

**Studies on Asymmetric Hetero-Michael Addition
Utilizing Various Modes of Organocatalytic Activation**

Yukihiro Fukata

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Contents

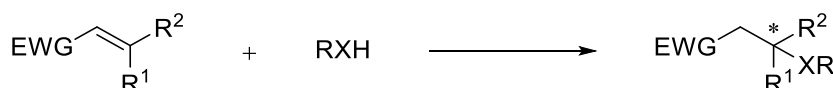
General Introduction	1
Chapter 1	19
Asymmetric Synthesis of 1,3-Oxazolidines via Intramolecular Aza-Michael Addition by Bifunctional Organocatalysts	
Chapter 2	61
Procedure-Controlled Enantioselectivity Switch in Organocatalytic 2-Oxazolidinone Synthesis	
Chapter 3	85
Asymmetric Isomerization of ω -Hydroxy- α,β -Unsaturated Thioesters into β -Mercaptolactones by a Bifunctional Amino thiourea Catalyst	
Chapter 4	117
Facile Net Cycloaddition Approach to Optically Active 1,5-Benzothiazepines	
Chapter 5	157
Isothiourea-Catalyzed Enantioselective Formal [4+3] Cycloaddition Affording 3-Substituted 1,5-Benzothiazepines	
Publication List	193
Acknowledgment	194

Abbreviations

α	observed optical rotation	k	kilo
Å	ångström	K	kelvin
Ac	acetyl	ln	logarithmus naturalis
aq	Aqueous	m	multiplet (spectral)
br	broad (spectral)	M	molar (1 M = 1 mol dm ⁻³)
Bu	butyl	Me	methyl
Bn	benzyl	mg	milligram(s)
<i>c</i>	concentration	MHz	megahertz
°C	degrees Celsius	min	minute(s)
calcd	calculated	mL	milliliter(s)
Cbz	benzyloxycarbonyl	mm	millimeter(s)
Cy	cyclohexyl	mmol	millimole(s)
δ	chemical shift in perts per million	mol	mole(s)
d	doublet (spectral)	mp.	melting point
d	day(s)	MS	molecular sieves
Δ	delta	Naph	naphthyl
dr	diastereomer ratio	nm	nanometer(s)
<i>E</i>	<i>entgegen</i> (means “opposite”)	Nu	nucleophile
Ed(s)	editor(s)	<i>o</i>	ortho
<i>ee</i>	enantiomeric excess	<i>p</i>	para
<i>ent</i>	enantiomer	pp.	page(s)
equiv	equivalent(s)	Ph	phenyl
<i>er</i>	enantiomer ratio	ppm	parts per million (spectral)
ESI	electrospray ionization	Pr	propyl
Et	ethyl	q	quartet (spectral)
EWG	electron-withdrawing group	<i>R</i>	rectus
<i>G</i>	Gibbs free energy	R	gas constant
h	hour(s)	rt	room temperature (<i>ca.</i> 25 °C)
<i>H</i>	enthalpy	s	singlet
HPLC	high performance liquid chromatography	<i>S</i>	sinister
HRMS	high-resolution mass spectrum	<i>S</i>	entropy
Hz	hertz (s ⁻¹)	sept	septet
<i>i</i>	iso	t	triplet
IR	infrared (spectral)	<i>t (tert)</i>	tertiary
<i>J</i>	coupling constant (spectral)	Ts	tosyl
J	Joule	TLC	thin-layer chromatography
		<i>Z</i>	<i>zusammen</i> (means “together”)

General Introduction

The asymmetric conjugate addition of heteroatom-centered nucleophiles, such as alcohols, amines, and thiols, to electron-deficient olefins, known as hetero-Michael reactions, can be considered one of the most powerful and reliable tools for the formation of heteroatom-substituted stereogenic centers (Scheme 1). Numerous examples of these reactions have been demonstrated, including as key strategic transformations in total syntheses. Moreover, a number of enantioselective hetero-Michael reactions have been developed over the last few decades.¹⁻⁴

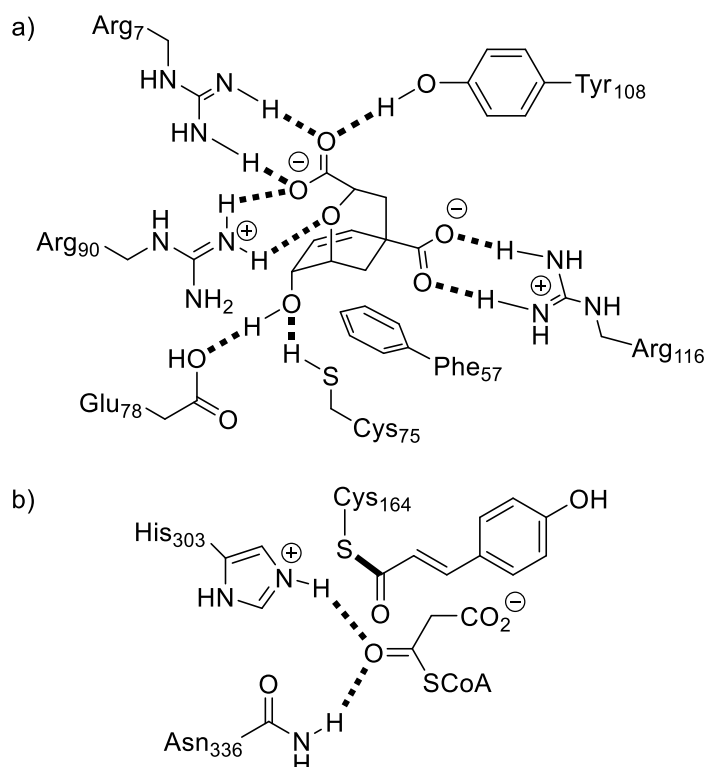


Scheme 1. Hetero-Michael addition reaction.

However, achieving high enantioselectivities for intramolecular reactions remains difficult as such reactions proceed via noncatalytic pathways owing to the rapid reaction rate of the intramolecular cyclization process. In addition, enantioselective reactions of α,β -unsaturated carboxylic acid derivatives, such as simple conjugated esters and amides, are also challenging because of the difficulty of constructing a suitable chiral environment. On the other hand, various modes of noncovalent bond interactions, such as hydrogen bonding, electrostatic effects, π - π interactions, cation- π interactions, van der Waals forces, and so on, are involved enzyme-catalyzed biosynthesis.⁵ While these noncovalent interactions play a crucial role in stereoselectivity, covalent bond interactions are also important in enzymatic pathways (Scheme 2). Depending on the reaction and the substrates, enzymes utilize all of these interactions and consequently they can accomplish high stereoselectivity.

During the last decade, organocatalysis, which mimics natural enzymes, has been one of the most rapidly growing and competitive fields in asymmetric catalysis.^{6,7} Numerous organocatalysts that activate substrates through covalent and noncovalent interactions have been

designed that contribute toward the development of enantioselective hetero-Michael addition reactions.^{8,9} An effective approach to overcoming the problems mentioned above is the utilization of the variety of available organocatalytic modes of activation depending on the reaction and substrate of interest.



Scheme 2. a) Noncovalent interactions between a transition state analog and active site residues of chorismate mutase (dashed line) and b) covalent interaction in the reaction of chalcone synthase (bold line).

1. Organocatalytic asymmetric intramolecular hetero-Michael reactions

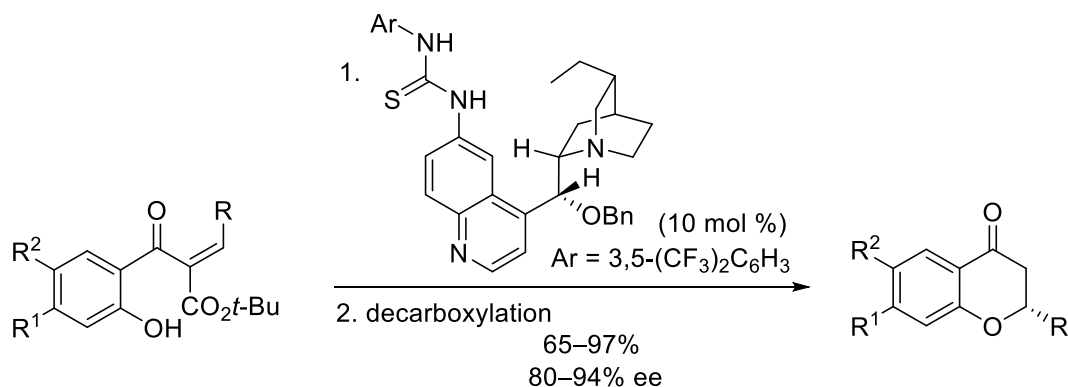
The stereocontrolled construction of chiral heterocycles is a topic of paramount importance in modern organic synthesis because of the prevalence of chiral mono- and polycyclic systems in natural products and pharmaceuticals. The intramolecular version of the organocatalytic asymmetric hetero-Michael reaction is one of the most efficient methods of preparing optically

active heterocycles in a single step.

1.1. Intramolecular oxa-Michael reactions by noncovalent activation

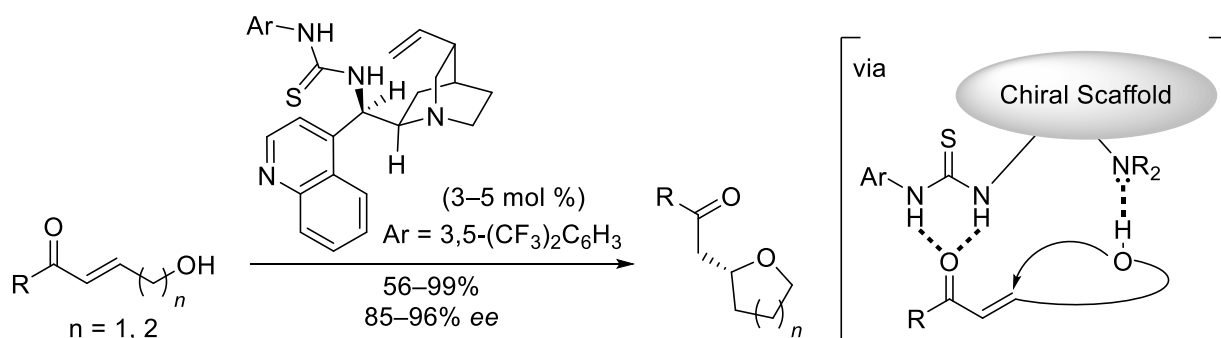
In organocatalytic asymmetric hetero-Michael reactions, chiral secondary and primary amines, which utilize the formation of iminium intermediates as a Michael acceptor, have often been employed. While these aminocatalysts have been proven to be powerful tools for enantioselective intramolecular aza-Michael reactions,^{2e,10} intramolecular oxa-Michael reactions are far less developed. The enantioselectivity of aza-Michael reactions is largely controlled by the substituents on the nucleophilic nitrogen atom through steric repulsion or π -interactions. On the other hand, because such substituents are absent from oxa-Michael reaction substrates, these strategies can only be applied to starting materials that bear an appropriate substituent near the alcohol moiety.^{11,12} Thus, to develop a more effective methodology for intramolecular hetero-Michael reactions, another type of organocatalytic activation is required.

An effective method for asymmetric intramolecular oxa-Michael reactions utilizes the activation of substrates through noncovalent bonds because multipoint recognition through these attractive interactions allows ready construction of an adequate chiral environment, regardless of the steric factor of the substrates.¹³ Moreover, the mild character of such noncovalent bonds easily maintains this chiral environment. Various noncovalent organocatalysts,¹⁴ represented by urea/thiourea-type bifunctional catalysts, have been utilized for asymmetric hetero-Michael reactions to date. In 2007, Scheidt demonstrated a chiral thiourea-cinchonine-based bifunctional catalyst that catalyzed the intramolecular oxa-Michael addition of phenol derivatives to produce chiral flavanones, which are important structures in antitumor and anti-inflammatory therapeutic agents, and chromanones in high yields with good to excellent enantioselectivities (Scheme 3).¹⁵

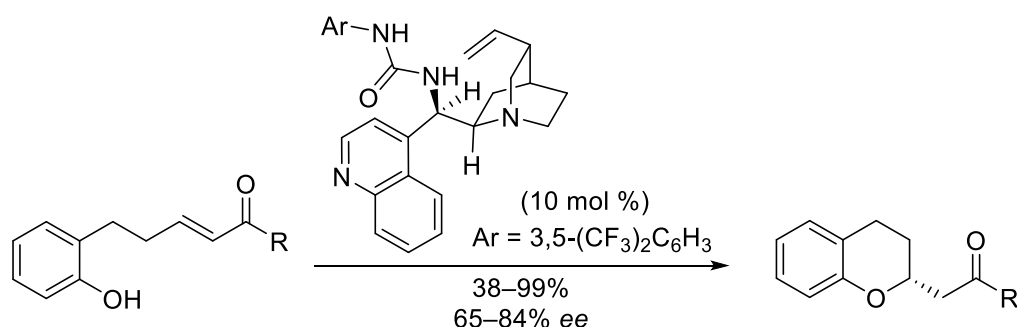


Scheme 3. Bifunctional aminothiurea-catalyzed chiral chromanone synthesis.

Asano and Matsubara reported enantioselective intramolecular oxa-Michael additions of γ - and δ -hydroxy- α,β -unsaturated ketones to afford optically active 2-substituted tetrahydrofurans and tetrahydropyrans in 2011 (Scheme 4).^{16,17} Their research group envisioned that this bifunctional catalyst-mediated hydrogen bonding would also be effective for the synthesis of chiral 2-substituted chromanes (Scheme 5).¹⁸ In the proposed transition states of these noncovalent processes, the Lewis basic oxygen atom in the carbonyl group of the substrate interacts with the thiourea group of the catalyst, and the tertiary amine of the quinuclidine moiety coordinates the nucleophilic hydroxyl group through the hydrogen bonding. Such multipoint recognition through hydrogen bonding is understood to have a large influence on the enantioselectivity of these oxa-Michael reactions.



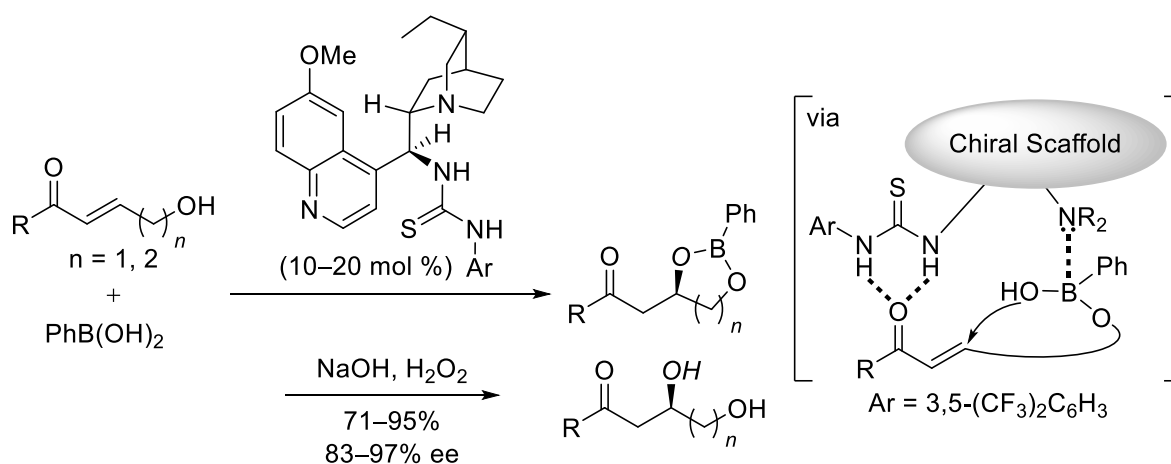
Scheme 4. Organocatalytic enantioselective intramolecular oxa-Michael reactions.



Scheme 5. Asymmetric synthesis of optically active chromanes.

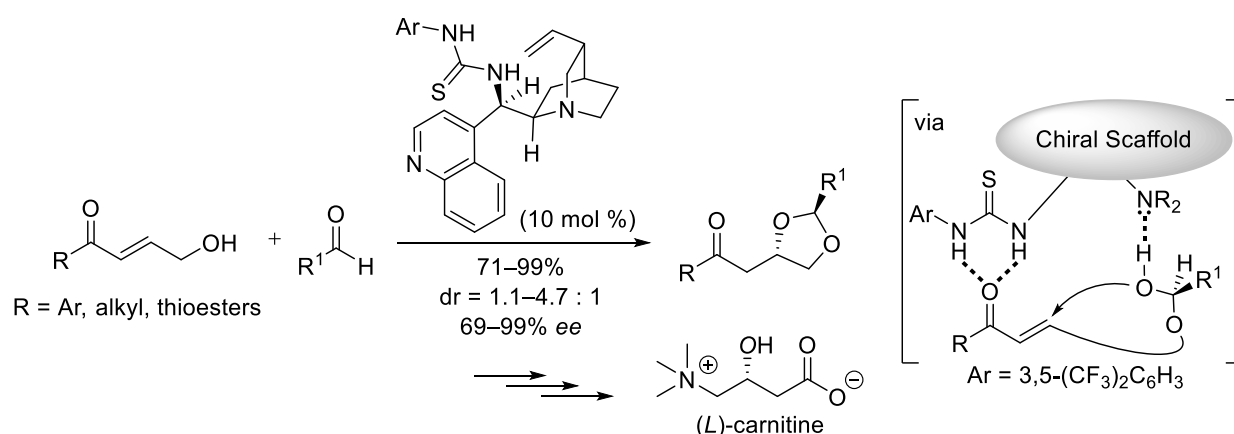
1.1.1. Reactions via hemiacetal/hemiester intermediates

The enantioselective intramolecular oxa-Michael addition of hemiacetals/hemiester offers an alternative method for formal hydration of enones, as nonenzymatic enantioselective Michael addition of water has remained very limited.¹⁹ This limitation is mainly due to the reversibility of the Michael addition process. Intramolecularization by tethering the nucleophile to the electrophile was found to be an efficient way of overcoming this problem. In 2008, Falck reported asymmetric intramolecular oxa-Michael reactions of boronic acid hemiesters triggered by a bifunctional organocatalyst (Scheme 6).²⁰ Oxidative cleavage of the resulting dioxaborolane consequently gave rise to chiral 1,2- and 1,3-diols in high yields with high enantioselectivities.



Scheme 6. Intramolecular oxa-Michael reactions of boronic acid hemiester intermediates.

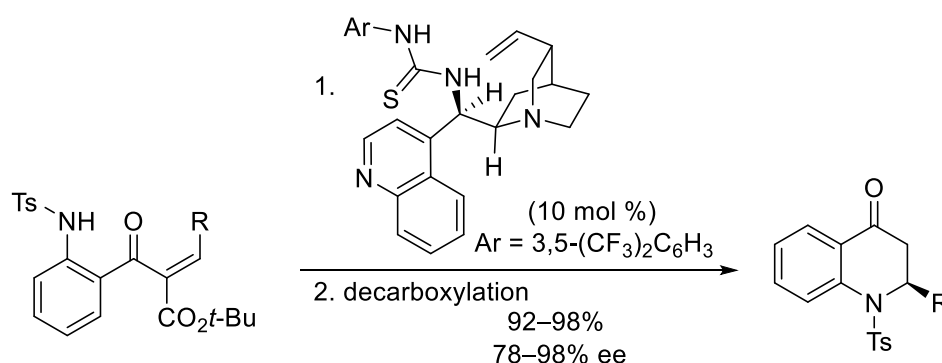
Asano and Matsubara reported formal cycloaddition reactions of γ -hydroxy- α,β -unsaturated carbonyl compounds and aldehydes via hemiacetal intermediates catalyzed by bifunctional catalysts (Scheme 7).²¹ The obtained product could be converted to (*L*)-carnitine, which is an important bioactive agent, and its hydroxyl group, which was introduced by oxa-Michael addition, was maintained.



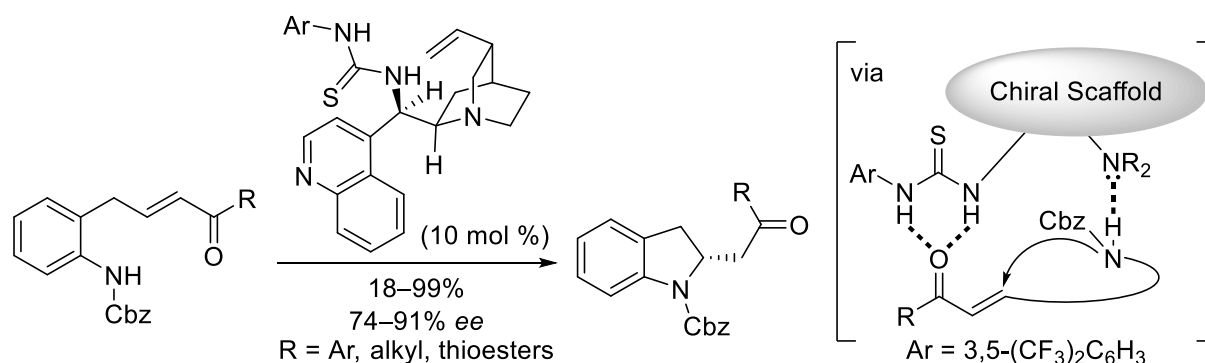
Scheme 7. Intramolecularization during an enantioselective oxa-Michael reaction via a hemiacetal intermediate.

1.2. Intramolecular aza-Michael reactions by noncovalent activation

Utilizing noncovalent bonds has been found to be effective not only for asymmetric intramolecular oxa-Michael reactions, but also for asymmetric aza-Michael reactions. In 2010, Lu reported an enantioselective intramolecular aza-Michael addition of tosylamide as the nitrogen nucleophile to a conjugated keto-ester as the Michael acceptor to afford chiral tetrahydroquinolines by bifunctional organocatalyst in high yields with excellent enantioselectivities (Scheme 8).²² Asano and Matsubara revealed the synthesis of chiral indolines using a urea-type bifunctional organocatalyst in 2013 (Scheme 9).²³ Notably, conjugated thioesters, to which an iminium intermediate cannot be applied, could also be employed in this reaction.



Scheme 8. Asymmetric intramolecular aza-Michael reaction via noncovalent activation.

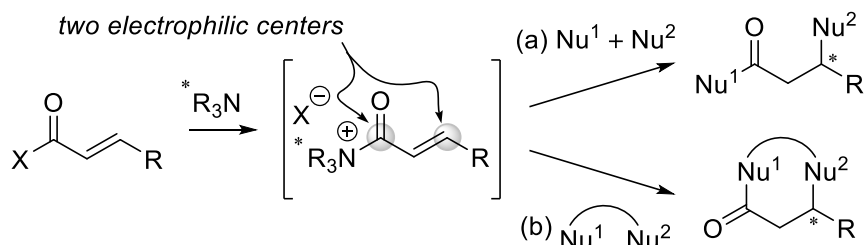


Scheme 9. Intramolecular aza-Michael addition for the synthesis of chiral indolines.

2. Covalent bond-activation of conjugated carboxylic acid derivatives via α,β -unsaturated acylammonium intermediates

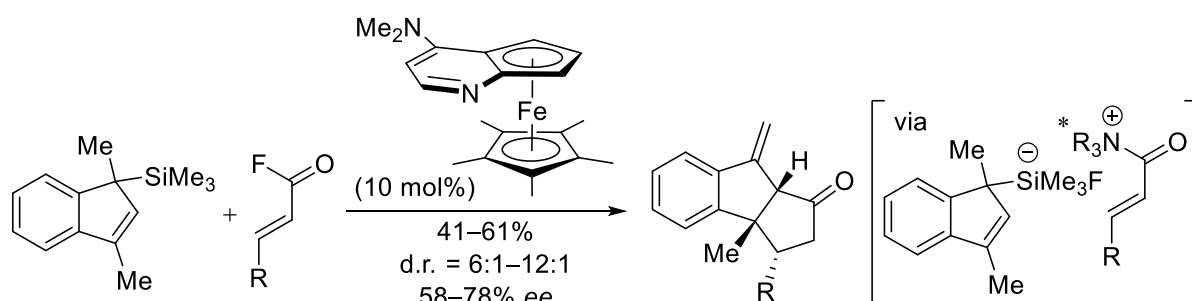
Although catalytic enantioselective intermolecular hetero-Michael addition employing enones and enals is well established, the use of simple conjugated esters remains challenging for both intra- and intermolecular reactions, with the exception of several successful examples.^{24,25,26} The activation of simple conjugated esters through only noncovalent interactions, such as hydrogen bonding, seems to be insufficient for efficient asymmetric induction. Thus, to achieve high enantioselectivities in hetero-Michael reactions of α,β -unsaturated carboxylic acid derivatives, modified Michael acceptors, such as 2-acylpyrazoles,²⁷ 2-acyloxazolidinones,²⁸ boronic acid anhydride,²⁹ and activated imides,³⁰ have been employed, as they interact with the catalyst more

strongly.



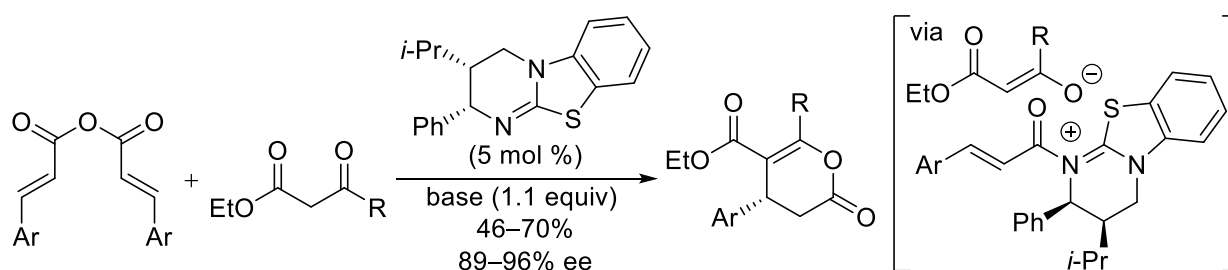
Scheme 10. Reactions of α,β -unsaturated acylammonium intermediates with nucleophiles (a) two nucleophiles and (b) one molecule with two nucleophilic sites.

On the other hand, the formation of α,β -unsaturated acylammonium intermediates using nucleophilic organocatalysts with activated conjugated carboxylic acid derivatives is expected to involve rigid catalyst–substrate interactions through a covalent bond.³¹ Recently, remarkable progress has been shown in several studies utilizing such intermediates, which will hopefully lead to a novel approach toward asymmetric hetero-Michael reactions. This strategy is also attractive in terms of synthetic transformations for the rapid assembly of complex organic molecules because such intermediates, which have two electrophilic sites, have the potential to react with two nucleophiles in a single step (Scheme 10, a). Moreover, by using a substrate with two nucleophilic sites in the same molecule, a tandem net cycloaddition reaction can be achieved to synthesize a cyclic product (Scheme 10, b).

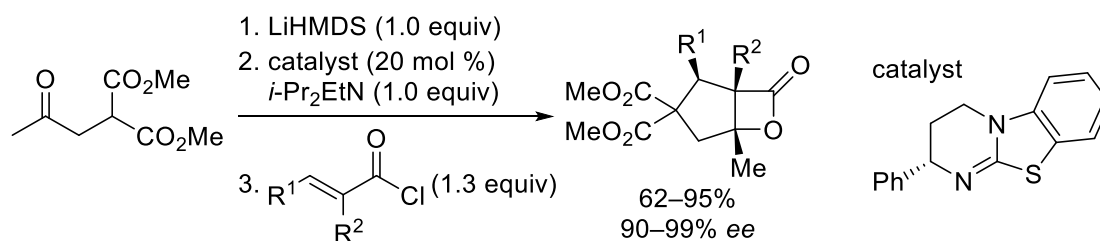


Scheme 11. Formal [3+2] cycloaddition via a chiral α,β -unsaturated acylammonium intermediate.

Net cycloaddition with an α,β -unsaturated acylammonium intermediate was first demonstrated by Fu for asymmetric net [3+2] annulations leading to diquinanes in 2006 (Scheme 11).³² In 2013, Smith reported the use of similar intermediates generated from conjugated mixed anhydrides in combination with 1,3-dicarbonyl compounds to obtain enol-lactones through an enantioselective tandem Michael-enol-lactonization process (Scheme 12).³³ Romo has reported several attractive tandem processes to construct optically active γ - or δ -lactams,^{34a} cyclopentanes,^{34b} and other molecules via chiral α,β -unsaturated acylammonium salts (Scheme 13).³⁴



Scheme 12. Tandem Michael-enol-lactonization via a conjugated acylammonium salt.



Scheme 13. Enantioselective synthesis of cyclopentanes via an α,β -unsaturated acylammonium intermediate.

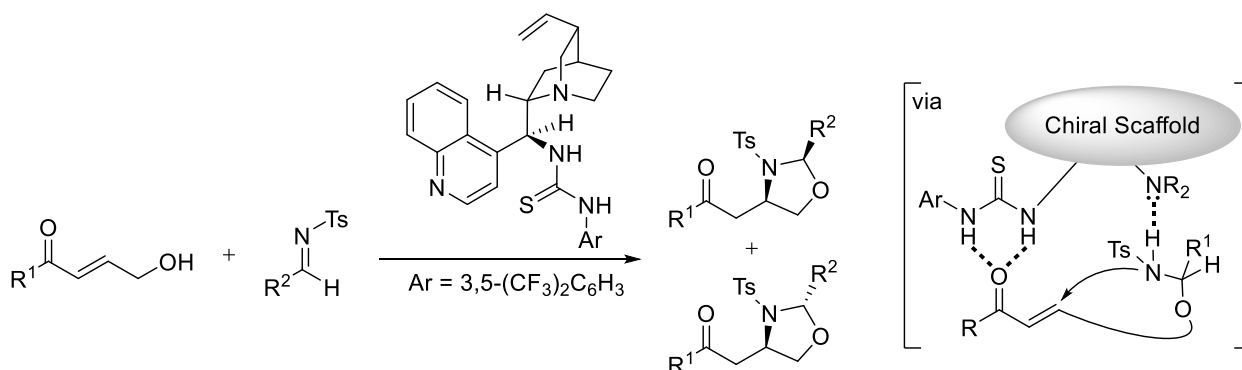
As reviewed above, organocatalytic activations via α,β -unsaturated acylammonium intermediates are effective for Michael additions of carbon-centered nucleophiles to realize net cycloadditions. These approaches are believed to have potential as a new method for asymmetric hetero-Michael reactions.

3. Overview of this thesis

The author investigated organocatalytic asymmetric hetero-Michael reactions to develop new methods for enantioselective construction of chiral heterocycles utilizing noncovalent and covalent bond activation. Each catalytic reaction was efficiently developed by tailoring the selection of the organocatalytic modes of activation depending on the reaction and substrate.

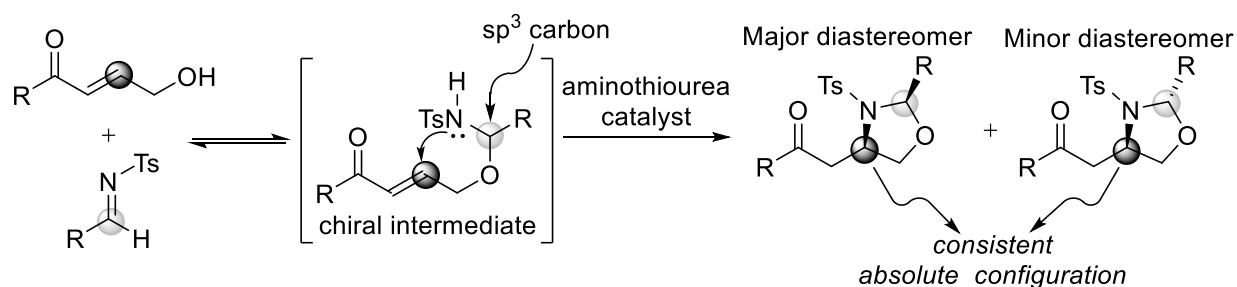
3.1. Asymmetric synthesis of chiral azacycles via intramolecular aza-Michael reactions with bifunctional organocatalysts (Chapters 1 and 2)

As reviewed above, the use of noncovalent bonds is effective to achieve enantioselective intramolecular hetero-Michael additions, and this method can also be extended to asymmetric formal [3+2] cycloadditions, including asymmetric intramolecular oxa-Michael addition processes (Scheme 6 and 7).^{20,21} In Chapter 1, the author describes an enantioselective formal [3+2] cycloaddition, including an asymmetric intramolecular aza-Michael reaction via chiral alkoxyamine intermediates generated from γ -hydroxy- α,β -unsaturated ketones and imines, carried out utilizing noncovalent bond-activation (Scheme 14).³⁵ The author developed an efficient route for synthesis of optically active nitrogen-containing heterocycles, 1,3-oxazolidines, as a mixture of diastereomers.



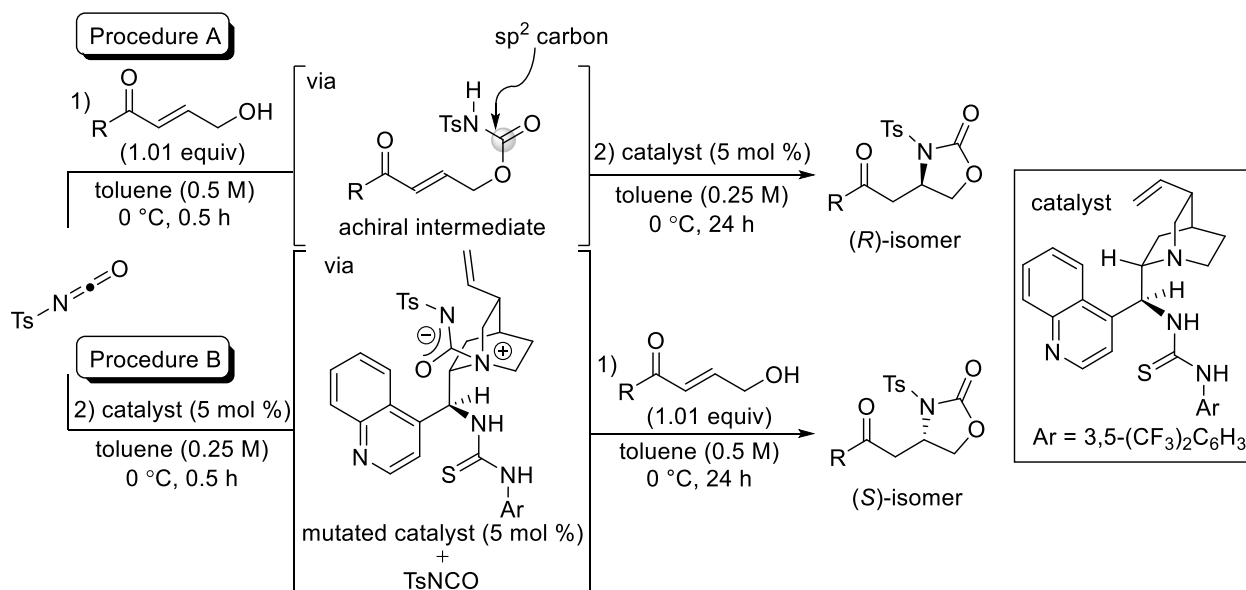
Scheme 14. Organocatalytic enantioselective formal [3+2] cycloaddition via an alkoxyamine intermediate.

The absolute configurations at the β -position of the carbonyl group in both diastereomers of the products were the same according to X-ray structure analysis (Scheme 15). This fact suggests that the stereochemistry of the products was mainly determined by the intramolecular aza-Michael addition step, regardless of the chirality of the intermediates.



Scheme 15. Stereochemistry of both diastereomers of the products.

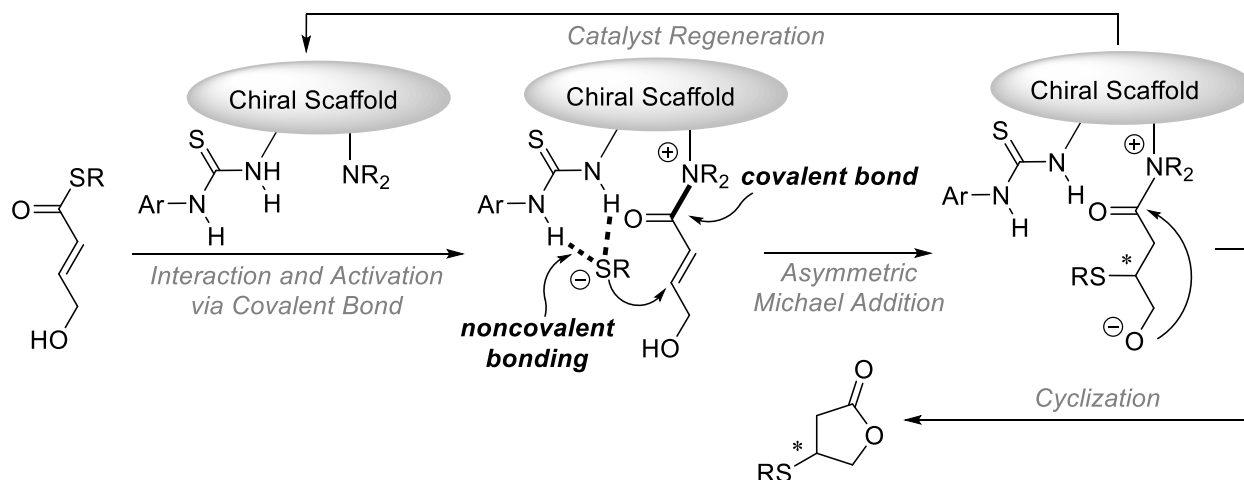
On the basis of the results described in Chapter 1, the author thought that isocyanates could be employed instead of imines, as described in Chapter 2, because enantioselective aza-Michael addition catalyzed by a cinchona-alkaloid-derived aminothiurea catalyst is expected to proceed even from an achiral carbamate intermediate.³⁶ This process is more practical for enantioselective amination of the β -position of the carbonyl group than the method described in Chapter 1 because there is no possibility to form diastereomers. In fact, chiral 2-oxazolidinones were obtained enantioselectively (Scheme 16, Procedure A). Surprisingly, the enantioselectivity switched when the sequence of adding the reagents and catalyst was changed, although the reaction components including the cinchona-alkaloid derived catalyst and the reaction conditions, were the same (Scheme 16, Procedure B). Spectroscopic studies indicated that the formation of a mutated catalyst, which is composed of a 1:1 adduct of the catalyst and isocyanate, caused this unusual enantioselectivity switch. Due to this reversal of enantioselectivity, both enantiomers could be synthesized selectively without changing the reaction components, including the enantiomer of the catalyst.



Scheme 16. Procedure-controlled enantioselectivity switch in the organocatalytic synthesis of chiral 2-oxazolidinones.

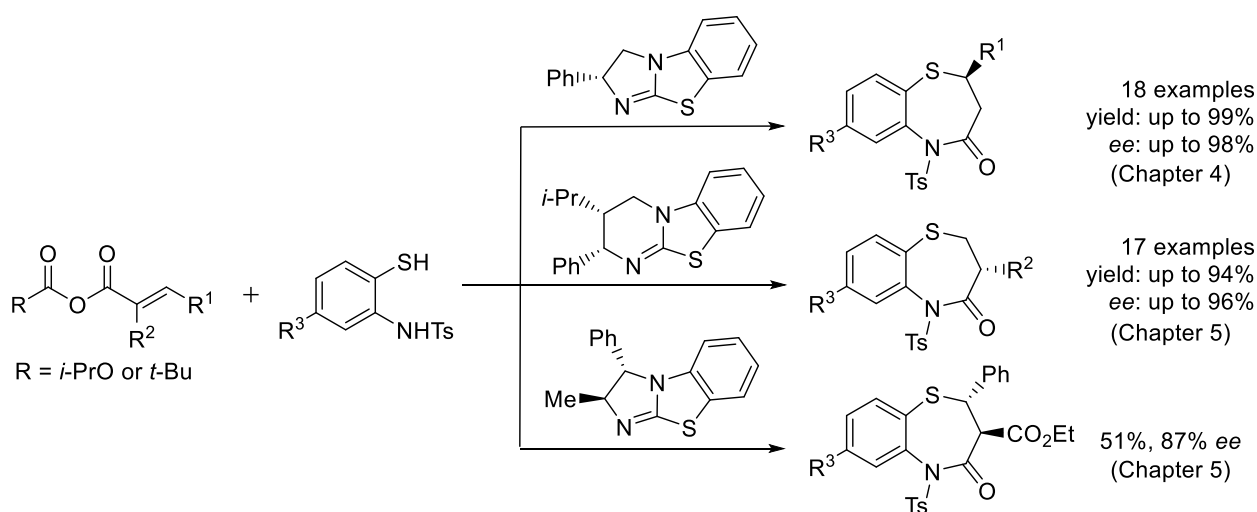
3.2. Organocatalytic sulfa-Michael reactions of α,β -unsaturated carboxylic acid derivatives via covalent bond-activation (Chapters 3–5)

The author attempted to utilize α,β -unsaturated acylammonium intermediates for asymmetric hetero-Michael reactions of α,β -unsaturated carboxylic acid derivatives. In Chapter 3, the author describes the isomerization of ω -hydroxy- α,β -unsaturated thioesters via α,β -unsaturated acylammonium intermediates using an aminothiurea catalyst to provide optically active β -mercaptolactones (Scheme 17).³⁷ The catalyst interacts with the substrate through the cooperative action of covalent bond formation at the amino group and noncovalent bonding at the thiourea group. Eyring plots showed that the enantioselectivity of this reaction depended dominantly on the differential activation entropy in various organic solvents. Thus, the potential for enantiodivergent synthesis could be demonstrated by carrying out the reaction in a different solvent system, as the governing factor for the enantioselectivity changed with the differential activation enthalpy.



