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Catalytic Asymmetric 1,6-Michael Addition of Arylthiols to 3-Methyl-4-nitro-5-alkenyl-isoxazoles with Bifunctional Catalysts

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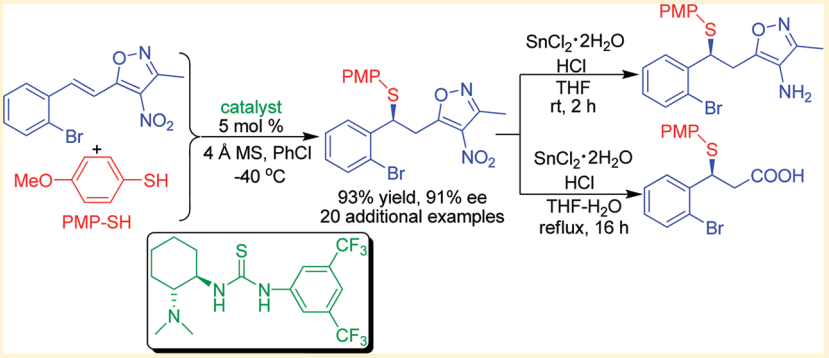
Supporting Information

ABSTRACT:



An enantioselective 1,6-Michael addition reaction of arylthiols to a wide range of 3-methyl-4-nitro-5-alkenyl-isoxazoles catalyzed by readily available Takemoto's thiourea catalyst has been developed. This reaction provides a useful catalytic method for the synthesis of optically active chiral sulfur compounds bearing a 4-nitroisoxazol-5-yl moiety in high to excellent yields (up to 97%) and high enantioselectivities (up to 91% ee). Significantly, the potential utilities of the protocol had been further demonstrated by gram-scale reaction and the versatile conversions of some resulting products into other functionalized and useful compounds.

INTRODUCTION

The optically active chiral thiols and sulfides are a key structural feature of several classes of pharmaceuticals and natural products and are extremely versatile building blocks that can undergo synthetically useful transformations,[1] as well as have very important applications in asymmetric synthesis serving as ligands for metal-based catalysts,[2] as catalysts themselves,[3] and as chiral auxiliaries.[3a,4] The catalytic asymmetric sulfa-Michael addition of thiols to electro-deficient olefins represents a straightforward and versatile approach toward such valuable optically active sulfur-containing compounds.[5] As a consequence of this, many different catalytic enantioselective versions of this fundamental transformation have been reported, which use metal-based chiral complex catalysts or organocatalysts.[6,7] However, to the best of our knowledge, the Michael acceptors have generally been limited to nitroolefins, enones, α,β-unsaturated aldehydes, α,β-unsaturated ketones, and carboxylic acid derivatives among all the reported methods. Moreover, the reported methods have also mainly focused on the conjugate addition of thiols to the β position (1,4-Michael addition) of electro-deficient olefins. In contrast, we are not aware of any method for catalytic enantioselective δ addition (1,6-Michael addition) of sulfur nucleophiles to electro-deficient olefins.[8] Accordingly, the development of efficient synthetic protocols for the 1,6-Michael addition of thiols to new electro-deficient Michael acceptors is highly desirable and particularly attractive.

As part of our research program relevant to the development of synthetic methods with asymmetric organocatalysis,[9] we recently developed a simple and efficient method for the enantioselective 1,6-Michael addition reaction of anthrone to a series of 3-methyl-4-nitro-5-alkenyl-isoxazoles with a bifunctional thiourea-tertiary amine as catalyst.[9i] 3-Methyl-4-nitro-5-alkenyl-isoxazoles, developed by Adamo and coworkers,[10] are able to be regarded as cinnamate equivalents that show high reactivity toward stabilized nucleophiles.[8,9i,11] Therefore, we take two facts into consideration: one is that 3-methyl-4-nitro-5-alkenyl-isoxazole compounds are very

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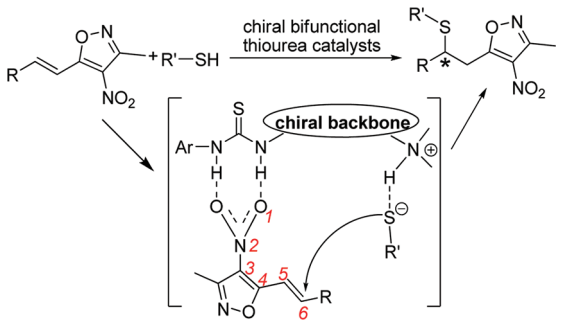
Scheme 1. Strategy of Bifunctional Thiourea-tertiary Amine Catalyzed 1,6-Michael Additions of Sulfur Nucleophiles to 3-Methyl-4-nitro-5-alkenyl-isoxazoles



attractive 1,6-Michael acceptors,[8,9i,11] and the other is that the nitro moiety of these compounds is a strong electro-withdrawing group that can be readily transformed into an amino group,[11d,12] and the 4-nitroisoxazol-5-yl core is able to be readily converted to a carboxylic acid group.[11a,13,14] Especially, based on the research that 3-methyl-4-nitro-5-alkenyl-isoxazoles have been successfully applied to the 1,6-Michael addition of various nucleophiles by us and Adamo,[8,9i,11] we envisaged that the corresponding 1,6-Michael addition of sulfur nucleophiles might be readily accessed by the bifunctional thiourea-tertiary amine catalysts with the synergistic cooperative activation of the nucleophilic thiols and electrophilic 3-methyl-4-nitro-5-alkenyl-isoxazoles (Scheme 1). Herein, we present our results on the organocatalytic asymmetric 1,6-Michael addition reaction of arylthiols to 3-methyl-4-nitro-5-alkenyl-isoxazoles, leading to a new array of enantioenriched sulfur-containing compounds in high to excellent yields (up to 97%) and high enantioselectivities (up to 91% ee), and further on the versatile conversions of the resulting adducts into other functionalized compounds.

RESULTS AND DISCUSSION

Initially, the DABCO-catalyzed test reaction between benzenethiol (**2a**) and (*E*)-3-methyl-4-nitro-5-styrylisoxazole (**3a**) was conducted in CH_2Cl_2 at room temperature. It is pertinent to note that the reaction proceeded smoothly to completion even in 5 min for delivering the desired product **4a** in quantitative yield. Encouraged by this preliminary reaction, the corresponding asymmetric version of the same reaction was promptly investigated at room temperature with readily available Takemoto's thiourea catalyst **1a**. Gratifyingly, compound **4a** could also be produced in quantitative yield within 5 min but with only 4% ee (Table 1, entry 1). After detailed analysis, we thought that the unduly high reaction activity was unfavorable to the asymmetric induction of catalyst **1a**. Therefore, the reaction was carried out at −30 °C and still gave **4a** in 92% yield with 50% ee after 8 h (Table 1, entry 2). To our delight, the enantioselectivity could be further improved to 72% by adding 100 mg of activated 4 Å molecular sieves (MS) as additive (Table 1, entry 3).[15] The most likely reason for this was that the 4 Å molecular sieves were able to remove the trace amount of residual water in the reaction system because we found that the dried solvent was of paramount importance for the enantioselectivity. Subsequently, some other chiral bifunctional thiourea-tertiary amine catalysts **1b**−**k** with diversely structured scaffold were further investigated under the same reaction conditions (Table 1, entries 4−13).[16] It was found that the thiourea catalysts **1a**−**c** and **1g** derived from cyclohexane-diamine showed high catalytic activity but poor stereochemical induction with **1b**−**c** and **1g** (Table 1, entries 4, 5, and 9) and good enantioselectivity with **1a** (Table 1, entry 3). Meanwhile, catalysts **1d**−**f** possessing a chiral 1,2-diphenylethylene-diamine (DPEN) skeleton showed lower catalytic activity than catalysts bearing a cyclohexane-diamine skeleton and induced particularly low enantioselectivities (Table 1, entries 6−8). In particular, catalysts **1e** and **1f** including a pyrrolidine ring gave the Michael adduct as a nearly racemic mixture (Table 1, entries 7−8). Additionally, thiourea cinchona alkaloid catalysts **1h**−**k** were also demonstrated to be inferior to **1a** in regard to enantioselectivity (Table 1, entries 10−13 vs entry 3); among them, reaction with **1h** as catalyst generated the product also as a nearly racemic mixture, and the exact reason for this was unclear (Table 1, entry 10). Consequently, via the various thiourea catalysts probed, catalyst **1a** was demonstrated to be the superior one in regard to the enantioselectivity (Table 1, entry 3).

