1H), 3.19 (td, J=11.9, 3.4 Hz, 1H), 2.80 (s, 6H), 2.06 (m, 1H), 1.89 (m, 2H), 1.73 (m, 1H), 1.48–1.28 (m, 4H), 1.42 (s, 18H). ^{13}C NMR (126 MHz, MeOD) δ 163.3, 152.3, 145.6, 126.1, 121.9, 69.9, 50.8, 40.2, 36.0, 34.2, 31.8, 25.6, 25.2, 24.0. HRMS (ESI) calcd for $C_{23}H_{39}N_3O_3S$ $[MH]^+$ 438.27849; found 438.27807.

*4.2.15. Urea **12o** (Table 2).* The general procedure (B) was followed using *tert*-butanesulfonamide (126 mg, 0.920 mmol), potassium hydride (110 mg, 2.80 mmol), 1,1′-carbonyldiimidazole (149 mg, 0.920 mmol), and (*R*,*R*)-diamine ***S*-1** (131 mg, 0.923 mmol). Urea **12o** was purified by silica gel chromatography (90:9:1 CH_2Cl_2/MeOH/NH_4OH). Product **12o** was isolated as a white solid (211 mg, 75% yield), mp 189 °C. IR: 2933, 2862, 1705, 1585, 1514, 1478, 1450, 1388, 1324, 1282, 1216, 1132, 1091, 1066, 864 cm^{-1}. ^1H NMR (400 MHz, MeOD) δ 3.85–3.66 (m, 1H), 3.05 (m, 1H), 2.80 (s, 6H), 2.07 (m, 2H), 1.92 (m, 1H), 1.78 (m, 1H), 1.55–1.45 (m, 1H), 1.44–1.39 (s, 9H), 1.33 (m, 3H). ^{13}C NMR (126 MHz, MeOD) δ 162.3, 70.6, 60.2, 51.8, 40.7, 34.5, 26.1, 25.7, 25.5, 24.4. HRMS (ESI) calcd for $C_{13}H_{27}N_3O_3S$ $[MH]^+$ 306.18459; found 306.18450.

4.3. Representative procedure for racemic addition of thioacetic acid to *trans*-β-nitrostyrene

To a solution of *trans*-β-nitrostyrene (30 mg, 0.20 mmol) in diethyl ether (1.0 mL) was added one drop of triethylamine. The solution was cooled to −15 °C. Thioacetic acid (0.029 mL, 0.40 mmol) was added. The reaction mixture was stirred at −15 °C for 4 h, then quenched at that temperature by addition of saturated $NaHCO_{3(aq)}$ (1 mL). The mixture was then diluted with ether (2 mL) and washed with saturated $NaHCO_{3(aq)}$ (2×2 mL). The crude product was purified by silica gel chomatography (9:1 hexanes/EtOAc).

4.4. Representative procedure for enantioselective addition of thioacetic acid to *trans*-β-nitrostyrenes

A mixture of *trans*-β-nitrostyrene (30 mg, 0.20 mmol) and sulfinyl urea catalyst (0.010 mmol) in cyclopentyl methyl ether (2.0 mL) was cooled to −78 °C. Thioacetic acid (0.029 mL, 0.40 mmol) was added. The reaction mixture was stirred at −78 °C for 48 h, then quenched at that temperature by addition of saturated $NaHCO_{3(aq)}$ (1 mL). The mixture was then diluted with diethyl ether (1 mL) and allowed to warm with shaking until the aqueous layer was thawed. The layers were separated and the organic layer was washed quickly with saturated $NaHCO_{3(aq)}$ (3×1 mL). The crude ether solution was eluted immediately through a silica gel plug with diethyl ether. The resulting solution was concentrated in vacuo. The crude product was purified by silica gel chromatography (90:9:1 hexanes/EtOAc/AcOH). Enantiomeric excess was determined by chiral HPLC analysis.