Scheme 17. Organocatalytic isomerization of ω -hydroxy- α,β -unsaturated thioesters.

The author discovered highly stereoselective net [4+3] cycloaddition reactions via the reaction of α,β -unsaturated acylammonium intermediates with 2-aminobenzenethiols, which have two nucleophilic heteroatoms (Scheme 18).^{38,39} This protocol can be applied for the divergent synthesis of 1,5-benzothiazepines, which are representative skeletons in the field of pharmaceutical science, with various substitution patterns. Hence, this synthetic approach is expected to significantly contribute toward the construction of a library of 1,5-benzothiazepines for assay evaluation in drug discovery. These reactions are described in Chapters 4 and 5.



Scheme 18. Net cycloaddition approach for the construction of a library of chiral 1,5-benzothiazepines.

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Instrumental and Materials

^1H and ^{13}C Nuclear magnetic resonance spectra were taken on a Varian UNITY INOVA 500 (^1H , 500 MHz; ^{13}C , 125.7 MHz) spectrometer using tetramethylsilane as an internal standard for ^1H NMR ($\delta = 0$ ppm) and CDCl_3 as an internal standard for ^{13}C NMR ($\delta = 77.0$ ppm). ^1H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, br = broad, m = multiplet), coupling constants (Hz), integration. ^{19}F NMR spectra were measured on a Varian Mercury 200 (^{19}F , 188 MHz) spectrometer with hexafluorobenzene as an internal standard ($\delta = 0$ ppm). Mass spectra were recorded on a Thermo Scientific Exactive (ESI, APCI) spectrometers. High performance liquid chromatography (HPLC) was performed with a SHIMADZU Prominence. Infrared (IR) spectra were determined on a SHIMADZU IR Affinity-1 spectrometer. Melting points were determined using a YANAKO MP-500D. Optical rotations were measured on a HORIBA SEPA-200. X-ray data were taken on Bruker Smart APEX X-Ray diffractometer, Rigaku XtalAB mini diffractometer and Rigaku R-Axis RAPID diffractometer equipped with a CCD detector. TLC analyses were performed by means of Merck Kieselgel 60 F₂₅₄ (0.25 mm) Plates. Visualization was accomplished with UV light (254 nm) and/or such as an aqueous alkaline KMnO_4 solution followed by heating. Flash column chromatography was carried out using Kanto Chemical silica gel (spherical, 40–50 μm). Unless otherwise noted, commercially available reagents were used without purification.

Chapter 1

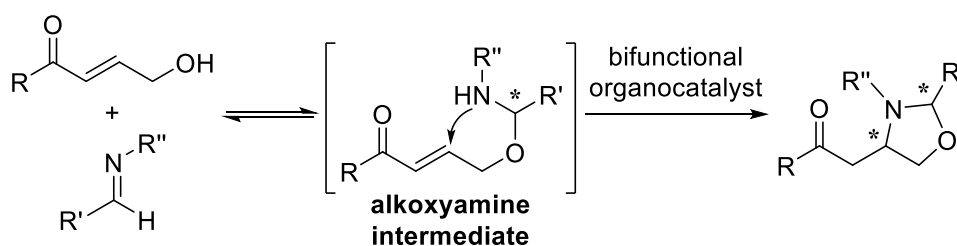
Asymmetric Synthesis of 1,3-Oxazolidines via Intramolecular Aza-Michael Addition by Bifunctional Organocatalysts

An enantioselective formal [3+2] cycloaddition, including asymmetric intramolecular aza-Michael reaction via chiral alkoxyamine intermediates generated from γ -hydroxy- α,β -unsaturated carbonyls and imines, carried out in the presence of cinchona-alkaloid-thiourea-based bifunctional catalysts. This protocol gives easy access to a wide range of chiral 1,3-oxazolidines.

Introduction

Asymmetric 1,3-oxazolidine frameworks are found in natural products and pharmaceutical compounds.¹ They are also utilized as versatile chiral intermediates leading to β -amino carbonyl compounds, as well as synthetic reagents such as chiral auxiliaries and ligands.² Therefore, the development of an efficient route to various asymmetric 1,3-oxazolidine derivatives is highly desirable. Nevertheless, their synthesis is mainly based on optically active starting materials, and there are very few examples of the catalytic enantioselective synthesis methods.³

Asano and Matsubara developed several asymmetric cycloetherification reactions mediated by bifunctional organocatalysts, which can facilitate multipoint recognition via hydrogen bonding in the intramolecular oxa-Michael addition step.^{4,5} This methodology could also be extended to the formal [3+2] cycloaddition of γ -hydroxy- α,β -unsaturated carbonyls with aldehydes via hemiacetal intermediates.^{4b,4c} Inspired by these results, the author attempted to use this formal cycloaddition approach for the development of an efficient route to nitrogen-containing chiral heterocycles (Scheme 1).⁶ In this Chapter, the author present a novel asymmetric organocatalytic formal [3+2] cycloaddition method for the synthesis of 1,3-oxazolidines using cinchona-alkaloid-thiourea-based bifunctional organocatalysts.⁷



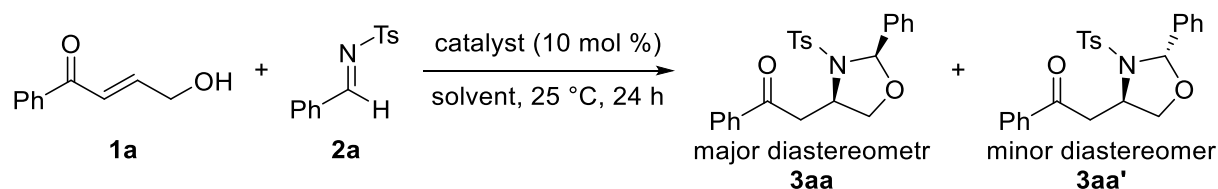
Scheme 1. Formal cycloaddition route to 1,3-oxazolidines using bifunctional organocatalyst.

Results and Discussion

The reaction of (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) with (*E*)-*N*-benzylidene-4-

methylbenzenesulfonamide (**2a**) in the presence of 10 mol % cinchonidine-derived bifunctional catalyst **4a** in CHCl₃ at 25 °C was first examined (Table 1). As expected, 1,3-oxazolidines were formed as a diastereomer mixture with modest enantioselectivity in 83% yield (entry 1). Screening of various solvents revealed that less polar solvents are more efficient for the stereoselectivity (entries 8–10).⁸ When the reaction was carried out in toluene at 0 °C, the enantioselectivity was improved to 64% *ee* (entry 11). Notably, even when the catalyst loading was reduced to 1 mol %, the stereoselectivity remained unchanged (entry 12). No dramatic improvement in the stereoselectivity was observed when the reaction temperature was decreased to –20 °C, and the yield decreased considerably (entry 13). Catalyst screening identified that **4c** efficiently aided the formation of the opposite enantiomer of **3aa** in good yield and with high stereoselectivity (entry 15).

Table 1. Optimization of conditions^a

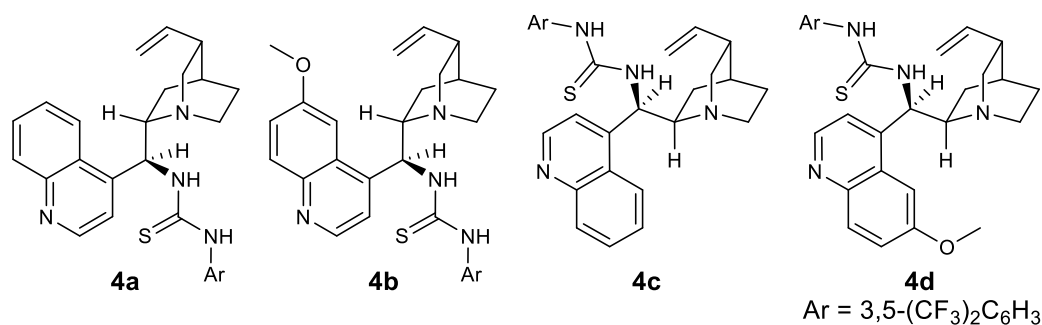


entry	catalyst	solvent	yield (%) ^b	dr ^c	ee (3aa , 3aa') (%)
1	4a	CHCl ₃	83	2.4:1	43, 30
2	4a	Et ₂ O	78	3.0:1	59, 44
3	4a	THF	53	2.4:1	46, 46
4	4a	CPME	77	2.6:1	51, 51
5	4a	DME	63	2.4:1	55, 48
6	4a	CH ₃ CN	79	2.7:1	54, 19
7	4a	EtOAc	79	2.7:1	47, 22
8	4a	benzene	93	5.6:1	53, 22
9	4a	toluene	85	4.5:1	54, 32

Table 1. (continued)

10	4a	xylene	89	4.3:1	56, 37
11 ^d	4a	toluene	95	2.4:1	64, 59
12 ^{d,e}	4a	toluene	46	2.5:1	64, 60
13 ^f	4a	toluene	62	2.4:1	67, 62
14 ^d	4b	toluene	53	3.0:1	53, 48
15 ^d	4c	toluene	84	9.1:1	–63, –40
16 ^d	4d	toluene	59	10:1	–62, –24

^aReactions were run using **1a** (0.25 mmol), **2a** (0.25 mmol), and catalyst (0.025 mmol) in solvent (0.5 mL). ^bIsolated yields. ^cDiastereomeric ratios were determined by ¹H NMR. ^dReaction was run at 0 °C. ^eReaction was run using 1 mol % of **4a** (0.0025 mmol). ^fReaction was run at –20 °C.



With the optimized conditions in hand, scope of substrates were examined (Table 2). γ -Hydroxy- α,β -unsaturated ketones **1** could be readily prepared from commercially available materials by reported procedure.⁹ Using **1a** as the substrate, the feasibility of extending the reaction to various imines **2** were examined (entries 1–9).¹⁰ The corresponding products were obtained with similar stereoselectivity, regardless of the electronic nature of the imine (entries 2 and 3). An imine bearing *p*-bromophenyl group also afforded the corresponding product (entry 4). In addition, imines with *o*-tolyl, 1-naphthyl, and 2-thienyl substituents gave the cycloadducts with high diastereoselectivity (entries 5–7). Notably, high enantioselectivity of up to 87% *ee* was achieved when using imines with alkyl substituents (entries 8 and 9). The reactions of various enones with imines **2a** and **2f** were also investigated (entries 10–23). In most cases, **2f** gave the corresponding 1,3-oxazolidines with high diastereoselectivity. Both electron-rich and electron-

deficient enones afforded the desired cycloaddition products (entries 10–13). A substrate bearing *p*-bromophenyl group was tolerated, but *o*-tolyl- and 1-naphthyl-substituted enones gave low enantioselectivity (entries 14–19). Further, heterocycle- or alkyl-substituted enones gave the corresponding 1,3-oxazolidines with acceptable stereoselectivity (entries 20–23). The absolute configuration of **3af** (the major diastereomer) was determined by X-ray analysis,¹¹ and the configurations of all other examples were assigned analogously.

Table 2. Scope of substrates^a

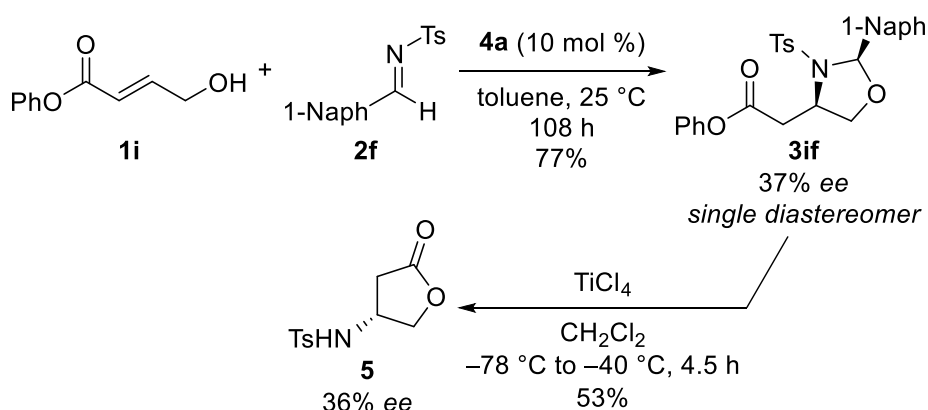
entry	R ¹	R ²	3	yield (%) ^b	dr ^c	ee (3aa , 3aa') (%) ^d
1	Ph	Ph	3aa	95	2.4:1	64
2 ^e	Ph	4-CH ₃ OC ₆ H ₄	3ab	75	3.7:1	65
3	Ph	4-CF ₃ C ₆ H ₄	3ac	70	4.3:1	66
4	Ph	4-BrC ₆ H ₄	3ad	84	3.1:1	51
5	Ph	2-CH ₃ C ₆ H ₄	3ae	74	5.3:1	57
6	Ph	1-naphthyl	3af	95	7.2:1	55
7	Ph	2-thienyl	3ag	55	9.3:1	53
8	Ph	cyclohexyl	3ah	99	1.9:1	74
9	Ph	<i>t</i> -Bu	3ai	62	2.6:1	87
10	4-CH ₃ OC ₆ H ₄	Ph	3ba	58	2.2:1	63
11	4-CH ₃ OC ₆ H ₄	1-naphthyl	3bf	88	5.3:1	55
12	4-CF ₃ C ₆ H ₄	Ph	3ca	71	4.8:1	66
13	4-CF ₃ C ₆ H ₄	1-naphthyl	3cf	95	11:1	60
14	4-BrC ₆ H ₄	Ph	3da	84	4.0:1	68
15	4-BrC ₆ H ₄	1-naphthyl	3df	87	11:1	60

Table 2. (continued)

16	2-CH ₃ C ₆ H ₄	Ph	3ea	55	11:1	23
17	2-CH ₃ C ₆ H ₄	1-naphthyl	3ef	90	11:1	19
18	1-naphthyl	Ph	3fa	93	11:1	24
19	1-naphthyl	1-naphthyl	3ff	87	11:1	20
20	2-thienyl	Ph	3ga	74	2.6:1	61
21	2-thienyl	1-naphthyl	3gf	91	7.2:1	49
22	C ₆ H ₅ (CH ₂) ₂	Ph	3ha	45	3.3:1	65
23 ^f	C ₆ H ₅ (CH ₂) ₂	1-naphthyl	3hf	54	6.3:1	65

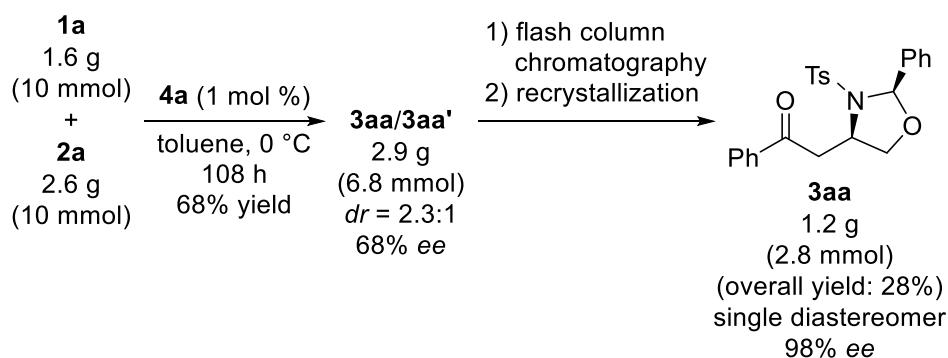
^aReactions were run using **1** (0.25 mmol), **2** (0.25 mmol), and **4a** (0.025 mmol) in toluene (0.5 mL). ^bIsolated yields. ^cDiastereomeric ratios were determined by ¹H NMR. ^dValues are for the major diastereomers of **3**. ^eReaction was run at 25 °C. ^fReaction was run for 48 h.

The γ -hydroxy- α,β -unsaturated ester **1i** could also be used in this protocol. The reaction of **1i** with imine **2f** afforded **3if** as a single diastereomer, albeit with low enantioselectivity (Scheme 2). Subsequent treatment of **3if** with titanium tetrachloride gave β -tosylamino- γ -butyrolactone (**5**).¹² The absolute configuration of **5** was assigned as (*R*) by comparing the optical rotation with the literature value.^{12e,13}

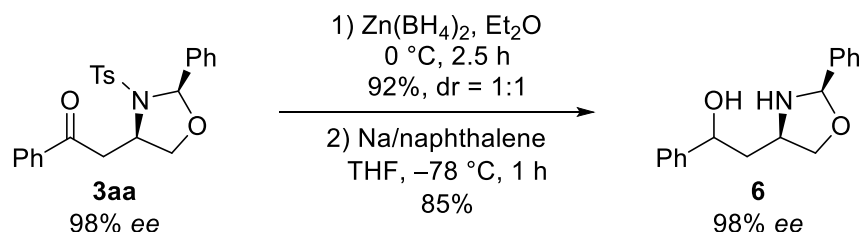


Scheme 2. Formal [3+2] cycloaddition of γ -hydroxy- α,β -unsaturated ester **1i** with **2f** and further transformation to β -amino- γ -butyrolactone **5**.

Although a major limitation of this reaction is its moderate stereoselectivity, we could establish the catalytic synthesis of enantioenriched **3aa** on a gram scale (Scheme 3). Formal [3+2] cycloaddition of **1a** (1.6 g, 10 mmol) with **2a** (2.6 g, 10 mmol) in the presence of 1 mol % **4a** afforded **3aa**/**3aa'** (2.9 g, 6.8 mmol, 68% yield) in 2.3:1 diastereomeric ratio, with 68% *ee* for the major diastereomer **3aa**. Separation of the major diastereomer by flash silica gel column chromatography using toluene/EtOAc/hexane (v/v/v = 30/1/10) as an eluent and subsequent one-time recrystallization with 2-propanol gave 1.2 g of **3aa** (2.8 mmol, overall yield: 28%) with 98% *ee*. Besides, the tosyl group could be removed after reduction of the carbonyl group by the treatment with sodium naphthalenide to afford **6** in high yield without any erosion of optical purity (Scheme 4).



Scheme 3. Asymmetric synthesis of 1,3-oxazolidine **3aa** on a gram scale.



Scheme 4. Deprotection of **3aa**.¹⁴

Conclusion

In summary, the author has developed a novel efficient route to a wide range of optically active 1,3-oxazolidines via organocatalytic formal [3+2] cycloaddition. Despite its moderate stereoselectivity, this protocol is expected to contribute significantly to the construction of a 1,3-oxazolidine library. In addition, the author demonstrated that bifunctional organocatalysts can aid the asymmetric synthesis of nitrogen-containing heterocycles via intramolecular aza-Michael addition.

Experimental Section

Materials.

Unless otherwise noted, commercially available reagents were used without purification. Imines **2** were prepared according to the literature.¹⁵

General procedure for asymmetric [3+2] cycloaddition reaction

In a 5-mL vial, after the mixture of γ -hydroxy- α,β -unsaturated ketone **1** (0.25 mmol) and imine **2** (0.25 mmol) in toluene (0.5 mL) was stirred for 10 min at 0 °C, catalyst **4a** (0.025 mmol) was added. The mixture was stirred at 0 °C for 24 h. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **4a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using toluene/EtOAc/hexane (v/v/v = 30/1/9) as an eluent afforded each diastereomer of the corresponding oxazolidine **3**. Racemic compounds were prepared using triethylamine as a catalyst.

Procedure for asymmetric [3+2] cycloaddition reaction on a gram scale

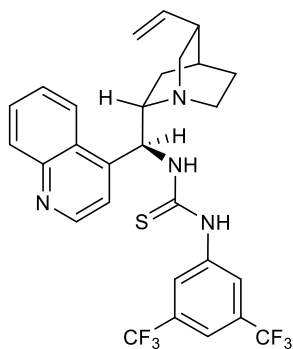
In a 50-mL round bottom flask, after the mixture of γ -hydroxy- α,β -unsaturated ketone **1a** (1.6

g, 10 mmol) and imine **2a** (2.6 g, 10 mmol) in toluene (20 mL) for 10 min at 0 °C, catalyst **4a** (56 mg, 0.1 mmol) was added. The mixture was stirred at 0 °C for 108 h. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **4a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using toluene/EtOAc/hexane (v/v/v = 30/1/10) as an eluent afforded the major diastereomer of **3aa** as a white solid (1.9 g, 4.5 mmol, 67% *ee*) and the minor diastereomer of **3aa** as a white solid (0.75 g, 1.8 mmol, 64% *ee*), respectively. After subsequent one-time recrystallization with 2-propanol, evaporating the solvent after removal of the precipitate gave 1.2 g of **3aa** with with 98% *ee* (2.8 mmol, overall yield: 28%).

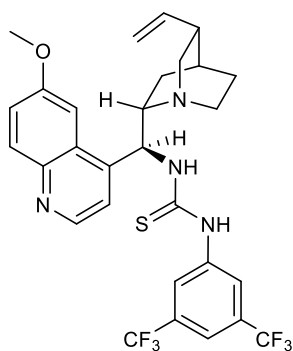
Procedure for preparation of bifunctional catalysts 4

Bifunctional organocatalysts **4** were prepared by the literature procedure.^{7c} Cinchonidine (1.5 g, 5 mmol) and triphenylphosphine (1.6 g, 6 mmol) were dissolved in THF (25 mL), and the solution was cooled to 0 °C. Diethyl azodicarboxylate (1.0 g, 6 mmol) was subsequently added. To the resulting solution was added dropwise the solution of diphenyl phosphoryl azide (1.3 mL, 6 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to ambient temperature. After being stirred for 24 h, it was heated to 50 °C and stirred for 10 h. Triphenylphosphine (1.7 g, 6.5 mmol) was added again, and the mixture was stirred at 50 °C for additional 15 h. After the solution was cooled to ambient temperature, H₂O (0.5 mL) was added, and the solution was stirred for 24 h. The solvents were removed in vacuo, and the residue was dissolved in CH₂Cl₂/10% aqueous hydrochloric acid (25 mL/25 mL). The aqueous phase was separated and washed with CH₂Cl₂ (25 mL × 4). It was subsequently made alkaline with aqueous ammonia, and the aqueous phase was extracted with CH₂Cl₂ (25 mL × 4). The combined organic layers were dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using EtOAc/CH₃OH (v/v = 9/1) then CHCl₃/CH₃OH (v/v = 8/2) as an eluent gave the corresponding 9-amino(9-deoxy)cinchona alkaloids. Next, to the solution of the obtained 9-amino(9-deoxy)cinchona alkaloid in THF (6 mL) was slowly added a solution of 3,5-

bis(trifluoromethyl)phenyl isothiocyanate (1 equiv) in THF (4 mL) at ambient temperature. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using $\text{CHCl}_3/\text{CH}_3\text{OH}$ (v/v = 95/5) as an eluent gave the corresponding bifunctional organocatalyst **4**.

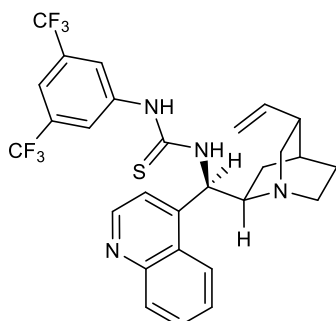


4a. White solid; 44% yield (1.2 g) (for 2 steps from cinchonidine). $[\alpha]_{\text{D}}^{23} -101.0$ (*c* 1.24, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.80 (br s, 1H), 8.35 (br s, 1H), 8.14 (d, $J = 8.5$ Hz, 1H), 7.80 (s, 2H), 7.74 (dd, $J = 8.0, 7.5$ Hz, 1H), 7.69 (s, 1H), 7.63 (dd, $J = 8.0, 7.5$ Hz, 1H), 7.27 (br s, 1H), 5.78 (br s, 1H), 5.67 (m, 1H), 4.98 (m, 2H), 3.26 (m, 1H), 3.20 (br s, 1H), 3.17 (dd, $J = 13.5, 10.5$ Hz, 1H), 2.78 (m, 2H), 2.33 (br s, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.33 (m, 1H), 0.93 (br s, 1H). ^{13}C NMR (CDCl_3) δ 180.9, 149.9, 148.5, 145.9, 140.7, 139.9, 132.6 (q, $J = 33.6$ Hz), 130.4, 129.5, 127.0, 123.6, 122.9 (q, $J = 273.0$ Hz), 119.1, 118.9, 115.0, 61.5, 56.5, 54.9, 41.1, 39.2, 27.5, 27.1, 25.7. Mp. 122.8–123.1 °C. IR (neat): 3240, 3081, 2946, 2366, 1510, 1473, 1384, 1281, 1181, 1135, 990, 958, 884, 849, 755, 683 cm^{-1} . HRMS Calcd for $\text{C}_{28}\text{H}_{26}\text{F}_6\text{N}_4\text{S}$: $[\text{M}+\text{H}]^+$, 565.1861. Found: m/z 565.1855.

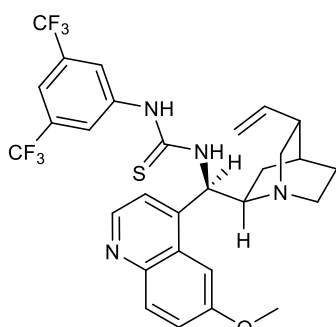


4b. White solid; 27% yield (0.80 g) (for 2 steps from quinine). $[\alpha]_{\text{D}}^{23} -99.0$ (*c* 1.24, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.60 (br s, 1H), 8.00 (d, $J = 8.5$ Hz, 1H), 7.82 (br s, 2H), 7.68 (s, 1H), 7.62 (br s, 1H), 7.39 (d, $J = 8.5$ Hz, 1H), 7.18 (br s, 1H), 5.84 (br s, 1H), 5.70 (m, 1H), 5.01 (m, 2H), 3.96 (s, 3H), 3.37 (br s, 1H), 3.30 (br s, 1H), 3.18 (m, 1H), 2.79 (br s, 2H), 2.35 (br s, 1H), 1.72 (s, 1H), 1.68 (m, 2H), 1.41 (m, 1H), 0.92 (br s, 1H). ^{13}C NMR (CDCl_3) δ 181.0, 158.2, 147.4, 144.8, 144.0, 140.6, 140.0, 132.6 (q, $J = 33.6$ Hz), 131.8, 127.9, 123.6, 122.9 (q, $J = 273.0$ Hz), 122.0, 118.8, 115.1, 102.1, 61.2, 55.7, 54.9, 41.3, 39.0, 27.5, 27.1, 25.7. Mp. 121.0–121.5 °C. IR (neat): 3220, 2946, 2360, 1623, 1510, 1475, 1384, 1279, 1180, 1134, 1032, 959, 917, 885, 850, 683 cm^{-1} . HRMS Calcd for $\text{C}_{29}\text{H}_{28}\text{F}_6\text{N}_4\text{OS}$: $[\text{M}+\text{H}]^+$,

595.1966. Found: m/z 595.1961.



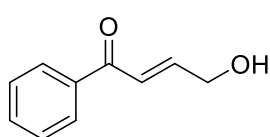
4c. White solid; 36% yield (1.0 g) (for 2steps from cinchonine). $[\alpha]_D^{23} +163.3$ (c 1.23, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.83 (br s, 1H), 8.28 (br s, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 7.85 (br s, 2H), 7.56 (dd, $J = 7.5, 7.5$ Hz, 1H), 7.68 (s, 1H), 7.64 (dd, $J = 7.5, 7.5$ Hz, 1H), 7.29 (br s, 1H), 5.81 (br s, 2H), 5.14 (m, 2H), 3.21 (br s, 1H), 3.00 (m, 3H), 2.92 (br s, 1H), 2.36 (m, 1H), 1.66 (s, 1H), 1.59 (m, 2H), 1.22 (br s, 1H), 0.95 (m, 1H). ^{13}C NMR (CDCl_3) δ 181.3, 150.0, 148.6, 145.8, 140.2, 139.3, 132.5 (q, $J = 33.6$ Hz), 130.5, 129.5, 127.1, 126.7, 123.4, 122.9 (q, $J = 273.1$ Hz), 122.8, 119.0, 118.7, 115.5, 61.8, 55.7, 48.5, 47.0, 38.9, 27.3, 26.0, 24.9. Mp. 189.9–190.3 °C. IR (KBr): 3428, 3246, 2944, 2360, 1622, 1588, 1512, 1474, 1386, 1281, 1183, 1126, 960, 882, 848, 752, 682 cm^{-1} . HRMS Calcd for $\text{C}_{28}\text{H}_{26}\text{F}_6\text{N}_4\text{S}$: $[\text{M}+\text{H}]^+$, 565.1861. Found: m/z 565.1855.



4d. White solid; 41% yield (1.2 g) (for 2steps from quinidine). $[\alpha]_D^{23} +122.6$ (c 1.33, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.65 (br s, 1H), 8.02 (d, $J = 9.0$ Hz, 1H), 7.86 (s, 2H), 7.67 (s, 1H), 7.59 (br s, 1H), 7.40 (d, $J = 9.0$ Hz, 1H), 7.23 (br s, 1H), 5.86 (br s, 2H), 5.19 (br s, 1H), 5.15 (d, $J = 9.5$ Hz, 1H), 3.97 (s, 3H), 3.22 (br s, 1H), 3.10 (br s, 1H), 3.03 (m, 2H), 2.94 (m, 1H), 2.38 (m, 1H), 1.70 (s, 1H), 1.61 (m, 2H), 1.27 (br s, 1H), 1.02 (m, 1H). ^{13}C NMR (CDCl_3) δ 181.0, 158.1, 147.3, 144.7, 144.5, 140.1, 139.6, 132.5 (q, $J = 33.6$ Hz), 131.6, 128.0, 123.5, 122.9 (q, $J = 273.0$ Hz), 122.3, 118.7, 115.3, 101.7, 61.4, 55.6, 48.5, 47.1, 38.7, 27.1, 26.1, 25.0. Mp. 125.0–125.2 °C. IR (KBr): 3221, 2944, 2361, 1735, 1623, 1511, 1475, 1384, 1278, 1177, 1134, 1034, 959, 916, 884, 850, 826, 682 cm^{-1} . HRMS Calcd for $\text{C}_{29}\text{H}_{28}\text{F}_6\text{N}_4\text{OS}$: $[\text{M}+\text{H}]^+$, 595.1966. Found: m/z 595.1961.

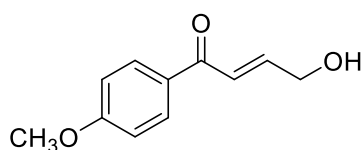
General procedure for preparation of γ -hydroxy- α,β -unsaturated carbonyls **1**

γ -Hydroxy- α,β -unsaturated carbonyls **1** were prepared by literature procedures.^{4c,9} The characterization results of **1** are as blow.

(*E*)-4-Hydroxy-1-phenylbut-2-en-1-one (1a**):** CAS RN [156386-82-2].

White solid. ^1H NMR (C_6D_6) δ 7.92 (m, 2H), 7.11 (m, 1H), 7.09 (dt, J = 15.5, 2.0 Hz, 1H), 7.04 (m, 2H), 6.99 (dt, J = 15.5, 3.5 Hz, 1H), 3.75 (br s, 2H). ^{13}C NMR (C_6D_6) δ 189.3, 147.3, 138.5, 132.6, 128.9, 128.7, 123.5,

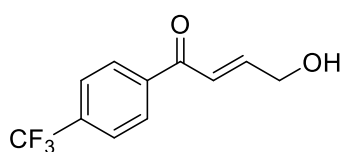
62.1.

(*E*)-4-Hydroxy-1-(4-methoxyphenyl)but-2-en-1-one (1b**):** CAS RN [112533-12-7].

White solid. ^1H NMR (C_6D_6) δ 8.00 (m, 2H), 7.15 (m, 1H), 7.07 (dt, J = 15.0, 3.5 Hz, 1H), 6.64 (m, 2H), 3.77 (m, 2H), 3.16 (s, 3H).

^{13}C NMR (C_6D_6) δ 188.6, 163.6, 146.3, 131.5, 131.2, 123.4, 114.1,

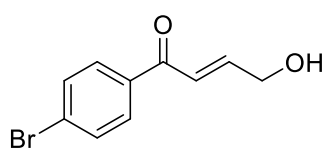
62.2, 54.9.

(*E*)-6-Hydroxy-1-(4-trifluoromethylphenyl)but-2-en-1-one (1c**):** CAS RN [1158843-58-3].

Colorless oil. ^1H NMR (C_6D_6) δ 7.66 (m, 2H), 7.26 (m, 2H), 6.98 (m, 1H), 6.93 (m, 1H), 3.82 (m, 2H), 1.58 (br s, 1H). ^{13}C NMR

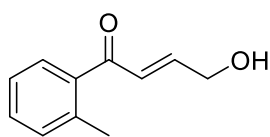
(C_6D_6) δ 188.8, 148.6, 141.0, 133.8 (q, J = 32.7 Hz), 129.0, 125.7 (q,

J = 3.9 Hz), 124.4 (q, J = 272.5 Hz), 123.3, 62.0. ^{19}F NMR (C_6D_6) δ 99.4.

(*E*)-1-(4-Bromophenyl)-4-hydroxybut-2-en-1-one (1d**):** CAS RN [557085-43-5].

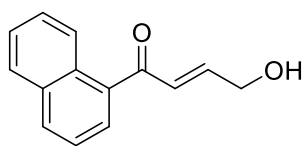
White solid. ^1H NMR (C_6D_6) δ 7.53 (m, 2H), 7.16 (m, 2H), 6.91 (m, 2H), 3.68 (m, 2H), 0.69 (t, J = 5.5 Hz, 1H). ^{13}C NMR (C_6D_6) δ 188.1,

147.6, 137.0, 132.0, 130.3, 128.4, 123.0, 62.0.

(E)-4-Hydroxy-1-(2-methylphenyl)but-2-en-1-one (1e): CAS RN [1362860-46-5].

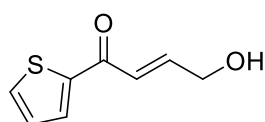
Pale yellow oil. ^1H NMR (C_6D_6) δ 7.31 (dd, $J = 7.0, 1.5$ Hz, 1H), 7.04 (ddd, $J = 7.5, 7.5, 1.5$ Hz, 1H), 6.94 (m, 2H), 6.72 (dt, $J = 16.0, 2.0$ Hz, 1H), 6.56 (dt, $J = 16.0, 4.0$ Hz, 1H), 3.66 (m, 2H), 2.41 (s, 3H), 0.87 (br s, 1H).

^{13}C NMR (C_6D_6) 194.8, 149.7, 139.5, 137.6, 131.6, 130.5, 128.6, 128.4, 125.6, 61.8, 20.5.

(E)-4-Hydroxy-1-(naphthalen-1-yl)but-2-en-1-one (1f): CAS RN [1362860-47-6].

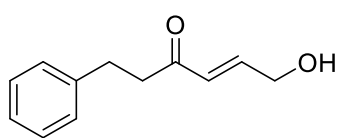
Pale yellow oil. ^1H NMR (C_6D_6) δ 8.64 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.56 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.47 (dd, $J = 7.0, 1.5$ Hz, 1H), 7.29 (ddd, $J = 8.5, 7.0, 1.5$ Hz, 1H), 7.20 (ddd, $J = 8.0, 7.0, 1.0$ Hz, 1H), 7.07 (dd, $J = 8.0, 7.0$ Hz, 1H), 6.91 (m, 2H), 6.66 (dt, $J = 15.5, 4.0$ Hz, 1H), 3.75 (br s, 2H), 1.76 (br s, 1H).

^{13}C NMR (C_6D_6) 194.7, 148.7, 137.2, 134.3, 131.7, 131.2, 128.62, 128.59, 127.70, 127.67, 126.6, 126.4, 61.9.

(E)-4-Hydroxy-1-(thiophen-2-yl)but-2-en-1-one (1g): CAS RN [1191258-98-6].

Pale yellow oil. ^1H NMR (C_6D_6) δ 7.35 (dd, $J = 4.0, 1.0$ Hz, 1H), 7.04 (m, 2H), 6.88 (dd, $J = 5.0, 1.0$ Hz, 1H), 6.54 (dd, $J = 5.0, 4.0$ Hz, 1H), 3.80 (m, 2H), 1.59 (br s, 1H).

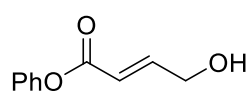
^{13}C NMR (C_6D_6) δ 181.7, 147.0, 145.9, 133.7, 132.0, 128.1, 123.3, 62.0.

(E)-6-Hydroxy-1-phenylhex-4-en-3-one (1h): CAS RN [1158843-60-7].

Colorless oil. ^1H NMR (C_6D_6) δ 7.12 (m, 2H), 7.03 (m, 3H), 6.41 (dt, $J = 16.0, 4.0$ Hz, 1H), 6.16 (dt, $J = 16.0, 2.0$ Hz, 1H), 3.62 (m, 2H), 2.87 (t, $J = 8.0$ Hz, 2H), 2.45 (t, $J = 8.0$ Hz, 2H), 0.91 (t, $J = 6.5$ Hz, 1H).

^{13}C NMR (C_6D_6) δ 197.8, 144.6, 141.9, 128.8, 128.7, 128.4, 126.3, 61.7, 42.4, 30.2.

(E)-Phenyl 4-hydroxybut-2-enoate (1i): CAS RN [1376702-19-0].

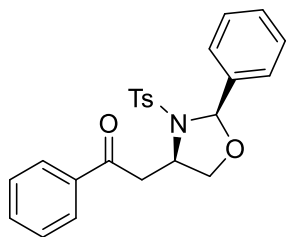


Colorless oil. ^1H NMR (CDCl_3) δ 7.41 (m, 2H), 7.28–7.23 (m, 2H), 7.15 (m, 2H), 6.33 (dt, $J = 15.5, 2.5$ Hz, 1H), 4.42 (m, 2H), 2.23 (br s, 1H). ^{13}C NMR (CDCl_3) δ 164.8, 150.6, 149.2, 129.4, 125.8, 121.5, 119.3, 61.8. TLC: R_f 0.37 (hexane/EtOAc = 1:1). IR (neat): 3443, 3043, 2903, 2361, 1736, 1658, 1592, 1493, 1299, 1275, 1196, 1164, 1145, 1097, 1023, 954, 918, 730, 689 cm^{-1} . HRMS Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_3$: $[\text{M}+\text{H}]^+$, 179.0703. Found: m/z 179.0698.

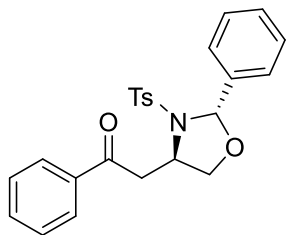
Characterization Data of Products

1-Phenyl-2-(2-phenyl-3-tosyloxazolidin-4yl)-ethanone.

Yield: 95% (99.8 mg), dr = 2.4:1.