Having identified the readily available Takemoto's thiourea catalyst **1a** as the best one among the catalysts probed, optimization of other reaction conditions for the process was carried out next. First, the effect of solvent on the 1,6-Michael addition reactions was examined (Table 1, entries 14−18), and it was found that the use of chlorobenzene as a reaction medium was superior to others.[15] In this solvent, the highest enantioselectivity (81% ee) was obtained (Table 1, entry 18). Afterward, the effects of catalyst loading (Table 1, entries 19−20) and substrate concentration (Table 1, entries 21−22) on the process were determined. Evidently, the optimal results could be obtained with 10 mol % of catalyst **1a** for 0.1 mmol of **3a** in 3.0 mL of solvent. Finally, we found that the amount of 4 Å molecular sieves had significant influence on the yield and enantioselectivity (Table 1, entries 23−24). Notably, when the reaction was performed with 200 mg of freshly activated 4 Å molecular sieves under the conditions as illustrated in entry 18 of Table 1, hardly any improvement in the enantioselectivity was observed. As a result, these studies provided a standard reaction protocol: addition of benzenethiol (**2a**) to a solution of 3-methyl-4-nitro-5-alkenyl-isoxazoles in chlorobenzene in the presence of 10 mol % **1a** at −40 °C with 200 mg of activated 4 Å molecular sieves (Table 1, entry 24).

With optimized reaction conditions in hand, we next explored the scope of the process with respect to the 3-methyl-4-nitro-5-alkenyl-isoxazoles component. As shown in Table 2, the reaction scope generally proved to be broad to the Michael acceptor 3-methyl-4-nitro-5-styrylisoxazoles. We found that various electron-rich and -poor reagents **3** with different substitution patterns on the phenyl ring were equally good substrates (Table 2, entries 1−10). In the cases of **3j** and **3k** with the methoxyl group substituent on the phenyl ring as substrate, the corresponding products were obtained in good yields with good enantioselectivities (Table 2, entries 9−10). In addition, more sterically demanding substrates **3l** and **3m** also smoothly gave rise to the formation of products **4l** and **4m** in good yields and ee's (Table 2, entries 11−12). At the same time, heteroaromatic 3-methyl-4-nitro-5-styrylisoxazole **3n** was readily accommodated to the standard reaction conditions (Table 2, entry 13). More importantly, we also verified

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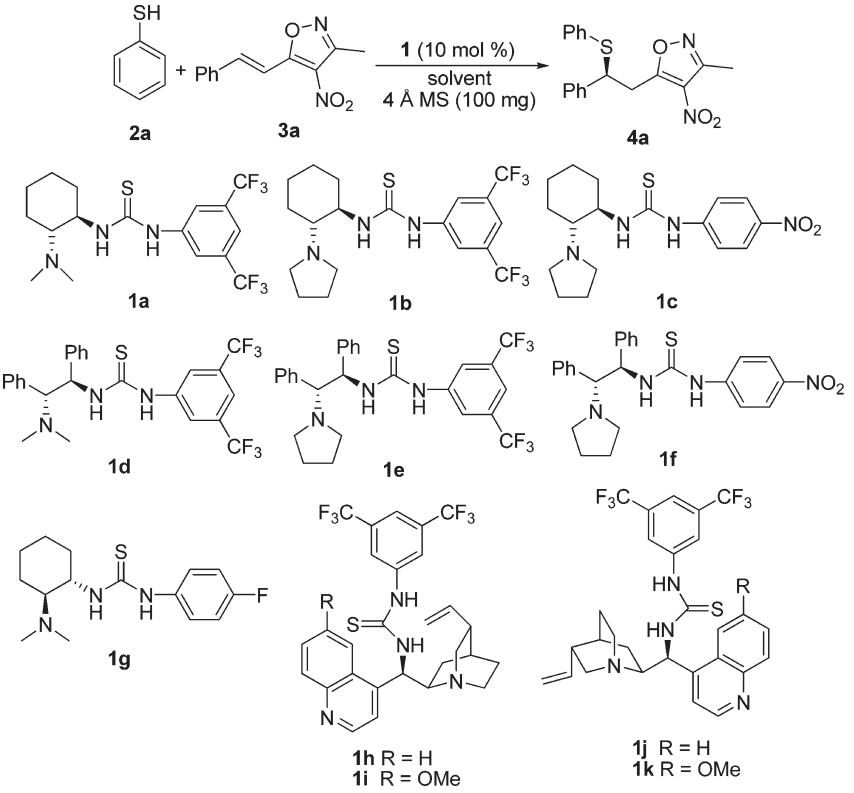
Table 1. Effect of Reaction Parameters on the Catalytic Asymmetric 1,6-Michael Addition of Benzenethiol (2a) to 3-Methyl-4-nitro-5-styrylisoxazole (3a)[a]



entry	1	solvent	T (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	DCM	rt	5 min	quant.	4[d]
2	**1a**	DCM	−30	8	92	50[d]
3	**1a**	DCM	−30	8	93	72
4	**1b**	DCM	−30	8	95	35
5	**1c**	DCM	−30	8	91	20
6	**1d**	DCM	−30	8	83	37
7	**1e**	DCM	−30	8	71	2[e]
8	**1f**	DCM	−30	8	50	8[e]
9	**1g**	DCM	−30	8	94	27[e]
10	**1h**	DCM	−30	8	98	2[e]
11	**1i**	DCM	−30	8	71	49
12	**1j**	DCM	−30	8	68	56[e]
13	**1k**	DCM	−30	8	94	54[e]
14	**1a**	$CHCl_3$	−30	8	81	44
15	**1a**	DCE	−30	8	93	68
16	**1a**	toluene	−30	8	52	44
17	**1a**	THF	−30	8	85	13
18	**1a**	PhCl	−30	8	91	81
19	**1a**	PhCl	−30	8	76	81[f]
20	**1a**	PhCl	−30	8	93	76[g]
21	**1a**	PhCl	−30	8	82	79[h]
22	**1a**	PhCl	−30	8	90	81[i]
23	**1a**	PhCl	−30	8	76	75[j]
24	**1a**	PhCl	−40	30	93	84[k]

[a] Unless noted, reactions were carried out with **2a** (0.2 mmol), **3a** (0.1 mmol), **1** (10 mol %), and freshly activated 4 Å MS (100 mg) in solvent (3.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] No additive 4 Å MS. [e] Opposite enantiomer was obtained as the major product. [f] 5 mol % of **1a** was used. [g] 20 mol % of **1a** was used. [h] Run in 1.0 mL of chlorobenzene. [i] Run in 6.0 mL of chlorobenzene. [j] Freshly activated 4 Å MS (50 mg) were used. [k] Freshly activated 4 Å MS (200 mg) were used. DCM = Dichloromethane, DCE = 1,2-Dichloroethane.

