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Asymmetric Isomerization of ω-Hydroxy-α,β-Unsaturated Thioesters into β-Mercaptolactones by a Bifunctional Aminothiourea Catalyst

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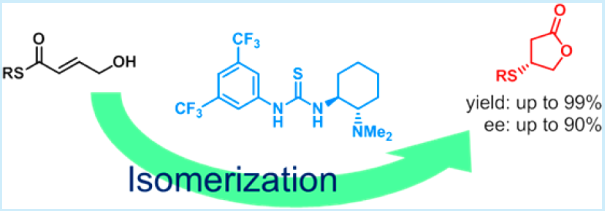
Supporting Information

ABSTRACT: We present a novel methodology for the asymmetric synthesis of β-mercaptolactones via isomerization of ω-hydroxy-α,β-unsaturated thioesters by means of a bifunctional aminothiourea catalyst. The catalyst interacts with the substrate through the cooperative action of both a covalent bond at the amino group and noncovalent bonding at the thiourea group. The potential for an enantiodivergent synthesis could also be demonstrated by carrying out the reaction in a different solvent system.

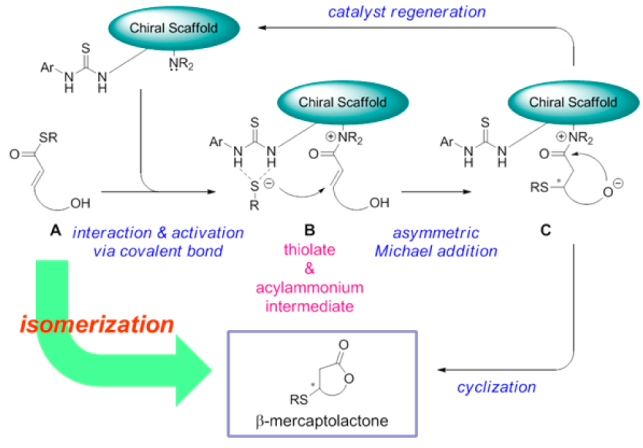


Organocatalysis has seen tremendous progress through the exploration of various catalytic functional groups and the exploitation of a variety of molecular interactions. In the design of organocatalytic reactions, it is important to utilize covalent and noncovalent interactions thoughtfully. Examples of this are rife in biosynthesis, in which enzymes employ both interactions situationally: for example, polyketide synthase fixes substrates such as acetyl-CoA through a covalent interaction at the catalytic site,[1] while noncovalent interactions including hydrogen bonding also play crucial roles in a range of enzymatic processes.[2]

Asymmetric sulfa-Michael addition is one of the most powerful methods for the synthesis of chiral sulfur-containing compounds,[3] which are found in various organisms and play important roles in biological and medicinal chemistry.[4] However, asymmetric hetero-Michael additions to α,β-unsaturated esters generally suffer from low enantioselectivity in contrast to reactions of α,β-unsaturated ketones,[5,6] and only a limited number of successful asymmetric sulfa-Michael additions starting from esters have been reported.[7] In light of these previous studies, the activation of simple esters through only a noncovalent interaction such as hydrogen bonding seems to be insufficient for reasonable asymmetric induction. Thus, modified α,β-unsaturated carboxylic acid derivatives have been employed in order to furnish specifically strong interactions to attain the effective transmission of chiral information:[8] α,β-unsaturated acyl oxazolidinones,[8a−g] acyl pyrazoles,[8h] imides,[8i] and thioamides[8j] have been demonstrated as useful substrates for asymmetric sulfa-Michael additions mediated by chiral hydrogen-bond donor catalysts or Lewis acid catalysts.

In this context, we attempted to explore an alternative catalytic pathway to realize a rigid catalytic interaction in a direct access to the desired esters. As it is a powerful synthetic strategy to design an organocatalytic isomerization of appropriate substrates,[9] we designed an isomerization of ω-hydroxy-α,β-unsaturated thioesters **A** by means of a bifunctional aminothiourea catalyst[10] to afford a cyclic ester bearing a mercapto group at the β-position (Scheme 1). Such products have been catalytically synthesized with only slight enantioselectivity before.[5b,7b] Since carboxylic acid derivatives allow for an addition−elimination reaction by a nucleophilic catalyst, their treatment with a tertiary amine catalyst may lead to the generation of an ion pair intermediate **B**, which includes a thiolate anion and an acylammonium ion, in which the catalyst is fixed through a covalent bond to offer an efficient chiral environment. In addition, the cationic intermediate is considered to be more reactive as a Michael acceptor than the substrate **A**[11] and can undergo the stereoselective sulfa-

Scheme 1. Reaction Design via Organocatalytic Isomerization of ω-Hydroxy-α,β-Unsaturated Thioesters



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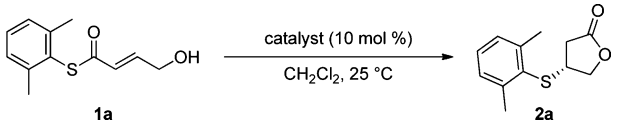
Michael addition of the thiolate interacting with the thiourea in the catalyst.[12] As the Michael addition removes the rigidity of the (*E*)-olefinic moiety, subsequent cyclization may be facilitated to form the desired cyclic ester and regenerate the catalyst.