Major diastereomer (3aa): 98% *ee* (after recrystallization from 2-propanol), white solid. $[\alpha]_{\text{D}}^{26} -33.3$ (c 1.65, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.87 (m, 2H), 7.82 (m, 2H), 7.34–7.46 (m, 7H), 6.22 (s, 1H), 4.31 (dddd, $J = 13.5, 9.0, 6.0, 3.0$ Hz, 1H), 4.15 (dd, $J = 9.5, 7.5$ Hz, 1H), 3.90 (dd, $J = 18.0, 3.0$ Hz, 1H), 3.53 (dd, $J = 9.0, 6.0$ Hz, 1H), 3.00 (dd, $J = 18.5, 11.0$ Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.0, 144.4, 138.4, 136.0, 133.9, 133.6, 130.0, 128.7, 128.66, 128.5, 128.2, 128.0, 126.6, 91.3, 71.5, 56.0, 44.6, 21.6. Mp. 42.2–43.2 $^\circ\text{C}$. TLC: R_f 0.34 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3062, 2876, 1680, 1597, 1493, 1450, 1373, 1352, 1215, 1165, 1118, 1091, 1002, 951, 815, 756, 690, 671, 593 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 422.1421. Found: m/z 422.1420. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 40 $^\circ\text{C}$): $t_{\text{major}} = 29.7$ min, $t_{\text{minor}} = 34.5$ min.

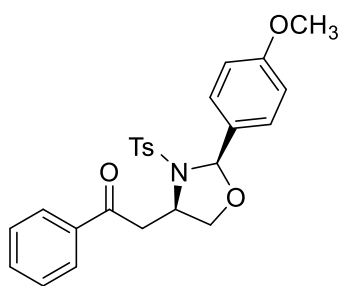


Minor diastereomer (2S,4R) (3aa'): 88% *ee* (after recrystallization from 2-propanol), white solid. $[\alpha]_{\text{D}}^{26} -56.0$ (c 0.67, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.09 (m, 2H), 7.59 (m, 1H), 7.70 (m, 1H), 7.60 (m, 2H), 7.39–7.14 (m, 9H), 6.25 (s, 1H), 4.76 (m, 1H), 4.56 (ddd, $J = 9.0, 4.0, 1.5$ Hz, 1H), 4.26 (ddd, $J = 17.5, 3.0, 1.0$ Hz, 1H), 3.98 (dd, $J = 9.5, 3.5$ Hz, 1H), 3.54 (dd, $J = 17.5, 10.0$

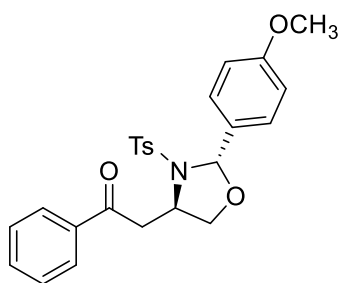
Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.2, 143.1, 137.8, 136.8, 136.4, 133.6, 129.1, 129.0, 128.7, 128.08, 128.02, 127.9, 126.9, 91.8, 71.8, 55.8, 42.2, 21.4. Mp. 111.9–113.0 °C. TLC: R_f 0.25 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 3038, 2927, 1671, 1581, 1450, 1346, 1155, 1093, 1025, 947, 690, 673, 541, 508 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 422.1421. Found: m/z 422.1420. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 49.4 min, t_{major} = 54.4 min.

2-(2-(4-(Methoxy)phenyl)-3-tosyloxazolidin-4-yl)-1-phenylethanone.

Yield: 75% (84.8 mg), dr = 3.7:1.



Major diastereomer (3ab): 65% *ee*, white solid. $[\alpha]_{\text{D}}^{26} +8.62$ (c 0.58, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.88 (m, 2H), 7.80 (m, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.54 (m, 2H), 7.45 (m, 2H), 7.37 (m, 2H), 6.15 (s, 1H), 4.29 (m, 1H), 4.11 (dd, J = 9.5, 7.0 Hz, 1H), 3.89 (dd, J = 18.0, 3.5 Hz, 1H), 3.54 (dd, J = 9.5, 6.0 Hz, 1H), 3.05 (dd, J = 18.0, 10.5 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.0, 159.9, 144.4, 135.9, 133.7, 133.6, 130.2, 130.0, 128.6, 127.95, 127.93, 127.90, 113.8, 91.1, 71.3, 55.8, 55.2, 44.6, 21.6. Mp. 80.1–81.1 °C. TLC: R_f 0.21 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2950, 1683, 1609, 1597, 1512, 1448, 1351, 1249, 1162, 1093, 1030, 820, 756, 671, 604, 584 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_5\text{S}$: $[\text{M}+\text{H}]^+$, 452.1526. Found: m/z 452.1518. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.6 min, t_{minor} = 13.8 min.

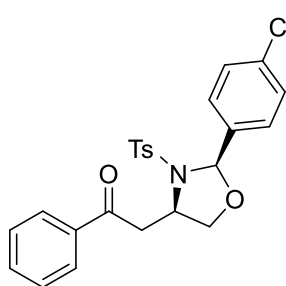


Minor diastereomer (3ab'): 26% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -26.3$ (c 0.38, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.00 (m, 2H), 7.61 (t, J = 7.0 Hz, 1H), 7.50 (m, 2H), 7.23 (m, 2H), 7.07–7.05 (m, 4H), 6.66 (m, 2H), 6.08 (s, 1H), 4.67 (m, 1H), 4.47 (ddd, J = 9.5, 6.0, 1.5 Hz, 1H), 4.16 (ddd, J = 18.0, 3.0, 1.0 Hz, 1H), 3.87 (dd, J = 9.0, 3.0 Hz, 1H), 3.79 (s, 3H), 3.44 (dd, J = 18.0, 10.5 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.4, 160.2, 143.0, 137.9, 136.3, 129.3, 129.1, 128.7, 128.1, 126.9, 113.3, 91.4, 71.7, 55.7, 55.3, 42.4, 21.5. Mp.

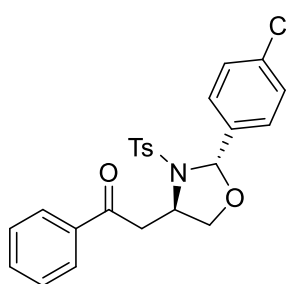
108.3–111.0 °C. TLC: R_f 0.10 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2924, 1669, 1611, 1597, 1517, 1343, 1253, 1211, 1176, 1156, 1091, 925, 830, 812, 670, 604, 542 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_5\text{S}$: $[\text{M}+\text{H}]^+$, 452.1526. Found: m/z 452.1518. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 25.4 min, t_{minor} = 30.2 min.

2-(3-Tosyl-2-(4-(trifluoromethyl)phenyl)oxazolidin-4-yl)-1-phenylethanone.

Yield: 70% (86.1 mg), dr = 4.3:1.



Major diastereomer (3ac): 66% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -17.2$ (*c* 6.40, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.86 (m, 2H), 7.80 (m, 2H), 7.67 (m, 2H), 7.58 (tt, J = 7.0, 2.5, 1.5 Hz, 1H), 7.45 (m, 2H), 7.39 (m, 2H), 6.21 (s, 1H), 4.29 (m, 1H), 4.19 (dd, J = 9.0, 7.0 Hz, 1H), 3.90 (dd, J = 18.0, 3.0 Hz, 1H), 3.50 (dd, J = 9.5, 6.5 Hz, 1H), 2.96 (dd, J = 18.5, 11 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (CDCl_3) δ 197.7, 144.8, 142.5, 135.9, 133.7, 133.5, 131.0 (q, J = 32.2 Hz), 130.8, 130.2, 128.7, 128.0, 127.1, 125.5 (q, J = 3.77 Hz), 124.0 (q, J = 272.0 Hz), 90.6, 71.2, 56.0, 44.5, 21.6. ^{19}F NMR (CDCl_3) δ 98.6. Mp. 154.3–155.3 °C. TLC: R_f 0.35 (toluene/EtOAc = 30:1). IR (KBr): 2956, 2930, 2897, 1730, 1678, 1599, 1451, 1408, 1373, 1344, 1324, 1219, 1166, 1129, 1066, 1014, 951, 901, 673, 596, 555 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{23}\text{F}_3\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 490.1294. Found: m/z 490.1289. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 5.3 min, t_{minor} = 5.6 min.

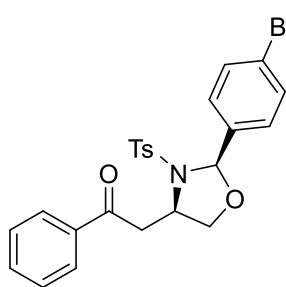


Minor diastereomer (3ac'): 34% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -25.6$ (*c* 1.56, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.00 (m, 2H), 7.62 (m, 1H), 7.51 (m, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.23 (m, 2H), 7.02 (m, 2H), 6.15 (s, 1H), 4.72 (m, 1H), 4.50 (ddd, J = 9.0, 6.0, 1.0 Hz, 1H), 4.16 (ddd, J = 18.0, 3.5, 1.5 Hz, 1H), 3.93 (dd, J = 9.0, 3.5 Hz, 1H), 3.44 (dd, J = 18.0, 10.0 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.0, 143.6, 140.6, 137.7,

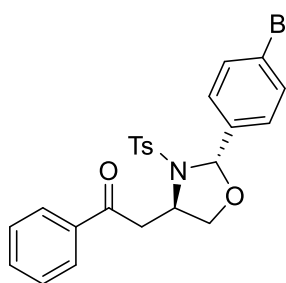
136.3, 133.7, 131.2 (q, $J = 32.6$ Hz), 129.3, 128.8, 128.4, 128.1, 126.8, 124.9 (q, $J = 3.77$ Hz), 123.8 (q, $J = 272.5$ Hz), 90.7, 72.2, 56.1, 42.0, 21.3. ^{19}F NMR (CDCl_3) δ 98.3. Mp. 174.5–175.5 °C. TLC: R_f 0.31 (toluene/EtOAc = 30:1). IR (KBr): 2957, 2928, 1672, 1598, 1449, 1426, 1372, 1348, 1327, 1161, 1126, 1068, 689 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{23}\text{F}_3\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 490.1294. Found: m/z 490.1289. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 40 °C): $t_{\text{major}} = 8.2$ min, $t_{\text{minor}} = 11.6$ min.

2-(2-(4-Bromophenyl)-3-tosyloxazolidin-4-yl)-1-phenylethanone.

Yield: 84% (104 mg), dr = 3.1:1.



Major diastereomer (3ad): 51% *ee*, white solid. $[\alpha]_{\text{D}}^{26} +1.78$ (c 7.04, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.87 (m, 2H), 7.80 (m, 2H), 7.57 (m, 1H), 7.52 (m, 4H), 7.45 (m, 2H), 7.38 (m, 2H), 6.14 (s, 1H), 4.29 (m, 1H), 4.15 (dd, $J = 9.0, 7.0$ Hz, 1H), 3.88 (dd, $J = 18.0, 3.0$ Hz, 1H), 3.50 (dd, $J = 9.5, 6.5$ Hz, 1H), 2.97 (dd, $J = 18.0, 10.5$ Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (CDCl_3) δ 197.8, 144.6, 137.6, 135.9, 133.65, 133.60, 131.6, 130.1, 128.7, 128.4, 127.98, 127.96, 123.0, 90.7, 71.6, 55.9, 44.5, 21.6. Mp. 57.0–58.0 °C. TLC: R_f 0.37 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2875, 1681, 1597, 1486, 1449, 1352, 1215, 1164, 1091, 1002, 814, 756, 714, 689, 672, 595 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{26}\text{BrN}_2\text{O}_4\text{S}$: $[\text{M}+\text{NH}_4]^+$, 517.0791. Found: m/z 517.0776. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 40 °C): $t_{\text{major}} = 4.9$ min, $t_{\text{minor}} = 5.5$ min.

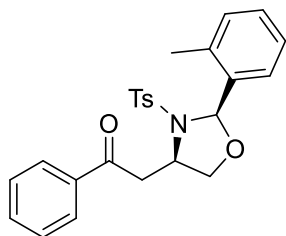


Minor diastereomer (3ad'): 45% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -22.9$ (c 2.40, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.99 (m, 2H), 7.60 (m, 1H), 7.49 (m, 2H), 7.26 (m, 4H), 7.09 (m, 2H), 7.03 (m, 2H), 6.06 (s, 1H), 4.67 (m, 1H), 4.45 (ddd, $J = 9.0, 6.0, 1.0$ Hz, 1H), 4.15 (ddd, $J = 18.0, 3.5, 1.0$ Hz, 1H), 3.88 (dd, $J = 9.0, 4.0$ Hz, 1H), 3.41 (dd, $J = 17.5, 10.0$ Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.0, 143.5, 137.8, 136.3, 135.8, 133.6, 131.1, 129.6, 129.2, 128.7, 128.1, 126.9, 123.4, 90.9, 72.0, 55.9, 42.0, 21.5. Mp. 146.5–148.0 °C. TLC: R_f 0.27

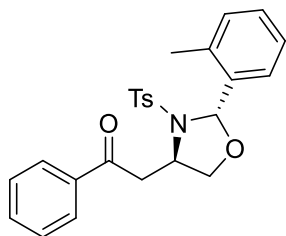
(toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3050, 2925, 2853, 2360, 1681, 1598, 1417, 1374, 1339, 1212, 1153, 1093, 1070, 931, 810, 758, 687, 599, 540 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{26}\text{BrN}_2\text{O}_4\text{S}$: $[\text{M}+\text{NH}_4]^+$, 517.0791. Found: m/z 517.0776. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 7.3 min, t_{minor} = 8.8 min.

2-(2-(2-Methylphenyl)-3-tosyloxazolidin-4-yl)-1-phenylethanone.

Yield: 74% (80.3 mg), dr = 5.3:1.



Major diastereomer (3ae): 57% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -6.89 (*c* 2.99, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.97 (m, 2H), 7.80 (m, 2H), 7.74 (m, 1H), 7.60 (m, 1H), 7.49 (m, 1H), 7.38 (m, 1H), 7.28 (m, 2H), 7.20 (m, 1H), 6.20 (s, 1H), 4.38 (m, 1H), 3.99 (dd, J = 18.0, 3.0 Hz, 1H), 3.96 (dd, J = 10.5, 6.5 Hz, 1H), 3.57 (dd, J = 9.5, 5.0 Hz, 1H), 3.66 (dd, J = 18.0, 10.5 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3) δ 198.3, 143.3, 137.7, 137.4, 136.4, 133.6, 130.5, 129.1, 129.0, 128.95, 128.7, 128.1, 127.8, 127.1, 125.3, 128.9, 71.2, 56.1, 42.6, 21.4, 19.1. Mp. 51.0–52.0 °C. TLC: R_f 0.38 (toluene/EtOAc = 30:1). IR (KBr): 2925, 1681, 1597, 1449, 1352, 1324, 1214, 1166, 1092, 1028, 1013, 1002, 937, 816, 755, 670, 597, 594, 553 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 436.1577. Found: m/z 436.1577. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, flow rate = 3.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 9.6 min, t_{minor} = 15.3 min.

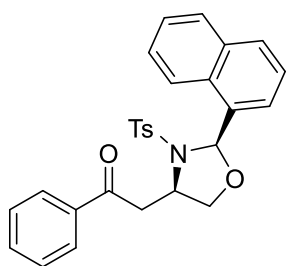


Minor diastereomer (3ae'): 53% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -40.6 (*c* 1.17, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.01 (m, 2H), 7.61 (m, 1H), 7.51 (m, 2H), 7.27 (m, 2H), 7.18–7.14 (m, 2H), 7.08–7.09 (m, 3H), 6.91–6.87 (m, 2H), 6.32 (s, 1H), 4.74 (m, 1H), 4.41 (ddd, J = 9.0, 6.0, 1.0 Hz, 1H), 4.16 (ddd, J = 18.0, 3.0, 1.0 Hz, 1H), 3.83 (dd, J = 9.0, 3.0 Hz, 1H), 3.44 (dd, J = 17.5, 10.0 Hz, 1H), 2.42 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (CDCl_3) δ 197.7, 136.4, 133.4, 128.6, 128.0, 105.2, 72.4, 70.1, 43.3, 26.9, 17.9. Mp. 38.0–39.0 °C. TLC: R_f 0.36 (toluene/EtOAc = 30:1). IR (KBr): 2923, 1681, 1598, 1580, 1494, 1449, 1344, 1214, 1159, 1091, 991, 932, 814, 756, 669, 596, 543 cm^{-1} . HRMS

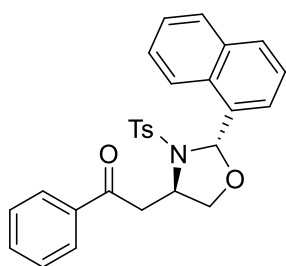
Calcd for $C_{25}H_{26}NO_4S$: $[M+H]^+$, 436.1577. Found: m/z 436.1577. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97/3, flow rate = 3.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.8 min, t_{minor} = 16.6 min.

2-(2-(1-Naphthalen-1-yl)-3-tosyloxazolidin-4-yl)-1-phenylethanone.

Yield: 98% (107 mg), dr = 7.1:1.



Major diastereomer (2*R*,4*R*) (3af): 55% *ee*, white solid. $[\alpha]_D^{26} +27.3$ (*c* 10.1, CH_2Cl_2). 1H NMR ($CDCl_3$) δ 8.27 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.98 (m, 2H), 7.91–7.87 (m, 4H), 7.61–7.52 (m, 4H), 7.48 (m, 2H), 7.41 (m, 2H), 6.82 (s, 1H), 4.47 (m, 1H), 4.16 (dd, J = 11.0, 3.0 Hz, 1H), 4.14 (dd, J = 6.5, 3.0 Hz, 1H), 3.54 (dd, J = 9.0, 6.0 Hz, 1H), 3.39 (dd, J = 18.0, 10.5 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.8, 144.5, 136.0, 133.9, 133.6, 133.5, 133.2, 131.0, 130.1, 129.8, 128.63, 128.59, 128.00, 127.97, 126.3, 125.8, 125.2, 124.8, 124.1, 90.5, 70.9, 56.4, 43.7, 21.5. Mp. 38.4–39.4 °C. TLC: R_f 0.29 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3056, 1681, 1597, 1448, 1352, 1215, 1164, 1091, 1002, 807, 671, 593, 551 cm^{-1} . HRMS Calcd for $C_{28}H_{26}NO_4S$: $[M+H]^+$, 472.1577. Found: m/z 472.1574. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 14.4 min, t_{major} = 17.3 min.

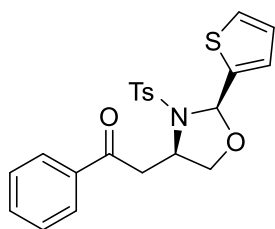


Minor diastereomer (3af'): 54% *ee*, white solid. $[\alpha]_D^{26} -35.2$ (*c* 1.42, CH_2Cl_2). 1H NMR ($CDCl_3$) δ 8.11 (m, 1H), 8.00 (m, 2H), 7.80 (m, 2H), 7.62 (m, 1H), 7.51 (m, 2H), 7.47 (m, 2H), 7.32 (m, 3H), 7.26 (m, 1H), 6.98 (m, 2H), 6.85 (s, 1H), 4.85 (m, 1H), 4.41 (ddd, J = 9.0, 6.0, 1.0 Hz, 1H), 4.22 (ddd, J = 18.0, 3.0, 1.0 Hz, 1H), 3.89 (dd, J = 9.5, 3.5 Hz, 1H), 3.47 (dd, J = 17.5, 10.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 198.1, 143.3, 137.3, 136.4, 133.7, 133.6, 131.2, 130.7, 130.0, 129.0, 128.8, 128.5, 128.1, 127.2, 126.6, 126.4, 125.6, 124.4, 123.6, 89.8, 71.1, 56.3, 42.0, 21.4. Mp. 45.9–46.9 °C. TLC: R_f 0.22 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 1684, 1597, 1559, 1339, 1215, 1158, 1092, 806, 759, 596, 546 cm^{-1} . HRMS

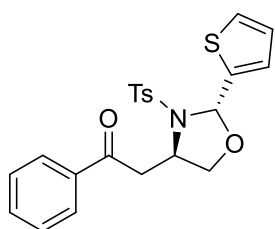
Calcd for $C_{28}H_{26}NO_4S$: $[M+H]^+$, 472.1577. Found: m/z 472.1574. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 94/6, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 15.6 min, t_{minor} = 24.0 min.

2-(2-(Thiophen-2-yl)-3-tosyloxazolidin-4-yl)-1-phenylethanone.

Yield: 55% (58.8 mg), dr = 9.3:1.



Major diastereomer (3ag): 53% *ee*, white solid. $[\alpha]_D^{26}$ -6.13 (*c* 4.08, CH_2Cl_2). 1H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.79 (m, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 7.38 (m, 2H), 7.33 (m, 1H), 7.26 (m, 1H), 7.02 (m, 1H), 6.39 (s, 1H), 4.28 (m, 1H), 4.18 (dd, J = 9.5, 3.0 Hz, 1H), 3.94 (dd, J = 18.0, 3.0 Hz, 1H), 3.67 (dd, J = 9.5, 3.5 Hz, 1H), 3.25 (dd, J = 18.0, 10.5 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 197.9, 144.6, 142.8, 136.0, 133.6, 130.1, 128.7, 128.0, 127.97, 127.2, 126.7, 126.5, 88.5, 71.7, 56.0, 44.5, 21.6. Mp. 40.7–42.0 °C. TLC: R_f 0.33 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2873, 1676, 1597, 1448, 1374, 1345, 1215, 1164, 1113, 1090, 1002, 938, 815, 694, 671, 594, 552 cm^{-1} . HRMS Calcd for $C_{22}H_{22}NO_4S_2$: $[M+H]^+$, 428.0985. Found: m/z 428.0982. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 55/45, flow rate = 0.7 mL/min, λ = 254 nm, 40 °C): t_{major} = 9.1 min, t_{minor} = 10.8 min.



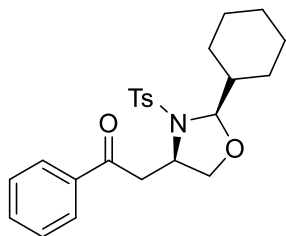
Minor diastereomer (3ag'): 38% *ee*, colorless oil. $[\alpha]_D^{26}$ -25.9 (*c* 0.58, CH_2Cl_2). 1H NMR ($CDCl_3$) δ 7.92 (m, 2H), 7.80 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 7.38 (m, 2H), 7.34 (m, 1H), 7.26 (m, 2), 7.02 (dd, J = 5.0, 3.5 Hz, 1H), 6.39 (s, 1H), 4.27 (m, 1H), 4.18 (dd, J = 9.5, 7.0 Hz, 1H), 3.93 (dd, J = 17.5, 3.0 Hz, 1H), 3.67 (dd, J = 9.0, 6.0 Hz, 1H), 3.24 (dd, J = 18.0, 9.5 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 198.0, 144.6, 142.9, 136.0, 133.8, 133.7, 130.1, 128.7, 128.1, 128.0, 127.2, 126.7, 126.6, 88.6, 71.8, 56.0, 44.5, 21.6. Mp. 42.0–43.5 °C. TLC: R_f 0.30 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3106, 2872, 1676, 1598, 1448, 1412, 1345, 1215, 1163, 1113, 1090, 1002, 937, 754, 671, 594, 553 cm^{-1} . HRMS Calcd for $C_{22}H_{22}NO_4S_2$: $[M+H]^+$, 428.0985. Found: m/z 428.0982. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 55/45, flow

rate = 0.7 mL/min, λ = 254 nm, 40 °C): t_{minor} = 11.5 min, t_{major} = 12.2 min.

2-(2-Cyclohexyl-3-tosyloxazolidin-4-yl)-1-phenylethanone.

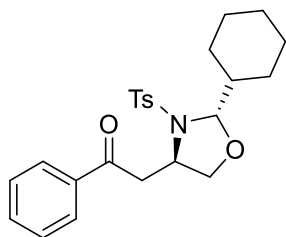
The diastereomers could not be separated.

Yield: 99% (106 mg), dr = 1.9:1, white solid. Mp. 79.1–82.0 °C. TLC: R_f 0.31 (toluene/EtOAc/hexane/ = 30:1:9). HRMS Calcd for $C_{24}H_{30}NO_4S$: $[M+H]^+$, 428.1890. Found: m/z 428.1889. IR (KBr): 2928, 2854, 1682, 1589, 1581, 1494, 1449, 1350, 1214, 1165, 1093, 1013, 1002, 815, 689, 668, 596, 552 cm^{-1} .



Major diastereomer (3ah): 74% *ee*. ^1H NMR (CDCl_3) δ 7.95 (m, 2H), 7.74 (m, 2H), 7.57 (m, 1H), 7.48 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.76 (d, J = 6.0 Hz, 1H), 4.17 (m, 1H), 3.76 (dd, J = 17.5, 3.0 Hz, 1H), 3.70 (dd, J = 9.5, 6.5 Hz, 1H), 3.61 (dd, J = 8.5, 6.5 Hz, 1H), 3.23 (dd, J = 18.0, 10.5

Hz, 1H), 2.43 (s, 3H), 1.94–1.70 (m, 4H), 1.68–1.60 (m, 1H), 1.58–1.50 (m, 1H), 1.29–1.14 (m, 3H), 1.12–1.04 (m, 2H). ^{13}C NMR (CDCl_3) δ 198.0, 144.1, 136.1, 133.6, 133.4, 129.9, 128.7, 128.0, 127.9, 95.8, 72.2, 55.5, 44.6, 41.8, 29.0, 26.6, 26.3, 25.7, 25.6, 21.5. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 10.1 min, t_{minor} = 15.3 min.

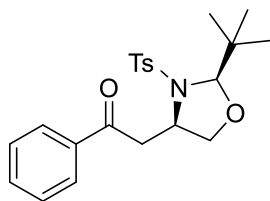


Minor diastereomer (3ah'): 59% *ee*. ^1H NMR (CDCl_3) δ 7.92 (m, 2H), 7.78 (m, 2H), 7.60 (m, 1H), 7.47 (m, 2H), 7.31 (d, J = 8.5 Hz, 2H), 5.13 (d, J = 2.5 Hz, 1H), 4.47 (m, 1H), 4.09 (ddd, J = 8.5, 5.5, 1.5 Hz, 1H), 4.01 (ddd, J = 18.0, 4.0, 1.5 Hz, 1H), 3.68 (dd, J = 8.5, 3.0 Hz, 1H), 3.27 (dd, J

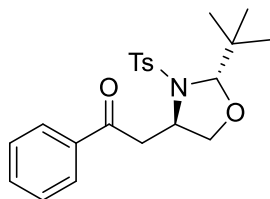
= 18.0, 10.5 Hz, 1H), 2.42 (s, 3H), 1.85–1.75 (m, 4H), 1.60–1.58 (m, 1H), 1.29–1.22 (m, 1H), 1.20–1.04 (m, 3H), 0.94–0.77 (m, 2H). ^{13}C NMR (CDCl_3) δ 198.1, 143.5, 138.9, 136.3, 133.8, 129.6, 128.6, 127.9, 126.9, 94.7, 70.7, 55.8, 41.7, 41.0, 29.3, 26.2, 26.1. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 18.9 min, t_{minor} = 23.0 min.

2-(2-(*tert*-Butyl)-3-tosyloxazolidin-4-yl)-1-phenylethanone.

Yield: 62% (61.7 mg), dr = 2.6:1.



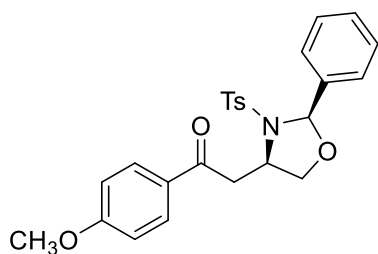
Major diastereomer (3ai): 87% *ee*, white solid. $[\alpha]_D^{26} -89.3$ (*c* 0.70, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.94 (m, 2H), 7.76 (m, 2H), 7.60 (m, 1H), 7.48 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 4.87 (s, 1H), 4.30 (m, 1H), 3.75 (dd, *J* = 18.0, 2.5 Hz, 1H), 3.68–3.62 (m, 2H), 3.34 (dd, *J* = 18.0, 11.0 Hz, 1H), 2.44 (s, 3H), 1.08 (s, 9H). ¹³C NMR (CDCl₃) δ 198.0, 144.3, 136.1, 133.6, 133.4, 130.0, 128.7, 128.4, 128.0, 99.5, 71.5, 56.8, 44.1, 36.8, 26.5, 21.5. Mp. 44.8–47.8 °C. TLC: R_f 0.27 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2960, 2873, 1683, 1598, 1581, 1449, 1355, 1324, 1214, 1166, 1129, 1090, 1001, 963, 815, 757, 669, 560 cm⁻¹. HRMS Calcd for C₂₂H₂₈NO₄S: [M+H]⁺, 402.1734. Found: *m/z* 402.1738. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 92.5/7.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 3.5 min, *t*_{minor} = 4.6 min.



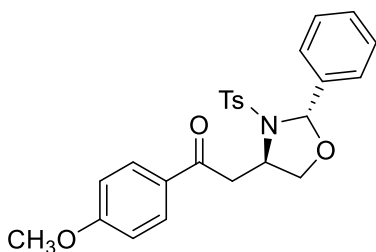
Minor diastereomer (3ai'): 29% *ee*, white solid. $[\alpha]_D^{26} +36.5$ (*c* 0.48, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.83–7.79 (m, 4H), 7.58 (m, 1H), 7.45 (m, 2H), 7.27 (m, 1H), 5.94 (s, 1H), 4.31 (m, 1H), 4.22 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.11 (dd, *J* = 18.0, 4.5 Hz, 1H), 3.12 (dd, *J* = 10.0, 7.5 Hz, 1H), 2.97 (dd, *J* = 17.5, 9.0 Hz, 1H), 2.38 (s, 3H), 1.07 (s, 9H). ¹³C NMR (CDCl₃) δ 195.7, 144.0, 139.5, 136.1, 133.5, 130.0, 128.7, 127.9, 127.4, 99.0, 71.2, 56.1, 37.8, 36.3, 26.0, 21.5. Mp. 45.5–46.5 °C. TLC: R_f 0.22 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2973, 2878, 1689, 1598, 1482, 1449, 1399, 1348, 1303, 1229, 1162, 1113, 1002, 946, 814, 755, 689, 668, 596, 539 cm⁻¹. HRMS Calcd for C₂₂H₂₈NO₄S: [M+H]⁺, 402.1734. Found: *m/z* 402.1738. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 92.5/7.5, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 4.9 min, *t*_{minor} = 5.6 min.

2-(2-Phenyl-3-tosyloxazolodin-4-yl)-1-(4-(methoxy)phenyl)ethanone.

Yield: 58% (64.5 mg), dr = 2.2:1.



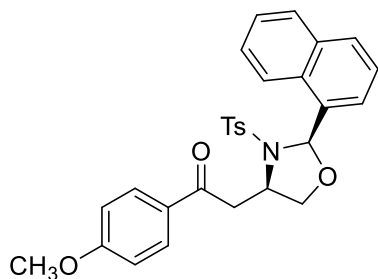
Major diastereomer (3ba): 63% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -18.1$ (*c* 5.24, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.85 (m, 2H), 7.83 (m, 2H), 7.42 (m, 2H), 7.41–7.34 (m, 3H), 6.90 (m, 2H), 6.21 (s, 1H), 4.28 (m, 1H), 4.14 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.86 (s, 3H), 3.85 (dd, *J* = 18.0, 3.5 Hz, 1H), 3.52 (dd, *J* = 9.0, 7.5 Hz, 1H), 2.94 (dd, *J* = 18.0, 11.0 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 196.4, 163.8, 144.4, 138.3, 133.7, 130.3, 130.1, 129.0, 128.7, 128.5, 127.9, 126.6, 113.7, 91.1, 71.5, 56.0, 55.4, 44.3, 21.6. Mp. 55.5–56.2 °C. TLC: *R*_f 0.30 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2941, 2875, 2361, 1751, 1669, 1600, 1576, 1457, 1419, 1352, 1319, 1263, 1220, 1164, 1116, 1091, 1010, 992, 950, 831, 738, 664, 592 cm⁻¹. HRMS Calcd for C₂₅H₂₆NO₅S: [M+H]⁺, 452.1526. Found: *m/z* 452.1515. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 12.8 min, *t*_{minor} = 14.3 min.



Minor diastereomer (3ba'): 58% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -22.6$ (*c* 1.33, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.98 (m, 2H), 7.23 (m, 2H), 7.17–7.15 (m, 4H), 7.05 (m, 2H), 6.97 (m, 2H), 6.15 (s, 1H), 4.64 (m, 1H), 4.45 (ddd, *J* = 9.5, 6.0, 1.0 Hz, 1H), 4.11 (ddd, *J* = 17.5, 2.5, 1.0 Hz, 1H), 3.90 (s, 3H), 3.89 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.99 (dd, *J* = 17.5, 5.0 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (CDCl₃) δ 196.8, 163.9, 143.1, 137.7, 136.7, 130.4, 129.4, 129.2, 129.0, 128.0, 127.9, 126.9, 113.8, 91.7, 71.9, 55.8, 55.5, 41.9, 21.5. Mp. 125.1–126.1 °C. TLC: *R*_f 0.21 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3010, 2894, 2368, 1663, 1600, 1576, 1507, 1458, 1419, 1339, 1329, 1287, 1260, 1211, 1158, 1112, 1093, 1025, 987, 922, 828, 814, 766, 678, 593, 538 cm⁻¹. HRMS Calcd for C₂₅H₂₆NO₅S: [M+H]⁺, 452.1526. Found: *m/z* 452.1515. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 19.6 min, *t*_{minor} = 22.1 min.

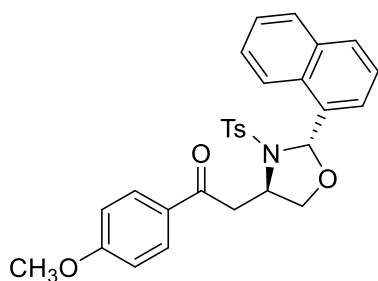
2-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-1-(4-(methoxy)phenyl)ethanone.

Yield: 88% (110 mg), dr = 5.3:1.



Major diastereomer (3bf): 55% *ee*, white solid. $[\alpha]_D^{26} +27.1$ (c 1.29, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.24 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.93 (m, 2H), 7.90 (m, 2H), 7.86 (m, 2H), 7.57–7.50 (m, 3H), 7.41 (m, 2H), 6.94 (m, 2H), 6.78 (s, 1H), 4.42 (m, 1H), 4.11–4.06 (m, 2H), 3.69 (s, 3H), 3.52 (dd, *J* = 9.5, 6.0 Hz, 1H),

3.32 (dd, *J* = 18.0, 11.0 Hz, 1H), 2.49 (s, 3H). ¹³C NMR (CDCl₃) δ 196.3, 163.8, 144.5, 133.9, 133.4, 133.3, 130.9, 130.3, 130.1, 129.8, 129.1, 128.6, 128.0, 126.3, 125.8, 125.2, 124.8, 124.1, 113.8, 90.5, 70.9, 56.5, 55.5, 43.4, 21.6. Mp. 76.5–77.5 °C. TLC: *R*_f 0.16 (toluene/EtOAc/hexane = 30:1:9). IR (neat): 3061, 2935, 2361, 1669, 1599, 1575, 1510, 1351, 1262, 1221, 1166, 1120, 1091, 1037, 803, 668, 592, 551 cm⁻¹. HRMS Calcd for C₂₉H₂₈NO₅S: [M+H]⁺, 502.1683. Found: *m/z* 502.1676. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{minor} = 18.2 min, *t*_{major} = 19.7 min.

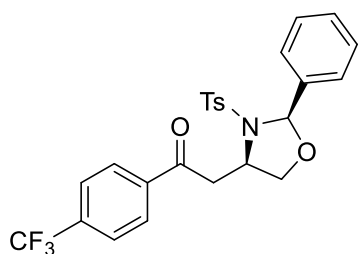


Minor diastereomer (3bf'): 55% *ee*, white solid. $[\alpha]_D^{26} -31.6$ (c 1.58, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.11 (m, 1H), 7.98 (m, 2H), 7.79 (m, 2H), 7.47 (m, 2H), 7.35–7.32 (m, 3H), 7.26 (m, 1H), 6.99–6.96 (m, 4H), 6.84 (s, 1H), 4.83 (m, 1H), 4.40 (ddd, *J* = 9.0, 6.0, 1.0 Hz, 1H), 4.15 (ddd, *J* = 17.5, 3.0, 1.0 Hz, 1H), 3.90 (dd, *J* = 9.0,

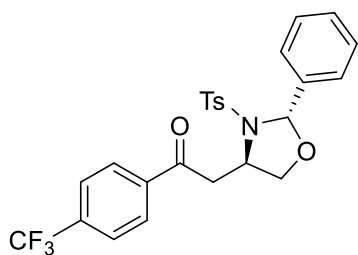
3.0 Hz, 1H), 3.89 (s, 3H), 3.41 (dd, *J* = 17.0, 10.0 Hz, 1H), 2.31 (s, 3H). ¹³C NMR (CDCl₃) δ 196.5, 163.8, 143.3, 137.2, 133.6, 131.1, 130.6, 130.4, 129.9, 129.4, 129.0, 128.5, 127.2, 126.5, 126.3, 125.6, 124.3, 123.6, 113.8, 89.7, 71.0, 56.3, 55.5, 41.6, 21.4. Mp. 31.0–32.0 °C. TLC: *R*_f 0.09 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3052, 2956, 1669, 1600, 1575, 1511, 1419, 2340, 1262, 1159, 1028, 989, 832, 804, 786, 672, 596, 546 cm⁻¹. HRMS Calcd for C₂₉H₂₈NO₅S: [M+H]⁺, 502.1683. Found: *m/z* 502.1676. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 20.0 min, *t*_{minor} = 30.6 min.

2-(2-Phenyl-3-tosyloxazolodin-4-yl)-1-(4-(trifluoromethyl)phenyl)ethanone.

Yield: 81% (86.5 mg), dr = 4.8:1.



Major diastereomer (3ca): 66% *ee*, white solid. $[\alpha]_D^{26} -10.5$ (*c* 6.66, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.00 (m, 2H), 7.80, (m, 2H), 7.70 (m, 2H), 7.62 (m, 2H), 7.41–7.35 (m, 5H), 6.22 (s, 1H), 4.30 (m, 1H), 4.16 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.91 (dd, *J* = 17.5, 3.5 Hz, 1H), 3.52 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.01 (dd, *J* = 18.0, 10.0 Hz, 1H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 197.0, 144.6, 138.4, 138.1, 134.7 (*q*, *J* = 32.7 Hz), 133.5, 130.1, 128.8, 128.5, 128.4, 127.9, 126.5, 125.7 (*q*, *J* = 3.4 Hz), 123.3 (*q*, *J* = 273.0 Hz), 91.2, 71.3, 55.7, 44.9, 21.6. ¹⁹F NMR (CDCl₃) δ 98.5. Mp. 51.4–52.4 °C. TLC: *R_f* 0.43 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 2957, 2895, 1688, 1684, 1599, 1512, 1493, 1457, 1449, 1411, 1354, 1324, 1213, 1165, 1129, 1111, 1061, 1015, 996, 951, 831, 816, 767, 739, 707, 697, 677, 594, 563, 536, 502 cm⁻¹. HRMS Calcd for C₂₅H₂₃F₃NO₄S: [M+H]⁺, 490.1294. Found: *m/z* 490.1284. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t_{major}* = 6.1 min, *t_{minor}* = 8.1 min.

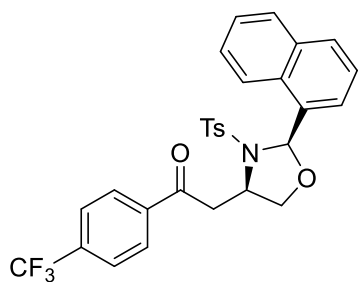


Minor diastereomer (3ca'): 41% *ee*, white solid. $[\alpha]_D^{26} -24.4$ (*c* 2.05, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.11 (m, 2H), 7.77 (m, 2H), 7.19 (m, 2H), 7.17–7.14 (m, 4H), 7.03 (m, 2H), 6.14 (s, 1H), 4.68 (m, 1H), 4.48 (ddd, *J* = 9.0, 4.5, 1.0 Hz, 1H), 4.20 (ddd, *J* = 18.0, 3.0, 1.0 Hz, 1H), 3.90 (dd, *J* = 9.0, 3.5 Hz, 1H), 3.45 (dd, *J* = 18.0, 10.0 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (CDCl₃) δ 197.4, 143.3, 138.8, 137.5, 136.4, 134.8 (*q*, *J* = 32.7 Hz), 129.2, 128.5, 128.1, 127.9, 126.9, 125.8 (*q*, *J* = 3.77 Hz), 123.4 (*q*, *J* = 272.5 Hz), 91.8, 71.7, 55.4, 42.6, 21.4. ¹⁹F NMR (CDCl₃) δ 98.6. Mp. 141.2–142.2 °C. TLC: *R_f* 0.39 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3067, 2865, 2369, 1684, 1559, 1507, 1507, 1459, 1410, 1374, 1340, 1327, 1213, 1155, 1121, 1111, 1065, 1015, 993, 916, 834, 744, 705, 674, 592, 538 cm⁻¹. HRMS Calcd for C₂₅H₂₃F₃NO₄S: [M+H]⁺, 490.1294. Found: *m/z* 490.1284. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C):

$t_{\text{major}} = 10.0$ min, $t_{\text{minor}} = 29.7$ min.