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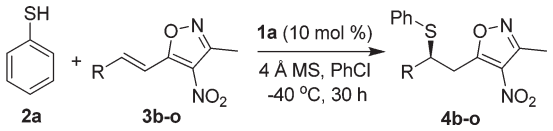
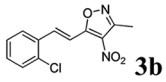
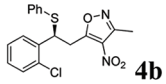
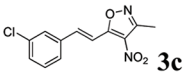
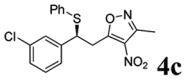
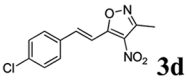
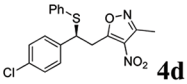
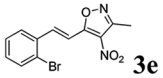
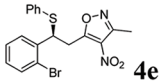
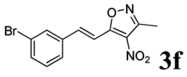
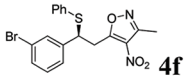
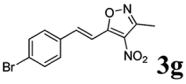
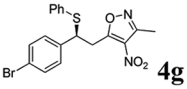
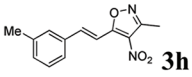
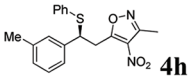
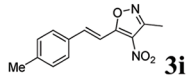
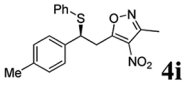
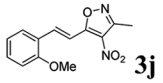
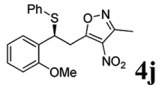
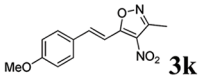
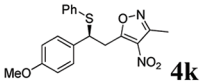
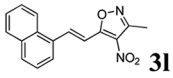
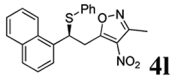
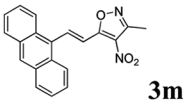
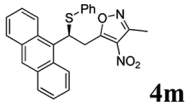
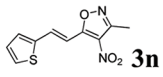
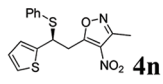
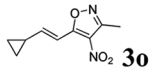
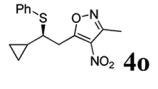
Table 2. Scope of 1a-Catalyzed 1,6-Michael Addition of Benzenethiol (2a) to Various 3-Methyl-4-nitro-5-alkenyl-isoxazoles[a]



entry	3	4	yield (%)[b]	ee (%)[c]
1	 **3b**	 **4b**	96	89
2	 **3c**	 **4c**	86	85
3	 **3d**	 **4d**	93	84
4	 **3e**	 **4e**	96	91[d]
5	 **3f**	 **4f**	89	81
6	 **3g**	 **4g**	90	81
7	 **3h**	 **4h**	91	82
8	 **3i**	 **4i**	92	84
9	 **3j**	 **4j**	75	78
10	 **3k**	 **4k**	71	74
11	 **3l**	 **4l**	82	86
12	 **3m**	 **4m**	74	71
13	 **3n**	 **4n**	70	72
14	 **3o**	 **4o**	95	80

[a] Unless noted, reactions were carried out with **2a** (0.2 mmol), **3** (0.1 mmol), **1a** (10 mol %), and freshly activated 4 Å MS (200 mg) in PhCl (3.0 mL) at −40 °C for 30 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Run for 45 h with 5 mol % of **1a**.

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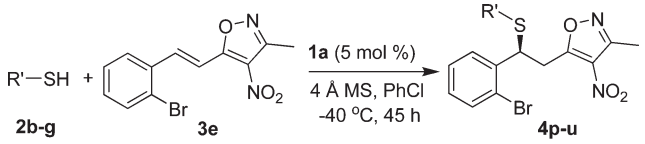
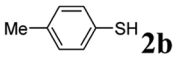
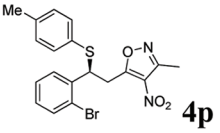
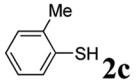
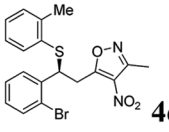
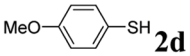
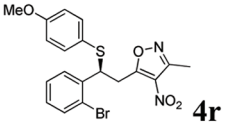
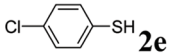
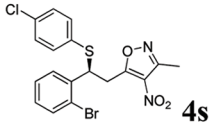
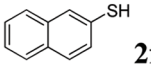
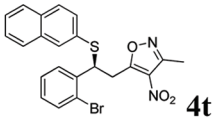
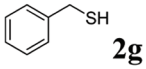
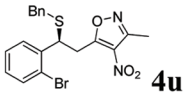
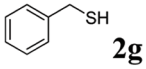
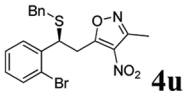
Table 3. Scope of 1a-Catalyzed 1,6-Michael Additions of Various Thiols to 3e[a]



entry	2	4	yield (%)[b]	ee (%)[c]
1	 **2b**	 **4p**	96	90
2	 **2c**	 **4q**	83	91
3	 **2d**	 **4r**	93	91
4	 **2e**	 **4s**	95	81
5	 **2f**	 **4t**	97	88(99)[d]
6	 **2g**	 **4u**	47	13[e]
7	 **2g**	 **4u**	43	45[f]

[a] Unless noted, reactions were carried out with **2** (0.2 mmol), **3e** (0.1 mmol), **1a** (5 mol %), and freshly activated 4 Å MS (200 mg) in PhCl (3.0 mL) at −40 °C for 45 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The data in parentheses mean the ee value of product after a single recrystallization from anhydrous ethanol. [e] Run at room temperature without 4 Å MS. [f] Run at room temperature with freshly activated 4 Å MS (200 mg).

that isoxazole derivative **3o**, in which the R group was represented by a cyclopropyl group, was a viable substrate for this asymmetric transformation, affording the corresponding product **4o** in 95% yield with 80% ee (Table 2, entry 14).

In light of the previous investigation (Table 2, entry 4) in which substrate **3e** reacted with benzenethiol (**2a**) in the presence of 5 mol % of catalyst **1a** furnishing the corresponding product **4e** in 96% yield and up to 91% ee just with an extended reaction time of 45 h, we attempted to probe the effect of altering the structure of the thiol on the reactivity and enantioselectivity of the reaction. As shown in Table 3, some arenethiols, regardless of their electronic and steric properties, underwent efficient reactions affording corresponding adducts in excellent yields (83−97%) with high enantioselectivities (81−91% ee). As revealed from entries 1−3, electron-rich thiols reacted efficiently with over 90% enantioselectivity. In contrast, electro-deficient thiol reacted also efficiently but with a little poor enantioselectivity (Table 3, entry 4). Meanwhile, naphthalene-2-thiol smoothly gave rise to the desired product in 97% yield with 88% ee, and the ee value of product **4t** could be readily improved to 99% after a single recrystallization from anhydrous ethanol (Table 3, entry 5). However, we found that the reactivity of less active alkanethiols **2g** was poor, and the desired adduct could not be observed under the standard reaction conditions. Even though the reaction was carried out at room temperature, the product could be obtained only in 47% yield with very poor enantioselectivity (Table 3, entry 6) and in 43% yield with 45% ee value by adding 200 mg 4 Å molecular sieves (Table 3, entry 7). Notably, it can be deduced that the molecular sieves plays

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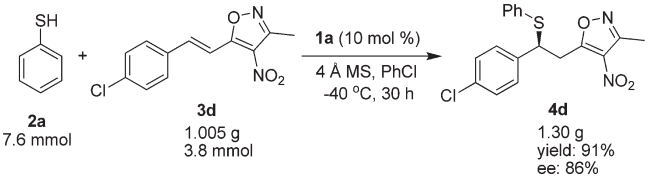
an important role in improving the enantioselectivity for the reaction.