4.4.1. trans-1-Thioacetyl-2-nitro-cyclohexane ***11a*** *(Scheme 2).* The general procedure was followed using *trans*-1-nitrocyclohexene (13 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol), and thioacetic acid (14 μL, 0.20 mmol) in cyclopentyl methyl ether (1 mL) to afford product **11a** (19 mg, 95% yield) with >99% diastereomeric purity as a colorless oil. IR: 2943, 2862, 1693, 1543, 1448, 1373, 1353, 1301, 1269, 1244, 1112, 999, 953, 911, 859, 758, 625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 4.66 (dt, J=7.9, 4.1 Hz, 1H), 4.25 (s, 1H), 2.33 (s, 3H), 2.09 (dd, J=8.4, 5.1 Hz, 3H), 1.88–1.79 (m, 1H), 1.74–1.56 (m, 3H), 1.52–1.42 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 85.2, 42.9, 30.6, 29.9, 28.8, 23.3, 21.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_8H_{13}NO_3S$, 226.05084; found, 226.05033. $[\alpha]_D^{20}$ −52.2 (c 1.0, $CHCl_3$). The ee was determined to be 94% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ=210 nm): t_R (**11a** major)=11.1 min, t_R (**11a** minor)=8.0 min.

4.4.2. 1-Thioacetyl-2-nitro-cyclopentane ***2l*** *(Scheme 2).* The general procedure was followed using *trans*-1-nitrocyclopentene (11 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol), and thioacetic acid (21 μL, 0.30 mmol) in cyclopentyl methyl ether (2.5 mL) to afford a 65:35 diastereomeric mixture of product **11b** (15 mg, 80% yield) as a colorless oil. IR: 2960, 1694, 1548, 1449, 1369, 1355, 1324, 1272, 1128, 955, 628 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (only peaks corresponding the the major isomer are listed) 5.12 (dd, J=9.0, 4.5 Hz, 1H), 4.81–4.77 (m, 1H), 4.28 (dd, J=12.5, 7.5 Hz, 1H), 3.90 (dt, J=14.0, 7.1 Hz, 1H), 2.41–2.22 (m, 6H), 2.13–2.06 (m, 1H), 2.01 (d, J=11.9 Hz, 1H), 1.84–1.68 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (peaks corresponding to both the major and minor diastereomers are listed) 195.1, 194.6, 91.6, 89.3, 46.6, 45.1, 32.5, 31.8, 31.3, 30.4, 30.4, 29.6, 24.2, 22.8. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_7H_{11}NO_3S$, 212.03519; found, 212.03510. The ee for the major diastereomer was determined to be 93% by chiral HPLC analysis (Chiralcel AD-H, hexane/isopropanol 97/3, 1.0 mL/min, λ=210 nm): t_R (**11b** major)=16.3 min, t_R (**11b** minor)=9.8 min.

4.4.3. 1-Thioacetyl-2-nitro-cycloheptane ***11c*** *(Scheme 2).* The general procedure was followed using *trans*-1-nitrocycloheptene (14 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol), and thioacetic acid (14 μL, 0.20 mmol) in cyclopentyl methyl ether (1 mL) to afford a 80:20 diastereomeric mixture of product **11c** (18 mg, 82% yield) as a colorless oil. IR: 2933, 2862, 1691, 1545, 1457, 1374, 1354, 1297, 1107, 953, 854, 771, 628 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (only peaks corresponding the the major isomer are listed) 4.89–4.78 (m, 1H), 4.72 (dd, J=11.8, 7.7 Hz, 1H), 4.25 (t, J=12.5 Hz, 1H), 2.36 (s, 3H), 2.26–2.15 (m, 2H), 1.92 (dd, J=16.3, 6.7 Hz, 1H), 1.82–1.68 (m, 3H), 1.67–1.56 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (peaks corresponding to both the major and minor diastereomers are listed) 194.2, 91.2, 89.1, 46.3, 45.3, 32.7, 32.5, 31.6, 30.9, 30.5, 28.3, 27.1, 26.6, 26.4, 23.5, 23.1. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_9H_{15}NO_3S$, 218.08454; found, 218.08447. The ee of the major diastereomer was determined to be 86% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 99/1, 1.0 mL/min, λ=210 nm): t_R (**11c** major)=17.3 min, t_R (**11c** minor)=10.5 min.