2-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-1-(4-(trifluoromethyl)phenyl)ethanone.

Yield: 95% (128 mg), dr = 11:1.

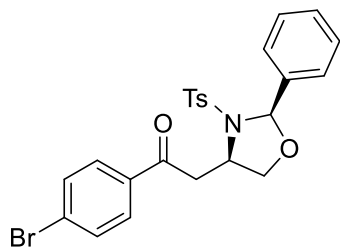


Major diastereomer (3cf): 60% *ee*, white solid. $[\alpha]_{\text{D}}^{26} +29.7$ (*c* 1.58, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.25 (d, *J* = 8.0 Hz, 1H), 8.06–8.03 (m, 3H), 7.90–7.89 (m, 3H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.73 (m, 2H), 7.58–7.51 (m, 3H), 7.42 (m, 2H), 6.80 (s, 1H), 4.45 (m, 1H), 4.14 (dd, *J* = 18.5, 3.0 Hz, 1H), 4.11 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.52

(dd, *J* = 9.5, 6.0 Hz, 1H), 3.37 (dd, *J* = 18.0, 10.5, 1H), 2.49 (s, 3H). ¹³C NMR (CDCl₃) δ 197.0, 144.7, 138.5, 134.7 (q, *J* = 32.7 Hz), 133.9, 133.2, 133.1, 130.9, 130.2, 129.9, 128.6, 128.4, 128.0, 126.4, 125.9, 125.7 (q, *J* = 3.77 Hz), 125.1, 124.8, 124.0, 123.4 (q, *J* = 273.0 Hz), 90.6, 70.7, 56.2, 44.0, 21.6. ¹⁹F NMR (CDCl₃) δ 97.9. Mp. 71.0–72.0 °C. TLC: *R*_f 0.40 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3066, 2874, 1688, 1599, 1512, 1410, 1353, 1324, 1165, 1129, 1066, 997, 803, 735, 677, 594, 551 cm⁻¹. HRMS Calcd for C₂₉H₂₄ClF₃NO₄S: [M+Cl]⁺, 574.1061. Found: *m/z* 574.1053. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): $t_{\text{minor}} = 24.4$ min, $t_{\text{major}} = 25.4$ min.

2-(2-Phenyl-3-tosyloxazolidin-4-yl)-1-(4-bromophenyl)ethanone.

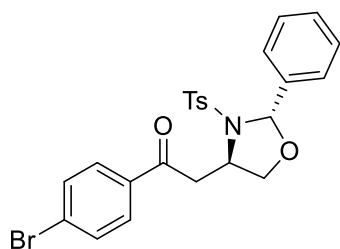
Yield: 84% (109 mg), dr = 4.0:1.



Major diastereomer (3da): 68% *ee*, white solid. $[\alpha]_{\text{D}}^{26} -11.3$ (*c* 5.07, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.91 (m, 1H), 7.80–7.77 (m, 3H), 7.71 (m, 2H), 7.61 (m, 2H), 7.58 (m, 2H), 7.42–7.33 (m, 3H), 6.20 (s, 1H), 4.28 (m, 1H), 4.15 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.83 (dd, *J* = 18.0,

3.5 Hz, 1H), 3.50 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.95 (dd, *J* = 18.0, 10.5 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 196.9, 144.6, 136.5, 132.0, 130.2, 130.1, 129.8, 129.5, 128.8, 128.5, 127.9, 127.8, 127.0, 126.5, 71.3, 55.8, 44.5, 21.6. Mp. 31.1–31.5 °C. TLC: *R*_f 0.45 (toluene/EtOAc/hexane

= 30:1:9). IR (KBr): 3067, 2869, 2301, 1684, 1599, 1586, 1356, 1291, 1211, 1189, 1176, 1165, 1119, 1096, 992, 970, 921, 815, 743, 664, 596, 575, 555 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{BrNO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 500.0526. Found: m/z 500.0529. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 9.2 min, t_{minor} = 10.8 min.

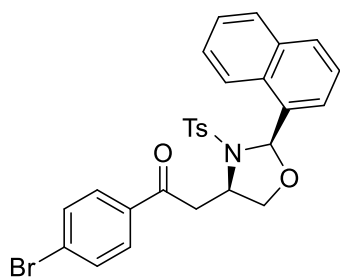


Minor diastereomer (3da'): 54% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -33.0 (*c* 1.06, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.86 (m, 2H), 7.65 (m, 2H), 7.43 (m, 1H), 7.25 (m, 2H), 7.21–7.13 (m, 4H), 7.03 (m, 2H), 6.13 (s, 1H), 4.65 (m, 1H), 4.46 (ddd, J = 9.0, 6.0, 1.5 Hz, 1H), 4.12 (ddd, J = 18.0,

3.5, 1.5 Hz, 1H), 3.88 (dd, J = 9.0, 3.0 Hz, 1H), 3.40 (dd, J = 18.0, 10.0 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (CDCl_3) δ 197.3, 143.2, 137.6, 136.5, 135.0, 132.1, 129.6, 129.14, 129.11, 128.0, 127.9, 126.9, 91.8, 71.7, 55.6, 42.3, 21.5. Mp. 136.0–136.8 °C. TLC: R_f 0.41 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3032, 2890, 2367, 1730, 1683, 1585, 1458, 1405, 1345, 1213, 1158, 1153, 1098, 1070, 988, 913, 819, 677, 594, 539 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{BrNO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 500.0526. Found: m/z 500.0529. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 14.5 min, t_{minor} = 26.0 min.

2-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-1-(4-bromophenyl)ethanone.

Yield: 87% (119 mg), *dr* = 11:1.



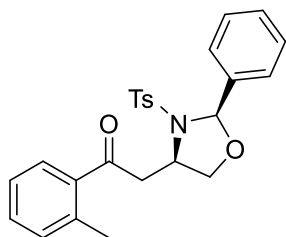
Major diastereomer (3df): 60% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ +33.8 (*c* 1.11, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.24 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 7.0 Hz, 1H), 7.90 (m, 2H), 7.85 (m, 2H), 7.80 (m, 2H), 7.61 (m, 2H), 7.57–7.51 (m, 3H), 7.41 (m, 2H), 6.78 (s, 1H), 4.42 (m, 1H), 4.11–4.06 (m, 2H), 3.50 (dd, J = 9.5, 6.5 Hz, 1H), 3.32 (dd, J = 18.0,

10.0 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (CDCl_3) δ 196.8, 144.6, 134.6, 133.9, 133.2, 133.1, 132.0, 130.9, 130.1, 129.9, 129.5, 128.9, 128.6, 128.0, 126.4, 125.9, 125.1, 124.8, 124.0, 90.5, 70.8, 56.2, 43.7, 21.6. Mp. 175.2–176.2 °C. TLC: R_f 0.37 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 2871, 1965, 1679, 1586, 1396, 1376, 1350, 1320, 1215, 1164, 1123, 1087, 1069, 1035, 993, 815,

808, 779, 679, 654, 596, 553 cm^{-1} . HRMS Calcd for $\text{C}_{28}\text{H}_{25}\text{BrNO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 550.0682. Found: m/z 550.0678. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} = 7.6 min, t_{major} = 8.5 min.

2-(2-Phenyl-3-tosyloxazolidin-4-yl)-1-(2-methylphenyl)ethanone.

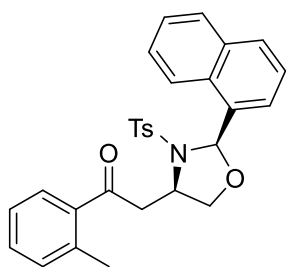
Yield: 55% (58.7 mg), dr = 11:1.



Major diastereomer (3ea): 23% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -4.17 (*c* 6.59, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.82 (m, 2H), 7.63–7.60 (m, 3H), 7.43–7.35 (m, 5H), 7.26 (m, 1H), 7.23 (m, 1H), 7.17 (m, 1H), 6.21 (s, 1H), 4.30 (m, 1H), 4.14 (dd, J = 9.5, 3.0 Hz, 1H), 3.82 (dd, J = 18.0, 3.0 Hz, 1H), 3.53 (dd, J = 9.5, 6.0 Hz, 1H), 2.96 (dd, J = 18.0, 10.5 Hz, 1H), 2.48 (s, 3H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 201.3, 144.4, 138.8, 138.2, 135.9, 133.7, 132.2, 132.1, 130.1, 129.0, 128.7, 128.5, 127.9, 126.6, 125.8, 91.2, 71.5, 56.0, 46.9, 21.7, 21.6. Mp. 108.5–109.5 °C. TLC: R_f 0.37 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3064, 2972, 2931, 2878, 2363, 1683, 1676, 1600, 1570, 1492, 1351, 1287, 1207, 1166, 1112, 1090, 1011, 982, 926, 821, 759, 741, 692, 596, 537, 555, 516 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{26}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 436.1577. Found: m/z 436.1580. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 6.3 min, t_{minor} = 7.4 min.

2-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-1-(2-methylphenyl)ethanone.

Yield: 90% (110 mg), dr = 11:1.

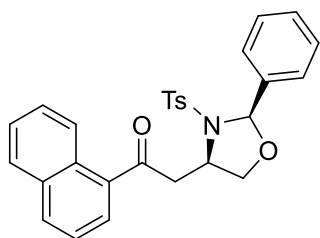


Major diastereomer (3ef): 19% *ee*, yellow solid. $[\alpha]_{\text{D}}^{26}$ +8.14 (*c* 8.60, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.26 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.0 Hz, 1H), 7.91–7.77 (m, 4H), 7.75 (dd, J = 8.0, 1.0 Hz, 1H), 7.58–7.51 (m, 3H), 7.43–7.40 (m, 3H), 7.30 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 7.5 Hz, 1H), 6.80 (s, 1H), 4.46 (m, 1H), 4.10 (dd, J = 9.0, 6.5 Hz, 1H), 4.07 (dd, J = 14.5, 3.0 Hz, 1H), 3.54 (dd, J = 9.5, 6.0 Hz, 1H), 3.32 (dd, J = 18.0, 9.5 Hz, 1H), 2.50 (s, 3H). ^{13}C

NMR (CDCl₃) δ 201.3, 144.5, 138.6, 136.1, 133.9, 133.4, 133.2, 132.2, 132.0, 130.9, 130.1, 129.8, 129.1, 128.6, 128.0, 126.3, 125.84, 125.80, 125.1, 124.8, 124.0, 90.5, 70.9, 56.5, 46.1, 21.6. Mp. 60.0–61.0 °C. TLC: R_f 0.42 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3060, 2874, 2367, 1676, 1599, 1507, 1457, 1353, 1213, 1164, 1120, 1090, 1038, 991, 981, 802, 758, 668, 594, 551 cm⁻¹. HRMS Calcd for C₂₉H₂₈NO₄S: [M+H]⁺, 486.1734. Found: *m/z* 486.1736. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{minor} = 5.0 min, *t*_{major} = 5.8 min.

2-(2-Phenyl-3-tosyloxazolidin-4-yl)-1-(naphthalene-1-yl)etanone.

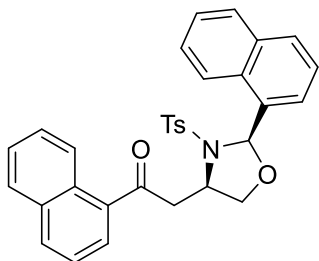
Yield: 93% (110 mg), dr = 11:1.



Major diastereomer (3fa): 24% *ee*, white solid. $[\alpha]_D^{26}$ -9.05 (*c* 4.97, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.66 (d, *J* = 3.0 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.89 (m, 2H), 7.84 (m, 2H), 7.64 (m, 2H), 7.59 (m, 1H), 7.54 (m, 1H), 7.50 (m, 1H), 7.37 (m, 1H), 7.28 (m, 2H), 7.19 (m, 2H), 6.25 (s, 1H), 4.42 (m, 1H), 4.22 (dd, *J* = 9.5, 7.0 Hz, 1H), 4.02 (dd, *J* = 18.0, 3.5 Hz, 1H), 3.64 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.10 (dd, *J* = 18.0, 10.5 Hz, 1H), 2.48 (s, 3H). ¹³C NMR (CDCl₃) δ 201.6, 144.5, 138.2, 133.9, 133.72, 133.67, 130.08, 130.00, 128.99, 128.96, 128.7, 128.5, 128.3, 128.0, 126.6, 126.5, 125.5, 125.3, 124.3, 91.2, 71.5, 56.1, 47.3, 21.6. Mp. 92.9–93.9 °C. TLC: R_f 0.42 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3435, 3061, 2878, 2363, 2343, 1739, 1669, 1663, 1507, 1350, 1291, 1164, 1120, 1094, 1023, 973, 949, 802, 774, 735, 668, 650, 536 cm⁻¹. HRMS Calcd for C₂₈H₂₆NO₄S: [M+H]⁺, 472.1577. Found: *m/z* 472.1581. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 9.0 min, *t*_{minor} = 12.2 min.

2-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-1-(naphthalene-1-yl)ethanone.

Yield: 87% (113 mg), dr = 11:1.

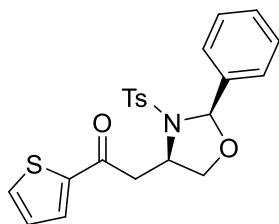


Major diastereomer (3ff): 20% *ee*, yellow solid. $[\alpha]_D^{26} +4.40$ (*c* 8.60, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.69 (d, *J* = 7.5 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.06–8.00 (m, 3H), 7.93–7.88 (m, 5H), 7.62–7.51 (m, 6H), 7.44 (d, *J* = 8.0 Hz, 1H), 6.84 (s, 1H), 4.58 (m, 1H), 4.26 (dd, *J* = 18.0, 3.5 Hz, 1H), 4.18 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.65 (dd, *J* = 9.5, 6.0 Hz,

1H), 3.48 (dd, *J* = 18.0, 10.5 Hz, 1H), 2.50 (s, 3H). ¹³C NMR (CDCl₃) δ 201.5, 144.5, 134.0, 133.88, 133.86, 133.6, 133.4, 133.1, 130.9, 130.1, 129.9, 129.8, 128.8, 128.6, 128.5, 128.2, 128.0, 126.5, 126.3, 125.8, 125.5, 125.2, 124.8, 124.3, 124.1, 90.5, 70.9, 56.6, 46.5, 21.6. Mp. 82.2–83.2 °C. TLC: *R*_f 0.38 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3462, 2921, 2855, 1719, 1653, 1598, 1507, 1472, 1351, 1305, 1234, 1164, 1096, 1061, 948, 845, 803, 775, 666 cm⁻¹. HRMS Calcd for C₃₂H₂₈NO₄S: [M+H]⁺, 522.1734. Found: *m/z* 522.1738. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 7.8 min, *t*_{minor} = 9.4 min.

2-(2-Phenyl-3-tosyloxazolidin-4-yl)-1-(thiophen-2-yl)ethanone.

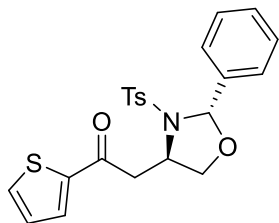
Yield: 74% (79.0 mg), dr = 2.6:1.



Major diastereomer (3ga): 61% *ee*, white solid. $[\alpha]_D^{26} -15.8$ (*c* 5.71, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.81 (m, 2H), 7.64 (m, 2H), 7.60 (m, 2H), 7.41 (m, 2H), 7.40–7.34 (m, 3H), 7.10 (m, 2H), 6.21 (s, 1H), 4.27 (m, 1H), 4.10 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.80 (dd, *J* = 17.5, 3.5 Hz, 1H), 3.57 (dd, *J*

= 9.5, 6.0 Hz, 1H), 2.95 (dd, *J* = 17.0, 10.5 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 190.5, 144.5, 143.2, 138.2, 134.3, 133.6, 132.7, 130.0, 128.7, 128.4, 128.2, 127.9, 126.5, 91.2, 71.2, 55.7, 44.8, 21.6. Mp. 39.6–41.0 °C. TLC: *R*_f 0.29 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 2923, 2875, 1657, 1598, 1518, 1448, 1416, 1352, 1220, 1164, 1118, 1091, 1011, 949, 858, 815, 735, 698, 665, 598, 550 cm⁻¹. HRMS Calcd for C₂₂H₂₂NO₄S₂: [M+H]⁺, 428.0985. Found:

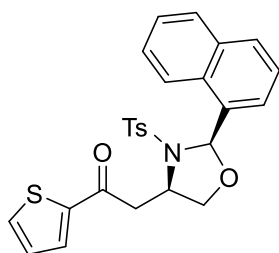
m/z 428.0979. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 8.8 min, t_{minor} = 11.6 min.



Minor diastereomer (3ga'): 41% *ee*, white solid. $[\alpha]_D^{26}$ -25.9 (*c* 2.90, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.83 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.69 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.26 (m, 1H), 7.23 (m, 2H), 7.18 (m, 2H), 7.17–7.14 (m, 3H), 7.04 (m, 2H), 6.14 (s, 1H), 4.63 (m, 1H), 4.42 (ddd, *J* = 9.0, 5.5, 1.0 Hz, 1H), 4.09 (ddd, *J* = 17.0, 3.0, 1.0 Hz, 1H), 3.94 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.38 (dd, *J* = 17.0, 10.5 Hz, 1H), 2.35 (s, 3H). ¹³C NMR (CDCl₃) δ 190.9, 143.6, 143.2, 137.6, 136.6, 134.2, 132.7, 129.14, 129.06, 128.4, 128.0, 127.9, 126.9, 91.7, 71.6, 55.5, 42.6, 21.4. Mp. 40.4–42.4 °C. TLC: *R*_f 0.20 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 3035, 2954, 2922, 2895, 1654, 1598, 1458, 1416, 1343, 1213, 1159, 1093, 949, 917, 814, 759, 699, 673, 596, 539 cm⁻¹. HRMS Calcd for C₂₂H₂₂NO₄S₂: [M+H]⁺, 428.0985. Found: m/z 428.0979. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 13.8 min, t_{minor} = 19.5 min.

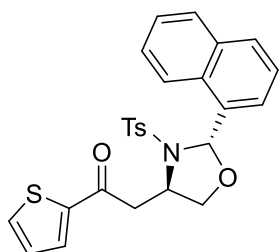
2-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-1-(thiophen-2-yl)ethanone.

Yield: 91% (108 mg), dr = 7.2:1.



Major diastereomer (3gf): 49% *ee*, white solid. $[\alpha]_D^{26}$ +21.0 (*c* 7.97, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.01 (dd, *J* = 7.0, 0.5 Hz, 1H), 7.89 (m, 2H), 7.86 (m, 2H), 7.77 (dd, *J* = 4.0, 1.0 Hz, 1H), 7.66 (dt, *J* = 3.5, 1.0 Hz, 1H), 7.58–7.50 (m, 3H), 7.41 (m, 2H), 7.14 (m, 1H), 6.79 (s, 1H), 4.40 (m, 1H), 4.09 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.05 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.56 (dd, *J* = 9.0, 6.5 Hz, 1H), 3.31 (dd, *J* = 17.0, 10.5 Hz, 1H), 2.48 (s, 3H). ¹³C NMR (CDCl₃) δ 190.5, 144.6, 143.2, 134.3, 133.9, 133.3, 133.1, 132.7, 130.9, 130.1, 129.9, 128.6, 128.3, 128.0, 126.3, 125.8, 125.2, 124.8, 124.0, 90.5, 70.7, 56.2, 44.0, 21.6. Mp. 31.6–32.0 °C. TLC: *R*_f 0.26 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 2923, 2875, 1657, 1598, 1518, 1448, 1416, 1352, 1220, 1164, 1118, 1091, 1011, 949, 858, 815, 735, 698, 665, 598,

550 cm^{-1} . HRMS Calcd for $\text{C}_{26}\text{H}_{24}\text{NO}_4\text{S}_2$: $[\text{M}+\text{H}]^+$, 478.1141. Found: m/z 478.1141. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 8.8 min, t_{minor} = 11.6 min.

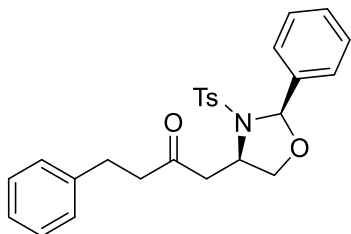


Minor diastereomer (3gf'): 8% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -11.4 (*c* 1.10, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.10 (m, 1H), 7.82 (dd, J = 3.5, 1.0 Hz, 1H), 7.80 (m, 2H), 7.70 (dd, J = 5.0, 1.0 Hz, 1H), 7.46 (m, 2H), 7.34–7.31 (m, 3H), 7.26 (m, 2H), 7.19 (dd, J = 5.0, 4.0 Hz, 1H), 6.98 (m, 2H), 6.84 (s, 1H), 4.82 (m, 1H), 4.36 (ddd, J = 9.0, 4.0, 1.0 Hz, 1H), 4.12 (ddd, J = 12.5,

3.0, 1.0 Hz, 1H), 3.94 (dd, J = 9.5, 3.5 Hz, 1H), 3.40 (dd, J = 17.0, 10.0 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (CDCl_3) δ 190.8, 143.4, 137.1, 134.3, 133.7, 132.7, 131.1, 130.6, 130.0, 129.1, 128.5, 128.4, 127.2, 126.5, 126.4, 125.6, 124.3, 123.5, 89.7, 70.8, 56.1, 42.4, 21.4. Mp. 40.0–41.0 °C. TLC: R_f 0.20 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3065, 3035, 2954, 2922, 2895, 1654, 1598, 1458, 1416, 1343, 1213, 1159, 1093, 949, 917, 814, 759, 699, 673, 596, 539 cm^{-1} . HRMS Calcd for $\text{C}_{26}\text{H}_{24}\text{NO}_4\text{S}_2$: $[\text{M}+\text{H}]^+$, 478.1141. Found: m/z 478.1141. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 13.8 min, t_{minor} = 19.5 min.

1-(2-Phenyl-3-tosyloxazolidin-4-yl)-4-phenylbutan-2-one.

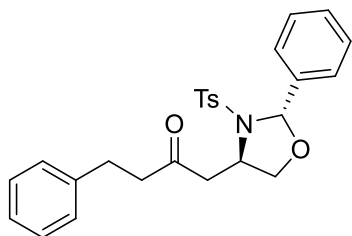
Yield: 45% (46.3 mg), *dr* = 3.3:1.



Major diastereomer (3ha): 65% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -2.13 (*c* 2.35, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.76 (m, 2H), 7.54 (m, 2H), 7.49–7.34 (m, 6H), 7.25 (m, 2H), 7.13 (m, 2H), 6.14 (s, 1H), 4.10 (m, 1H), 4.00 (dd, J = 9.5, 7.0 Hz, 1H), 3.33 (dd, J = 9.5, 6.5 Hz, 1H), 3.25 (dd, J = 17.5, 3.5 Hz, 1H), 2.86–2.60 (m, 4H), 2.47 (s, 3H). ^{13}C NMR (CDCl_3) δ 208.0,

144.5, 138.2, 131.3, 130.1, 128.7, 128.50, 128.46, 128.2, 128.1, 127.9, 126.5, 126.2, 91.1, 71.2, 55.1, 48.4, 44.2, 29.5, 21.6. Mp. 83.8–84.8 °C. TLC: R_f 0.27 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3031, 2868, 2360, 1710, 1598, 1455, 1362, 1351, 1319, 1304, 1291, 1212, 1164, 1092,

1077, 1030, 1014, 953, 783, 758, 702, 672, 595, 551, 541 cm^{-1} . HRMS Calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 450.1734. Found: m/z 450.1722. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96/4, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 14.0 min, t_{minor} = 17.3 min.

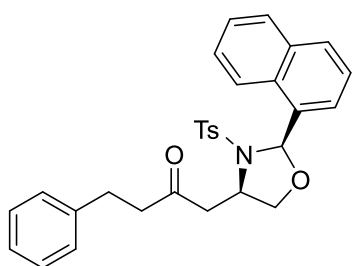


Minor diastereomer (3ha'): 42% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ -7.08 (*c* 1.06, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.30 (m, 2H), 7.22 (m, 2H), 7.20–7.14 (m, 5H), 7.11 (m, 2H), 7.03 (m, 2H), 6.05 (s, 1H), 4.46 (m, 1H), 3.43 (ddd, J = 9.0, 6.0, 1.0 Hz, 1H), 3.70 (dd, J = 9.0, 4.0 Hz, 1H), 3.55 (dd, J = 18.0, 3.0 Hz, 1H), 2.95–2.74 (m, 5H), 2.35 (s, 3H). ^{13}C NMR (CDCl_3) δ 208.1,

143.1, 140.6, 137.6, 136.5, 129.11, 129.07, 128.6, 128.3, 128.0, 127.9, 126.8, 126.2, 91.7, 71.7, 54.8, 46.0, 44.6, 29.6, 21.5. Mp. 97.3–98.1 °C. TLC: R_f 0.20 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3420, 2924, 2360, 1710, 1599, 1454, 1399, 1344, 1160, 1091, 804, 704, 673, 595, 546 cm^{-1} . HRMS Calcd for $\text{C}_{26}\text{H}_{28}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$, 450.1734. Found: m/z 450.1722. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96/4, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 20.4 min, t_{minor} = 27.2 min.

1-(2-(Naphthalene-1-yl)-3-tosyloxazolidin-4-yl)-4-phenylbutan-2-one.

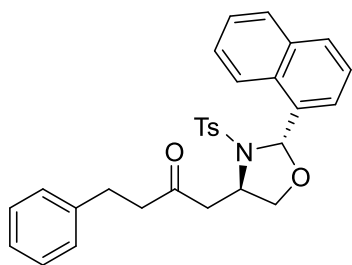
Yield: 54% (67.2 mg), *dr* = 6.3:1.



Major diastereomer (3hf): 65% *ee*, white solid. $[\alpha]_{\text{D}}^{26}$ +28.6 (*c* 0.70, CH_2Cl_2). ^1H NMR (CDCl_3) δ 8.20 (m, 1H), 7.89–7.87 (m, 3H), 7.81 (m, 2H), 7.56–7.49 (m, 3H), 7.40 (m, 2H), 7.26 (m, 2H), 7.19 (m, 1H), 7.15 (m, 2H), 6.70 (s, 1H), 4.22 (m, 1H), 3.94 (dd, J = 9.5, 7.0 Hz, 1H), 3.48 (dd, J = 17.5, 3.5 Hz, 1H), 3.34 (dd, J = 9.5,

6.5 Hz, 1H), 2.91–2.69 (m, 5H), 2.49 (s, 3H). ^{13}C NMR (CDCl_3) δ 207.9, 144.6, 140.4, 133.9, 133.3, 133.1, 130.9, 130.1, 129.9, 128.6, 128.5, 128.2, 128.0, 126.4, 126.2, 125.9, 125.1, 124.8, 124.0, 90.4, 70.6, 55.6, 47.6, 44.3, 29.5, 21.6. Mp. 35.8–37.8 °C. TLC: R_f 0.33 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3465, 2363, 1714, 1653, 1598, 1507, 1495, 1456, 1352, 1165, 1092, 1003, 802, 781, 668, 596, 551 cm^{-1} . HRMS Calcd for $\text{C}_{30}\text{H}_{30}\text{NO}_4\text{S}$: $[\text{M}+\text{H}]^+$,

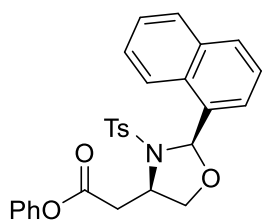
500.1890. Found: m/z 500.1883. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 98/2, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 65.0 min, t_{minor} = 68.4 min.



Minor diastereomer (3hf'): 25% *ee*, white solid. $[\alpha]_D^{26}$ -4.59 (*c* 1.09, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.04 (m, 1H), 7.77 (m, 2H), 7.43 (m, 2H), 7.31 (m, 2H), 7.30–7.25 (m, 3H), 7.24 (m, 2H), 7.23–7.20 (m, 2H), 6.92 (m, 2H), 6.72 (s, 1H), 4.66 (m, 1H), 4.30 (ddd, J = 8.5, 6.0, 1.0 Hz, 1H), 3.71 (dd, J = 9.5, 4.0 Hz, 1H), 3.60 (ddd, J = 18.0,

3.5, 0.5 Hz, 1H), 2.96–2.76 (m, 5H), 2.28 (s, 3H). ¹³C NMR (CDCl₃) δ 207.9, 143.2, 140.6, 137.0, 133.6, 131.1, 130.4, 130.0, 129.0, 128.6, 128.5, 128.3, 127.0, 126.7, 126.3, 126.2, 125.6, 124.3, 123.5, 89.9, 71.0, 55.3, 45.9, 44.6, 29.6, 21.4. Mp. 49.5–51.5 °C. TLC: R_f 0.22 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3420, 2924, 2360, 1710, 1599, 1454, 1399, 1344, 1160, 1091, 804, 704, 673, 595, 546 cm⁻¹. HRMS Calcd for C₃₀H₃₀NO₄S: [M+H]⁺, 500.1890. Found: m/z 500.1883. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96/4, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 27.9 min, t_{minor} = 50.9 min.

Phenyl-2-((2*R*,4*R*)-2-(naphthalene-1-yl)-3-tosyloxazolidin-4-yl)acetate (3if).



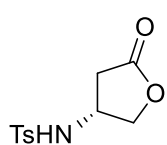
Yield: 77% (94.0 mg), single diastereomer, 37% *ee*, white solid. $[\alpha]_D^{26}$ +13.0 (*c* 3.86, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.21 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.89 (m, 2H), 7.85 (m, 2H), 7.57–7.52 (m, 3H), 7.40–7.37 (m, 4H), 7.26 (m, 1H), 7.11 (m, 2H), 6.77 (s, 1H), 4.39 (m, 1H), 3.97 (dd, J = 9.0, 6.0 Hz, 1H), 3.65 (dd, J = 9.5, 6.0 Hz, 1H), 3.55 (dd, J = 17.0, 4.5 Hz, 1H), 2.98 (dd, J = 17.5, 9.5 Hz, 1H), 2.48 (s, 3H). ¹³C NMR (CDCl₃) δ 169.4, 150.3, 144.6, 134.0, 133.6, 132.9, 131.0, 130.1, 130.01, 129.95, 129.5, 128.7, 128.1, 126.4, 126.1, 125.9, 125.3, 124.9, 124.0, 121.4, 91.0, 70.5, 56.2, 39.2, 21.6. Mp. 165.0–166.0 °C. TLC: R_f 0.24 (toluene/EtOAc/hexane = 30:1:9). IR (KBr): 3056, 2874, 1751, 1598, 1492, 1355, 1228, 1193, 1165, 1117, 1039, 910, 802, 731, 684, 667, 596, 549 cm⁻¹. HRMS Calcd for C₂₈H₂₆NO₅S: [M+H]⁺, 488.1526. Found: m/z 488.1526. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 96/4, flow rate = 2.0 mL/min, λ =

254 nm, 40 °C): $t_{\text{minor}} = 26.5$ min, $t_{\text{major}} = 28.0$ min.

Procedure for synthesis of **5**

To a stirred solution of **3if** (0.023 g, 0.047 mmol) in CH₂Cl₂ (5 mL) was added titanium tetrachloride (0.052 mL, 0.5 mmol) at –78 °C, and the mixture was stirred at –78 °C for 1 h and at –40 °C for additional 3 h. H₂O was added to the solution, and the mixture was stirred at 0 °C for 30 min and subsequently warmed to ambient temperature. The mixture was extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave (*R*)-4-methyl-*N*-(5-oxotetrahydrofuran-3-yl)benzenesulfonamide (**5**).

(*R*)-4-Methyl-*N*-(5-oxotetrahydrofuran-3-yl)benzenesulfonamide (5**):** CAS RN [162518-06-1].



Yield: 53% (6.3 mg), 36% *ee*, white solid. ¹H NMR (CDCl₃) δ 7.74 (d, *J* = 8.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 5.70 (br s, 1H), 4.38 (dd, *J* = 11.0, 7.5 Hz, 1H), 4.14 (m, 2H), 2.64 (dd, *J* = 18.5, 8.0 Hz, 1H), 2.44 (s, 3H), 2.35 (dd, *J* = 18.5, 5.5 Hz, 1H). ¹³C NMR (CDCl₃) δ 174.9, 144.4, 136.5, 129.6, 127.0, 73.1, 49.8, 34.8, 21.6. TLC: R_f 0.27 (hexane/EtOAc = 1/1). HRMS Calcd for C₁₁H₁₇N₂O₄S: [M+NH₄]⁺, 273.0904. Found: *m/z* 273.0904. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): $t_{\text{major}} = 12.1$ min, $t_{\text{minor}} = 16.0$ min.

The absolute configuration of **5** was assigned as (*R*) by comparing the optical rotation with the literature value.^{12e}

[α]_D²⁵ +7.25 (*c* 0.69, EtOH) [lit.^{12e} (*R*)-4-methyl-*N*-(5-oxotetrahydrofuran-3-yl)benzenesulfonamide: [α]_D²⁵ +15.5 (*c* 1.0, EtOH)].

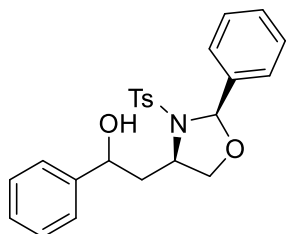
Procedure for reduction of **3aa**

Zinc borohydride solution was prepared by the literature procedure.¹⁶ To a stirred solution of

3aa (0.055 g, 0.13 mmol) in Et₂O (1 mL) was added zinc borohydride solution (in Et₂O, 0.2 M, 2 mL) at 0 °C, and the mixture was stirred for 2.5 h at 0 °C. Saturated aqueous NH₄Cl was added to quench the reaction, and the mixture was extracted with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using CH₂Cl₂/EtOAc (v/v = 25/1) as an eluent gave both isolated diastereomers of 1-phenyl-2-(2-phenyl-3-tosyloxazolidin-4yl)ethanol (dihydro-**3aa**).

1-Phenyl-2-(2-phenyl-3-tosyloxazolidin-4yl)ethanol (dihydro-3aa).

Yield: 92% (50.4 mg), dr = 1:1.



Diastereomer 1: 98% *ee*, white solid. $[\alpha]_D^{25} -15.2$ (*c* 1.15, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.57–7.62 (m, 4H), 7.29–7.39 (m, 10H), 7.26 (d, *J* = 4.0 Hz, 1H), 6.19 (s, 1H), 4.82 (m, 1H), 3.86 (m, 1H), 3.79 (m, 1H), 3.58 (m, 1H), 2.44 (s, 3H), 2.43 (m, 1H), 2.13 (m, 1H), 1.84 (m, 1H). ¹³C

NMR (CDCl₃) δ 144.2, 143.5, 138.3, 133.6, 129.9, 128.64, 128.56, 128.4, 128.0, 127.7, 126.7, 125.7, 91.5, 71.7, 70.8, 56.9, 43.2, 21.6. Mp. 37.5–38.5 °C. TLC: *R*_f 0.31 (CH₂Cl₂/EtOAc = 25:1). IR (KBr): 3555, 2880, 1598, 1494, 1448, 1351, 1164, 1110, 1013, 947, 811, 753, 673, 588 cm⁻¹. HRMS Calcd for C₂₄H₂₆NO₄S: [M+H]⁺, 424.1577. Found: *m/z* 424.1568. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} = 15.2 min, *t*_{minor} = 18.8 min.

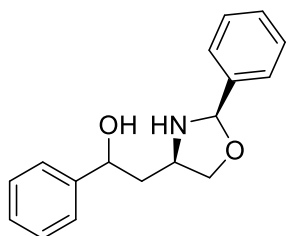
Diastereomer 2: 98% *ee*, white solid. $[\alpha]_D^{25} +81.7$ (*c* 1.53, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.83 (m, 2H), 7.60 (m, 2H), 7.36–7.42 (m, 5H), 7.26–7.35 (m, 2H), 7.22 (m, 1H), 7.16 (m, 2H), 6.31 (s, 1H), 5.05 (m, 1H), 4.24 (m, 1H), 5.32–5.58 (m, 2H), 3.39 (d, *J* = 4.5 Hz, 1H), 2.48 (s, 3H), 1.59–1.66 (m, 2H). ¹³C NMR (CDCl₃) δ 144.7, 143.7, 138.5, 133.8, 130.1, 128.7, 128.5, 128.3, 127.9, 127.1, 126.2, 125.2, 91.6, 70.9, 69.8, 59.6, 44.6, 21.7. Mp. 41.0–42.0 °C. TLC: *R*_f 0.45 (CH₂Cl₂/EtOAc = 25:1). IR (KBr): 3527, 3031, 1598, 1494, 1450, 1348, 1164, 1091, 1008, 815, 699, 597, 553 cm⁻¹. HRMS Calcd for C₂₄H₂₅NO₄S: [M+H]⁺, 424.1577. Found: *m/z* 424.1568.

HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} = 12.1 min, t_{minor} = 14.9 min.

Procedure for synthesis of 6

To a stirred solution of naphthalene (0.13 g, 1 mmol) in THF (2 mL) was added sodium (0.035g, 1.5 mmol) at room temperature, and the mixture was stirred for 1 h to give a deep green solution of sodium naphthalenide. To a stirred solution of an isolated diastereomer (diastereomer 1) of dihydro-**3aa** (0.026 g, 0.06 mmol) in THF (1 mL) was added the sodium naphthalenide solution (0.5 mL) at -78 °C, and the mixture was stirred for 1 h at -78 °C. Saturated aqueous NaHCO₃ was added to quench the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using CHCl₃/MeOH (v/v = 10/1) as an eluent gave 1-phenyl-2-(2-phenyloxazolidin-4yl)ethanol (**6**).

1-Phenyl-2-(2-phenyloxazolidin-4yl)ethanol (**6**).



Yield: 85% (13.7 mg), 98% *ee*, yellow oil. $[\alpha]_D^{25} -11.9$ (*c* 1.05, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.23–7.36 (m, 10H), 4.91 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.95 (d, *J* = 6.0 Hz, 1H), 3.79–3.83 (m, 2H), 3.56 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.06 (m, 1H), 1.73–1.84 (m, 1H), 1.70 (m, 1H). ¹³C NMR (CDCl₃)

δ 144.9, 139.1, 128.6, 128.35, 128.29, 127.4, 127.2, 125.6, 74.6, 62.5, 58.6, 50.6, 40.5. TLC: *R*_f 0.10 (CHCl₃/MeOH = 10:1). IR (KBr): 3347, 2920, 1647, 1452, 1119, 1003, 749, 699, 479, 407, 362 cm⁻¹. HRMS Calcd for C₁₇H₂₀NO₂: [M+H]⁺, 270.1489. Found: *m/z* 270.1488. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 97.5/2.5, flow rate = 4.5 mL/min, λ = 254 nm, 40 °C): t_{major} = 19.6 min, t_{minor} = 21.2 min.

Table 3. Dependence of stereoselectivity on reaction time^a

$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{toluene, 25 } ^\circ\text{C, } t \text{ h}]{\mathbf{4a} \text{ (10 mol \%)}} \mathbf{3aa} + \mathbf{3aa'}$				
entry	<i>t</i> (h)	yield (%) ^b	dr ^c	ee (3aa , 3aa') (%)
1	0.5	35	3.2:1	55, 41
2	5	89	3.3:1	54, 40
3	24	86	4.5:1	54, 32
4	140	84	>50:1	48, n.d.

^aReactions were run using **1a** (0.25 mmol), **2a** (0.25 mmol), and **4a** (0.025 mmol) in toluene (0.5 mL). ^bIsolated yields. ^cDiastereomeric ratios were determined by ¹H NMR.