The significance of the current protocol and the high catalytic efficiency of **1a** were further demonstrated by a gram-scale experiment under the standard reaction conditions. As highlighted in Scheme 2, 10 mol % of **1a** was sufficient for the completion of the reaction of **2a** addition to **3d** within 30 h, and the corresponding adduct **4d** was obtained smoothly in 91% yield with 86% ee value. It is worthwhile to note that these results obtained in gram-scale reaction are very similar to those observed in a previous investigation (entry 3 of Table 2).

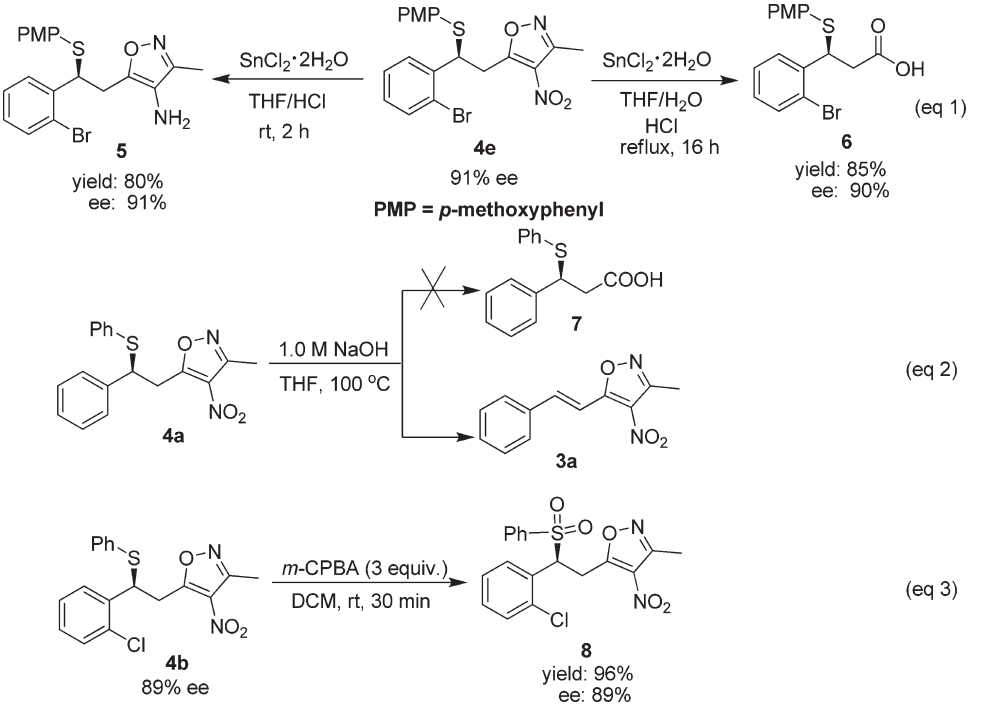
After completing the research of methodology for the catalytic asymmetric 1,6-Michael additions of various thiols to a wide range of 3-methyl-4-nitro-5-alkenyl-isoxazoles and the investigation into the gram-scale reaction, we attempted to demonstrate the significance of the current protocol by the versatile transformation of some Michael adducts into other functionalized and useful compounds (Scheme 3). For example, the nitro group of compound **4e** could be readily reduced to an amino group in **5** with tin dichloride at room temperature (Scheme 3, eq 1, left).[17] Interestingly, the 4-nitroisoxazol-5-yl core of **4e** could be converted into a carboxylic acid group in compound **6** with the promotion of tin dichloride in a mixture solvent of THF/H_2O after refluxing 16 h (Scheme 3, eq 1, right).[17] However, treatment of Michael adduct **4a** with 1.0 M aqueous NaOH in THF according to the procedure,[13a] described by Sarti-Fantoni and co-workers, could not deliver the desired product β-thio-carboxylic acid **7** (Scheme 3, eq 2, up) but furnishes the corresponding starting material, Michael acceptor **3a** (Scheme 3, eq 2, down). We assumed that a retro-Michael reaction probably took place during the course of the reaction process. In addition, the potential synthetic usefulness of our methodology was also demonstrated by the transformation of Michael adduct **4b** into sulfone **8** with the oxidation of 3-chlorobenzoperoxoic acid in dichloromethane (Scheme 3, eq 3).[17]

Similarly, as shown in Scheme 4, for adduct **4a**, which had been obtained with 84% ee, we were also able to transform it into the corresponding acidic derivative **7** with retention of stereochemistry.[17] This allowed us to establish the absolute configuration of the stereocenter that had been generated in the 1,6-Michael addition reaction as *S* configuration in **4a** by comparison of the optical rotation of **7** with the reported value of the same compound.[18] On the basis of this absolute configuration result, we tentatively propose a transition state for the reaction. As shown in Scheme 4, a double hydrogen bonding interaction might be formed between two N−H of thiourea and the nitro group of the Michael acceptor. Synchronously, another single hydrogen-bonding interaction would be generated between the protonated tertiary amine group and nucleophilic thiol. Subsequently, the Michael donor thiol approaches the Michael acceptor from its *si* face to afford the desired adduct **4a** with *S* configuration. According to the stereostructure obtained for compound **4a**, additionally, all the products in this work were delivered with the same thiourea catalyst **1a** and via the same reaction mechanism, and the configuration of all other products in this work was tentatively established by analogy. Notably, in view of the reported procedure,[18,19] we know that compound **7** could be

Scheme 2. Asymmetric 1,6-Michael Addition Reaction of 2a to 3d in Gram Scale



Scheme 3. Transformation of Some Adducts into Other Functionalized Compounds



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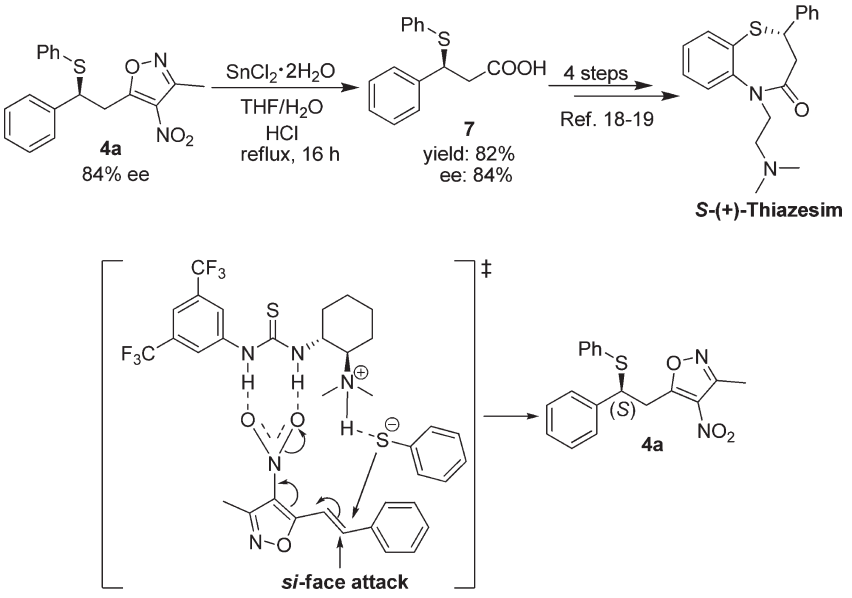
Scheme 4. Confirmation of the Absolute Configuration of 4a and Proposed Transition State for the Reaction and the Potential Application in the Synthesis of *S*-(+)-Thiazesim



easily transformed into *S*-(+)-thiazesim,[20] the simplest member of the benzothiazepin family, via four steps of normal reactions.