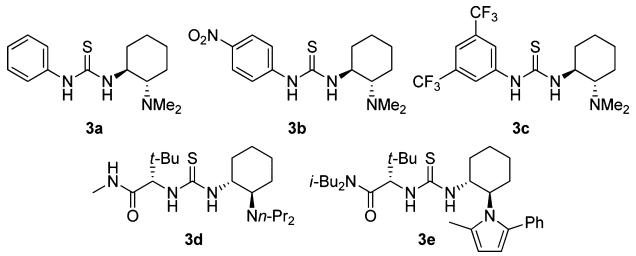
On the basis of this reaction design, a study was initiated by treating γ-hydroxy-α,β-unsaturated thioester **1a** with aminothiourea catalyst **3a**. As expected, the desired lactone **2a** was obtained in high yield with moderate enantioselectivity (Table 1, entry 1). Catalysts **3b** and **3c**, which bear electron-withdrawing groups on the thiourea moiety, attained higher enantioselectivity (Table 1, entries 2 and 3). Catalyst **3d** afforded the product in high yield, but the enantioselectivity was only slight (Table 1, entry 4). In addition, catalyst **3e**, which has no nucleophilic nitrogen atom, proved to be inactive for this transformation (Table 1, entry 5). These results imply that the bifunctionality consisting of an anion receptor and a nucleophilic amino group is crucial for catalysis of the reaction.[13] The concentration of the reaction mixture also had a large effect on the enantioselectivity (Table 1, entries 3 and 6–8).

Table 1. Isomerization of γ-Hydroxy-α,β-Unsaturated Thioester 1a by Aminothiourea Catalyst[a]



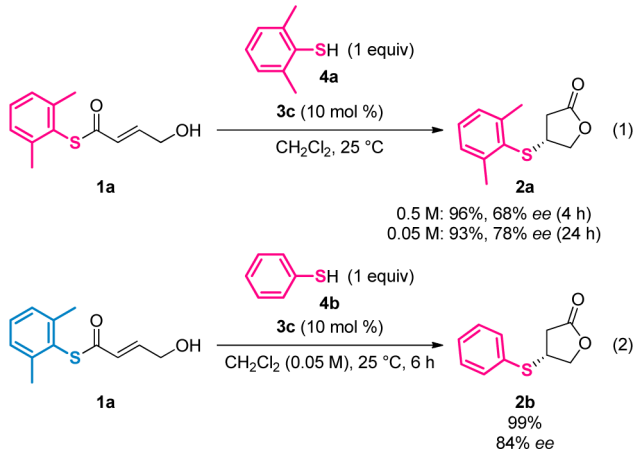
entry	catalyst	concn (M)	time (h)	yield (%)[b]	ee (%)
1	**3a**	0.5	24	95	40
2	**3b**	0.5	24	97	59
3	**3c**	0.5	24	99	66
4	**3d**	0.5	24	92	3
5	**3e**	0.5	24	<1	–
6	**3c**	0.1	96	98	74
7	**3c**	0.05	144	83	76
8	**3c**	0.03	336	72	74

[a]Reactions were run using **1a** (0.15 mmol) and the catalyst (0.015 mmol) in CH_2Cl_2. [b]Isolated yields.



In addition, when the reaction was performed in the presence of 2,6-dimethylbenzenethiol (**4a**) at 25 °C, the enantioselectivity grew slightly higher (Scheme 2, eq 1). It is also notable that the addition of **4a** dramatically accelerated the reaction: the reaction proceeded to completion in 24 h even at 0.05 M, whereas a much longer time was required in the absence of **4a** (Table 1, entry 7). Furthermore, the reaction starting from **1a** in the presence of a less-substituted thiol exclusively afforded the product that incorporated the mercapto group derived from the external thiol (Scheme 2, eq 2). Probably due to its bulkiness, the thiolate anion generated initially could be readily exchanged with the external thiol during the conversion from **B** to **C** shown in Scheme 1.