(Note: the shift of diastereomeric ratio could not be observed at 0 °C.)

Table 4. Screening of protecting groups of imines^a

Reaction scheme: 1a + 2 (R = Ts, 4-NO₂C₆H₄SO₂, 3-NO₂C₆H₄SO₂, 2-NO₂C₆H₄SO₂, 2,4,6-(CH₃)₃C₆H₄SO₂, CH₃SO₂) $\xrightarrow[\text{toluene, 0 } ^\circ\text{C, 24 h}]{\text{4a (10 mol \%)}}$ 3 (major diastereomer) + 3' (minor diastereomer)					
entry	R (2)		yield (%) ^b	dr ^c	ee (3 , 3') (%)
1	Ts	2a	95	2.4:1	64, 59
2	4-NO ₂ C ₆ H ₄ SO ₂ (4-Ns)	2j	92	3.0:1	39, n.d.
3	3-NO ₂ C ₆ H ₄ SO ₂ (3-Ns)	2k	65	4.8:1	48, 8
4	2-NO ₂ C ₆ H ₄ SO ₂ (2-Ns)	2l	52	>30:1	33, n.d.
5	2,4,6-(CH ₃) ₃ C ₆ H ₄ SO ₂	2m	77	14:1	59, 77
6	CH ₃ SO ₂ (Ms)	2n	95	1:1	57, 26

^aReactions were run using **1a** (0.25 mmol), **2** (0.25 mmol), and **4a** (0.025 mmol) in toluene (0.5 mL). ^bIsolated yields. ^cDiastereomeric ratios were determined by ¹H NMR.

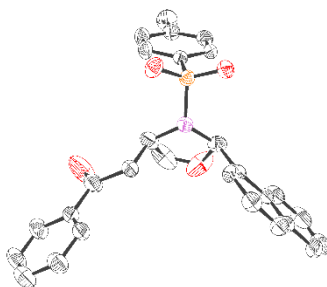


Figure 1. ORTEP drawing of **3af** ($C_{22}H_{19}NO_3S_2$, $M = 471.55$, $T = 273(2)$ K).

Crystal System	Tetragonal	
Radiation	Mo-K α ($\lambda = 0.71073$ Å)	
Space group	P4 ₃ 2 ₁ 2	
Crystal Dimensions	0.10 × 0.080 × 0.060 mm	
Unit cell dimensions	$a = 11.3101(16)$ Å	$\alpha = 90^\circ$
	$b = 11.3101(16)$ Å	$\beta = 90^\circ$
	$c = 38.841(8)$ Å	$\gamma = 90^\circ$
Volume	4968.5(14) Å ³	
Z	8	
D_{calc}	1.261 Mg/m ³	
θ range for data collection	1.88 to 27.03°.	
Reflections collected	29935	
Independent reflections	5435 [$R_{\text{int}} = 0.0289$]	
No. Variables	308	
Goodness-of-fit on F^2	1.030	
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0489$, $wR_2 = 0.1271$	
R indices (all data)	$R_1 = 0.0596$, $wR_2 = 0.1343$	
Flack Parameter	0.03(9)	

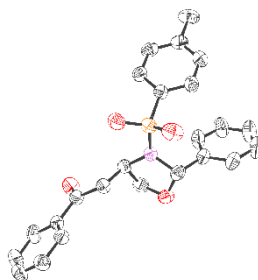


Figure 2. ORTEP Drawing of **3aa'** ($C_{24}H_{23}NO_4S$, $M = 421.49$ $T = 273(2)$ K)).

Wavelength	Mo-K α ($\lambda = 0.71073$ Å)
Crystal system	Monoclinic
Space group	P2 ₁
Crystal Dimensions	0.10 × 0.070 × 0.060 mm

Unit cell dimensions	$a = 10.1238(14) \text{ \AA}$ $b = 13.8355(18) \text{ \AA}$ $c = 15.717(2) \text{ \AA}$	$\alpha = 90^\circ$ $\beta = 102.154(2)^\circ$ $\gamma = 90^\circ$
Volume	$2152.1(5) \text{ \AA}^3$	
Z value	4	
D_{calc}	1.301 Mg/m^3	
θ range for data collection	1.98 to 27.03°	
Reflections collected	13120	
Independent reflections	7349 [$R_{\text{int}} = 0.0199$]	
No. Variables	543	
Goodness-of-fit on F^2	1.043	
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0435$, $wR_2 = 0.1103$	
R indices (all data)	$R_1 = 0.0512$, $wR_2 = 0.1158$	
Flack Parameter	$-0.05(5)$	

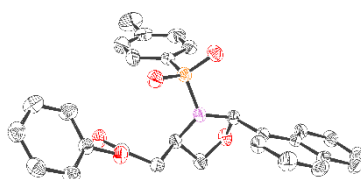


Figure 3. ORTEP Drawing of **3if** ($\text{C}_{28}\text{H}_{25}\text{NO}_5\text{S}$, $M = 487.55$, $T = 298(2) \text{ K}$).

Wavelength	Mo-K α ($\lambda = 0.71073 \text{ \AA}$)	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Crystal Dimensions	$1.00 \times 0.60 \times 0.50 \text{ mm}$	
Unit cell dimensions	$a = 13.2838(12) \text{ \AA}$ $b = 15.5091(14) \text{ \AA}$ $c = 12.3383(11) \text{ \AA}$	$\alpha = 90^\circ$ $\beta = 103.4920(10)^\circ$ $\gamma = 90^\circ$
Volume	$2471.8(4) \text{ \AA}^3$	
Z value	4	
D_{calc}	1.310 Mg/m^3	
θ range for data collection	1.58 to 27.04°	
Reflections collected	14116	
Independent reflections	5384 [$R_{\text{int}} = 0.0263$]	
No. Variables	317	
Goodness-of-fit on F^2	1.211	
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0619$, $wR_2 = 0.1297$	
R indices (all data)	$R_1 = 0.0707$, $wR_2 = 0.1360$	

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 13. The relative configuration of **3if** was determined by X-ray analysis.
 14. The reduction of **3aa** with Zn(BH₄)₂ gave a diastereomer mixture (1/1). One of the isolated diastereomers of the alcohol obtained by reduction was used for subsequent deprotection.
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Chapter 2

Procedure-Controlled Enantioselectivity Switch in Organocatalytic 2-Oxazolidinone Synthesis

Aminothiourea-based bifunctional organocatalysts allowed enantioselective formal [3+2] cycloadditions of γ -hydroxy- α,β -unsaturated carbonyls with isocyanates to afford optically active 2-oxazolidinones, which are important frameworks found in a wide range of bioactive compounds and chiral auxiliaries for asymmetric synthesis. It was found that the absolute configurations of the products can be controlled without changing the reaction components, but simply by changing the order of addition of the reactants.

Introduction

Protein function can be altered by post-translational modification or by genetic mutation as a result of chemical damage or ionizing radiation. Post-translational modification of biological catalysts, such as phosphorylation of enzymes like Smurf1^{1a} or MEK,^{1b} can dramatically alter the selectivity of the enzyme and downstream biological events. In chemical synthesis, asymmetric catalysts, especially biomimetic organocatalysts, may undergo similar functional switches in response to environmental changes.² For example, reversal of enantioselectivity by using a single chiral source has been accomplished in several reactions simply by changing an achiral component (e.g., the solvent) or using additional achiral additives.^{3,4}

Chiral 2-oxazolidinones are important frameworks found in a wide range of bioactive compounds⁵ and chiral auxiliaries for asymmetric synthesis.⁶ In Chapter 1, the author described asymmetric formal [3 + 2] cycloaddition reactions via intermediates generated in situ from γ -hydroxy- α,β -unsaturated carbonyls with imines (Scheme 1).⁷ In the presence of cinchona-alkaloid-based aminothiourea catalysts (Figure 1),⁸ those intermediates underwent intramolecular aza-Michael addition with practical enantioselectivity to afford a diastereomeric mixture. Thus inspired, he envisioned that reactions of an isocyanate with γ -hydroxy- α,β -unsaturated carbonyl compounds could also be carried out enantioselectively to furnish chiral 2-oxazolidinones (Scheme 1).⁹ Moreover, the use of a heterocumulene as a nitrogen source would circumvent the generation of diastereomers, thereby allowing more effective enantioselective amination of the β -carbon.

In the present study, the author found that a slight change in the reaction procedure led to a reversal of the enantioselectivity, even when the chiral catalyst, substrates, and solvent used were unaltered. Herein he presents a novel asymmetric reaction to afford 2-oxazolidinones in which a procedure-controlled enantioselectivity switch was observed when using a single cinchona-alkaloid-derived organocatalyst. To the best of my knowledge, there has been no previous report of such an inversion behavior that requires no change in the reaction components.

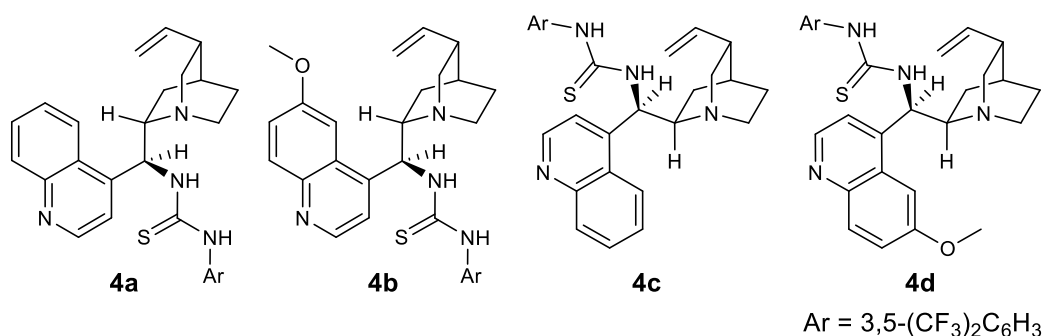
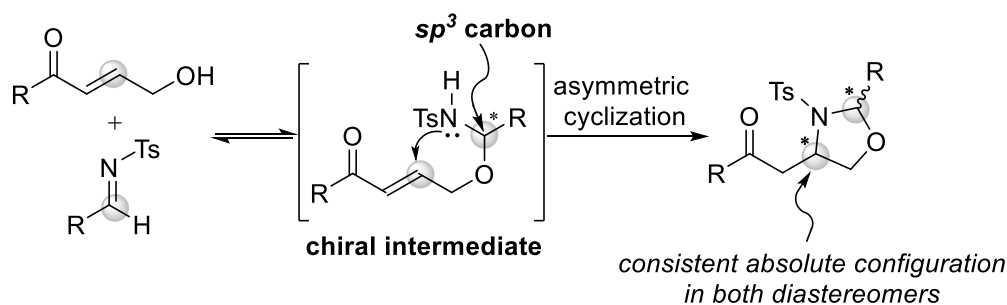
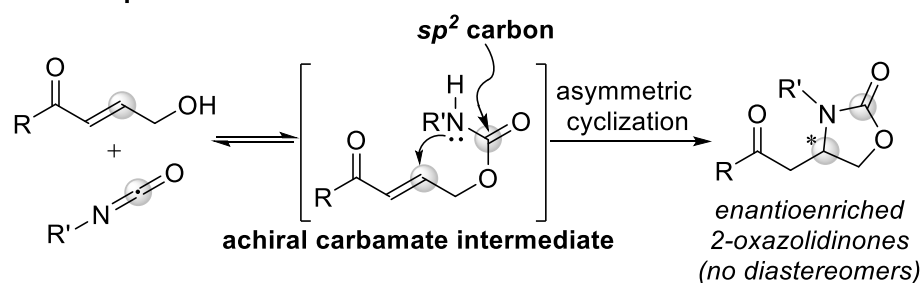


Figure 1. Cinchona-alkaloid-derived aminothiurea catalysts.

In Chapter 1



This Chapter

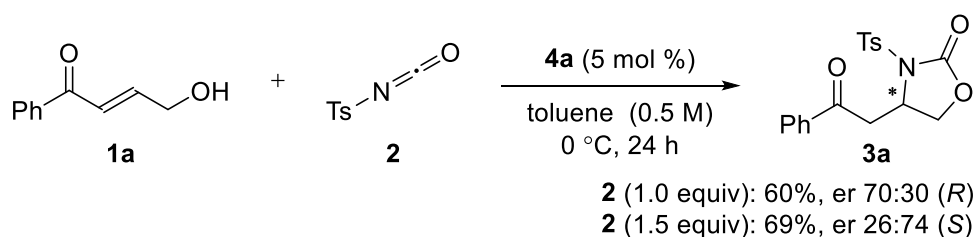


Scheme 1. Formal [3+2] Cycloaddition via asymmetric intramolecular hetero-Michael addition by aminothiurea catalysts.

Results and Discussion

The author initially carried out the cycloaddition of (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and 4-methylbenzenesulfonyl isocyanate (**2**) using 5 mol % cinchonidine-derived catalyst **4a** (Scheme 2). The reaction was effected by mixing the starting materials and the catalyst in one

portion in toluene at 0 °C. The addition of 1.0 equiv of **2** resulted in the formation of the (*R*)-2-oxazolidinone (*R*)-**3a** in an enantiomeric ratio (er) of 70:30, while the use of 1.5 equiv of **2** afforded (*S*)-**3a** with an er of 26:74.



Scheme 2. Effect of the amount of isocyanate **2** in the formal [3+2] cycloaddition of **1a** with **2**.

To gain insight into the unusual effect of an excess amount of the isocyanate on the stereoselectivity, spectroscopic studies were carried out. ^1H NMR analysis of a solution of **2** and **4a** in toluene- d_8 indicated that the signals associated with the protons adjacent to the quinuclidine nitrogen of **4a** were shifted downfield in the presence of **2** (Figure 3 in the Experimental Section). In addition, ^{13}C NMR analysis of the solution revealed the disappearance of the sp carbon of **2** in the presence of **4a** (Figure 4 in the Experimental Section). Furthermore, high-resolution mass spectrometry analysis of a solution of **2** and **4a** (20:1 mixture) detected their 1:1 adduct (found, m/z 762.2000; calcd for $[\text{M} + \text{H}]^+$, 762.2002) but not oligomeric $n:1$ adducts ($n > 1$) (Scheme 6 in the Experimental Section). These results strongly suggested that **4a** was mutated by **2** to form a zwitterionic 1:1 adduct by addition of the quinuclidine nitrogen of **4a** to **2** (Figure 2),¹⁰ which had a significant influence on the stereoselectivity. Thus, the author modified the reaction procedure as follows: **1a** (1.01 equiv) was first treated with **2** (1.0 equiv) until the latter was completely consumed, generating the carbamate intermediate; subsequently, **4a** (5 mol %) was added (Scheme 3, procedure A).^{11,12} This sequential protocol yielded (*R*)-**3a** with improved enantioselectivity. In contrast, when **4a** (5 mol %) was mutated by treatment with **2** (1.0 equiv) before the addition of 1.01 equiv of **1a** (Scheme 3, procedure B), the opposite enantiomer, (*S*)-**3a**, was obtained selectively.¹³ We carried out the aforementioned reaction protocols in the presence of catalysts

derived from other readily available cinchona alkaloids (Table 1) and found that all of them led to reversal of the enantioselectivity.

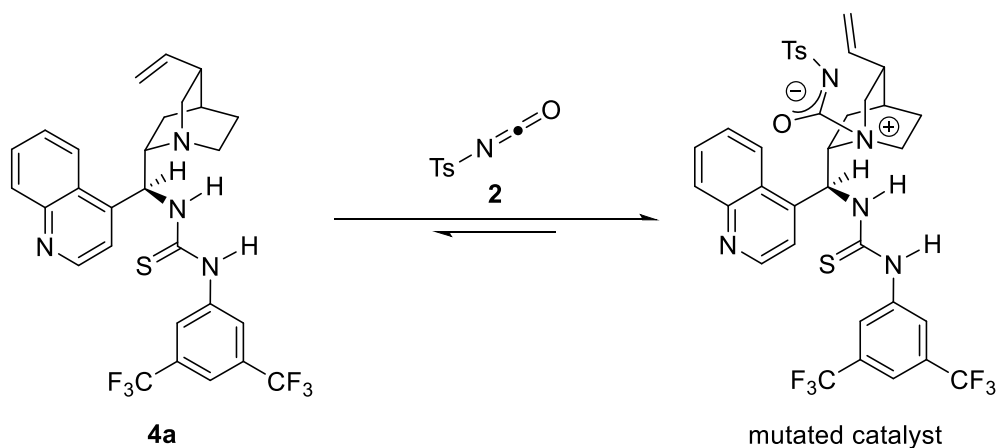
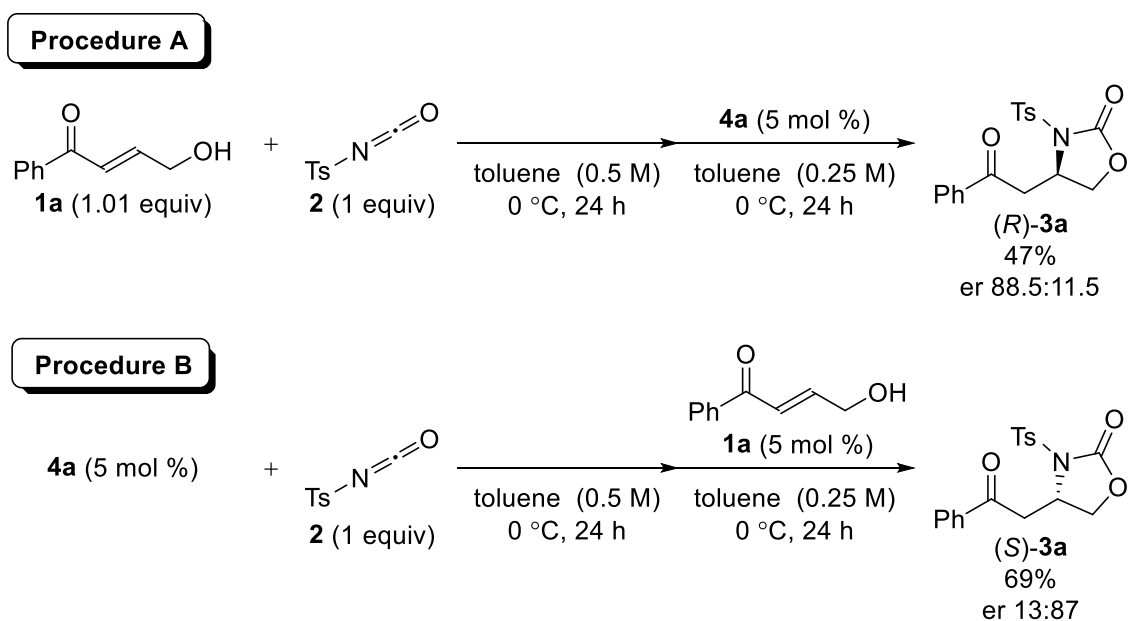
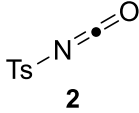


Figure 2. Proposed structure of the catalyst mutated by **2**.



Scheme 3. Enantioselectivity switch in the formal [3+2] cycloaddition using sequential protocols.

Table 1. Investigation of the enantioselectivity switch with cinchona-alkaloid-based catalysts **4**^a

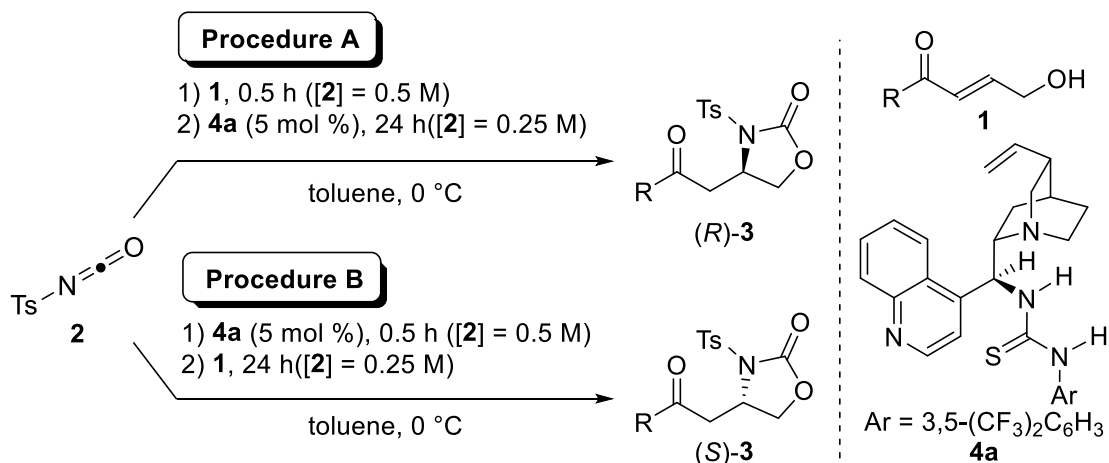
 2 Procedure A 1) 1a, 0.5 h ([2] = 0.5 M) 2) 4 (5 mol %), 24 h ([2] = 0.25 M) toluene, 0 °C 3a Procedure B 1) 4 (5 mol %), 0.5 h ([2] = 0.5 M) 2) 1a, 24 h ([2] = 0.25 M) toluene, 0 °C <i>ent</i>-3a					
entry	catalyst	Procedure A		Procedure B	
		yield (%) ^b	<i>er</i>	yield (%) ^b	<i>er</i>
1	4a	47	88.5:11.5 (<i>R</i>)	69	13:87 (<i>S</i>)
2	4b	75	79:21 (<i>R</i>)	57	20:80 (<i>S</i>)
3	4c	53	26:74 (<i>S</i>)	50	83:17 (<i>R</i>)
4	4d	61	20.5:79.5 (<i>S</i>)	46	82:18 (<i>R</i>)

^aReactions were carried out using **1a** (0.253 mmol), **2a** (0.25 mmol), and the catalyst (0.0125 mmol) in the toluene. ^bIsolated yields.

With the established procedures and conditions using **4a** as a single catalyst, the author explored the substrate scope (Table 2). Reversal of enantioselectivity was observed in all of the reactions with γ -hydroxy- α,β -unsaturated ketones **1a–h** (entries 1–8). Both electron-rich and electron-deficient substrates were tolerated under the employed reaction conditions (entries 2 and 3). A substrate bearing a *p*-bromo group also selectively afforded both enantiomers of the 2-oxazolidinone product (entry 4). In addition, enones bearing bulky biphenyl and naphthyl groups yielded the corresponding products with high enantioselectivity (entries 5 and 6), and a heterocycle-substituted substrate also allowed for the enantiodivergent synthesis (entry 7). An aliphatic ketone could also be used in the reaction, although the enantioselectivity with procedure A was modest in comparison with that in other cases (entry 8). However, in the reaction using a γ -hydroxy- α,β -unsaturated ester, the same 2-oxazolidinone enantiomer was obtained as the major

product in both procedures, and higher enantioselectivity was observed with procedure B (entry 9).

Table 2. Substrate scope^a

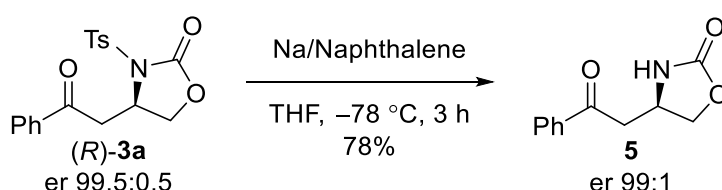


entry	R (3)	Procedure A		Procedure B	
		yield (%) ^b	<i>er</i>	yield (%) ^b	<i>er</i>
1	Ph (3a)	47	88.5:11.5 (<i>R</i>)	69	13:87 (<i>S</i>)
2	4-CH ₃ OC ₆ H ₄ (3b)	67	73:27 (<i>R</i>)	49	25.5:74.5 (<i>S</i>)
3	4-CF ₃ C ₆ H ₄ (3c)	79	80.5:19.5 (<i>R</i>)	71	6.5:93.5 (<i>S</i>)
4	4-BrC ₆ H ₄ (3d)	95	81:19 (<i>R</i>)	74	14:86 (<i>S</i>)
5	4-PhC ₆ H ₄ (3e)	27	89.5:10.5 (<i>R</i>)	19	15.5:84.5 (<i>S</i>)
6	2-naphthyl (3f)	66	91:9 (<i>R</i>)	49	18:82 (<i>S</i>)
7	2-thienyl (3g)	53	81.5:18.5 (<i>R</i>)	53	16.5:83.5 (<i>S</i>)
8	PhCH ₂ CH ₂ (3h)	83	68:32 (<i>R</i>)	73	17.5:82.5 (<i>S</i>)
9	PhO (3i)	73	55:45 (<i>R</i>)	30	88:12 (<i>R</i>)

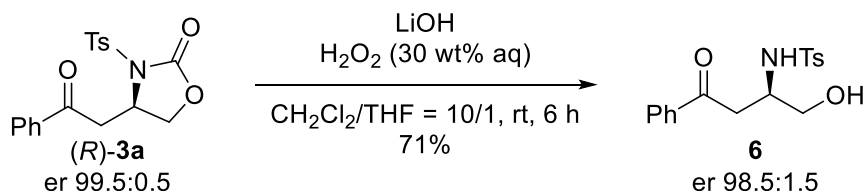
^aReactions were carried out using **1a** (0.253 mmol), **2a** (0.25 mmol), and the catalyst (0.0125 mmol) in the toluene. ^bIsolated yields.

To demonstrate the utility of the products as valuable synthetic intermediates, transformations of (*R*)-**3a** with high optical purity obtained after one-time recrystallization were carried out. The tosyl group of **3a** could be removed by treatment with sodium naphthalenide to afford **5** without

significant loss of optical purity (Scheme 4). In addition, treatment of (*R*)-**3a** with lithium hydroxide and hydrogen peroxide gave optically active 1,2-amino alcohol **6** (Scheme 5). Thus, the proposed 2-oxazolidinone synthesis protocol and transformation methods would constitute a facile, practical enantiodivergent route to optically active 2-oxazolidinones and chiral 1,2-amino alcohols. The absolute configuration of **5** was determined by comparing its optical rotation with the literature value¹⁴, and the configurations of all other products were assigned analogously.



Scheme 4. Deprotection of **3a**.



Scheme 5. Synthesis of chiral 1,2-amino alcohol **6**.

Conclusion

In summary, the author developed a novel cinchona-alkaloid-driven aminothiurea catalyzed formal [3+2] cycloaddition of γ -hydroxy- α,β -unsaturated ketones with isocyanate for the synthesis of chiral 2-oxazolidinones. Notably, the two enantiomers could be synthesized selectively without changing the reaction components (chiral catalyst, substrate, and solvent). Enantioselectivity was controlled only by changing the sequence of adding the reagents and the catalyst. Formation of the covalent bond between the catalyst and substrate critically changes the

enantioselectivity compared to utilize the noncovalent bond. The proposed reaction protocols are particularly valuable for catalysts derived from chiral natural products, including cinchona alkaloids, since these compounds are available in only one enantiomeric form.

Experimental Section

Materials.

Unless otherwise noted, commercially available reagents were used without purification. Substrates **1a–1d**, and **1f–1i** were prepared according to the literature,^{7c,15} Bifunctional organocatalyst **4** were prepared by the method described in Chapter 1.

General procedure for asymmetric formal [3+2] cycloaddition reaction

Procedure A

In a 5-mL vial, after the mixture of γ -hydroxy- α,β -unsaturated ketone **1** (0.253 mmol) in toluene (0.5 mL) was stirred at 0 °C, isocyanate **2** (0.25 mmol) was added and stirred for 30 min. Subsequently, cinchonidine-derived bifunctional catalyst **4a** (0.0125 mmol) and toluene (0.5 mL) was added. The mixture was stirred at 0 °C for additional 24 h. The reaction mixture was diluted with CH₂Cl₂, and the solution was sequentially purified by flash silica gel column chromatography using EtOAc/hexane (v/v = 1/1) as an eluent to afford the corresponding oxazolidinone **3**. Racemic compounds were prepared using triethylamine as a catalyst.

Procedure B

In a 5-mL vial, after the mixture of isocyanate **2** (0.25 mmol) and cinchonidine-derived bifunctional catalyst **4a** (0.0125 mmol) in toluene (0.5 mL) was stirred for 30 min at 0 °C, γ -hydroxy- α,β -unsaturated ketone **1** (0.253 mmol) and toluene (0.5 mL) was added. The mixture was stirred at 0 °C for additional 24 h. The reaction mixture was diluted with CH₂Cl₂, and the solution was sequentially purified by flash silica gel column chromatography using EtOAc/hexane

(v/v = 1/1) as an eluent to afford the corresponding oxazolidinone **3**.

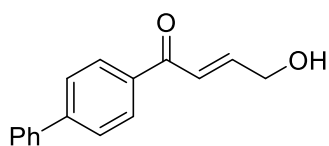
Procedure for preparation of γ -hydroxy- α,β -unsaturated ketone **1e**

The mixture of 1-([1,1'-biphenyl]-4-yl)-2-bromoethanone (2.75 g, 10 mmol) and triphenylphosphine (2.9 g, 11 mmol) in benzene (10 mL) was stirred at ambient temperature for 18 h. The reaction slurry was filtered, and the obtained solid was washed with benzene and dried under reduced pressure.

This salt was dissolved in a mixture of CH₂Cl₂ (80 mL) and 2N aqueous NaOH (50 mL), and the solution was stirred for 30 min. The organic phase was separated, washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Removal of the solvent under reduced pressure provided the corresponding stabilized ylide, 1-([1,1'-biphenyl]-4-yl)-2-(triphenylphosphoranylidene)ethanone, in nearly quantitative yield.

Next, the mixture of 1-([1,1'-biphenyl]-4-yl)-2-(triphenylphosphoranylidene)ethanone (0.58 g, 1.8 mmol) and glycoaldehyde dimer (0.12 g, 1 mmol) in THF (5 mL) was stirred at ambient temperature to 80 °C for 5 h. After being stirred, the solvent was evaporated. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave (*E*)-1-([1,1'-biphenyl]-4-yl)-4-hydroxybut-2-en-1-one (**1e**) in 74% yield (0.32 g) (overall).

(*E*)-1-([1,1'-Biphenyl]-4-yl)-4-hydroxybut-2-en-1-one (1e**)**

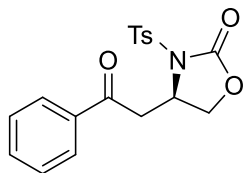


White solid. ¹H NMR (CDCl₃) δ 8.06 (m, 2H), 7.71 (m, 2H), 7.63 (m, 2H), 7.49 (m, 2H), 7.41 (m, 1H), 7.29 (dt, *J* = 16.0, 2.0 Hz, 1H), 7.18 (dt, *J* = 16.0, 3.5 Hz, 1H), 4.52 (m, 2H), 1.76 (t, *J* = 6.0 Hz, 1H). ¹³C

NMR (CDCl₃) δ 189.7, 146.7, 145.7, 139.9, 136.3, 129.2, 128.9, 128.2, 127.3, 123.7, 62.4. Mp. 46.2–47.2 °C. TLC: R_f 0.40 (hexane/EtOAc = 1:1). IR (KBr): 3415, 2910, 2360, 1659, 1609, 1403, 1305, 1210, 1102, 1009, 945, 910, 852, 760, 684, 600 cm⁻¹. HRMS Calcd for C₁₆H₁₅O₂: [M+H]⁺, 239.1067. Found: *m/z* 239.1067.

Characterization Data of Product

4-(2-Oxo-2-phenylethyl)-3-tosyloxazolidin-2-one (3a).

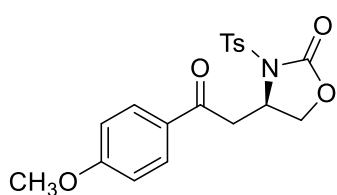


Procedure A: 47% yield (42.2 mg), er = 88.5:11.5 (after one-time recrystallization: er = 99.5:0.5). $[\alpha]_{\text{D}}^{25} -131.3$ (*c* 1.37, CH₂Cl₂).

Procedure B: 62% yield (42.2 mg), er = 13:87. $[\alpha]_{\text{D}}^{25} +88.5$ (*c* 1.45, CH₂Cl₂).

White solid. ¹H NMR (CDCl₃) δ 7.97–7.96 (m, 2H), 7.96–7.95 (m, 2H), 7.64 (tt, *J* = 7.5, 1.5 Hz, 1H), 7.52 (m, 2H), 7.37 (m, 2H), 4.90 (m, 1H), 4.66 (ddd, *J* = 8.5, 1.0 Hz, 1H), 4.18 (ddd, *J* = 18.0, 3.0, 1.0 Hz, 1H), 4.08 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.46 (dd, *J* = 18.0, 10.5 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 196.9, 152.2, 146.0, 135.5, 134.2, 129.9, 128.9, 128.4, 128.1, 68.9, 53.9, 44.1, 21.8. Mp. 167.2–168.2 °C. TLC: *R*_f 0.62 (hexane/EtOAc = 1:1). IR (KBr): 3444, 1772, 1680, 1597, 1451, 1390, 1363, 1348, 1321, 1221, 1193, 1172, 1135, 1011, 813, 768, 761, 690, 669, 602, 580, 543 cm⁻¹. HRMS Calcd for C₁₈H₁₈NO₅S: [M+H]⁺, 360.0900. Found: *m/z* 360.0888. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} (Procedure A) = 10.0 min, *t*_{minor} (Procedure A) = 12.6 min.

4-(2-(4-Methoxyphenyl)-2-oxoethyl)-3-tosyloxazolidin-2-one (3b).



Procedure A: 67% yield (65.5 mg), er = 73:27. $[\alpha]_{\text{D}}^{25} -35.7$ (*c* 1.05, CH₂Cl₂).

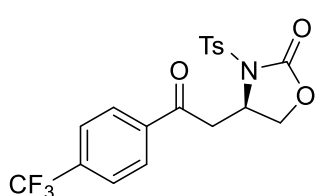
Procedure B: 49% yield (47.6 mg), er = 25.5:74.5. $[\alpha]_{\text{D}}^{25} +34.3$ (*c* 1.02, CH₂Cl₂).

White solid. ¹H NMR (CDCl₃) δ 7.96–7.95 (m, 2H), 7.93–7.92 (m, 2H), 7.37 (m, 2H), 6.98 (m, 2H), 4.86 (m, 1H), 4.64 (dd, *J* = 9.0 Hz, 1H), 4.12 (dd, *J* = 18.0, 3.0 Hz, 1H), 4.07 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.90 (s, 3H), 3.40 (dd, *J* = 18.0, 10.0 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 195.3, 164.2, 152.2, 145.9, 134.3, 130.4, 129.9, 128.7, 128.4, 114.0, 68.9, 55.6, 54.0, 43.6, 21.7. Mp. 154.0–155.0 °C. TLC: *R*_f 0.41 (hexane/EtOAc = 1:1). IR (KBr): 2972, 1784, 1762, 1664, 1600, 1571, 1512, 1421, 1393, 1363, 1314, 1263, 1227, 1187, 1170, 1139, 1090, 1012, 814, 763, 667, 596, 542 cm⁻¹. HRMS Calcd for C₁₉H₂₀NO₆S: [M+H]⁺, 390.1006. Found: *m/z* 390.0994. HPLC

(Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C):

t_{major} (Procedure A) = 13.7 min, t_{minor} (Procedure A) = 18.8 min.

4-(2-Oxo-2-(4-(trifluoromethyl)phenyl)ethyl)-3-tosyloxazolidin-2-one (3c).

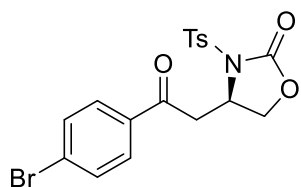


Procedure A: 79% yield (84.0 mg), er = 80.5:19.5. $[\alpha]_D^{25} -71.7$ (*c* 1.15, CH₂Cl₂).

Procedure B: 71% yield (76.0 mg), er = 6.5:93.5. $[\alpha]_D^{25} +85.5$ (*c* 1.17, CH₂Cl₂).

White solid. ¹H NMR (CDCl₃) δ 8.07 (m, 2H), 7.95 (m, 2H), 7.79 (m, 2H), 7.38 (m, 2H), 4.90 (m, 1H), 4.66 (ddd, *J* = 9.5, 8.5, 1.0 Hz, 1H), 4.19 (ddd, *J* = 18.0, 3.0, 1.0 Hz, 1H), 4.08 (dd, *J* = 8.5, 5.0 Hz, 1H), 3.46 (dd, *J* = 18.0, 10.0 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 196.0, 152.0, 146.1, 138.1, 135.3 (q, *J* = 32.6 Hz), 134.1, 128.47, 128.44, 126.0 (q, *J* = 3.9 Hz), 123.2 (q, *J* = 272.6 Hz), 109.7, 68.7, 53.6, 44.3, 21.8. ¹⁹F NMR (CDCl₃) δ 97.8. Mp. 204.1–205.1 °C. TLC: R_f 0.62 (hexane/EtOAc = 1:1). IR (KBr): 2929, 1765, 1685, 1411, 1368, 1326, 1311, 1199, 1187, 1171, 1150, 1135, 1065, 1007, 836, 816, 664, 597, 574, 549 cm⁻¹. HRMS Calcd for C₁₉H₁₇F₃NO₅S: [M+H]⁺, 428.0774. Found: *m/z* 428.0764. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} (Procedure A) = 15.1 min, t_{minor} (Procedure A) = 37.1 min.

4-(2-(4-Bromophenyl)-2-oxoethyl)-3-tosyloxazolidin-2-one (3d).



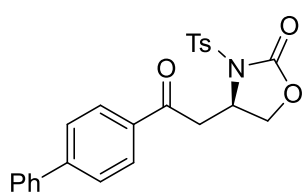
Procedure A: 95% yield (103.9 mg), er = 81:19. $[\alpha]_D^{25} -71.6$ (*c* 1.64, CH₂Cl₂).

Procedure B: 74% yield (42.2 mg), er = 14:86. $[\alpha]_D^{25} +82.8$ (*c* 1.485, CH₂Cl₂).

White solid. ¹H NMR (CDCl₃) δ 7.95 (m, 2H), 7.81 (m, 2H), 7.66 (m, 2H), 7.37 (m, 2H), 4.87 (m, 1H), 4.64 (dd, *J* = 9.5 Hz, 1H), 4.12 (dd, *J* = 18.0, 3.0 Hz, 1H), 4.05 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.42 (dd, *J* = 18.0, 10.5 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 195.9, 152.1, 146.0, 134.24,

134.18, 132.3, 129.9, 129.5, 128.4, 68.7, 53.7, 44.0, 21.8. Mp. 207.5–208.5 °C. TLC: R_f 0.58 (hexane/EtOAc = 1:1). IR (KBr): 2918, 1786, 1679, 1586, 1398, 1365, 1313, 1188, 1166, 1139, 1088, 1004, 986, 755, 665, 603, 581, 541 cm^{-1} . HRMS Calcd for $\text{C}_{18}\text{H}_{17}\text{BrNO}_5\text{S}$: $[\text{M}+\text{H}]^+$, 438.0005. Found: m/z 437.9993. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{major} (Procedure A) = 10.2 min, t_{minor} (Procedure A) = 21.6 min.

4-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)-3-tosyloxazolidin-2-one (3e).

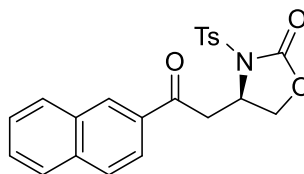


Procedure A: 27% yield (29.3 mg), er = 89.5:10.5. $[\alpha]_{\text{D}}^{18} -100.0$ (*c* 0.22, CH_2Cl_2).

Procedure B: 19% yield (20.3 mg), er = 15.5:84.5. $[\alpha]_{\text{D}}^{18} +83.3$ (*c* 0.18, CH_2Cl_2).

White solid. ^1H NMR (CDCl_3) δ 8.02 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 8.0 Hz, 2H), 7.73 (m, 2H), 7.65 (m, 2H), 7.50 (t, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 1H), 7.38 (m, 2H), 4.90 (m, 1H), 4.60 (dd, J = 9.0 Hz, 1H), 4.21 (dd, J = 18.5, 3.0 Hz, 1H), 4.10 (dd, J = 9.0, 4.5 Hz, 1H), 3.48 (dd, J = 18.5, 10.5 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (CDCl_3) δ 196.4, 146.8, 145.9, 139.5, 134.3, 129.9, 129.0, 128.6, 128.5, 128.4, 127.4, 127.2, 68.8, 53.9, 44.0, 21.7. Mp. 197.1–197.2 °C. TLC: R_f 0.55 (hexane/EtOAc = 1:1). IR (KBr): 3358, 3261, 3048, 2923, 1775, 1676, 1371, 1319, 1174, 1130, 1006, 762, 667, 601, 545 cm^{-1} . HRMS Calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_5\text{S}$: $[\text{M}+\text{H}]^+$, 436.1213. Found: m/z 436.1217. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): t_{minor} (Procedure A) = 26.8 min, t_{major} (Procedure A) = 31.7 min.