CONCLUSION

In conclusion, we have developed the first procedure for carrying out enantioselective organocatalytic 1,6-Michael addition of arylthiols to various 3-methyl-4-nitro-5-alkenyl-isoxazole compounds in the presence of a catalytic amount of chiral bifunctional thiourea-tertiary amine (10 or 5 mol %) in chlorobenzene at −40 °C. A wide range of chiral sulfur-containing compounds were obtained smoothly in high to excellent yields (up to 97%) and high enantioselectivities (up to 91% ee). These studies carried out in this report further demonstrate that 3-methyl-4-nitro-5-alkenyl-isoxazole belongs to a kind of promising Michael acceptor in organic synthesis.[8,9i,11] Significantly, the potential utilities of the protocol also had been demonstrated by gram-scale reaction and the versatile conversions of some resulting products into other functionalized and useful compounds with retention of stereochemistry. Further studies in our laboratories will focus on applying the 3-methyl-4-nitro-5-alkenyl-isoxazole compounds into asymmetric synthesis and expanding the synthetic utility of the related reactions.

EXPERIMENTAL SECTION

General Information. Various 3-methyl-4-nitro-5-alkenyl-isoxazoles substrates **3a**−**o** were synthesized according to the previously reported methods,[10] and the purity of these compounds was determined with ^{1}H NMR. NMR spectra were recorded on a 300 MHz spectrometer. ^{1}H NMR chemical shifts were reported in parts per million with tetramethylsilane (TMS) as the internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (in ppm) and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Splitting patterns that could not be clearly distinguished are designated as multiplets (m). Data for ^{13}C NMR are reported in parts per million. High-resolution mass spectral analyses (HRMS) were measured using ESI ionization. High-performance liquid chromatography (HPLC) analysis was performed on chiral columns. Optical rotations were measured in the solvent indicated. The solvents used in this work must be thoroughly dried solvents.

General Experimental Procedure for the 1,6-Michael Addition of Benzenethiol to Various 3-Methyl-4-nitro-5-alkenyl-isoxazoles Catalyzed by 1a (Table 2). In an ordinary tube equipped with a magnetic stirring bar, the solution of 3-methyl-4-nitro-5-alkenyl-isoxazoles **3** (0.1 mmol), catalyst **1a** (0.01 mmol), and freshly activated 4 Å MS (200 mg) in PhCl (2.0 mL) was stirred at −40 °C for 30 min, and then benzenethiol **2a** (0.2 mmol, 1.0 mL of cold benzenethiol solution in PhCl (−40 °C, *c* = 0.2 M)) was added. After the reaction mixture was stirred for 30 h at −40 °C, the reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (eluent: petroleum ether/ethyl acetate = 25:1) to give products **4**.

General Experimental Procedure for the 1,6-Michael Addition of Various Thiols to 3e Catalyzed by 1a (Table 3). In an ordinary tube equipped with a magnetic stirring bar, the solution of (*E*)-5-(2-bromostyryl)-3-methyl-4-nitro-isoxazole **3e** (0.1 mmol), catalyst **1a** (0.005 mmol), and freshly activated 4 Å MS (200 mg) in PhCl (2.0 mL) was stirred at −40 °C for 30 min, and then thiol **2** (0.2 mmol, 1.0 mL of cold benzenethiol solution in PhCl (−40 °C, *c* = 0.2 M)) was added. After the reaction mixture was stirred for 45 h at −40 °C, the reaction mixture was directly loaded onto a silica gel and purified by flash chromatography (eluent: petroleum ether/ethyl acetate = 25:1) to give products **4**.

(*S*)-3-Methyl-4-nitro-5-(2-phenyl-2-(phenylthio)ethyl)isoxazole (4a). White solid; 31.5 mg, 93% yield; 84% ee; $[\alpha]_D^{25} = -67.5$ (*c* 0.83, $CHCl_3$); mp 61.8−62.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.23 (m, 10H), 4.84 (t, *J* = 7.8 Hz, 1H), 3.81 (d, *J* = 7.8 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 34.4, 50.0, 127.3, 127.9, 128.1, 128.6, 128.8, 130.3, 132.7, 133.1, 138.9, 155.2, 171.4; IR (KBr) ν 3076, 2921, 1597, 1513, 1410, 1371, 1148, 829, 696. HRMS (ESI) calcd for $C_{18}H_{16}N_2NaO_3S$ $[M+Na]^+$: 363.0774. Found: 363.0765. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.9 min, t_{major} = 9.0 min.

(*S*)-5-(2-(2-Chlorophenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4b). Yellow solid; 35.8 mg, 96% yield; 89% ee;

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$[\alpha]_D^{25}$ = −33.8 (*c* 0.97, $CHCl_3$); mp 73.4−74.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.47 (m, 1H), 7.38−7.20 (m, 8H), 5.41 (t, *J* = 7.8 Hz, 1H), 3.86 (dd, *J* = 14.7, 7.8 Hz, 1H), 3.75 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 33.9, 46.0, 127.3, 128.0, 128.4, 128.7, 129.0, 129.2, 129.8, 130.6, 132.8, 133.3, 136.5, 155.4, 171.1; IR (KBr) ν 2926, 1606, 1521, 1477, 1419, 1381, 1364, 831, 756 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{15}ClN_2NaO_3S$ $[M+Na]^+$: 397.0384. Found: 397.0383. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 6.0 min, t_{minor} = 6.5 min.

(*S*)-5-(2-(3-Chlorophenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4c). Yellow solid; 32.2 mg, 86% yield; 85% ee; $[\alpha]_D^{25}$ = −66.5 (*c* 0.97, $CHCl_3$); mp 66.4−67.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.17 (m, 9H), 4.75 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 7.8 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 34.3, 49.7, 125.5, 127.6, 128.2, 129.0, 129.9, 130.5, 132.5, 133.2, 134.5, 141.2, 155.4, 171.1; IR (KBr) ν 2903, 1612, 1520, 1418, 1381, 1140, 830, 755, 693 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{15}ClN_2NaO_3S$ $[M+Na]^+$: 397.0384. Found: 397.0378. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.4 min, t_{major} = 8.9 min.

(*S*)-5-(2-(4-Chlorophenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4d). White solid; 34.9 mg, 93% yield; 84% ee; $[\alpha]_D^{25}$ = −74.3 (*c* 0.83, $CHCl_3$); mp 67.3−68.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 9H), 4.77 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 7.8 Hz, 2H), 2.45(s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 11.5, 34.2, 49.5, 128.2, 128.7, 128.8, 129.0, 130.4, 132.6, 133.2, 133.7, 137.6, 155.4, 171.2; IR (KBr) ν 3033, 1603, 1514, 1414, 1381, 1362, 1094, 831, 748 cm^{-1}. HRMS (ESI) Calcd for $C_{18}H_{15}ClN_2NaO_3S$ $[M+Na]^+$: 397.0384. Found: 397.0387. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.1 min, t_{major} = 13.7 min.

(*S*)-5-(2-(2-Bromophenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4e). Yellow solid; 40.3 mg, 96% yield; 91% ee; $[\alpha]_D^{25}$ = −29.6 (*c* 1.0, $CHCl_3$); mp 67.6−69.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.49 (m, 2H), 7.39−7.12 (m, 7H), 5.41 (t, *J* = 7.8 Hz, 1H), 3.84 (dd, *J* = 14.7, 7.8 Hz, 1H), 3.74 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 34.0, 48.7, 124.1, 127.9, 128.0, 128.6, 128.8, 129.0, 129.5, 132.8, 133.1, 138.1, 155.4, 171.0; IR (KBr) ν 3052, 2926, 1606, 1519, 1416, 1379, 1362, 831, 753 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{15}BrN_2NaO_3S$ $[M+Na]^+$: 440.9879. Found: 440.9881. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 6.2 min, t_{minor} = 6.9 min.