4.4.4. trans-1-Thioacetyl-2-nitro-3,4-dihydronaphthalene ***11d*** *(Scheme 2).* The general procedure was followed using *trans*-2-nitro-3,4-dihydronaphthalene (18 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol), and thioacetic acid (14 μL, 0.20 mmol) in cyclopentyl methyl ether (0.25 mL) to afford a 96:4 diastereomeric mixture of product **11d** (24 mg, 96% yield) as a colorless oil. IR: 2934, 2333, 1697, 1548, 1489, 1453, 1436, 1374, 1355, 1265, 1127, 952, 909, 729, 626 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 1H), 7.23 (t, J=3.5 Hz, 2H), 7.16–7.07 (m, 1H), 5.66 (d, J=4.3 Hz, 1H), 5.50 (t, J=5.8 Hz, 1H), 5.04 (ddd, J=10.7, 4.6, 3.2 Hz, 1H), 4.98–4.89 (m, 1H), 3.14–3.01 (m, 1H), 3.01–2.91 (m, 1H), 2.61–2.50 (m, 1H), 2.40 (s, 3H), 2.40–2.37 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 134.4, 134.3, 129.7, 129.2, 128.5, 127.6, 84.2, 44.9, 30.7, 27.2, 25.1. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{12}H_{13}NO_3S$, 252.06889; found, 252.06870. The ee of the major diastereomer was determined to be 90% by chiral HPLC analysis (Chiralcel AS-H, hexane/isopropanol 95/5, 1.0 mL/min, λ=210 nm): t_R (**11d** major)=25.4 min, t_R (**11d** minor)=17.6 min.

4.4.5. trans-1-Thioacetyl-2-nitro-3,4-dihydro-7-bromonaphthalene ***11e*** *(Scheme 2).* The general procedure was followed using *trans*-2-nitro-3,4-dihydro-7-bromonaphthalene (51 mg, 0.20 mmol), catalyst **7** (4.4 mg, 0.010 mmol), and thioacetic acid (29 μL, 0.40 mmol) in cyclopentyl methyl ether (0.5 mL) to afford a 95:5 diastereomeric mixture of product **11e** (64 mg, 98% yield) as a colorless oil. IR: 2939, 2326, 2084, 1695, 1591, 1546, 1480, 1435, 1373, 1354, 1265, 1149, 1125, 951, 733, 625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.30 (d, J=8.2 Hz, 1H), 6.95 (d, J=8.3 Hz, 1H), 5.51 (d, J=4.2 Hz, 1H), 5.05–4.89 (m, 1H), 2.94 (dt, J=17.3, 5.6 Hz, 1H), 2.88–2.77 (m, 1H), 2.49 (s, 1H), 2.41–2.28 (m, 1H), 2.38 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 136.4, 133.5, 132.2, 131.5, 130.8, 121.0, 84.0, 44.1, 30.8, 26.5, 25.2. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{12}H_{12}BrNO_3S$, 329.97940; found, 329.97937. The ee of the major diastereomer was determined to be 89% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 95/5, 1.0 mL/min, λ=210 nm): t_R (**11e** major)=14.8 min, t_R (**11e** minor)=11.1 min.