4-(2-(Naphthalen-2-yl)-2-oxoethyl)-3-tosyloxazolidin-2-one (3f).

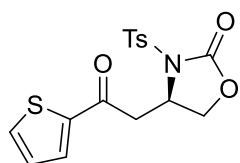


Procedure A: 66% yield (67.5 mg), er = 91:9. $[\alpha]_{\text{D}}^{25} -108.8$ (*c* 1.31, CH_2Cl_2).

Procedure B: 49% yield (50.0 mg), er = 18:82. $[\alpha]_{\text{D}}^{25} +88.2$ (*c* 1.19, CH_2Cl_2).

White solid. ^1H NMR (CDCl_3) δ 8.49 (m, 1H), 8.01–7.94 (m, 4H), 7.92 (d, $J = 3.5$ Hz, 2H), 7.65 (t, $J = 7.0$ Hz, 1H), 7.59 (t, $J = 7.0$ Hz, 1H), 7.37 (d, $J = 3.5$ Hz, 2H), 4.94 (m, 1H), 4.68 (dd, $J = 9.5$ Hz, 1H), 4.32 (dd, $J = 18.0, 3.0$ Hz, 1H), 4.14 (dd, $J = 9.5, 4.5$ Hz, 1H), 3.61 (dd, $J = 18.0, 9.5$ Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 196.8, 152.2, 145.9, 136.0, 134.4, 132.9, 132.4, 130.3, 129.9, 129.7, 129.1, 128.8, 128.5, 127.9, 127.2, 123.2, 68.9, 54.0, 44.1, 21.7. Mp. 213.8–214.5 °C. TLC: R_f 0.57 (hexane/EtOAc = 1:1). IR (KBr): 2923, 2852, 1770, 1670, 1402, 1374, 1351, 1319, 1176, 1119, 1050, 1005, 817, 754, 666, 589, 547 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{19}\text{NO}_5\text{SNa}$: $[\text{M}+\text{Na}]^+$, 432.0876. Found: m/z 432.0886. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 40 °C): t_{major} (Procedure A) = 11.8 min, t_{minor} (Procedure A) = 17.6 min.

4-(2-Oxo-2-(thiophen-2-yl)ethyl)-3-tosyloxazolidin-2-one (3g).

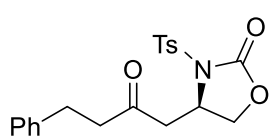


Procedure A: 53% yield (48.1 mg), er = 81.5:18.5. $[\alpha]_{\text{D}}^{25} -57.1$ (c 1.05, CH_2Cl_2).

Procedure B: 53% yield (48.3 mg), er = 16.5:83.5. $[\alpha]_{\text{D}}^{25} +70.4$ (c 1.03, CH_2Cl_2).

CH_2Cl_2).

White solid. ^1H NMR (CDCl_3) δ 7.95 (m, 2H), 7.78 (dd, $J = 3.5, 1.0$ Hz, 1H), 7.64 (dd, $J = 5.0, 1.0$ Hz, 1H), 7.37 (m, 2H), 7.19 (dd, $J = 5.0, 3.5$ Hz, 1H), 4.86 (m, 1H), 4.61 (ddd, $J = 9.0, 1.0$ Hz, 1H), 4.12 (dd, $J = 9.0, 4.5$ Hz, 1H), 4.10 (ddd, $J = 18.0, 3.0, 1.0$ Hz, 1H), 3.40 (dd, $J = 18.0, 10.5$ Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 189.4, 152.1, 146.0, 142.7, 135.0, 134.2, 133.1, 129.9, 128.5, 128.4, 68.7, 53.6, 44.2, 21.8. Mp. 224.8–225.8 °C. TLC: R_f 0.51 (hexane/EtOAc = 1:1). IR (KBr): 1777, 1654, 1423, 1368, 1363, 1315 1169 1134, 1090, 1003, 856, 811, 763, 740, 668, 602, 571, 543 cm^{-1} . HRMS Calcd for $\text{C}_{16}\text{H}_{16}\text{NO}_5\text{S}_2$: $[\text{M}+\text{H}]^+$, 366.0464. Found: m/z 366.0455. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 40 °C): t_{major} (Procedure A) = 10.7 min, t_{minor} (Procedure A) = 21.3 min.

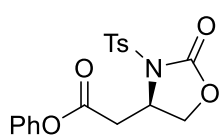
4-(2-Oxo-4-phenylbutyl)-3-tosyloxazolidin-2-one (3h).

Procedure A: 83% yield (80.8 mg), er = 68:32. $[\alpha]_{\text{D}}^{18} -24.4$ (*c* 1.54, CH₂Cl₂).

Procedure B: 73% yield (70.4 mg), er = 17.5:82.5. $[\alpha]_{\text{D}}^{18} +54.0$ (*c* 1.25, CH₂Cl₂).

CH₂Cl₂).

White solid. ¹H NMR (CDCl₃) δ 7.90 (m, 2H), 7.36 (m, 2H), 7.29 (m, 2H), 7.21 (m, 1H), 7.17 (m, 2H), 4.66 (m, 1H), 4.51 (dd, *J* = 9.5 Hz, 1H), 3.85 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.53 (dd, *J* = 18.5, 3.0 Hz, 1H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.80 (dd, *J* = 18.5, 1.5 Hz, 1H), 2.86–2.74 (m, 2H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 207.1, 152.0, 145.9, 140.1, 134.2, 129.9, 128.6, 128.4, 128.2, 126.4, 68.5, 53.1, 47.6, 44.1, 29.5, 21.7. Mp. 115.9–116.0 °C. TLC: R_f 0.58 (hexane/EtOAc = 1:1). IR (KBr): 3024, 2929, 1764, 1706, 1597, 1494, 1392, 1373, 1186, 1174, 1089, 813, 760, 676, 603, 577, 545 cm⁻¹. HRMS Calcd for C₂₀H₂₁NO₅SNa: [M+Na]⁺, 410.1033. Found: *m/z* 410.1019. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} (Procedure A) = 7.7 min, *t*_{minor} (Procedure A) = 10.0 min.

Phenyl 2-(2-oxo-3-tosyloxazolidin-4-yl)acetate (3i).

Procedure A: 73% yield (68.2 mg), er = 55:45.

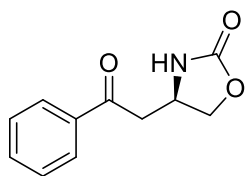
Procedure A: 30% yield (28.0 mg), er = 88:12. $[\alpha]_{\text{D}}^{18} +13.4$ (*c* 0.93, CH₂Cl₂).

White solid. ¹H NMR (CDCl₃) δ 7.98 (m, 2H), 7.41–7.37 (m, 4H), 7.28 (m, 2H), 7.06 (m, 2H), 4.83 (m, 1H), 4.58 (dd, *J* = 9.0 Hz, 1H), 4.23 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.57 (dd, *J* = 17.5, 3.5 Hz, 1H), 3.06 (dd, *J* = 17.5, 10.0 Hz, 1H), 2.54 (s, 3H). ¹³C NMR (CDCl₃) δ 168.4, 151.9, 150.0, 146.0, 134.4, 129.9, 129.6, 128.5, 126.3, 121.2, 67.9, 53.2, 38.8, 21.7. Mp. 144.8–145.8 °C. TLC: R_f 0.62 (hexane/EtOAc = 1:1). IR (KBr): 3053, 2959, 297, 1763, 1596, 1493, 1404, 1362, 1331, 1172, 1097, 1005, 934, 811, 740, 688, 660, 601, 579, 548 cm⁻¹. HRMS Calcd for C₁₈H₁₈NO₆S: [M+H]⁺, 376.0849. Found: *m/z* 376.0845. HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 40 °C): *t*_{major} (Procedure A) = 27.7 min, *t*_{minor} (Procedure A) = 57.0 min.

Procedure for synthesis of 5¹⁶

To a stirred solution of naphthalene (0.13 g, 1 mmol) in THF (2 mL) was added sodium (0.035 g, 1.5 mmol) at ambient temperature, and the mixture was stirred for 1 h to give a deep green solution of sodium naphthalenide. To a stirred solution of **3a** (0.0359 g, 0.11 mmol) in THF (1 mL) was added the sodium naphthalenide solution (0.8 mL) at $-78\text{ }^{\circ}\text{C}$, and the mixture was stirred for 3 h at $-78\text{ }^{\circ}\text{C}$. Saturated aqueous NaHCO_3 was added to quench the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (v/v = 20/1) as an eluent gave 4-(2-oxo-phenylethyl)oxazolidin-2-one (**5**).

(R)-4-(2-Oxo-phenylethyl)oxazolidin-2-one (5): CAS RN [154669-73-5].



Yield: 78% (17.5 mg), er = 99:1, yellow oil. $[\alpha]_{\text{D}}^{25} +3.43$ (*c* 0.88, MeOH).

^1H NMR (CDCl_3) δ 7.93 (m, 2H), 7.62 (m, 1H), 7.50 (m, 2H), 5.62 (br s, 1H), 4.67 (t, $J = 8.0$ Hz, 1H), 4.42 (m, 1H), 4.14 (m, 1H), 3.33 (m, 2H). ^{13}C NMR

(CDCl_3) δ 197.4, 158.8, 135.8, 134.0, 128.9, 128.0, 69.6, 48.6, 43.9. TLC: R_f 0.25 ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 20:1$). HPLC (Daicel Chiralpak AD-H, hexane/*i*-PrOH = 90/10, flow rate = 4.5 mL/min, $\lambda = 254$ nm, $40\text{ }^{\circ}\text{C}$): $t_{\text{minor}} = 10.2$ min, $t_{\text{major}} = 11.5$ min.

The absolute configuration of **5** was assigned as (*R*) by comparing the optical rotation with the literature value.¹⁴

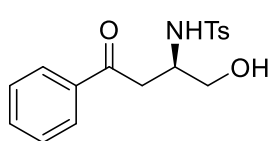
$[\alpha]_{\text{D}}^{25} +3.43$ (*c* 0.88, MeOH) [lit.¹⁴ (*R*)-4-(2-oxo-phenylethyl)oxazolidin-2-one: $[\alpha]_{\text{D}}^{25} +3.9$ (*c* 1.0, MeOH)].

Procedure for synthesis of 6¹⁷

To a stirred solution of lithium hydroxide (0.0527 g, 2.2 mmol) and aqueous 30 wt% H_2O_2 (0.0499 g, 4.4 mmol) in CH_2Cl_2 (1.1 mL)/THF (0.11 mL), **3a** (0.0400 g, 0.11 mmol) was added at ambient temperature, and the mixture was stirred for 6 h. Saturated aqueous NH_4Cl was added to

quench the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave 1,2-amino alcohol **6**.

***N*-(1-Hydroxy-4-oxo-4-phenylbutan-2-yl)-4-methylbenzenesulfonamide (**6**).**



Yield: 71% (26.4 mg), er = 98.5:1.5, colorless oil. $[\alpha]_D^{25} -30.0$ (*c* 2.07, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.83–7.81 (m, 2H), 7.75–7.72 (m, 2H), 7.58–7.54 (dt, *J* = 5.0, 1.5 Hz, 1H), 7.44–7.40 (m, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 5.63 (d, *J* = 7.5 Hz, 1H), 3.81 (m, 1H), 3.66 (m, 2H), 3.20 (d, *J* = 5.5 Hz, 2H), 2.47 (m, 1H), 2.36 (s, 3H), 1.75 (br s, 1H). ¹³C NMR (CDCl₃) δ 198.6, 143.5, 137.2, 136.2, 133.6, 129.7, 128.6, 128.1, 127.1, 64.0, 52.1, 39.7, 21.5. TLC: *R*_f 0.16 (hexane/EtOAc = 1/1). IR (neat): 3356, 3260, 2374, 1734, 1685, 1597, 1457, 1306, 1161, 1095, 908, 816, 761, 668, 546 cm⁻¹. HRMS Calcd for C₁₇H₂₀NO₄S: [M+H]⁺, 334.1108. Found: *m/z* 334.1114. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 80/20, flow rate = 0.5 mL/min, λ = 254 nm, 40 °C): *t*_{minor} = 27.3 min, *t*_{major} = 36.2 min.

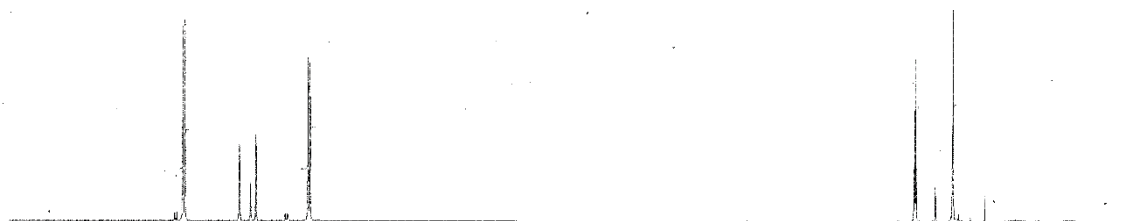
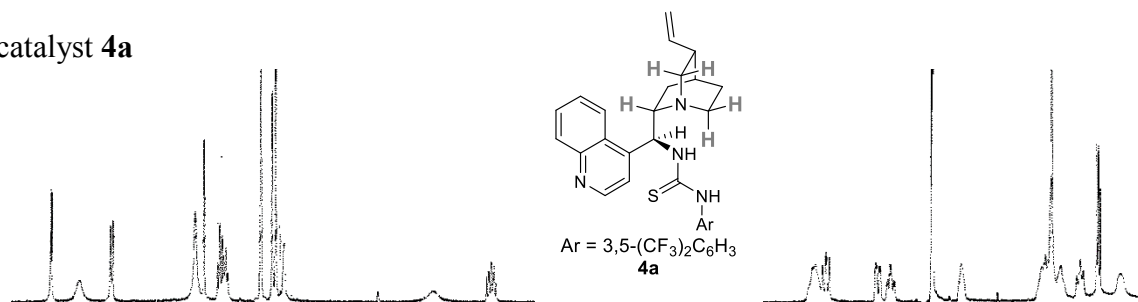
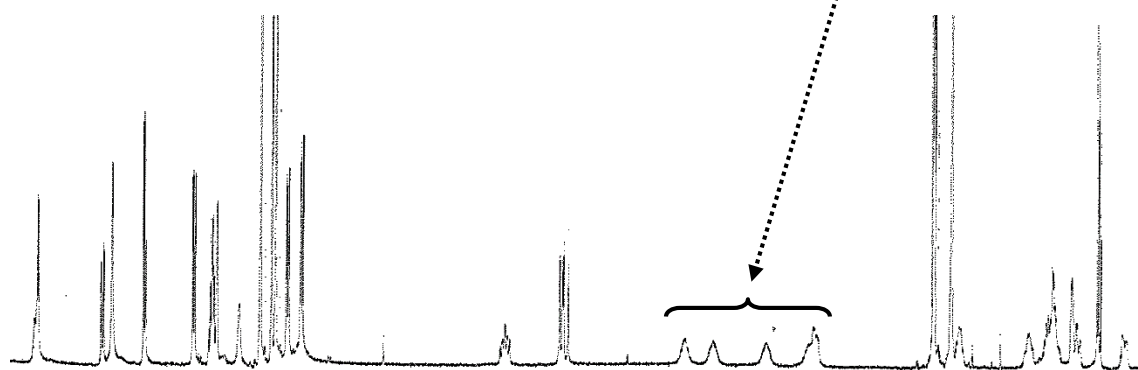
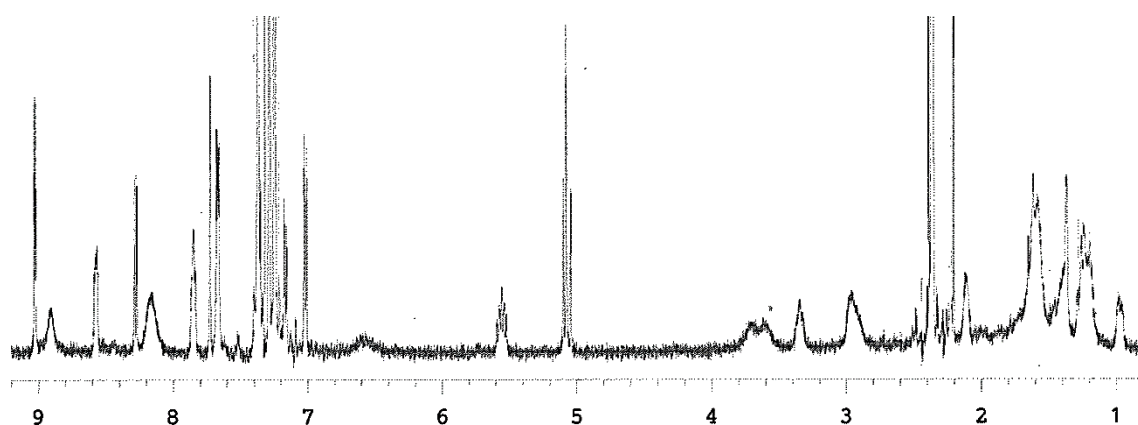
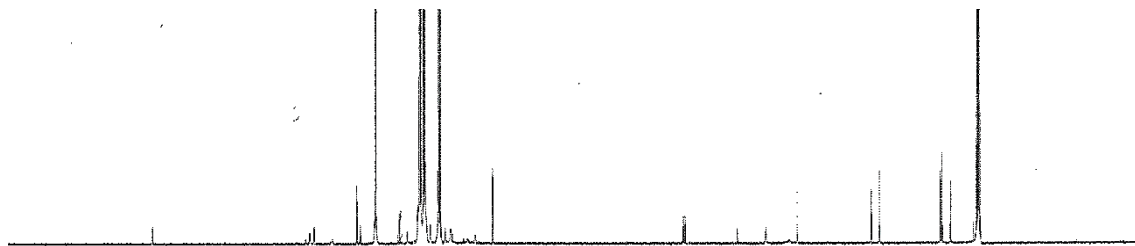
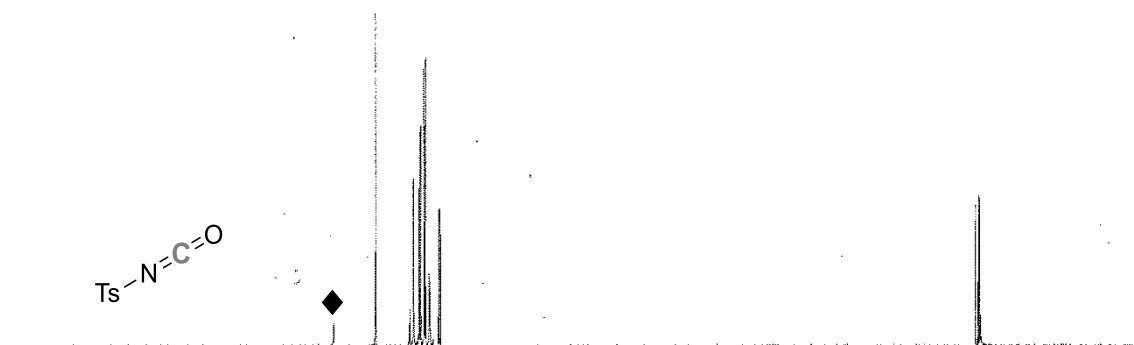
(a) tosyl isocyanate (**2**)(b) catalyst **4a**(c) mixture of **2** and **4a**(d) **4a'**

Figure 3. Independent ¹H NMR spectra of (a) tosyl isocyanate (**2**) and (b) catalyst **4a** and the spectra of (c) their 1:1 mixture and (d) the compound (**4a'**) obtained after concentration of the 1:1 mixture of **2** and **4a** (0.025 M, toluene-d₈, ambient temperature).

(a) catalyst **4a**



(b) tosyl isocyanate (**2**)



(c) mixture of **2** and **4a**

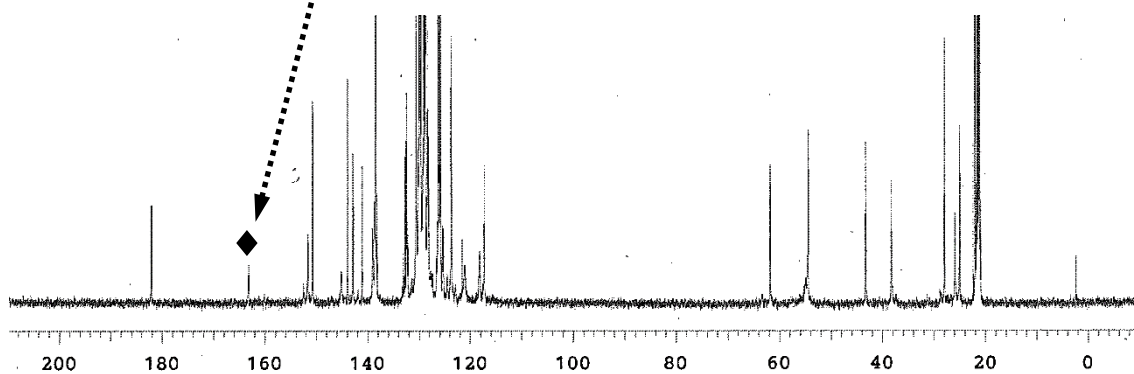
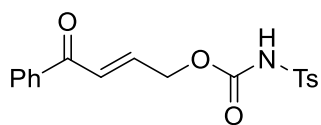
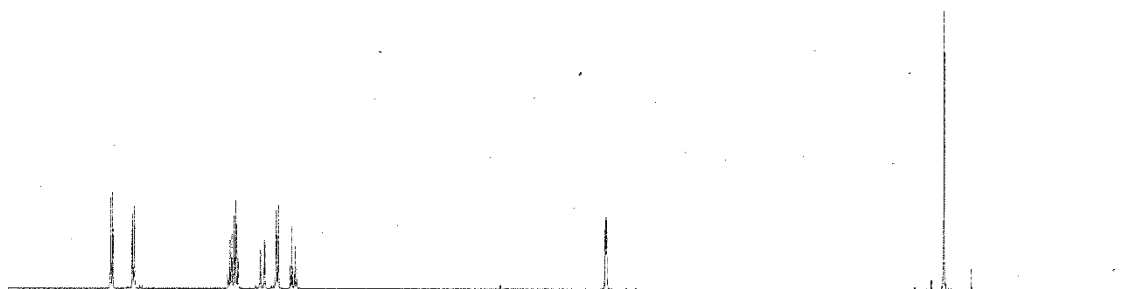


Figure 4. Independent ^{13}C NMR spectra of (a) catalyst **4a** and (b) tosyl isocyanate (**2**) and the spectra of (c) their 1:1 mixture and (0.025 M, toluene- d_8 , ambient temperature).

(a) mixture of **1a** and **2** (1.01:1)



carbamate intermediate



(b) 2-oxazolidinone **3a**

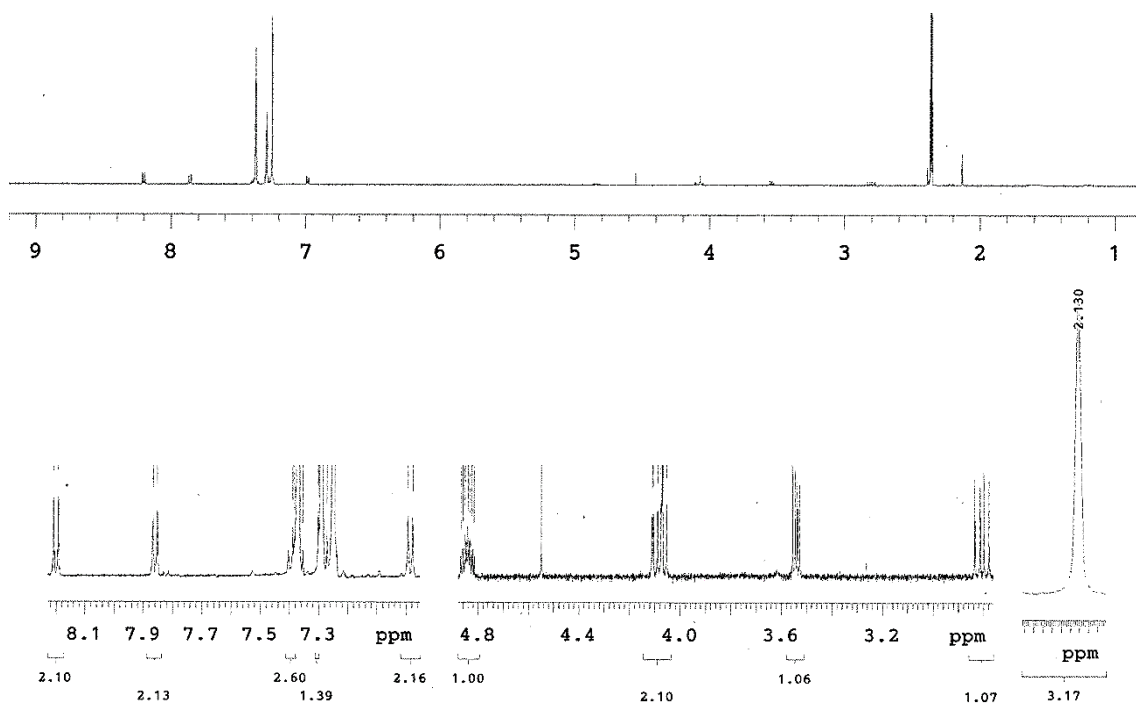
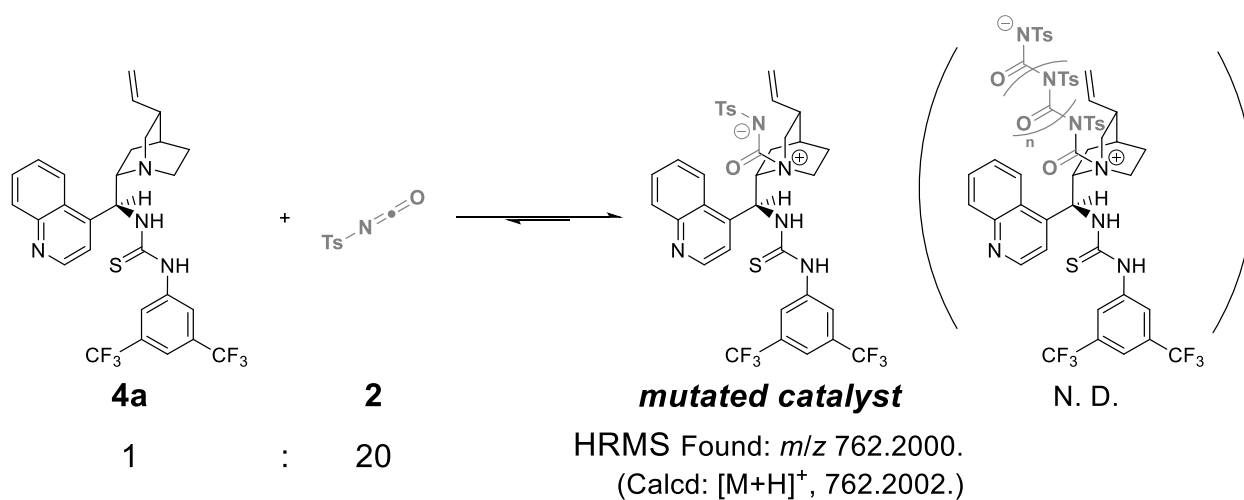


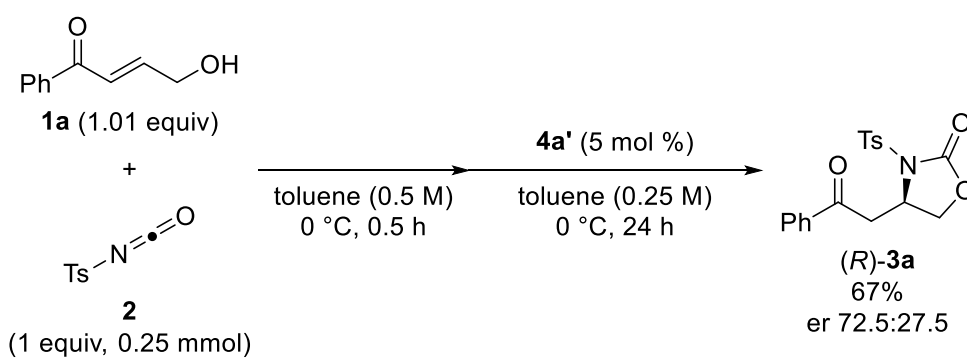
Figure 5. ^1H NMR spectra of (a) the 1.01:1 mixture of **1a** and **2** (0.5 M) and (b) 2-oxazolidinone **3a** (0.01 M) (toluene- d_8 , ambient temperature).

2-Oxazolidinone **3a** was not yet formed in the absence of any catalyst.



Scheme 6. HRMS analysis of the solution of **2** and **4a** (20:1 mixture).

The HRMS analysis (ESI) of the solution of **2** and **4a** (20:1 mixture) in EtOAc detected the molecular weight corresponding to their 1:1 adduct (found: m/z 762.2000; calcd: $[M+H]^+$, 762.2002.), but did not detect that corresponding to oligomeric $n:1$ ($n>1$) adducts.



Scheme 7. [3+2] Formal cycloaddition reaction using **4a'** in procedure A.

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11. The formation of the carbamate intermediate was confirmed by thin-layer chromatography analysis and a ^1H NMR study of a 1.01:1 mixture of **1a** and **2** in toluene- d_8 ; 2-oxazolidinone **3a** was not formed in the absence of catalyst (see Figure 5 for details).
12. Investigations revealed that 1.01 equiv of **1a** relative to **2** was efficient for reproducibility.
13. The mutated catalyst yielding (*S*)-**3a** easily decomposed at higher temperature; the concentration of the solution of a 1:1 mixture of **4a** and **2** gave **4a'**, which was different from that generated in situ (Figure 3). In addition, the use of **4a'** in procedure A did not bring about the enantioselectivity switch (Scheme 7).
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Chapter 3

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

A novel methodology for the asymmetric synthesis of β -mercaptolactones via isomerization of ω -hydroxy- α,β -unsaturated thioesters using an aminothiurea catalyst has been developed. The catalyst interacts with the substrate through the cooperative action of covalent bond at the amino group and noncovalent bonding at the thiourea group. Thus, the potential for enantiodivergent synthesis could be demonstrated by carrying out the reaction in a different solvent system.

Introduction

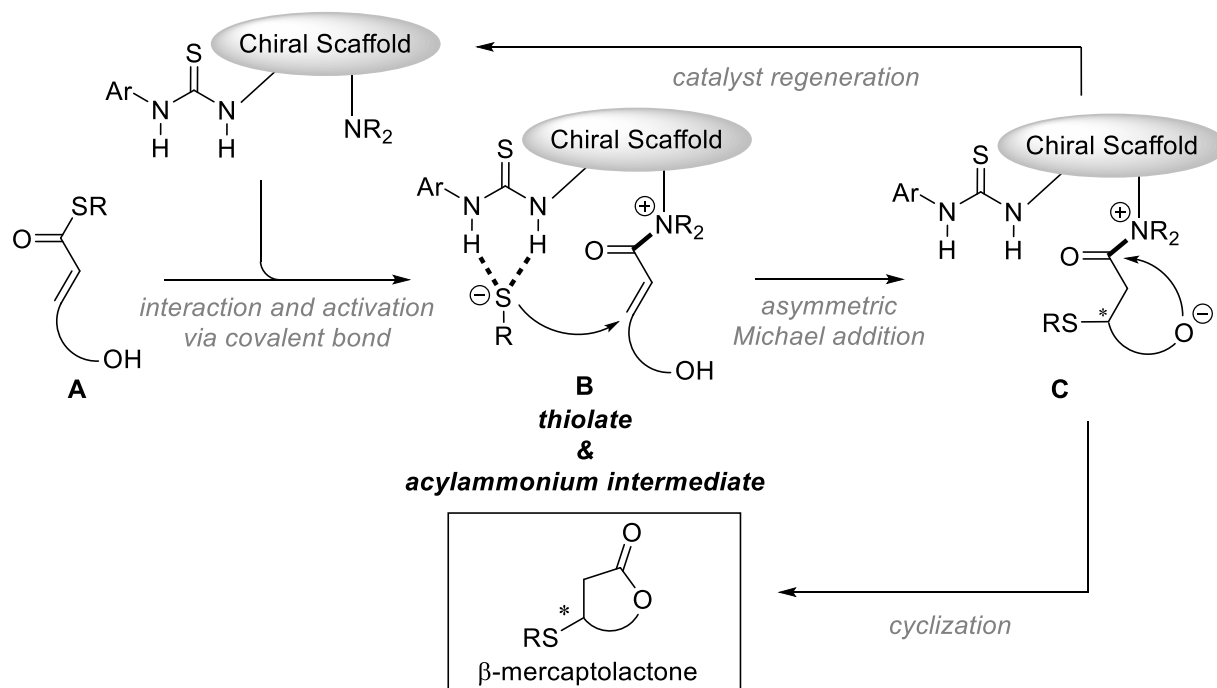
Organocatalysis has seen tremendous progress through the exploration of various catalytic functional groups and the exploitation of a variety of molecular interactions. In the design of organocatalytic reactions, it is important to utilize covalent and noncovalent interactions thoughtfully. Examples 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.

Results and Discussion

In this Chapter, the author 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 he designed an

isomerization of ω -hydroxy- α,β -unsaturated thioesters **A** by means of a bifunctional aminothiurea catalyst¹⁰ 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-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.

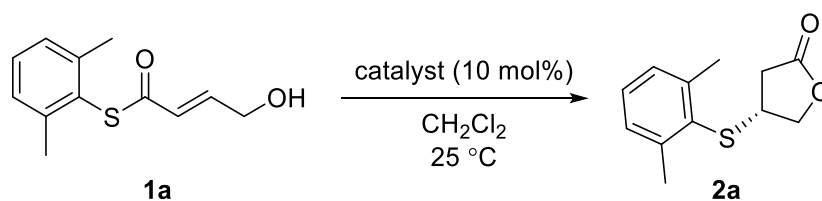


Scheme 1. Reaction design via organocatalytic isomerization of ω -hydroxy- α,β -unsaturated thioesters

On the basis of this reaction design, a study was initiated by treating γ -hydroxy- α,β -unsaturated

thioester **1a** with aminothiurea catalyst **3a** (Table 1). As expected, the desired lactone **2a** was obtained in high yield with moderate enantioselectivity (entry 1). Catalysts **3b** and **3c**, which bear electron withdrawing groups on the thiourea moiety, attained higher enantioselectivity (entries 2 and 3). Catalyst **3d** afforded the product in high yield, but the enantioselectivity was only slight (entry 4). In addition, catalyst **3e**, which has no nucleophilic nitrogen atom, proved to be inactive for this transformation (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. The concentration of the reaction mixture also had a large effect on the enantioselectivity (entries 3 and 6–8).

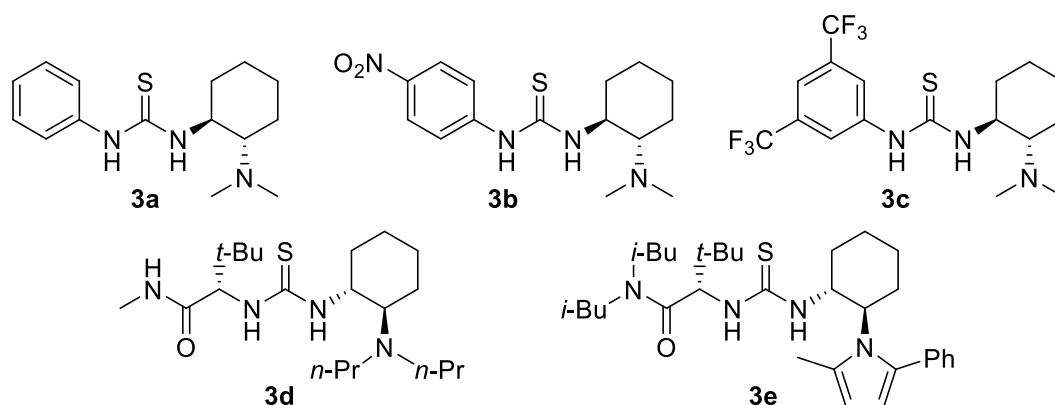
Table 1. Optimization of conditions^a



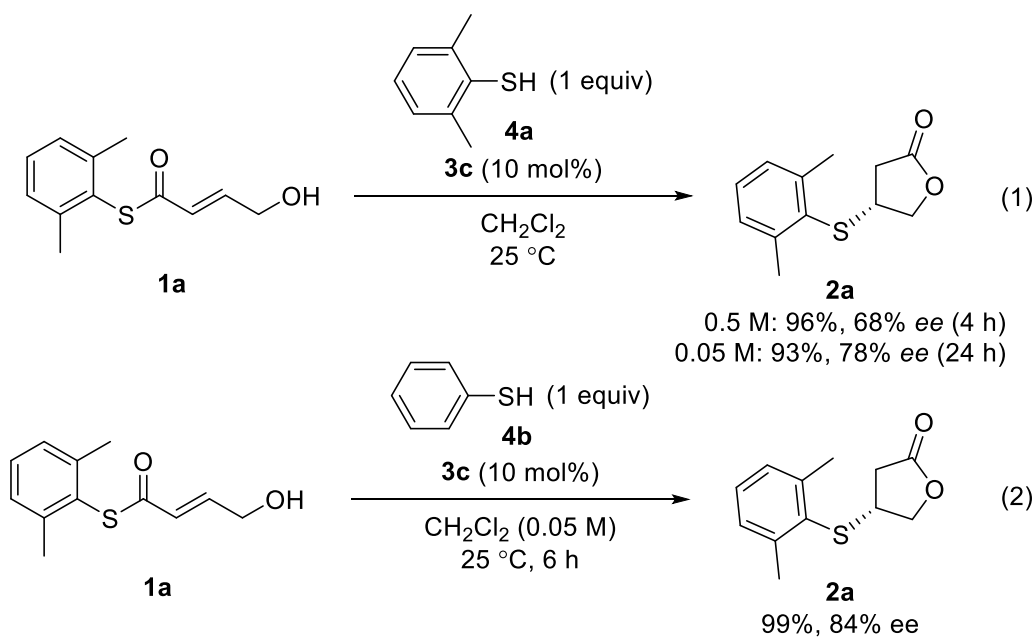
entry	catalyst	concn (M)	time (h)	yield (%) ^b	ee (%)
1	3a	0.5	24	95	40
2	3b	0.5	24	97	59
3	3c	0.5	24	99	66
4	3d	0.5	24	92	3
5	3e	0.5	24	<1	—
6	3c	0.1	96	98	74
7	3c	0.05	144	83	76
8	3c	0.03	336	72	74

^aReactions were carried out using **1a** (0.15 mmol) and the catalyst (0.015 mmol) in the CH₂Cl₂.

^bIsolated yields.



Using catalyst **3c**, the author investigated the effects of the reaction temperature; the enantioselectivity improved as the temperature increased (see Table 3 in the Experimental Section for details). The Eyring plot resulted in a straight line with a negative slope (see Figure 1 in the Experimental Section for details). 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.^{13–15}



Scheme 2. Reactions of **1a** in the presence of thiols.

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.