(*S*)-5-(2-(3-Bromophenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4f). Yellow solid; 37.2 mg, 89% yield; 81% ee; $[\alpha]_D^{25}$ = −56.9 (*c* 0.80, $CHCl_3$); mp 79.6−81.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39−7.13 (m, 8H), 4.73 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 7.8 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 34.3, 49.7, 122.6, 126.0, 128.3, 129.0, 130.2, 130.5, 131.2, 132.4, 133.2, 141.4, 155.4, 171.1; IR (KBr) ν 3054, 2905, 1605, 1517, 1375, 1136, 830, 753, 693 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{15}BrN_2NaO_3S$ $[M+Na]^+$: 440.9879. Found: 440.9862. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.6 min, t_{major} = 8.9 min.

(*S*)-5-(2-(4-Bromophenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4g). Yellow solid; 37.8 mg, 90% yield; 81% ee; $[\alpha]_D^{25}$ = −62.5 (*c* 0.65, $CHCl_3$); mp 103.5−104.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.32−7.26 (m, 5H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.75 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 7.8 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 34.2, 49.6, 121.9, 128.2, 129.0, 129.1, 130.4, 131.8, 132.5, 133.1, 138.1, 155.4, 171.1; IR (KBr) ν 3047, 2938, 1607, 1524, 1491, 1413, 1385, 822, 752 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{15}BrN_2NaO_3S$ $[M+Na]^+$: 440.9879. Found: 440.9870. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.8 min, t_{major} = 14.7 min.

(*S*)-3-Methyl-4-nitro-5-(2-(phenylthio)-2-*m*-tolylethyl)isoxazole (4h). Colorless oil; 32.4 mg, 91% yield; 82% ee; $[\alpha]_D^{25}$ = −61.2 (*c* 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.33 (m, 2H), 7.29−7.05 (m, 7H), 4.78 (t, *J* = 7.8 Hz, 1H), 3.79 (d, *J* = 7.8, 2H), 2.43 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 21.3, 34.6, 50.1, 124.3, 127.8, 128.0, 128.6, 128.8, 128.9, 132.8, 133.3, 138.4, 138.8, 155.3, 171.7; IR (KBr) ν 3014, 2924, 1604, 1521, 1377, 1133, 831, 755, 699 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_3S$ $[M+Na]^+$: 377.0930. Found: 377.0934. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 5.3 min, t_{major} = 6.9 min.

(*S*)-3-Methyl-4-nitro-5-(2-(phenylthio)-2-*p*-tolylethyl)isoxazole (4i). White solid; 32.7 mg, 92% yield; 84% ee; $[\alpha]_D^{25}$ = −62.7 (*c* 0.77, $CHCl_3$); mp 103.0−103.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.35 (m, 2H), 7.26−7.09 (m, 7H), 4.81 (t, *J* = 7.8 Hz, 1H), 3.79 (d, *J* = 7.8 Hz, 2H), 2.44 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 21.1, 34.6, 49.8, 126.9, 127.2, 127.7, 128.9, 129.4, 130.3, 132.7, 133.4, 135.9, 137.8, 155.3, 171.7; IR (KBr) ν 3021, 2969, 1601, 1529, 1414, 1383, 1127, 826, 743 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_3S$ $[M+Na]^+$: 377.0930. Found: 377.0927. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.9 min, t_{major} = 7.6 min.

(*S*)-5-(2-(2-Methoxyphenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4j). Yellow solid; 27.6 mg, 75% yield; 78% ee; $[\alpha]_D^{25}$ = −33.3 (*c* 0.75, $CHCl_3$); mp 71.0−72.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.22 (m, 7H), 6.92−6.83 (m, 2H), 5.32 (t, *J* = 7.8 Hz, 1H), 3.87 (dd, *J* = 14.7, 7.8 Hz, 1H), 3.82 (s, 2H), 3.76 (dd, *J* = 14.7, 7.8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 33.8, 43.6, 55.5, 110.7, 120.7, 127.2, 127.4, 128.8, 129.1, 132.2, 134.1, 155.2, 156.3, 171.9; IR (KBr) ν 3018, 2935, 1601, 1513, 1385, 1253, 1110, 831, 760 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_4S$ $[M+Na]^+$: 393.0879. Found: 393.0886. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 5.6 min, t_{major} = 6.2 min.

(*S*)-5-(2-(4-Methoxyphenyl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4k). Yellow solid; 26.2 mg, 71% yield; 74% ee; $[\alpha]_D^{25}$ = −17 (*c* 0.23, $CHCl_3$); mp 95.3−96.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.22 (m, 7H), 6.82−6.79 (m, 2H), 4.80 (t, *J* = 7.8 Hz, 1H), 3.77 (d, *J* = 7.8 Hz, 2H), 3.76 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 34.6, 49.5, 55.1, 114.0, 127.8, 128.5, 128.9, 130.8, 132.8, 133.3, 155.3, 159.1, 171.7; IR (KBr) ν 3004, 2969, 2836, 1608, 1513, 1364, 1255, 828, 748 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}N_2NaO_4S$ $[M+Na]^+$: 393.0879. Found: 393.0891. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 9.7 min, t_{major} = 10.8 min.

(*S*)-3-Methyl-5-(2-(naphthalen-1-yl)-2-(phenylthio)ethyl)-4-nitroisoxazole (4l). Yellow solid; 32.2 mg, 82% yield; 86% ee; $[\alpha]_D^{25}$ = −67.5 (*c* 1.15, $CHCl_3$); mp 108.7−110.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (m, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.62−7.23 (m, 9H), 5.74 (s, 1H), 3.94 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 34.5, 45.0, 122.5, 124.9, 125.2, 125.9, 126.7, 127.9, 128.8, 129.0, 129.1, 130.5, 132.9, 133.3, 133.9, 134.6, 155.3, 171.6; IR (KBr) ν 3066, 2935, 1601, 1511, 1377, 1363, 1127, 831, 736 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{18}N_2NaO_3S$ $[M+Na]^+$: 413.0930. Found: 413.0944. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 6.5 min, t_{major} = 7.2 min.

(*S*)-5-(2-(Anthracen-9-yl)-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4m). Yellow solid; 32.5 mg, 74% yield; 71% ee; $[\alpha]_D^{25}$ = −103.4 (*c* 0.55, $CHCl_3$); mp 153.5−154.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81−8.78 (m, 1H), 8.41−8.33 (m, 2H), 8.04−7.98 (m, 2H), 7.68−7.40 (m, 6H), 7.26−7.24 (m, 3H), 6.44−6.39 (m, 1H),

4.40 (dd, J = 14.4, 10.2 Hz, 1H), 3.91 (dd, J = 14.4, 6.0 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 34.7, 46.9, 122.3, 124.9, 125.0, 125.4, 125.9, 127.1, 127.8, 128.7, 128.8, 129.1, 129.4, 129.5, 129.8, 131.1, 131.3, 131.8, 132.3, 135.7, 155.1, 171.5; IR (KBr) ν 3066, 2935, 1601, 1511, 1377, 1363, 1127, 831, 736 cm^{-1}. HRMS (ESI) calcd for $C_{26}H_{20}N_2NaO_3S$ $[M+Na]^+$: 463.1087. Found: 463.1090. HPLC analysis: Chiralpak OD-H, *i*-propanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 6.2 min, t_{minor} = 6.7 min.