4.4.6. trans-1-Thioacetyl-2-nitro-3,4-dihydro-6-methoxynaphthalene ***11f*** *(Scheme 2).* The general procedure was followed using *trans*-2-nitro-3,4-dihydro-6-methoxynaphthalene (21 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol), and thioacetic acid (36 μL, 0.50 mmol) in cyclopentyl methyl ether (1 mL) to afford a 97:3 diastereomeric mixture of product **11f** (27 mg, 97% yield) as a yellow oil. IR: 2944, 2838, 2341, 1696, 1607, 1549, 1500, 1463, 1432, 1374, 1318, 1272, 1244, 1159, 1127, 1035, 951, 625 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J=8.6 Hz, 1H), 6.78 (d, J=8.4 Hz, 1H), 6.61 (s, 1H), 5.63 (d, J=4.1 Hz, 1H), 5.45 (m, 1H), 5.00 (dd, J=7.4, 3.7 Hz, 1H), 4.91 (s, 1H), 3.79 (s, 3H), 3.09–2.98 (m, 1H), 2.98–2.81 (m, 1H), 2.52 (dd, J=21.4, 15.3 Hz, 1H), 2.41–2.29 (m, 1H), 2.39 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.1, 159.2, 135.4, 130.6, 126.0, 113.8, 113.0, 83.9, 55.3, 44.3, 30.4, 27.2, 24.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{15}NO_3S$, 304.06140; found, 304.06163. The ee of the major diastereomer was determined to be 85% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 95/5, 1.0 mL/min, λ=210 nm): t_R (**11f** major)=17.9 min, t_R (**11f** minor)=13.9 min.

4.4.7. trans-1-Thioacetyl-2-nitro-3,4-dihydro-5,7-dimethylnaphthalene ***11g*** *(Scheme 2).* The general procedure was followed using *trans*-2-nitro-3,4-dihydro-5,7-dimethylnaphthalene (41 mg, 0.20 mmol), catalyst **7** (4.4 mg, 0.010 mmol), and thioacetic acid (29 μL, 0.40 mmol) in cyclopentyl methyl ether (0.5 mL) to afford a 96:4

diastereomeric mixture of product **11g** (50 mg, 90% yield) as a colorless oil. IR: 1698, 1549, 1482, 1432, 1375, 1355, 1265, 1125, 953, 908, 731, 702, 655, 624 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.90 (s, 1H), 5.60 (d, J=2.7 Hz, 1H), 5.03–4.88 (m, 1H), 4 2.87 (m, 1H), 2.73–2.60 (m, 1H), 2.60–2.52 (m, 1H), 2.34 (s, 3H), 2.30–2.24 (m, 1H), 2.24 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 137.1, 136.8, 134.3, 131.1, 129.9, 127.8, 83.9, 45.4, 30.8, 25.0, 24.8, 21.2, 19.9. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{17}NO_3S$, 280.10019; found, 280.10010. The ee of the major diastereomer was determined to be 90% by chiral HPLC analysis (Chiralcel IA, hexane/isopropanol 97/3, 1.0 mL/min, λ=210 nm): t_R (**11g** major)=12.1 min, t_R (**11g** minor)=8.9 min.

*4.4.8. 1-Thioacetyl-1-phenyl-2-nitropropane **11h** (Scheme 2).* The general procedure was followed using *trans*-β-methyl-β-nitrostyrene (16 mg, 0.10 mmol), catalyst **7** (2.2 mg, 0.0050 mmol), and thioacetic acid (21 μL, 0.30 mmol) in cyclopentyl methyl ether (2.5 mL) to afford a 67:33 diastereomeric mixture of product **11h** (23 mg, 96% yield) as a colorless oil. IR: 2941, 1696, 1549, 1492, 1451, 1386, 1356, 1293, 1124, 1094, 953, 864, 747, 698, 624 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ (peaks listed for both diastereomers) 7.34 (m, 5H), 5.17 (d, J=9.2 Hz, 0.67H), 5.14 (d, J=9.1 Hz, 0.33H), 5.05–4.95 (m, 1H), 2.40 (s, 2H), 2.35 (s, 1H), 1.71 (d, J=6.7 Hz, 2H), 1.51 (d, J=6.7 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ (peaks listed for both diastereomers) 192.4, 137.0, 129.1, 129.0, 128.6, 128.3, 128.0, 86.6, 86.1, 50.4, 50.3, 30.5, 30.5, 18.0, 17.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{13}NO_3S$, 262.05084; found, 262.05073. The ee of the major diastereomer was determined to be 94% by chiral HPLC analysis (Chiralcel AS-H, hexane/ethanol 98/2, 1.0 mL/min, λ=210 nm): t_R (**11h** major)=9.6 min, t_R (**11h** minor)=10.4 min.

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Supplementary data

Complete experimental procedures, product characterization, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.01.048.

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