Scheme 2. Reactions of 1a in the Presence of Thiols



We explored the substrate scope for the reaction at 25 °C and 0.05 M (Table 2). In several instances, the reactions were carried out both by a simple isomerization (method A) and by a reaction starting from the bulky thiol ester **1a** in the presence of the corresponding external thiol (method B); method B always afforded a higher reaction rate and higher enantioselectivity (Table 2, entries 1–6, 15, and 16). Notably, in method B for the reactions using **2b–2j**, the simple isomerization product **2a** was not generated (Table 2, entries 4 and 6–13). Reactions using electron-rich thiols afforded the corresponding products in higher enantioselectivity than in other cases (Table 2, entries 6, 7, and 9), although only an *ortho*-substituent decreased the enantiomeric excess (Table 2, entry 8). Electron-deficient thiols exhibited efficient reactivity and moderate to good enantioselectivity (Table 2, entries 10 and 11). Thiols bearing *p*-bromophenyl and 2-naphthyl groups were also tolerated and resulted in excellent yields with good enantioselectivity (Table 2, entries 12 and 13). A highly bulky thiol attained high enantioselectivity, but the yield was moderate due to the generation of byproduct **2a** through the competing simple isomerization (Table 2, entry 14). An aliphatic thiol ester or external thiol could also be applied in this process, albeit with moderate yield and selectivity, and byproduct **2a** was also obtained via method B in this case (Table 2, entries 15 and 16).

In addition, this reaction could also be applied to the synthesis of a δ-valerolactone (Scheme 3). The isomerization of δ-hydroxy-α,β-unsaturated thioester **5a** through method A afforded six-membered lactone **6a** in comparable enantioselectivity. Although the reaction was much slower than the formation of five-membered lactones, it was improved by the use of method B, and the enantioselectivity was also better in this case. The absolute configuration of **2b** was determined by comparing the optical rotation with the literature value[7b] (see SI for details), and the configurations for all other examples were assigned analogously.

Using catalyst **3c**, we investigated the effects of the reaction temperature; the enantioselectivity improved as the temperature increased (see Table S3 in the Supporting Information (SI) for details). The Eyring plot resulted in a straight line with a negative slope (see Figure S1a in the SI). This indicates that a single mechanism is maintained over the range of temperatures investigated and that this reaction has a manner of asymmetric induction in which the differential entropy of activation ($\Delta\Delta S^{\ddagger}$) is the determinant factor.[14–16]

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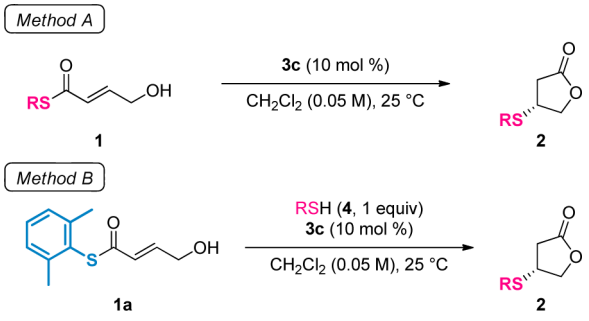
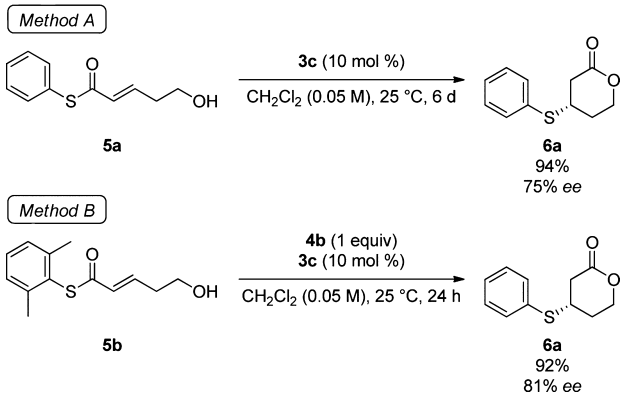
Table 2. Substrate Scope[a]