(*S*)-3-Methyl-4-nitro-5-(2-(phenylthio)-2-(thiophen-2-yl)-ethyl)isoxazole (4n). Yellow solid; 24.3 mg, 70% yield; 72% ee; $[\alpha]_D^{25}$ = −60.7 (*c* 0.47, $CHCl_3$); mp 72.9−74.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.20 (m, 6H), 6.87 (d, J = 3.3 Hz, 2H), 5.10 (t, J = 7.8 Hz, 1H), 3.83 (d, J = 7.8 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 35.5, 45.4, 125.3, 125.7, 126.7, 128.2, 132.7, 133.2, 142.7, 155.4, 171.1; IR (KBr) ν 3115, 2931, 1611, 1521, 1413, 1377, 831, 748, 724 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{14}N_2NaO_3S_2$ $[M+Na]^+$: 369.0338. Found: 369.0342. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 8.0 min, t_{major} = 10.5 min.

(*S*)-5-(2-Cyclopropyl-2-(phenylthio)ethyl)-3-methyl-4-nitroisoxazole (4o). Yellow solid; 29.0 mg, 95% yield; 80% ee; $[\alpha]_D^{25}$ = −27.8 (*c* 0.73, $CHCl_3$); mp 53.2−54.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.41 (m, 2H), 7.30−7.25 (m, 3H), 3.52 (d, J = 7.5 Hz, 2H), 2.89 (m, 1H), 2.47 (s, 3H), 1.01−0.66 (m, 1H), 0.65−0.50 (m, 2H), 0.39−0.0.34 (m, 1H), 0.18−0.15 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.4, 6.2, 11.5, 16.1, 34.6, 52.0, 127.8, 128.9, 132.7, 133.5, 155.3, 172.5; IR (KBr) ν 3082, 3003, 1602, 1516, 1377, 1362, 1128, 831, 751 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{16}N_2NaO_3S$ $[M+Na]^+$: 327.0774. Found: 327.0775. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 7.0 min, t_{major} = 8.8 min.

(*S*)-5-(2-(2-Bromophenyl)-2-(p-tolylthio)ethyl)-3-methyl-4-nitroisoxazole (4p). Yellow solid; 41.6 mg, 96% yield; 90% ee; $[\alpha]_D^{25}$ = −28.7 (*c* 1.13, $CHCl_3$); mp 93.8−95.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.45 (m, 2H), 7.32−7.05 (m, 6H), 5.35 (t, J = 7.8 Hz, 1H), 3.82 (dd, J = 14.7, 7.8 Hz, 1H), 3.72 (dd, J = 14.7, 7.8 Hz, 1H), 2.44 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 21.1, 33.9, 48.9, 124.0, 127.8, 128.5, 128.9, 129.3, 129.7, 133.0, 133.3, 138.1, 138.3, 155.3, 171.1; IR (KBr) ν 3063, 2924, 1601, 1511, 1381, 1129, 1025, 831, 774 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{17}BrN_2NaO_3S$ $[M+Na]^+$: 455.0035. Found: 455.0035. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 5.9 min, t_{minor} = 6.6 min.

(*S*)-5-(2-(2-Bromophenyl)-2-(*o*-tolylthio)ethyl)-3-methyl-4-nitroisoxazole (4q). Yellow solid; 35.9 mg, 83% yield; 91% ee; $[\alpha]_D^{25}$ = −24.4 (*c* 0.95, $CHCl_3$); mp 72.0−72.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.32 (m, 4H), 7.18−7.09 (m, 4H), 5.39 (t, J = 7.8 Hz, 1H), 3.84 (dd, J = 14.7, 7.8 Hz, 1H), 3.73 (dd, J = 14.7, 7.8 Hz, 1H), 2.44 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 20.6, 34.2, 47.8, 124.0, 126.5, 128.0, 128.2, 128.7, 129.4, 130.5, 131.9, 133.0, 133.5, 138.2, 140.7, 155.3, 171.0; IR (KBr) ν 3056, 2903, 1599, 1513, 1470, 1418, 1384, 831, 753 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{17}BrN_2NaO_3S$ $[M+Na]^+$: 455.0035. Found: 455.0021. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 5.2 min, t_{minor} = 5.6 min.

(*S*)-5-(2-(2-Bromophenyl)-2-(4-methoxyphenylthio)ethyl)-3-methyl-4-nitroisoxazole (4r). Yellow solid; 41.6 mg, 93% yield; 91% ee; $[\alpha]_D^{25}$ = −19.6 (*c* 1.33, $CHCl_3$); mp 101.8−102.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.50 (m, 1H), 7.40−7.37 (m, 1H) 7.31−7.26 (m, 3H) 7.12−7.10 (m, 1H), 6.78 (d, J = 8.7 Hz, 2H), 5.25 (t, J = 7.8 Hz, 1H), 3.82 (dd, J = 15.0, 7.8 Hz, 1H), 3.78 (s, 3H), 3.71 (dd, J = 15.0, 7.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.5, 33.7, 49.3, 55.2, 114.5, 122.7, 124.2, 127.8, 128.5, 129.3, 133.1, 136.0, 138.2, 155.4, 160.1, 171.3; IR (KBr) ν 3010, 2838, 1606, 1521, 1494, 1377, 1248, 831, 748 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{17}BrN_2NaO_4S$ $[M+Na]^+$: 470.9985. Found: 470.9982. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 8.0 min, t_{minor} = 9.4 min.

(*S*)-5-(2-(2-Bromophenyl)-2-(4-chlorophenylthio)ethyl)-3-methyl-4-nitroisoxazole (4s). Yellow solid; 43.0 mg, 95% yield; 81% ee; $[\alpha]_D^{25}$ = −29.5 (*c* 1.13, $CHCl_3$); mp 108.4−109.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.46 (m, 2H), 7.31−7.12 (m, 6H), 5.37 (t, J = 7.8 Hz, 1H), 3.84 (dd, J = 14.7, 7.8 Hz, 1H), 3.71 (dd, J = 14.7, 7.8 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 33.8, 48.8, 124.0, 128.0, 128.5, 129.1, 129.6, 131.1, 133.1, 134.1, 134.3, 137.7, 155.4, 170.7; IR (KBr) ν 3063, 2900, 1601, 1518, 1475, 1416, 1381, 1094, 831, 772 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{14}BrClN_2NaO_3S$ $[M+Na]^+$: 474.9489. Found: 474.9493. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 6.5 min, t_{minor} = 7.1 min.

(*S*)-5-(2-(2-Bromophenyl)-2-(naphthalen-2-ylthio)ethyl)-3-methyl-4-nitroisoxazole (4t). Yellow solid; 45.5 mg, 97% yield; 88% ee; $[\alpha]_D^{25}$ = −67.5 (*c* 1.15, $CHCl_3$); mp 108.9−110.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.80−7.72 (m, 3H), 7.56−7.47 (m, 5H), 7.34−7.29 (m, 1H), 7.15−7.13 (m, 1H), 5.57 (t, J = 7.8 Hz, 1H), 3.89 (dd, J = 14.7, 7.8 Hz, 1H), 3.75 (dd, J = 14.7, 7.8 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 34.2, 48.4, 124.0, 126.5, 126.6, 127.5, 128.0, 128.5, 128.7, 129.3, 129.5, 130.1, 131.5, 132.4, 133.1, 133.3, 138.1, 155.3, 170.9; IR (KBr) ν 3047, 2928, 1604, 1511, 1379, 1361, 1133, 831, 804, 780, 760 cm^{-1}. HRMS (ESI) calcd for $C_{22}H_{17}BrN_2NaO_3S$ $[M+Na]^+$: 491.0035. Found: 491.0040. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 9.2 min, t_{minor} = 10.0 min.