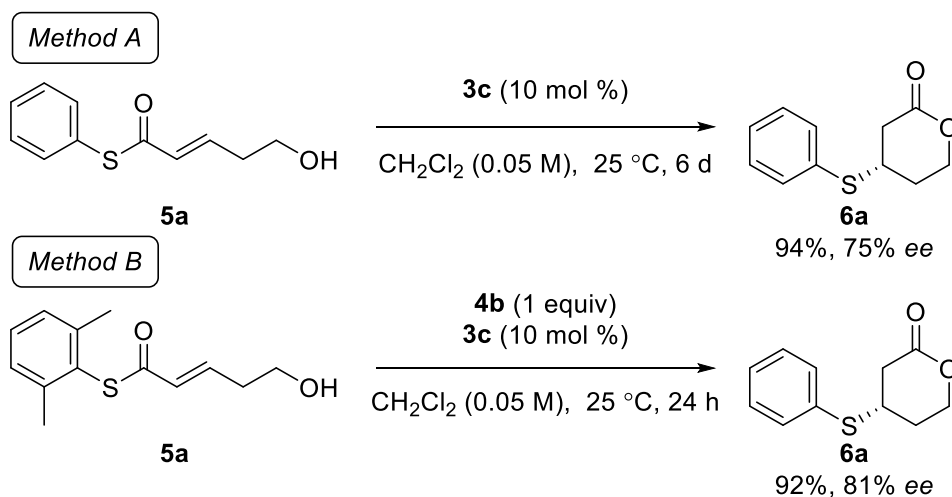
The author explored the substrate scope for the reaction at 25 °C and 0.05 M (Table 2). In several instances, the reactions were carried out both by a simple isomerization (method A) and by a reaction starting from the bulky thiol ester **1a** in the presence of the corresponding external thiol (method B); method B always afforded a higher reaction rate and higher enantioselectivity (entries 1–6, 15, and 16). Notably, in method B for the reactions using **2b–2j**, the simple isomerization product **2a** was not generated (entries 4 and 6–13). Reactions using electron-rich thiols afforded the corresponding products in higher enantioselectivity than in other cases (entries 6, 7, and 9), although only an ortho-substituent decreased the enantiomeric excess (entry 8). Electron-deficient thiols exhibited efficient reactivity and moderate to good enantioselectivity (entries 10 and 11). Thiols bearing pbromophenyl and 2-naphthyl groups were also tolerated and resulted in excellent yields with good enantioselectivity (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 (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 (entries 15 and 16).

Table 2. Substrate Scope^a

Method A				
Method B				
entry	R (2)	method	yield (%) ^b	ee (%)
1	2,6-(CH ₃) ₂ C ₆ H 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 ₃ OC ₆ H ₄ (2c)	A	99 (4 d)	69
6		B	97 (6 h)	89
7	3-CH ₃ OC ₆ H ₄ (2c)	B	99 (12 h)	86
8	2-CH ₃ OC ₆ H ₄ (2c)	B	92 (12 h)	76
9	3,4-(CH ₃ O) ₂ C ₆ H ₃ (2c)	B	94 (6 h)	90
10	4-CF ₃ C ₆ H ₄ (2c)	B	94 (6 h)	66
11	4-ClC ₆ H ₄ (2c)	B	99 (6 h)	77
12	4-BrC ₆ H ₄ (2c)	B	99 (6 h)	76
13	2-naphthyl (2c)	B	98 (6 h)	85
14 ^c	2,4,6-(<i>i</i> -Pr) ₃ C ₆ H ₂ (2c)	B	50 (24 h)	88
15	Bn (2l)	A	68 (10 d)	33
16 ^{d,e}		B	86 (36 h)	52

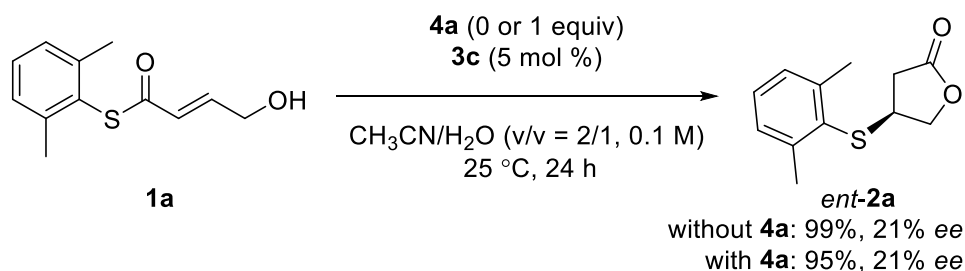
^aMethod A: reactions were run using **1a** (0.15 mmol) and the catalyst (0.015 mmol) in the CH₂Cl₂ (3.0 mL). Method B: reactions were run using **1a** (0.15 mmol), **4** (0.15 mmol), and the catalyst (0.015 mmol) in the CH₂Cl₂ (3.0 mL). ^bIsolated yields. ^c**2a** was also obtained in 37% yield with 80% *ee*. ^dReaction was run using 3 equiv of **4l** (0.45 mmol). ^e**2a** was also obtained in 14% yield with 80% *ee*.

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 Experimental Section for details), and the configurations for all other examples were assigned analogously.



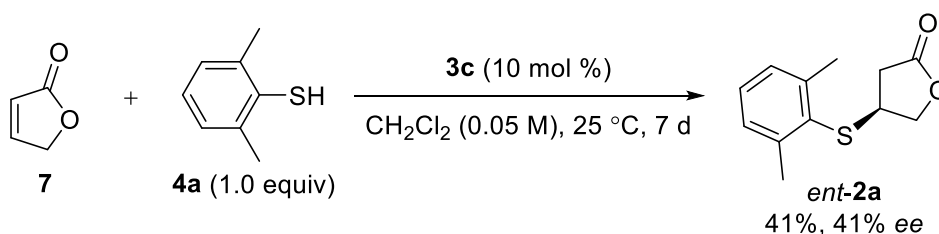
Scheme 3. Synthesis of δ -valerolactone.

Moreover, in order to demonstrate the potential of this reaction for an enantiodivergent synthesis using a single chiral catalyst, other solvent systems were investigated as an external factor to influence the enthalpy and entropy terms, as such observations have also been reported previously (see Table 8 and Figure 2 in the Experimental Section for details).^{15,16} 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 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$.

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 **1a** takes place mainly via the formation of **7** followed by the sulfa-Michael addition of **4a** mediated by the aminothiurea 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: $[\text{M}]^+$, 498.1644; see Scheme 6 in the Experimental Section 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.



Scheme 5. Sulfa-Michael addition to 2-furanone.

Conclusion

In summary, the author 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 aminothiurea 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 $\text{CH}_3\text{CN}/\text{H}_2\text{O}$. 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.

Experimental Section

Materials.

Unless otherwise noted, commercially available reagents were used without purification. Thiol **4k** was prepared according to the literature.¹⁷

General procedure for asymmetric isomerization of γ -hydroxy- α,β -unsaturated thioesters

In a 5-mL vial, we sequentially added γ -hydroxy- α,β -unsaturated thioester **1** (0.15 mmol), CH_2Cl_2 (3.0 mL), and aminothiurea catalyst **3c** (0.015 mmol). The mixture was stirred in an oil bath maintained at 25 °C for several hours. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3c**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/Et₂O (v/v = 3/1) as an eluent afforded the corresponding β -mercapto- γ -lactones **2**.

General procedure for asymmetric transformation of γ -hydroxy- α,β -unsaturated thioester **1a** in the presence of a thiol

In a 5-mL vial, we sequentially added γ -hydroxy- α,β -unsaturated thioester **1a** (0.15 mmol), CH_2Cl_2 (3.0 mL), aminothiurea catalyst **3c** (0.015 mmol), and thiols **4** (0.15 mmol). The mixture was stirred in an oil bath maintained at 25 °C for several hours. The reaction mixture was sequentially diluted with hexane/EtOAc (v/v = 1/1), passed through a short silica gel pad to remove **3c**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/Et₂O (v/v = 3/1) as an eluent afforded the corresponding β -mercapto- γ -lactones **2**. Racemic compounds were prepared using triethylamine as a catalyst.

Procedure for preparation of aminothiurea catalysts **3c**

Bifunctional organocatalysts **3c** were prepared by the literature procedure.^{18,19} To the solution of 1,3-dimethyl barbituric acid (3.12 g, 20 mmol) in Ac_2O (60 mL) was added concentrated sulfuric acid, and the mixture was refluxed at 160 °C for 1.5 h. The mixture was concentrated to make the volume approximately 1/4 of its original by evaporation at 65 °C, and then cooled to 0 °C. The precipitate was filtered off and washed with water and subsequently with acetone, and drying in vacuo gave 1,3-dimethyl-5-acetyl-barbituric acid as a yellow solid in 67% yield. The crude product was used for the next step without further purification.

The mixture of 1,3-dimethyl-5-acetyl-barbituric acid (1.98 g, 10 mmol) and (*S,S*)-cyclohexanediamine (1.14 g, 10 mmol) in CH_2Cl_2 (30 mL) was stirred at ambient temperature for 58 h. The solvents were removed in vacuo. Purification by flash silica gel column chromatography using $\text{CHCl}_3/\text{CH}_3\text{OH}$ (v/v = 20/1) as an eluent gave 5-((*E*)-1-(((1*S*,2*S*)-2-aminocyclohexyl)imino)ethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione as a yellow solid in 98% yield.

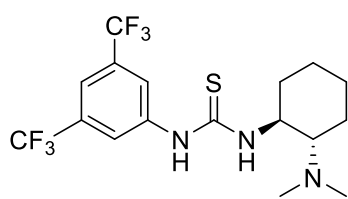
Subsequently, to the solution of 5-((*E*)-1-(((1*S*,2*S*)-2-aminocyclohexyl)imino)ethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1.59 g, 5.4 mmol) in CH_3CN (25 mL) was added 37% aqueous formaldehyde (2.01 mL, 27 mmol), and the mixture was stirred for 30 min. After

the addition of sodium cyanoborohydride (0.68 g, 11 mmol) followed by stirring for 40 min, AcOH (1 mL) was added to the solution, and the resulting mixture was stirred for 2 h. 1N Aqueous NaOH was added to the solution, and the mixture was extracted with CH₂Cl₂/CH₃OH (v/v = 50/1). The combined organic layers were washed with 1N aqueous NaOH, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using CHCl₃/CH₃OH (v/v = 95/5) as an eluent gave 5-((*E*)-1-(((1*S*,2*S*)-2-dimethylaminocyclohexyl)imino)ethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione as a yellow solid in 98% yield.

The mixture of 5-((*E*)-1-(((1*S*,2*S*)-2-dimethylaminocyclohexyl)imino)ethyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (1.84 g, 5.7 mmol) and KOH (2.26 g, 34 mmol) in EtOH (45 mL) was stirred at 60 °C for 36 h. The precipitate was filtered off and washed with CH₂Cl₂/CH₃OH (v/v = 40/1). The combined filtrate was washed with H₂O, dried over Na₂SO₄, and concentrated to afford (1*S*,2*S*)-*N,N*-dimethyl-1,2-diaminocyclohexane as a pale yellow oil in 86% yield. This crude product was used without further purification.

Next, to the solution of (1*S*,2*S*)-*N,N*-dimethyl-1,2-diaminocyclohexane (0.55 g, 3.9 mmol) in CH₂Cl₂ (10 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.06 g, 3.9 mmol) in CH₂Cl₂ (10 mL) at ambient temperature. The mixture was stirred overnight, and the solvents were removed in vacuo. Purification by flash silica gel column chromatography using CH₂Cl₂/CH₃OH (v/v = 10/1) as an eluent gave 1-(3,5-bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)thiourea (**3c**) in 63% yield.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((1*S*,2*S*)-2-(dimethylamino)cyclohexyl)thiourea (3c**):**
CAS RN [851477-20-8].



White solid; 53% yield (for the 4steps). ¹H NMR (CDCl₃) δ 7.84 (s, 2H), 7.61 (s, 1H), 3.94 (br s, 1H), 2.60 (br s, 1H), 2.48 (m, 1H), 2.30 (s, 6H), 1.92 (m, 1H), 1.84 (m, 1H), 1.74 (m, 1H), 1.37–1.07 (m, 4H). ¹³C NMR (CDCl₃) δ 179.2, 139.6, 132.3, 123.4, 122.9 (q, *J* = 274.0

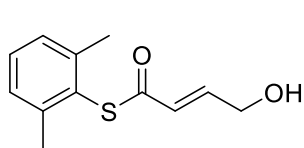
Hz), 118.5, 66.6, 55.9, 39.9, 32.7, 24.7, 24.4, 21.0.

General procedure for preparation of γ -Hydroxy- α,β -unsaturated thioesters **1a–1c, and **1l**.**

γ -Hydroxy- α,β -unsaturated thioesters **1a**, **1c**, and **1l** were prepared by literature procedure.²⁰

The characterization results are as below.

(*E*)-*S*-(2,6-Dimethylphenyl) 4-hydroxybut-2-enethioate (1a**).**



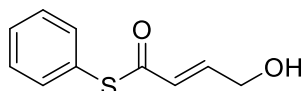
White solid. ^1H NMR (CDCl_3) δ 7.24 (dd, $J = 8.0, 6.5$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 2H), 7.03 (dt, $J = 15.5, 4.0$ Hz, 1H), 6.53 (dt, $J = 15.5, 2.0$ Hz, 1H), 4.39 (dd, $J = 4.0, 2.0$ Hz, 2H), 2.36 (s, 6H), 1.71 (br s, 1H). ^{13}C

NMR (CDCl_3) δ 187.0, 143.4, 142.9, 129.9, 128.3, 126.7, 126.4, 61.8, 21.7. Mp. 73.9–74.2 °C.

TLC: R_f 0.41 (hexane/EtOAc = 2:1). IR (KBr): 3424, 3054, 2910, 2826, 1682, 1636, 1462, 1438,

1374, 1255, 1102, 1036, 952, 910, 827, 775, 719, 620 cm^{-1} . HRMS Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 223.0784. Found: m/z 223.0784.

(*E*)-*S*-Phenyl 4-hydroxybut-2-enethioate (1b**).**



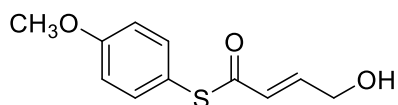
Pale yellow oil. ^1H NMR (CDCl_3) δ 7.47–7.41 (m, 5H), 7.03 (dt, $J = 15.5, 4.0$ Hz, 1H), 6.48 (dt, $J = 15.5, 2.0$ Hz, 1H), 4.35 (dd, $J = 4.0, 2.0$

Hz, 2H), 2.15 (br s, 1H). ^{13}C NMR (CDCl_3) δ 188.2, 144.1, 134.5, 129.4, 129.2, 127.3, 125.9,

61.6. TLC: R_f 0.19 (hexane/EtOAc = 2:1). IR (neat): 3423, 3060, 2918, 2850, 2369, 1774, 1678,

1634, 1479, 1441, 1141, 1099, 1037, 951, 823, 746, 690, 493 cm^{-1} . HRMS Calcd for $\text{C}_{10}\text{H}_{11}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 195.0474. Found: m/z 195.0472.

(*E*)-*S*-(4-Methoxyphenyl) 4-hydroxybut-2-enethioate (1c**).**

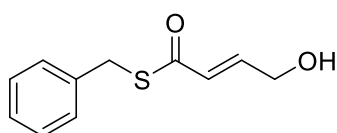


Yellow oil. ^1H NMR (CDCl_3) δ 7.36–7.33 (m, 2H), 7.04 (dt, $J = 15.5, 3.5$ Hz, 1H), δ 7.00–6.94 (m, 2H), 6.48 (dt, $J = 15.5, 2.0$

Hz, 1H), 4.39 (m, 2H), 3.83 (s, 3H), 1.67 (br s, 1H). ^{13}C NMR (CDCl_3) δ 188.9, 160.7, 143.6,

136.2, 126.0, 118.0, 114.9, 61.8, 55.4. TLC: R_f 0.30 (hexane/EtOAc = 1:1). IR (neat): 3426, 2941, 2838, 1773, 1682, 1635, 1593, 1495, 1290, 1250, 1174, 1102, 1095, 1033, 952, 828 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{SNa}$: $[\text{M}+\text{Na}]^+$, 247.0399. Found: m/z 247.0394.

(*E*)-*S*-Benzyl 4-hydroxybut-2-enethioate (1l).

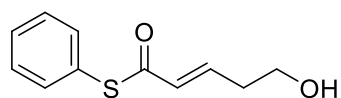


White solid. ^1H NMR (CDCl_3) δ 7.33–7.27 (m, 4H), 7.26–7.22 (m, 1H), 6.98 (dt, J = 15.5, 4.0 Hz, 1H), 6.41 (dt, J = 15.5, 2.0 Hz, 1H), 4.36 (ddd, J = 6.0, 4.0, 2.0 Hz, 2H), 4.21 (s, 2H), 1.63 (t, J = 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 189.0, 143.1, 137.5, 128.9, 128.6, 127.3, 126.6, 61.8, 33.1. Mp. 39.1–39.4 $^\circ\text{C}$. TLC: R_f 0.20 (hexane/EtOAc = 3:1). IR (KBr): 3354, 3089, 3066, 3030, 2917, 2856, 1946, 1876, 1800, 1678, 1633, 1497, 1440, 1395, 1262, 1099, 1045, 955, 902, 833, 771, 701, 612, 567, 479 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 209.0631. Found: m/z 209.0629.

Procedure for preparation of δ -hydroxy- α,β -unsaturated thioester 5a

The mixture of *S*-phenyl 2-(triphenylphosphoranylidene)ethanethioate (4.20 g, 10 mmol) and 3-((*tert*-butyldimethylsilyl)oxy)propanal (1.88 g, 10 mmol) in CH_2Cl_2 (30 mL) was stirred at 25 $^\circ\text{C}$ for 17 h. After the solvents were removed, purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 30/1) as an eluent gave (*E*)-*S*-phenyl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enethioate as a pale yellow oil in 38% yield.

To the stirred solution of (*E*)-*S*-phenyl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enethioate (1.23 g, 3.8 mmol) in CH_3CN (30 mL) was added aqueous HF (0.8 mL) at ambient temperature, and the mixture was stirred for 15 min. Aqueous NaHCO_3 was added to the solution, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave (*E*)-*S*-phenyl 5-hydroxypent-2-enethioate (**5a**) in 43% yield.

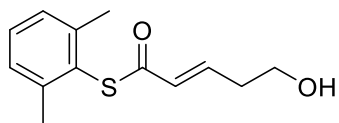
(*E*)-*S*-Phenyl 5-hydroxypent-2-enethioate (5a).

Pale yellow oil. ^1H NMR (CDCl_3) δ 7.45–7.41 (m, 5H), 6.99 (dt, J = 15.5, 7.0 Hz, 1H), 6.29 (dt, J = 15.5, 1.5 Hz, 1H), 3.80 (dt, J = 6.5, 5.0 Hz, 2H), 2.52 (dd, J = 6.5, 1.5 Hz, 1H), 2.49 (dd, J = 6.5, 1.5 Hz, 1H), 1.56 (t, J = 5.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 187.9, 142.5, 134.6, 129.8, 129.4, 129.7, 127.4, 60.8, 35.4. TLC: R_f 0.10 (hexane/EtOAc = 3:1). IR (neat): 3406, 3060, 2938, 2882, 1683, 1632, 1478, 1282, 1138, 1040, 965, 788, 746, 689 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 209.0631. Found: m/z 209.0628.

Procedure for preparation of δ -hydroxy- α,β -unsaturated thioester 5b

The mixture of *S*-phenyl 2-(triphenylphosphoranylidene)ethanethioate (3.91 g, 9.5 mmol) and 2-((triisopropylsilyl)oxy)acetaldehyde (1.77 g, 7.9 mmol) in THF (70 mL) was stirred at 50 °C for 24 h. After the solvents were removed, purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave (*E*)-*S*-phenyl 4-((triisopropylsilyl)oxy)but-2-enethioate as a pale yellow solid in 90% yield.

To the stirred solution of (*E*)-*S*-phenyl 4-((triisopropylsilyl)oxy)but-2-enethioate (2.50 g, 7.1 mmol) in CH_3CN (30 mL) was added aqueous HF (2.0 mL) at ambient temperature, and the mixture was stirred for 2 h. Aqueous NaHCO_3 was added to the solution, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3/1) as an eluent gave (*E*)-*S*-(2,6-dimethylphenyl) 5-hydroxypent-2-enethioate (**5b**) in 48% yield.

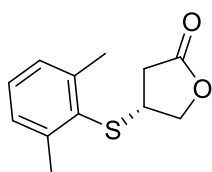
(*E*)-*S*-(2,6-Dimethylphenyl) 5-hydroxypent-2-enethioate (5b).

White solid. ^1H NMR (CDCl_3) δ 7.24 (dd, J = 8.0, 7.0 Hz, 1H), 7.16 (m, 2H), 7.00 (dt, J = 15.5, 7.0 Hz, 1H), 6.33 (dt, J = 15.5, 1.5 Hz, 1H), 3.81 (t, J = 6.0 Hz, 2H), 2.52 (dd, J = 6.0, 1.5 Hz, 1H), 2.49 (dd, J = 6.0, 1.5 Hz, 1H), 2.36 (s, 6H). ^{13}C NMR (CDCl_3) δ 187.1, 142.9, 142.1, 130.0, 129.9, 128.2,

126.6, 60.8, 35.4, 21.7. Mp. 41.2–41.9 °C. TLC: R_f 0.14 (hexane/EtOAc = 2:1). IR (neat): 3443, 3055, 3031, 2955, 2921, 2879, 2710, 1652, 1619, 1580, 1464, 1408, 1373, 1304, 1194, 1138, 1092, 1051, 973, 915, 810, 785, 656, 573 cm^{-1} . HRMS Calcd for $\text{C}_{13}\text{H}_{17}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 237.0944. Found: m/z 237.0941.

Characterization Data of Products

4-((2,6-Dimethylphenyl)thio)dihydrofuran-2(3*H*)-one (2a).



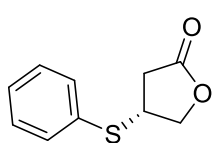
Method A: 83% yield (27.5 mg), 76% *ee*.

Method B: 93% yield (31.1 mg), 78% *ee*. $[\alpha]_{\text{D}}^{20} +29.7$ (*c* 3.11, CH_2Cl_2).

Scheme 5: 41% yield (13.6 mg), –41% *ee*. $[\alpha]_{\text{D}}^{20} -11.0$ (*c* 1.36, CH_2Cl_2).

White solid. ^1H NMR (CDCl_3) δ 7.18 (dd, J = 8.5, 6.0 Hz, 1H), 7.13 (m, 2H), 4.54 (dd, J = 10.0, 6.5 Hz, 1H), 4.21 (dd, J = 10.0, 4.0 Hz, 1H), 3.81 (m, 1H), 2.79 (dd, J = 17.5, 8.0 Hz, 1H), 2.53 (s, 6H), 2.53 (dd, J = 17.5, 5.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 175.1, 143.6, 130.3, 129.4, 128.5, 72.2, 41.5, 35.2, 22.1. Mp. 50.0–50.8 °C. TLC: R_f 0.30 (hexane/EtOAc = 2:1). IR (KBr): 3537, 3056, 2959, 2928, 2902, 2858, 1776, 1570, 1459, 1410, 1363, 1266, 1160, 1056, 1027, 969, 937, 844, 777, 680, 540 cm^{-1} . HRMS Calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 223.0787. Found: m/z 223.0778. HPLC (Daicel Chiralpak IB, hexane/*i*-PrOH = 97.5/2.5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 11.1 min, t_{minor} = 12.8 min.

(*S*)-4-(Phenylthio)dihydrofuran-2(3*H*)-one (2b).



Method A: 95% yield (27.7 mg), 77% *ee*.

Method B: 99% yield (29.2 mg), 84% *ee*. $[\alpha]_{\text{D}}^{20} +36.6$ (*c* 1.16, CHCl_3).

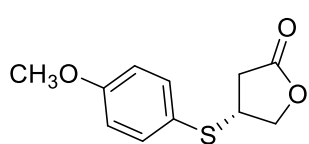
Colorless oil. ^1H NMR (CDCl_3) δ 7.45–7.41 (m, 2H), 7.38–7.32 (m, 3H), 4.54 (dd, J = 9.5, 6.5 Hz, 1H), 4.21 (dd, J = 9.5, 5.5 Hz, 1H), 4.00 (m, 1H), 2.89 (dd, J = 17.5, 8.0 Hz, 1H), 2.53 (dd, J = 17.5, 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 174.7, 132.8, 132.1, 129.5, 128.4, 72.6, 41.6, 35.0. TLC: R_f 0.31 (hexane/EtOAc = 2:1). IR (neat): 3546, 3074, 3058, 2993, 2962, 2905, 1779, 1584, 1481, 1439, 1411, 1372, 1262, 1168, 1092, 1063, 1025, 994, 940, 898, 844, 743, 692 cm^{-1} .

cm^{-1} . HRMS Calcd for $\text{C}_{10}\text{H}_{11}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 195.0474. Found: m/z 195.0471. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 11.4 min, t_{minor} = 27.1 min.

The absolute configuration of **2b** was assigned as (*R*) by comparing the optical rotation with the literature value.^{7b}

$[\alpha]_{\text{D}}^{20}$ +36.6 (*c* 1.16, CHCl_3) [lit. (*S*)-4-(phenylthio)dihydrofuran-2(3*H*)-one (7% *ee*): $[\alpha]_{\text{D}}^{20}$ -2.5 (*c* 1.16, CHCl_3)].

4-((4-Methoxyphenyl)thio)dihydrofuran-2(3*H*)-one (2c).

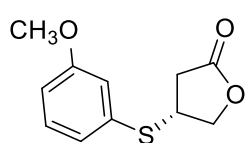


Method A: 99% yield (33.4 mg), 69% *ee*.

Method B: 97% yield (32.6 mg), 89% *ee*. $[\alpha]_{\text{D}}^{20}$ +39.9 (*c* 3.26, CH_2Cl_2).

Colorless oil. ^1H NMR (CDCl_3) 7.41 (m, 2H), 6.88 (m, 2H), 4.47 (dd, J = 9.5, 7.0 Hz, 1H), 4.18 (dd, J = 9.5, 5.5 Hz, 1H), 3.83 (m, 1H), 3.82 (s, 3H), 2.82 (dd, J = 17.5, 8.0 Hz, 1H), 2.49 (dd, J = 17.5, 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 175.0, 160.5, 136.3, 121.8, 115.0, 72.5, 55.4, 42.5, 34.8. TLC: R_f 0.20 (hexane/EtOAc = 2:1). IR (neat): 3546, 3067, 3001, 2962, 2904, 2838, 2534, 2045, 1778, 1592, 1494, 1465, 1408, 1370, 1288, 1248, 1173, 1027, 938, 898, 831, 681, 641 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_3\text{S}$: $[\text{M}+\text{H}]^+$, 225.0580. Found: m/z 225.0577. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 12.5 min, t_{minor} = 15.9 min.

4-((3-Methoxyphenyl)thio)dihydrofuran-2(3*H*)-one (2d).



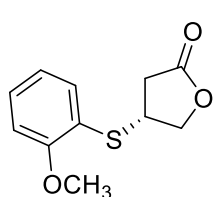
Method B: 99% yield (34.1 mg), 86% *ee*, colorless oil. $[\alpha]_{\text{D}}^{20}$ +49.3 (*c* 3.41,

CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.27 (t, J = 8.0 Hz, 1H), 6.98 (ddd, J = 7.5, 1.5, 1.0 Hz, 1H), 6.95 (dd, J = 2.5, 1.5 Hz, 1H), 6.86 (ddd, J = 7.5, 2.5, 1.0

Hz, 1H), 4.55 (dd, J = 9.5, 6.5 Hz, 1H), 4.21 (dd, J = 9.5, 5.5 Hz, 1H), 4.03 (m, 1H), 3.81 (s, 3H), 2.91 (dd, J = 18.0, 8.0 Hz, 1H), 2.54 (dd, J = 18.0, 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 174.9, 160.0,

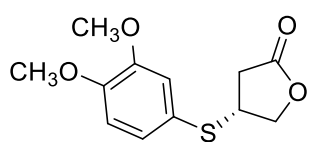
133.3, 130.3, 124.5, 117.9, 113.9, 72.6, 55.4, 41.4, 35.0. TLC: R_f 0.21 (hexane/EtOAc = 2:1). IR (neat): 3547, 3065, 3000, 2962, 2938, 2908, 2836, 2364, 1782, 1590, 1576, 1480, 1413, 1371, 1313, 1284, 1249, 1168, 1100, 1039, 1039, 942, 847, 776, 687 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_3\text{S}$: $[\text{M}+\text{H}]^+$, 225.0580. Found: m/z 225.0577. HPLC (Daicel Chiralpal IA, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 10.6 min, t_{minor} = 25.0 min.

4-((2-Methoxyphenyl)thio)dihydrofuran-2(3*H*)-one (2e).



Method B: 92% yield (30.9 mg), 76% *ee*, white solid. $[\alpha]_{\text{D}}^{27} +44.5$ (*c* 3.09, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.41 (dd, J = 7.5, 1.5 Hz, 1H), 7.36 (ddd, J = 8.5, 7.5, 1.5 Hz, 1H), 6.96 (dd, J = 7.5, 1.5 Hz, 1H), 6.93 (dd, J = 8.5, 1.5 Hz, 1H), 4.52 (dd, J = 10.0, 6.5 Hz, 1H), 4.21 (dd, J = 10.0, 5.0 Hz, 1H), 4.12 (m, 1H), 3.92 (s, 3H), 2.88 (dd, J = 18.0, 8.0 Hz, 1H), 2.53 (dd, J = 18.0, 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 175.3, 159.1, 135.0, 130.4, 121.2, 119.6, 111.1, 72.8, 55.8, 39.9, 35.1. Mp. 57.8–58.2 °C. TLC: R_f 0.21 (hexane/EtOAc = 2:1). IR (KBr): 3523, 3062, 3014, 2970, 2944, 2909, 2837, 2024, 1927, 2887, 1777, 1577, 1479, 1433, 1372, 1276, 1242, 1181, 1073, 1007, 854, 746, 686 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3\text{S}$: M^+ , 224.0507. Found: m/z 224.0510. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 9.1 min, t_{minor} = 10.0 min.

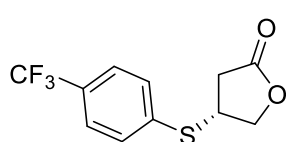
4-((3,4-Dimethoxyphenyl)thio)dihydrofuran-2(3*H*)-one (2f).



Method B: 94% yield (35.8 mg), 90% *ee*, colorless oil. $[\alpha]_{\text{D}}^{20} +41.9$ (*c* 3.58, CH_2Cl_2). ^1H NMR (CDCl_3) 7.06 (dd, J = 8.5, 2.5 Hz, 1H), 6.96 (d, J = 2.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 4.47 (dd, J = 10.0, 7.0 Hz, 1H), 4.19 (dd, J = 10.0, 5.0 Hz, 1H), 3.89–3.86 (m, 7H), 2.83 (dd, J = 18.0, 8.0 Hz, 1H), 2.50 (dd, J = 18.0, 6.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 175.0, 150.0, 149.2, 127.7, 122.0, 117.3, 111.6, 72.4, 56.0, 55.9, 42.6, 34.8. TLC: R_f 0.27 (hexane/EtOAc = 1:1). IR (neat): 2959, 2838, 1782, 1645, 1585, 1506, 1440, 1254, 1232, 1169, 1023, 879, 807, 762 cm^{-1} . HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4\text{SNa}$:

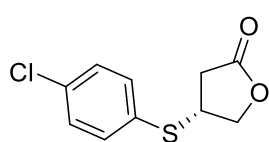
$[M+Na]^+$, 277.0505. Found: m/z 277.0498. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 95/5, flow rate = 4.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 25.5 min, t_{minor} = 27.0 min.

4-((4-(Trifluoromethyl)phenyl)thio)dihydrofuran-2(3*H*)-one (2g).

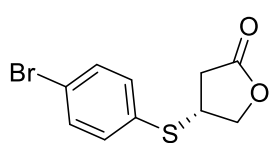


Method B: 94% yield (37.1 mg), 66% *ee*, white solid. $[\alpha]_D^{20}$ +19.5 (*c* 3.71, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.59 (m, 2H), 7.45 (m, 2H), 4.62 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.23 (dd, *J* = 9.5, 4.5 Hz, 1H), 4.15 (m, 1H), 2.99 (dd, *J* = 18.0, 8.0 Hz, 1H), 2.55 (dd, *J* = 18.0, 5.5 Hz, 1H). ¹³C NMR (CDCl₃) δ 174.3, 138.0, 130.6, 129.6 (q, *J* = 32.8 Hz), 126.2 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 272.1 Hz), 72.3, 40.7, 35.0. Mp. 60.7–61.3 °C. TLC: *R_f* 0.25 (hexane/EtOAc = 2:1). IR (KBr): 3528, 3092, 3031, 2996, 2974, 2921, 2642, 2313, 1923, 1786, 1608, 1499, 1404, 1328, 1264, 1171, 1127, 1065, 993, 941, 833, 780, 684, 595, 542, 496 cm⁻¹. HRMS Calcd for C₁₁H₉F₃O₂S: M⁺, 262.0275. Found: m/z 262.0273. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 11.7 min, t_{minor} = 13.0 min.

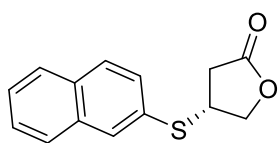
4-((4-Chlorophenyl)thio)dihydrofuran-2(3*H*)-one (2h).



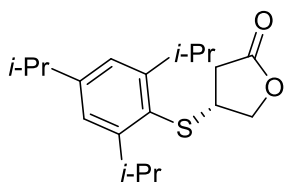
Method B: 99% yield (34.3 mg), 77% *ee*, white solid. $[\alpha]_D^{20}$ +37.2 (*c* 3.43, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.36 (m, 2H), 7.33 (m, 2H), 4.53 (dd, *J* = 10.0, 7.0 Hz, 1H), 4.19 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.98 (m, 1H), 2.90 (dd, *J* = 18.0, 3.0 Hz, 1H), 2.51 (dd, *J* = 18.0, 6.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 174.6, 134.8, 134.1, 130.6, 129.7, 72.4, 41.8, 34.9. Mp. 60.8–61.8 °C. TLC: *R_f* 0.24 (hexane/EtOAc = 2:1). IR (KBr): 2926, 2838, 1782, 1645, 1585, 1506, 1440, 1254, 1232, 1169, 1023, 879, 807, 762 cm⁻¹. HRMS Calcd for C₁₀H₉ClO₂SNa: $[M+Na]^+$, 250.9904. Found: m/z 250.9900. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 11.5 min, t_{minor} = 12.6 min.

4-((4-Bromophenyl)thio)dihydrofuran-2(3H)-one (2i).

Method B: 99% yield (41.7 mg), 76% *ee*, white solid. $[\alpha]_{\text{D}}^{20} +23.4$ (*c* 4.17, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.47 (m, 2H), 7.28 (m, 2H), 4.53 (dd, *J* = 10.0, 7.0 Hz, 1H), 4.19 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.99 (m, 1H), 2.90 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.51 (dd, *J* = 18.0, 6.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 174.5, 134.1, 132.6, 131.3, 122.8, 72.3, 41.7, 34.9. Mp. 59.4–60.1 °C. TLC: *R*_f 0.23 (hexane/EtOAc = 2:1). IR (KBr): 3013, 2991, 1763, 1474, 1413, 1388, 1374, 1263, 1173, 1092, 1065, 1005, 985, 938, 811 cm⁻¹. HRMS Calcd for C₁₀H₉BrO₂SNa: [M+Na]⁺, 294.9399. Found: *m/z* 294.9394. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{major} = 12.6 min, *t*_{minor} = 13.5 min.

4-(Naphthalen-2-ylthio)dihydrofuran-2(3H)-one (2j).

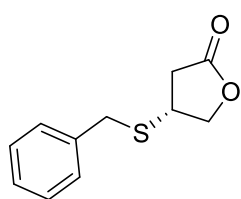
Method B: 98% yield (35.9 mg), 85% *ee*, white solid. $[\alpha]_{\text{D}}^{20} +31.3$ (*c* 3.59, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.91 (m, 1H), 7.85–7.78 (m, 3H), 7.55–7.50 (m, 2H), 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H), 4.56 (dd, *J* = 10.0, 6.5 Hz, 1H), 4.26 (dd, *J* = 10.0, 5.5 Hz, 1H), 4.12 (m, 1H), 2.94 (dd, *J* = 18.0, 8.0 Hz, 1H), 2.58 (dd, *J* = 18.0, 6.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 174.9, 133.5, 132.7, 132.0, 131.9, 129.5, 129.4, 129.2, 127.7, 127.5, 126.9, 72.5, 41.6, 35.0. Mp. 96.7–97.2 °C. TLC: *R*_f 0.25 (hexane/EtOAc = 2:1). IR (KBr): 3537, 3049, 3003, 2968, 2911, 1961, 1911, 1831, 1777, 1623, 1586, 1502, 1411, 1370, 1262, 1164, 1062, 988, 937, 816, 749, 686, 473 cm⁻¹. HRMS Calcd for C₁₄H₁₃O₂S: [M+H]⁺, 245.0631. Found: *m/z* 245.0626. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{major} = 13.7 min, *t*_{minor} = 18.3 min.

4-((2,4,6-Triisopropylphenyl)thio)dihydrofuran-2(3H)-one (2k).

Method B: 50% yield (24.2 mg), 88% *ee*, white solid. $[\alpha]_{\text{D}}^{20} +43.4$ (*c* 2.42, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.04 (s, 2H), 4.40 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.21 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.80 (sept, *J* = 7.0 Hz, 2H), 3.68 (m,

1H), 2.88 (sept, $J = 7.0$ Hz, 1H), 2.81 (dd, $J = 17.5, 7.5$ Hz, 1H), 2.47 (dd, $J = 17.5, 5.0$ Hz, 1H), 1.25 (d, $J = 7.0$ Hz, 6H), 1.23 (d, $J = 7.0$ Hz, 6H), 1.22 (d, $J = 7.0$ Hz, 6H). ^{13}C NMR (CDCl_3) δ 175.3, 153.5, 150.8, 124.6, 122.2, 72.0, 43.1, 35.0, 34.3, 31.6, 24.5, 24.3, 23.8. Mp. 103.1–103.3 °C. TLC: R_f 0.29 (hexane/EtOAc = 2:1). IR (KBr): 3524, 3044, 2966, 2928, 2908, 2868, 2307, 1775, 1600, 1560, 1461, 1412, 1362, 1255, 1165, 1063, 1027, 980, 937, 879, 842, 745, 682, 650, 546, 501 cm^{-1} . HRMS Calcd for $\text{C}_{19}\text{H}_{29}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 321.1883. Found: m/z 321.1877. HPLC (Daicel Chirapak IB, hexane/*i*-PrOH = 99/1, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 30 °C): $t_{\text{minor}} = 5.2$ min, $t_{\text{major}} = 5.8$ min.

4-(Benzylthio)dihydrofuran-2(3H)-one (2l).



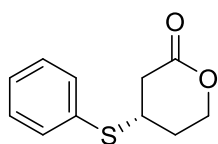
Method A: 68% yield (21.1 mg), 33% *ee*.

Method B: 86% yield (28.1 mg), 52% *ee*. $[\alpha]_{\text{D}}^{20} -1.8$ (c 2.81, CH_2Cl_2).

Colorless oil. ^1H NMR (CDCl_3) δ 7.36–7.26 (m, 5H), 4.36 (dd, $J = 9.5, 7.0$ Hz, 1H), 4.21 (dd, $J = 9.5, 6.5$ Hz, 1H), 3.79 (d, $J = 2.0$ Hz, 2H), 3.44 (m, 1H),

2.73 (dd, $J = 17.5, 8.0$ Hz, 1H), 2.53 (dd, $J = 17.5, 7.5$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 174.9, 137.3, 128.9, 128.7, 127.7, 73.0, 38.0, 36.1, 35.4. TLC: R_f 0.23 (hexane/EtOAc = 2:1). IR (neat): 3537, 3357, 3061, 3028, 2958, 2921, 2852, 1779, 1602, 1495, 1474, 1453, 1412, 1371, 1263, 1168, 1072, 1028, 943, 844, 771, 705 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 209.0631. Found: m/z 209.0627. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2 mL/min, $\lambda = 254$ nm, 30 °C): $t_{\text{minor}} = 9.4$ min, $t_{\text{major}} = 10.6$ min.

4-(Phenylthio)tetrahydro-2H-pyran-2-one (6a).



Method A: 94% yield (29.2 mg), 75% *ee*.

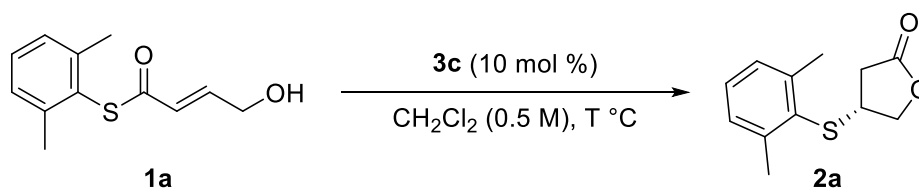
Method B: 92% yield (28.6 mg), 81% *ee*. $[\alpha]_{\text{D}}^{20} -20.1$ (c 2.86, CH_2Cl_2).