entry	R (2)	method	yield (%)[b]	ee (%)
1	2,6-$(CH_3)_2C_6H_3$ (**2a**)	A	83 (6 d)	76
2		B	93 (24 h)	78
3	Ph (**2b**)	A	95 (24 h)	77
4		B	99 (6 h)	84
5	4-$CH_3OC_6H_4$ (**2c**)	A	99 (4 d)	69
6		B	97 (6 h)	89
7	3-$CH_3OC_6H_4$ (**2d**)	B	99 (12 h)	86
8	2-$CH_3OC_6H_4$ (**2e**)	B	92 (12 h)	76
9	3,4-$(CH_3O)_2C_6H_4$ (**2f**)	B	94 (6 h)	90
10	4-$CF_3C_6H_4$ (**2g**)	B	94 (6 h)	66
11	4-ClC_6H_4 (**2h**)	B	99 (6 h)	77
12	4-BrC_6H_4 (**2i**)	B	99 (6 h)	76
13	2-naphthyl (**2j**)	B	98 (6 h)	85
14[c]	2,4,6-(*i*-Pr)$_3C_6H_4$ (**2k**)	B	50 (24 h)	88
15	Bn (**2l**)	A	68 (10 d)	33
16[d,e]		B	86 (36 h)	52

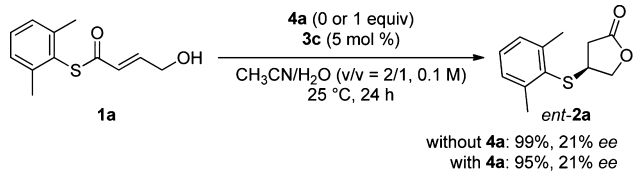
[a]Method A: reactions were run using **1** (0.15 mmol) and **3c** (0.015 mmol) in CH_2Cl_2 (0.3 mL). Method B: reactions were run using **1a** (0.15 mmol), **4** (0.15 mmol), and **3c** (0.015 mmol) in CH_2Cl_2 (0.3 mL). [b]Isolated yields. [c]**2a** was also obtained in 37% yield with 80% *ee*. [d]Reaction was run using 3 equiv of **4l** (0.45 mmol). [e]**2a** was also obtained in 14% yield with 80% *ee*.

Scheme 3. Synthesis of δ-Valerolactone



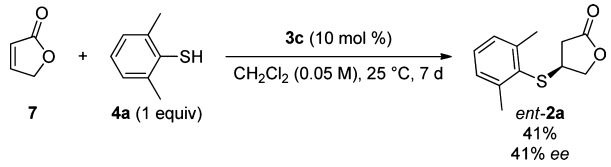
Moreover, in order to demonstrate the potential of this reaction for an enantiodivergent synthesis using a single chiral catalyst, we investigated other solvent systems as an external factor to influence the enthalpy and entropy terms, as such observations have also been reported previously (see Table S2 and Figure S2 in the SI for details).[16,17] Preliminary studies showed that a cosolvent system consisting of acetonitrile and water afforded the opposite enantiomer *ent*-**2a** both in the absence and in the presence of **4a**, albeit with modest enantiomeric excess (Scheme 4).

Scheme 4. Reactions Using 3c in CH_3CN/H_2O



To gain more information regarding the reaction mechanism, the sulfa-Michael addition of **4a** to 2-furanone (**7**) was carried out using **3c** as a catalyst in CH_2Cl_2; the absolute configuration of the obtained product was opposite to that of the product of the isomerization under the corresponding conditions (Scheme 5). This fact rules out the possibility that the isomerization of

Scheme 5. Sulfa-Michael Addition to 2-Furanone



1a takes place mainly via the formation of **7** followed by the sulfa-Michael addition of **4a** mediated by the aminothiourea catalyst. In addition, the HRMS analysis of a solution in which **1a** was subjected to a stoichiometric amount of **3c** detected a molecular ion peak corresponding to the acylammonium cation involved in **B** (found: *m*/*z* 498.1658; calcd: $[M]^+$, 498.1644; see Scheme S2 in the SI for details). Although a precise understanding of the mechanism requires additional studies, these and other experimental findings contain no contradiction to the reaction pathway we proposed in Scheme 1.

In summary, we have presented a novel method for the asymmetric synthesis of *β*-mercaptolactones via isomerization of *ω*-hydroxy-*α*,*β*-unsaturated thioesters mediated by a bifunctional aminothiourea catalyst. To our delight, the sulfur-containing cyclic esters were obtained in high yield with reasonably high enantioselectivity owing to a catalysis that exploited a covalent interaction cooperatively with anion binding; this is the first example of bifunctional catalysis utilizing the activation of electrophiles via *α*,*β*-unsaturated acylammonium intermediates and an interaction with anionic nucleophiles through a thiourea, thereby realizing a novel type of reaction. In addition, the potential of the system as an enantiodivergent synthetic method was also demonstrated by the choice of a specific solvent system such as CH_3CN/H_2O. Furthermore, the process in which the thiolate generated initially is exchanged with an external thiol suggests the high applicability of this reaction to various nucleophiles. Studies aiming at further applications of this synthetic methodology are currently underway in our laboratory, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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