(*S*)-5-(2-(Benzylthio)-2-(2-bromophenyl)ethyl)-3-methyl-4-nitroisoxazole (4u). Yellow solid; 18.6 mg, 43% yield; 45% ee; mp 61.2−61.9 °C; $[\alpha]_D^{25}$ = −30.4 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.60 (m, 1H), 7.51−7.48 (m, 1H), 7.36−7.28 (m, 1H), 7.27−7.18 (m, 5H), 7.16−7.13 (m, 1H), 4.87 (t, J = 7.8 Hz, 1H), 3.73 (dd, J = 14.7, 7.8 Hz, 1H), 3.61 (dd, J = 14.7, 8.4 Hz, 1H), 3.65 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 33.8, 36.2, 45.3, 123.9, 127.1, 128.1, 128.5, 128.8, 129.1, 129.3, 132.9, 136.9, 139.0, 155.3, 170.9; IR (KBr) ν 3052, 2938, 1607, 1517, 1416, 1380, 1024, 826, 752, 723 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{17}BrN_2NaO_3S$ $[M+Na]^+$: 455.0035. Found: 455.0044. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 6.3 min, t_{minor} = 7.1 min.

(−)-5-(2-(2-Bromophenyl)-2-(4-methoxyphenylthio)ethyl)-3-methylisoxazol-4-amine (5). To a solution of **4e** (0.419 g, 1.0 mmol) in 20 mL of THF was added $SnCl_2 \cdot 2H_2O$ (0.677 g, 3.0 mmol) and dropwised conc. HCl (1.0 mL). The reaction mixture was stirred at room temperature for 2 h, poured into a cold solution of 10% NaOH (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with water and then dried over Na_2SO_4 and finally concentrated. The residue mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3:1) to give compound **5** as a colorless oil in 335.5 mg. 80% yield; 91% ee; $[\alpha]_D^{25}$ = −19.6 (*c* 1.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.47 (m, 1H), 7.42−7.40 (m, 1H), 7.28−7.23 (m, 3H), 7.09−7.04 (m, 1H), 6.77−6.74 (m, 2H), 4.50 (t, J = 7.5 Hz, 1H), 3.76 (s, 3H), 3.30−3.16 (m, 2H), 2.39 (br, 2H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 31.5, 50.8, 55.2, 114.4, 122.1, 123.5, 124.5, 127.5, 128.7, 128.8, 132.9, 135.6, 139.8, 153.7, 154.9, 159.8; IR (KBr) ν 2926, 2852, 1646, 1494, 1468, 1401, 1387, 1250, 1028, 831, 750 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{19}BrN_2NaO_2S$ $[M+Na]^+$: 441.0243. Found: 441.0264. HPLC analysis: Chiralpak AD-H, ethanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 7.8 min, t_{minor} = 15.2 min.

(+)-3-(2-Bromophenyl)-3-(4-methoxyphenylthio)propanoic acid (6). The mixture of compound **4e** (1.0 mmol), $SnCl_2 \cdot 2H_2O$ (0.677 g, 3.0 mmol), THF (20.0 mL), water (20.0 mL), and 36% HCl (1.0 mL) was heated at reflux for 16 h and then cooled to room temperature. THF was evaporated in vacuo, and the water layer was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over $MgSO_4$. After evaporation of solvent, the residue mixture was purified by silica gel column chromatography (petroleum ether/ethyl acetate 3:1) to afford product **6** as a white solid in 312.2 mg. 85% yield; 90% ee; $[\alpha]_D^{25}$ = +24.5 (*c* 0.97, $CHCl_3$); mp 144.9−147.3 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.2 (br, 1H), 7.60−7.58 (m, 1H), 7.29−7.20 (m, 5H), 6.88 (d, *J* = 7.5 Hz, 2H), 4.84 (t, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 2.97−2.77 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 39.3, 48.2, 55.3, 114.7, 122.3, 124.1, 127.8, 128.5, 129.1, 132.8, 136.4, 139.4, 159.9, 171.6; IR (KBr) ν 2926, 2852, 1646, 1494, 1468, 1401, 1387, 1250, 1028, 831, 750 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{15}BrNaO_3S$ $[M+Na]^+$: 388.9817. Found: 388.9822. HPLC analysis: Chiralpak OD-H, *i*-propanol/hexane/TFA = 30:70:0.1, flow rate 1.0 mL/min, λ = 254 nm, t_{minor} = 4.3 min, t_{major} = 5.0 min.

(−)-3-Phenyl-3-(phenylthio)propanoic Acid (7). The mixture of compound **4a** (1.0 mmol), $SnCl_2 \cdot 2H_2O$ (0.677 g, 3.0 mmol), THF (20.0 mL), water (20.0 mL), and 36% HCl (1.0 mL) was heated at reflux for 16 h and then cooled to room temperature. THF was evaporated in vacuo, and the water layer was extracted with ethyl acetate (3 × 20 mL). The organic layer was dried over $MgSO_4$. After evaporation of solvent, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 3:1) to afford product **7** as a colorless oil in 212.0 mg, 82% yield; 84% ee; $[\alpha]_D^{25}$ = −121.9 (*c* 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.4 (br, 1H), 7.32−7.27 (m, 10H), 4.64 (t, *J* = 7.5 Hz, 1H), 3.50 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.5, 48.6, 127.5, 127.6, 127.9, 128.5, 128.8 133.3, 133.5, 140.1, 177.0; IR (KBr) ν 3042, 2908, 1703, 1404, 1243, 1172, 755, 692 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{14}NaO_2S$ $[M+Na]^+$: 281.0607. Found: 281.0610. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane/TFA = 9:91:0.03, flow rate 1.0 mL/min, λ = 220 nm, t_{major} = 7.8 min, t_{minor} = 8.5 min.

(+)-5-(2-(2-Chlorophenyl)-2-(phenylsulfonyl)ethyl)-3-methyl-4-nitroisoxazole (8). To a solution of **4b** (375 mg, 1.0 mmol) in CH_2Cl_2 (20.0 mL) was added 701 mg of *m*-CPBA (70%, 3.0 mmol), and the reaction was stirred at room temperature for 30 min. The solvent was evaporated, and the crude residue was treated with sat. $NaHCO_3$ solution (30 mL). The product **8** was obtained after purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate 1:2) as a white solid in 390.1 mg. 96% yield; 89% ee; $[\alpha]_D^{25}$ = +3.8 (*c* 0.85, $CHCl_3$); mp 114.8−116.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.58 (m, 4H), 7.44−7.12 (m, 5H), 5.57 (dd, *J* = 10.2, 5.4 Hz, 1H), 4.23 (dd, *J* = 15.3, 5.4 Hz, 1H), 4.10 (dd, *J* = 15.3, 10.5 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.4, 27.1, 61.5, 127.4, 128.4, 128.9, 129.0, 129.6, 129.7, 130.7, 134.3, 135.7, 136.5, 155.6, 169.6; IR (KBr) ν 3094, 2928, 1610, 1523, 1385, 1151, 831, 767, 738, 608 cm^{-1}. HRMS (ESI): calcd for $C_{18}H_{15}ClN_2NaO_5S$ $[M+Na]^+$: 429.0282. Found: 429.0283. HPLC analysis: Chiralpak AD-H, *i*-propanol/hexane = 20:80, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 17.4 min, t_{minor} = 22.5 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Detailed spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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