Colorless oil. ^1H NMR (CDCl_3) δ 7.46–7.42 (m, 2H), 7.36–7.30 (m, 3H), 4.51 (m, 1H), 4.27 (m, 1H), 3.57 (m, 1H), 2.91 (dd, $J = 17.5, 6.0$ Hz, 1H), 2.54 (dd, $J = 17.5, 8.5$ Hz, 1H), 2.21 (m, 1H), 1.88 (M, 1H). ^{13}C NMR (CDCl_3) δ 169.0, 133.4, 132.0, 129.3, 128.3, 67.1,

39.3, 36.6, 29.1. TLC: R_f 0.19 (hexane/EtOAc = 2:1). IR (neat): 3060, 2957, 2921, 2862, 1941, 1873, 1725, 1462, 1444, 1397, 1376, 1296, 1250, 1226, 1164, 1077, 1062, 975, 941, 890, 774, 636, 583, 529, 473 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{13}\text{O}_2\text{S}$: $[\text{M}+\text{H}]^+$, 209.0631. Found: m/z 209.0628. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 8.1 min, t_{minor} = 16.8 min.

Supplemental Data

Table 3. Effects of reaction temperature in the isomerization of **1a** in CH_2Cl_2 in the absence of **4a** (for Figure 1 (a))^a

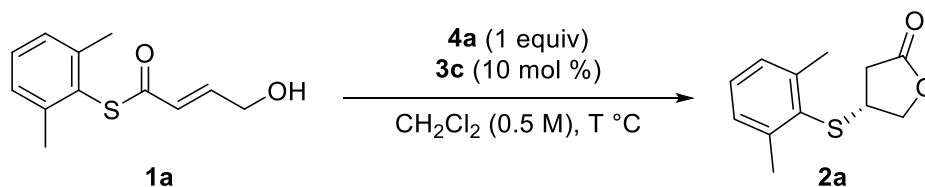


entry	T (°C)	time (h)	yield (%) ^b	ee (%)
1	−40	72	3	25
2	−30	72	8	36
3	−20	24	13	44
4	−10	24	29	51
5	0	24	88	58
6	10	24	86	64
7	25	24	99	66
8	40	4	70	68
9	60	4	96	69

^aReactions were run using **1a** (0.15 mmol) and **3c** (0.015 mmol) in CH_2Cl_2 (0.3 mL).

^bIsolated yields.

Table 4. Effects of reaction temperature in the isomerization of **1a** in CH₂Cl₂ in the presence of **4a** (for Figure 1 (b))^a



entry	T (°C)	time (h)	yield (%) ^b	ee (%)
1	−40	24	78	52
2	−30	24	92	51
3	−20	24	93	54
4	−10	24	99	60
5	0	24	94	63
6	10	24	97	66
7	25	24	96	68
8	40	4	98	69
9	60	2	92	70

^aReactions were run using **1a** (0.15 mmol), **3c** (0.015 mmol), and **4a** (0.15 mmol) in CH₂Cl₂ (0.3 mL). ^bIsolated yields.

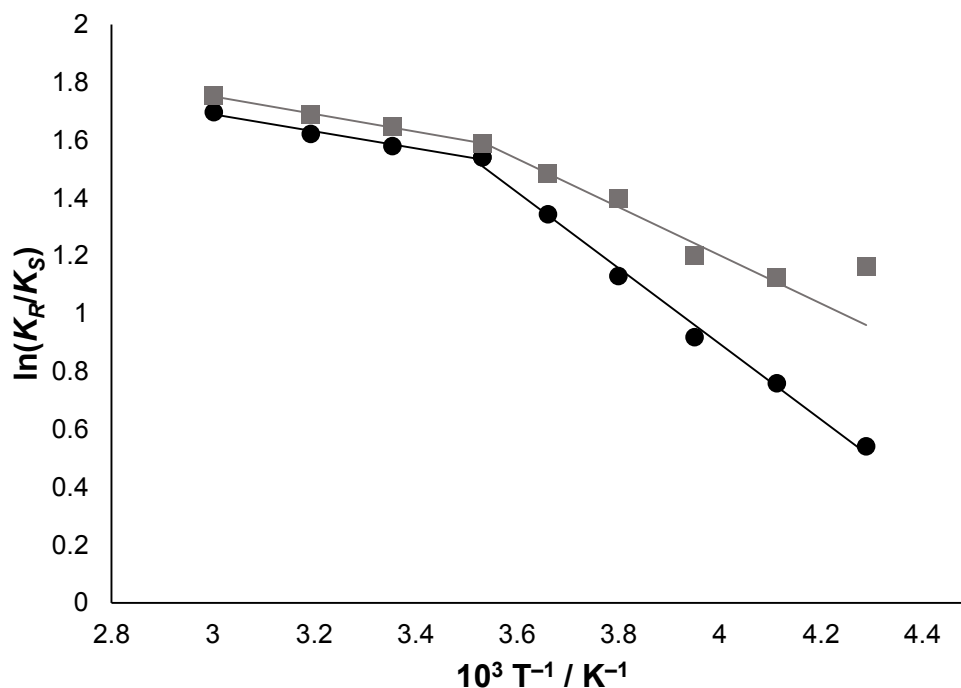


Figure 1. Eyring plots for the isomerization of **1a** (0.15 mmol) using **3c** (0.015 mmol) in CH_2Cl_2 (0.5 M) (a) in the absence of **4a** [●] and (b) in the presence of **4a** (0.15 mmol) [■]: $\ln(k_R/k_S) = -\Delta\Delta H^\ddagger_{R-S}/RT + \Delta\Delta S^\ddagger_{R-S}/R$.

Table 5. Differential activation parameters for the isomerization of **1a** in CH_2Cl_2

entry	4a	T (°C)	$\Delta\Delta H^\ddagger$ (KJ mol ⁻¹)	$\Delta\Delta S^\ddagger$ (J mol ⁻¹ K ⁻¹)
1	no	60 to 10	+2.43	+21.3
2	no	10 to -40	+10.9	+51.1
3	1 equiv	60 to 10	+2.54	+22.2
4	1 equiv	10 to -30	+6.94	+37.8

In the region of higher temperature (60–10 °C), the presence of **4a** slightly increased the value of $\Delta\Delta S^\ddagger$ (Table 4, entries 1 and 3), implying that the addition of **4a** improved the enantioselectivity by alleviating the entropic cost.

Table 6. Effects of reaction temperature in the isomerization of **1a** in CH₃CN/H₂O in the absence of **4a** (for Figure 2 (a))^a

1a $\xrightarrow[\text{CH}_3\text{CN}/\text{H}_2\text{O (v/v = 2/1, 0.1 M), T } ^\circ\text{C}]{\text{3c (5 mol \%)}}$ **ent-2a**

entry	T (°C)	time (h)	yield (%) ^b	ee (%)
1	−10	24	31	28
2	0	120	60	24
3	10	24	92	23
4	25	24	99	21
5	40	4	83	16
6	60	2	74	13

^aReactions were run using **1a** (0.15 mmol) and **3c** (0.0075 mmol) in CH₃CN/H₂O (v/v = 2/1, 1.5 mL). ^bIsolated yields.

Table 7. Effects of reaction temperature in the isomerization of **1a** in CH₃CN/H₂O in the presence of **4a** (for Figure 2 (b))^a

1a $\xrightarrow[\text{CH}_3\text{CN}/\text{H}_2\text{O (v/v = 2/1, 0.1 M), T } ^\circ\text{C}]{\text{4a (1 equiv) } \text{3c (5 mol \%)}}$ **ent-2a**

entry	T (°C)	time (h)	yield (%) ^b	ee (%)
1	−10	24	36	25
2	0	24	89	22
3	10	24	89	22
4	25	24	95	21

Table 7. (continued)

5	40	4	99	20
6	60	2	84	17

^aReactions were run using **1a** (0.15 mmol), **3c** (0.0075 mmol), and **4a** (0.15 mmol) in CH₃CN/H₂O (v/v = 2/1, 1.5 mL). ^bIsolated yields.

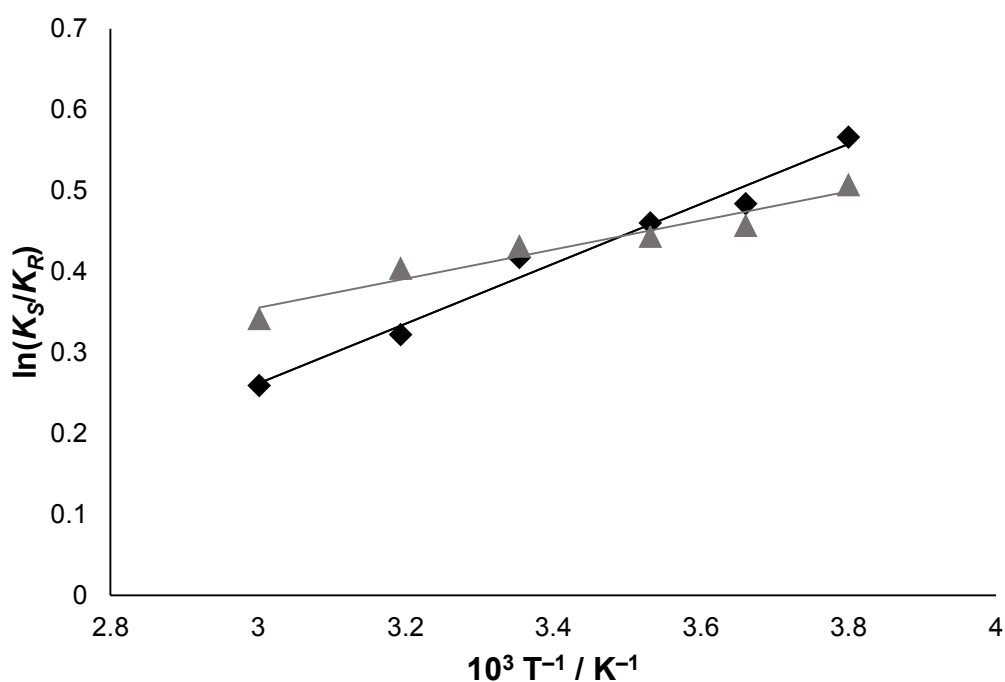


Figure 2. Eyring plots for the isomerization of **1a** (0.15 mmol) using **3c** (0.0075 mmol) in CH₃CN/H₂O (v/v = 2:1, 0.1 M) (a) in the absence of **4a** [♦] and (b) in the presence of **4a** (0.15 mmol) [▲]: $\ln(k_S/k_R) = -\Delta\Delta H^\ddagger_{S-R}/RT + \Delta\Delta S^\ddagger_{S-R}/R$.

Table 8. Differential activation parameters for the isomerization of **1a** in CH₃CN/H₂O

entry	4a	$\Delta\Delta H^\ddagger$ (KJ mol ⁻¹)	$\Delta\Delta S^\ddagger$ (J mol ⁻¹ K ⁻¹)
1	no	-3.08	-7.06
2	1 equiv	-1.49	-1.53

The Eyring plots of the reactions in CH₃CN/H₂O have linear lines with positive slopes (Figure 2), and the values of $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ are negative (Table 8). Thus, the $\Delta\Delta H^\ddagger$ term plays a dominant role in the stereodiscrimination in this solvent system, and the enantioselectivity switch can be attributed to the change of the governing factor which lowers $\Delta\Delta G^\ddagger$.

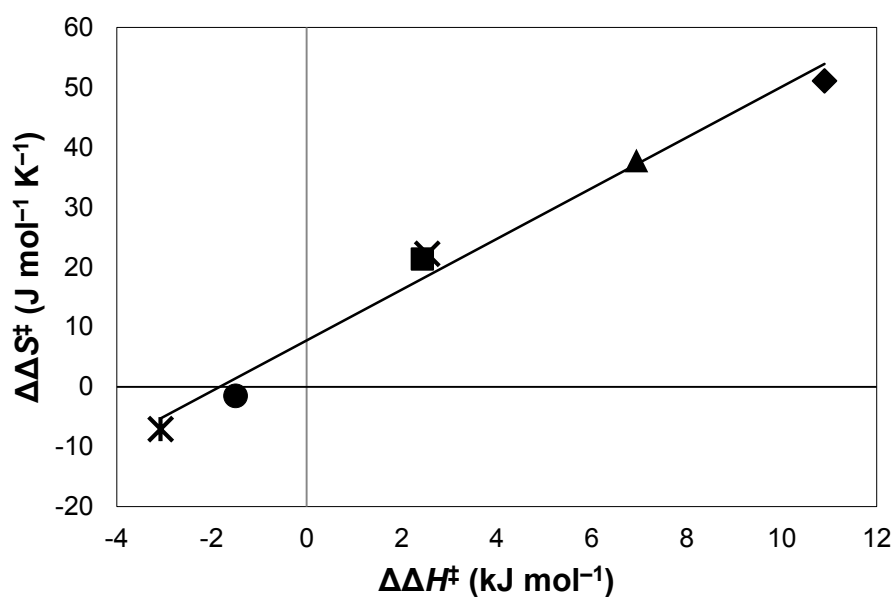
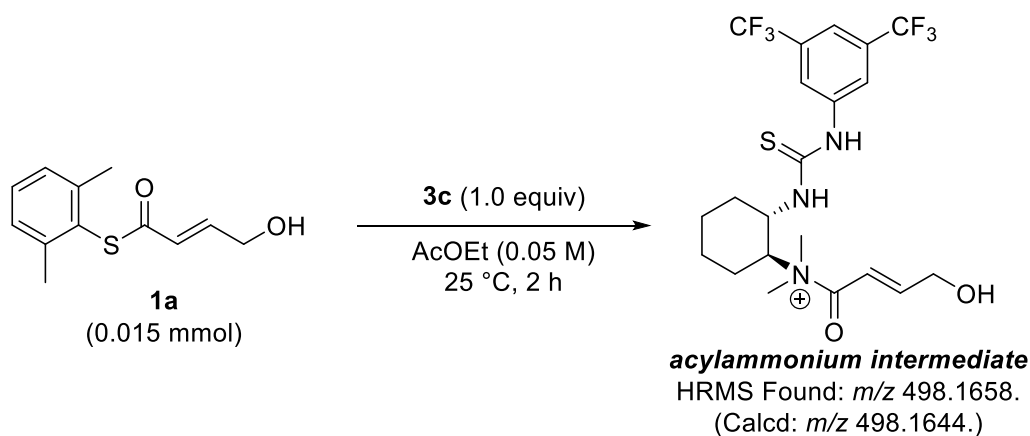


Figure 3. Enthalpy–entropy compensation plots using the $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ estimated for various conditions: isomerization of **1a** in CH₂Cl₂ (0.5 M) in the absence of **4a** (a) in a range from 60 °C to 10 °C (cross) and (b) in a range from 10 °C to -40 °C (diamond); isomerization of **1a** in CH₂Cl₂ in the presence of **4a** (c) in a range from 60 °C to 10 °C (square) and (d) in a range from 10 °C to -30 °C (triangle); isomerization of **1a** in CH₃CN/H₂O (v/v = 2/1, 0.1 M) (e) in the absence of **4a** (asterisk) and (f) in the presence of **4a** (circle).

The Eyring plots depicted in Figure 1 consist of two linear trends with an intersection known as an inversion temperature. They have been observed in a wide range of organic reactions.^{16b, 21} In addition, enthalpy–entropy compensation plots using the differential activation parameters ($\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$) shown in Tables 4 and 7 resulted in a straight line (Figure 3, $R^2 = 0.982$). According to previous reports, such a linear relationship in the enthalpy–entropy compensation plots can be evidence to indicate that the two linear trends in the Eyring plots did not result from changes in the reaction mechanism.²²



Scheme 6. HRMS analysis of the solution of **1a** in the presence of a stoichiometric amount of **3c**.

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Chapter 4

Facile Net Cycloaddition Approach to Optically Active 1,5-Benzothiazepines

The 1,5-benzothiazepine moiety is well-known as a versatile pharmacophore, and its derivatives are expected to have antagonism against numerous diseases. Thus, it is desirable to develop a synthetic route that enables facile enantioselective preparation of a wide range of such derivatives. Although the cycloaddition approach could be considered a possible route to these compounds, to date, there has been no precedent of such a protocol. This is the first example of a highly enantioselective net $[4 + 3]$ cycloaddition to afford 1,5-benzothiazepines by utilizing α,β -unsaturated acylammonium intermediates generated by chiral isothioureia catalysts, which undergo two sequential chemoselective nucleophilic attacks by 2-aminothiophenols. This protocol provided cycloadducts in extremely high regioselectivity, with a good-to-excellent stereoselectivity being achieved regardless of the steric and electronic properties of the substrates. This method therefore offers promising synthetic routes for the construction of a library of optically active 1,5-benzothiazepines for assay evaluation.

Introduction

1,5-Benzothiazepines are well-known as representative molecules in the field of pharmaceutical science (Figure 1) and are expected to exhibit antagonism against various diseases.¹

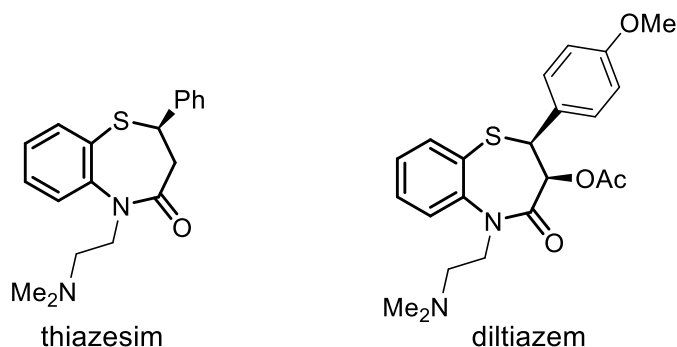
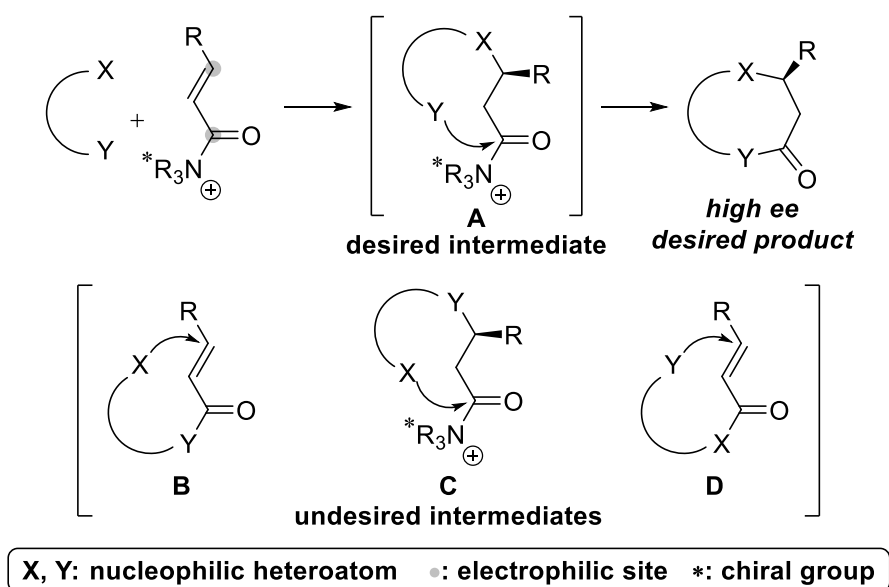


Figure 1. Representative pharmaceutical compounds containing the 1,5-benzothiazepine moiety.

Indeed, 1,5-benzothiazepines, such as thiazesim, originally attracted a great amount of attention as antidepressant agents. Later, thanks to a random screening program in a Japanese pharmaceutical company, calcium antagonism was unexpectedly observed, and diltiazem (Herbesser) was developed as an effective medication for the treatment of hypertension and angina and is currently used in more than 100 countries. These successful examples of the use of 1,5-benzothiazepines stress their great potential for application as pharmaceutical products. Thus, there exists a high demand for methods that allow rapid and divergent syntheses of such derivatives to support assay evaluation. To date, a few asymmetric syntheses have been reported through a multistep construction of the ring structure.² In this Chapter, an asymmetric cycloaddition approach is proposed for the diversity-oriented synthesis of 1,5-benzothiazepines.

Recently, the use of α,β -unsaturated acylammonium species in organocatalyzed transformations was reported, where they were employed as components bearing two electrophilic sites to allow annulations through sequential nucleophilic attacks by carbon and heteroatom, or two carbon nucleophiles, to take place.³ The α,β -unsaturated acylammonium species can therefore be

considered a promising candidate as the intermediate of a reaction with a molecule bearing two nucleophilic heteroatoms. However, despite the clear advantages in this type of transformation, a number of alternative pathways are possible when these reactants are employed.



Scheme 1. Net cycloaddition between α,β -unsaturated acylammonium ion and nucleophilic counterpart bearing two heteroatoms.

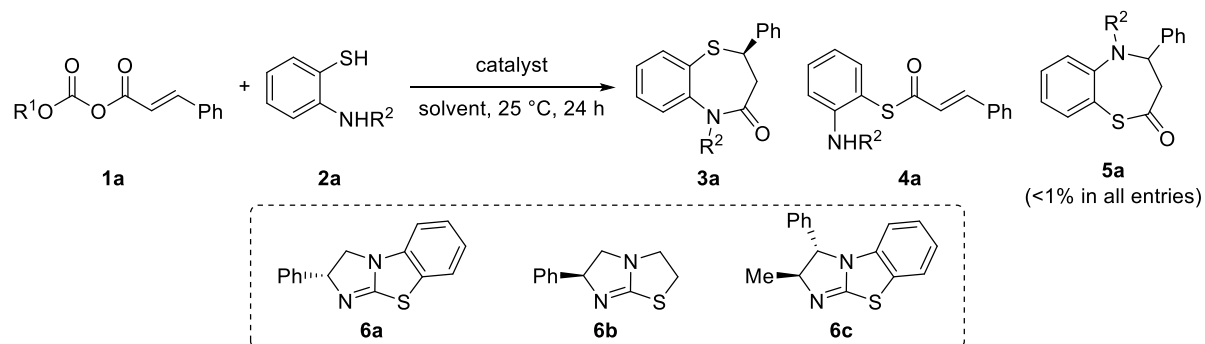
As shown in Scheme 1, besides the desired pathway via intermediate **A**, alternative pathways through undesired intermediates **B–D** could also take place to lower the enantioselectivity or generate the undesired regioisomer. Therefore, to achieve a highly enantio- and regioselective net cycloaddition, pathways **B–D** must be suppressed.

In Chapter 3, the author described an organocascade reaction via two nucleophilic attacks by different heteroatoms to α,β -unsaturated acylammonium species.⁴ In the course of this study, he noted the high chemoselectivity of the described intermediates, which exclusively captures a sulfur-centered nucleophile at the β -position via a sulfa-Michael addition. Thus, he proposed a net cycloaddition reaction of an α,β -unsaturated acylammonium salt, with a reagent containing both sulfur and nitrogen atoms, in hope that the reaction could proceed through the desired intermediate

corresponding to intermediate **A** in Scheme 1. In addition, the author expected that the stereoselectivity could also be attained by the use of a chiral nucleophilic organocatalyst.

Results and Discussion

The net cycloaddition reaction using α,β -unsaturated substrate **1a** and aminothiophenol **2a** with 10 mol % of benzotetramisole catalyst **6a** in toluene at 25 °C was investigated (Table 1).⁵ As expected, 1,5-benzothiazepine **3a** was obtained in high enantioselectivity, with no generation of the regioisomer being observed (entry 1). Catalyst screening revealed that **6a** was the most effective catalyst for achieving the highest enantioselectivity (entries 1–3). Optimization of the reaction solvents was also investigated, with CHCl_3 being identified as the most effective solvent for yielding high stereoselectivity (entries 4–8), whereas in THF, α,β -unsaturated thioester **4a** ($\text{R}^2 = \text{Ts}$) was obtained instead of the desired product (entry 6). The choice of the substituent (OR^1) on the carbonic anhydride was also important for the reaction yield, with alkyl substituents giving better yields than an aryl-containing substituent (entries 9 and 10).⁶ The use of 4 Å molecular sieves as an additive further improved the yield of the reaction (entry 11). The R^2 substituent on the nitrogen atom of aminothiophenol **2** was found to have an effect on the reaction pathway and thus influenced the identity of major product obtained from the reaction. Replacement of the tosyl group on the nitrogen atom of **2a** with a t-butoxycarbonyl group resulted in the formation of thioester **4b** ($\text{R}^2 = \text{Boc}$) (entry 12). To evaluate the effect of catalyst loading on the reaction, one reaction was run with a reduced catalyst loading of 5 mol % (entry 13). Even with this reduced catalyst loading, the desired product was obtained in similar yield and enantioselectivity. In addition, it was found that the catalyst loading could be reduced further to 0.5 mol % (entry 14), although a higher temperature, longer reaction time, and a slight excess of **2a** were required. Under these conditions, the use of halogenated solvents could also be avoided while keeping the enantioselectivity high (entry 14).

Table 1. Optimization of conditions^a

entry	catalyst (mol %)	R ¹ , R ²	solvent	Yield of 3a (%) ^b	Yield of 4a (%) ^b	ee of 3a (%)
1	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	toluene	86	<1	95
2	6b (10)	<i>i</i> -Pr (1a), Ts (2a)	toluene	38	<1	−78
3	6c (10)	<i>i</i> -Pr (1a), Ts (2a)	toluene	51	<1	−90
4	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	benzene	84	<1	94
5	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	EtOAc	74	<1	93
6	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	THF	<1	41	—
7	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	CH ₂ Cl ₂	87	<1	96
8	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	CHCl ₃	84	<1	97
9	6a (10)	Et (1b), Ts (2a)	CHCl ₃	76	<1	97
10	6a (10)	Bn (1c), Ts (2a)	CHCl ₃	35	<1	96
11 ^c	6a (10)	<i>i</i> -Pr (1a), Ts (2a)	CHCl ₃	98	<1	97
12 ^c	6a (10)	<i>i</i> -Pr (1a), Boc (2b)	CHCl ₃	<1	73	—
13 ^c	6a (5)	<i>i</i> -Pr (1a), Ts (2a)	CHCl ₃	95	<1	97
14 ^{c,d}	6a (0.5)	<i>i</i> -Pr (1a), Ts (2a)	toluene	87	<1	94

^aReactions were run using **1** (0.15 mmol), **2** (0.15 mmol), the catalyst, and the solvent (0.3 mL).

^bIsolated yields. ^cReactions were run using 75 mg of 4 Å molecular sieves. ^dReaction was run using 0.17 mmol of **2a** at 40 °C for 48 h.

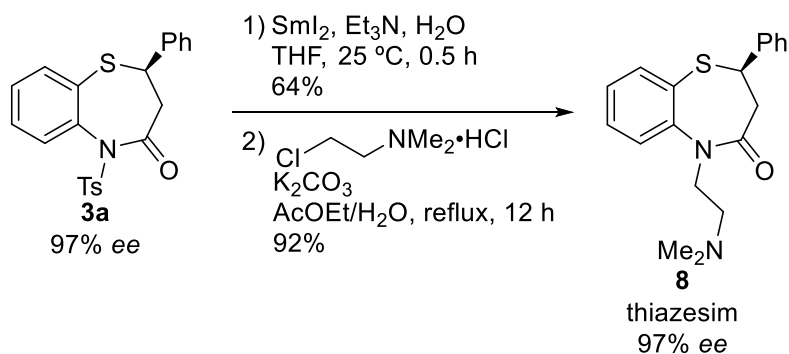
The substrate scope of the reaction with the use of 5 mol % **6a** as catalyst were explored (Table 2). Overall, good to excellent yields and enantioselectivities were obtained with a range of

substrates. Electron-rich aminothiophenols gave slightly higher enantioselectivities than electron-poor ones (**3a–3e**), which implies the possibility of cation- π interactions existing in the transition state of the enantiodetermining step. The electronic and steric characteristics of the substituents on the α,β -unsaturated carbonyl substrates did not have a large influence on the enantioselectivity of the reaction (**3f–3m**). In addition, various combinations of aminothiophenol and α,β -unsaturated carbonyl substrates yielded the corresponding products in high yields and enantioselectivities (**3n–3r**). These results indicate the high efficiency and generality of this net cycloaddition method by demonstrating that this protocol can provide access to a wide range of optically active 1,5-benzothiazepines. The absolute configuration of **3a** was determined by X-ray analysis (see the Experimental Section for details), and the configurations of all other examples were assigned analogously. By using the obtained cycloadduct **3a**, we also accomplished the asymmetric synthesis of thiazesim (**8**), a heterocyclic antidepressant (Scheme 2). Deprotection of **3a** with samarium iodide afforded the corresponding secondary amine 1,5-benzothiazepine **7** (not shown in Scheme 2) without a reduction in enantiomeric excess, with its optical rotation ($[\alpha]_{\text{D}}^{18}$ -448.4 (c 0.63, CHCl_3)) being consistent with the literature value of the (*R*)-isomer (see the Experimental Section for details).^{2b} Subsequent alkylation of **7** gave optically active thiazesim **8** in good yield.

Table 4-2. Substrate scope^a

Products ^b	
R = H (3a): 95%, 97% ee R = Me (3b): 94%, 97% ee R = OCH₃ (3c): 79%, 98% ee R = Cl (3d): 85%, 88% ee R = Br (3e): 87%, 90% ee	R = Me (3f): 82%, 98% ee R = OCH₃ (3h): 78%, 97% ee R = CF₃ (3i): 86%, 98% ee R = Br (3j): 99%, 97% ee
3g 76%, 94% ee	
3k 78%, 97% ee	3l 96%, 93% ee
	3m 99%, 97% ee
	3n 75%, 92% ee
3o 73%, 91% ee	3p 95%, 97% ee
	3q 94%, 93% ee
	3r 70%, 91% ee

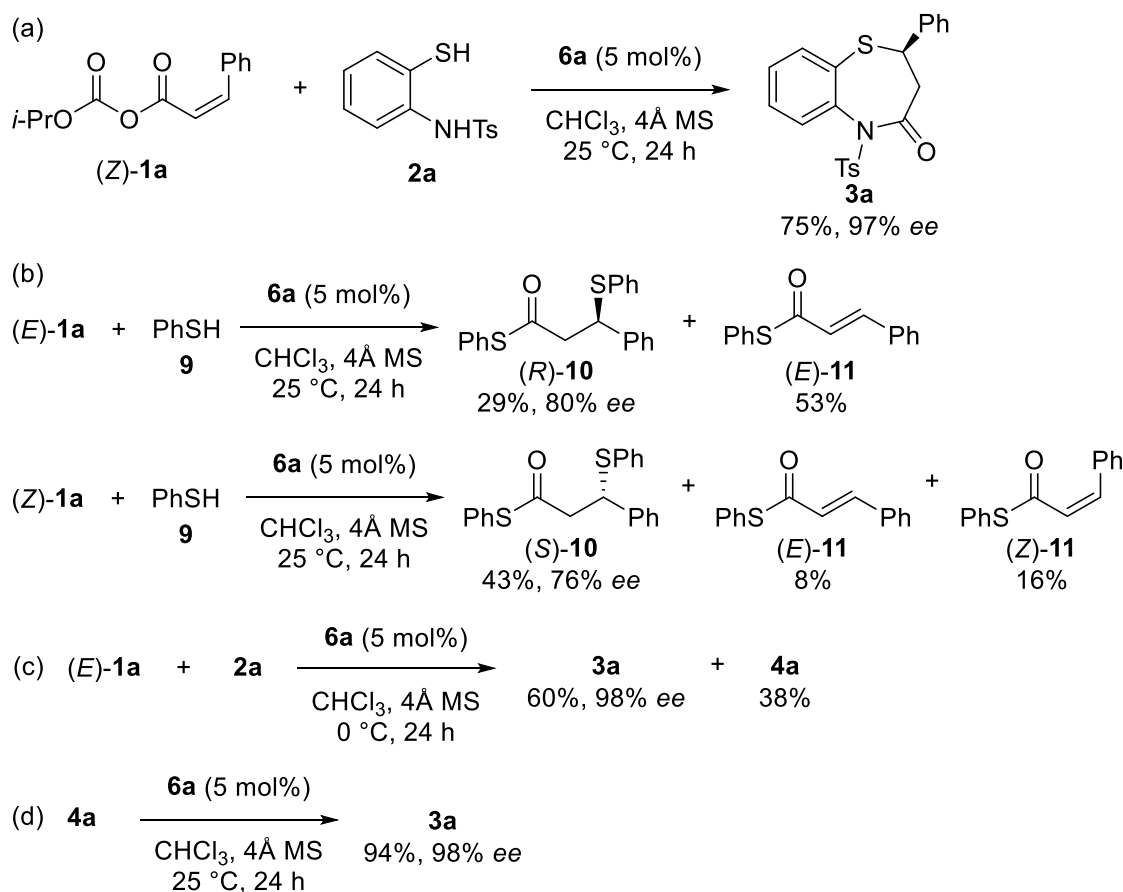
^aReactions were run using **1** (0.15 mmol), **2** (0.15 mmol), **6a** (0.0075 mmol), and 4 Å molecular sieves (75 mg) in CHCl₃ (0.3 mL). ^bYields represent material isolated after silica gel column chromatography.



Scheme 2. Synthesis of thiazesim (**8**)

To gain insight into the reaction mechanism, the net cycloaddition reaction was also carried out using α,β -unsaturated substrate **1a** in the (*Z*)-olefin configuration (Scheme 3a). The resulting cycloadduct was obtained in high enantioselectivity, and the absolute configuration was revealed to be (*R*)-configuration, which is consistent with the product obtained using the (*E*)-substrate. The reaction was then carried out in the presence of benzenethiol (**9**), instead of aminothiophenol **2a**, again using both the (*E*)- and (*Z*)-substrates of **1a** (Scheme 3b). In both cases, thioester products **10** and **11** were obtained, although different enantiomers of β -mercaptothioester **10** were obtained depending on the geometry of the starting materials. The α,β -unsaturated thioester (*E*)-**11** was also obtained for both substrates, whereas isomer (*Z*)-**11** was only obtained from the reaction from (*Z*)-**1a**. These results imply that the (*Z*)-substrate is capable of isomerizing to the (*E*)-form via a sulfa-Michael addition/C–C bond rotation/retro-sulfa-Michael addition process. In addition, when the reaction of **1a** with **2a** in CHCl_3 was carried out at 0 °C, α,β -unsaturated thioester **4a** was obtained as a side product (Scheme 3c), which implies that α,β -unsaturated thioesters (**4**) may be temporarily generated in situ under optimal conditions. Thus, the reaction starting from **4a** under the optimal conditions was tested, and the desired product **3a** was obtained in high yield and comparable enantioselectivity (Scheme 3d). These results suggest that the formation of **4** is also reversible, and thus it does not have an effect on the final outcome of the net cycloaddition. Furthermore, the formation of the α,β -unsaturated acylammonium intermediate was strongly supported by HRMS and NMR analyses of a solution of **1a** and a stoichiometric amount of **6a** in

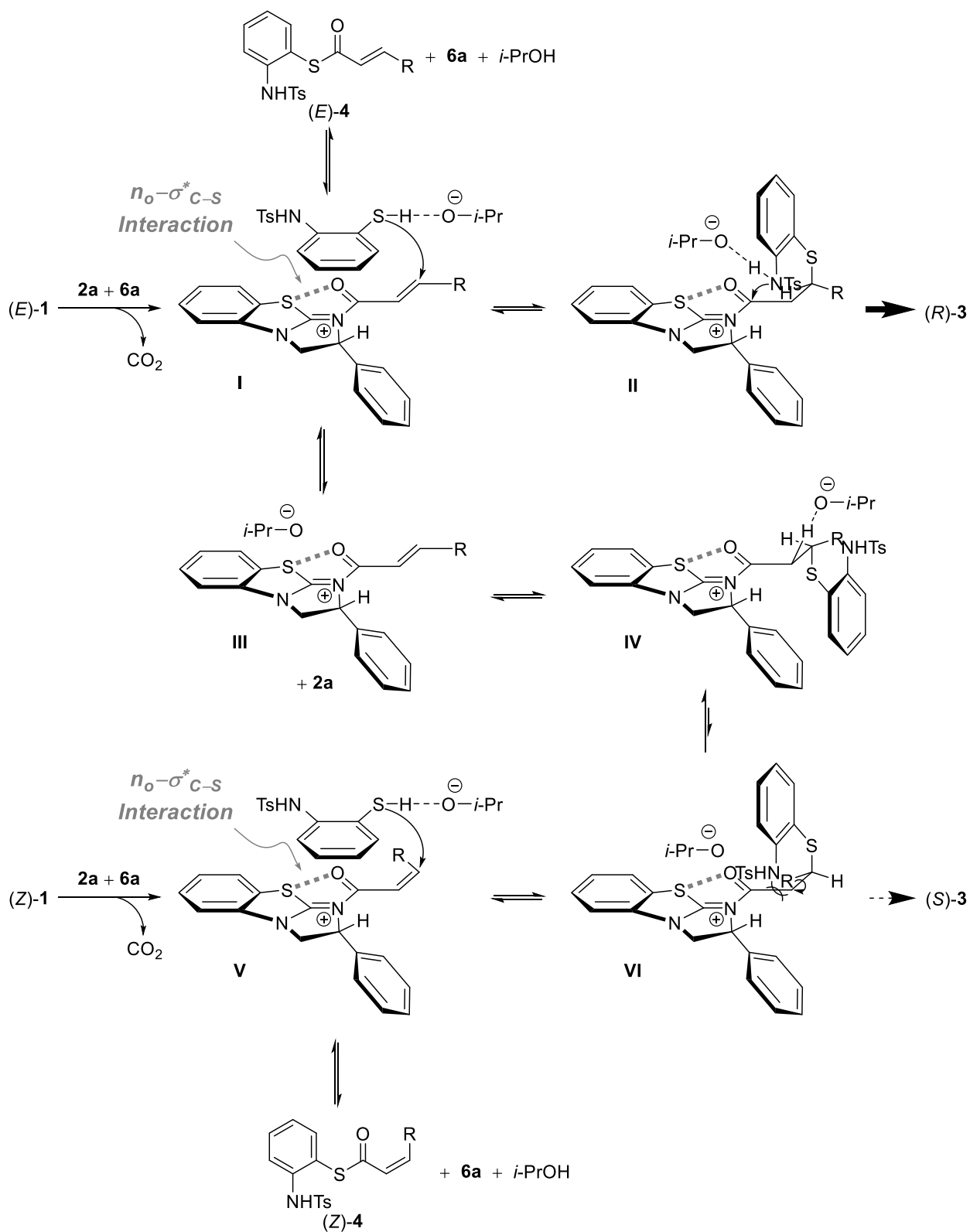
CDCl_3 , which then afforded **3a** after the subsequent addition of **2a** with enantioselectivity comparable to the catalytic reaction (see the Experimental Section for details).



Scheme 3. Mechanistic studies.

On the basis of the experimental results described above, the author propose the reaction mechanism for this transformation as outlined in Scheme 4. Starting from α,β -unsaturated (E)-**1**, it is expected that the acylammonium intermediate **I** forms and that the carbonyl group is fixed in position through an no to $\sigma^*_{\text{C-S}}$ interaction.⁷ The 2-aminothiophenol can then approach from the opposite side of the phenyl group on the catalyst for steric reasons, with this process possibly aided by the presence of a cation- π interaction.⁸ Subsequently, a sulfa-Michael addition followed by N-acylation affords the desired cycloadduct (R)-**3**. Alternatively, starting from substrate (Z)-**1**, acylammonium intermediate **V** is generated and subsequently undergoes the first sulfa-Michael

addition according to the results in Scheme 3, panel b. However, it is expected that the following cyclization may be inhibited by a favorable conformational change driven by the release of repulsion energy that exists in intermediate **VI**. Thus, from intermediate **IV**, bearing a more stable conformation, thiophenol **2a** eliminates to generate (*E*)-intermediate **III**, which again affords 1,5-benzothiazepine (*R*)-**3** via intermediates **I** and **II** (see also Scheme 3a). The enantioselectivity of this reaction therefore seems to be mainly controlled by the difference of cyclization rate between the intermediates **II** and **VI** and is also reinforced by the face-selective sulfa-Michael addition, where the selection system supported by the reversibility of sulfa-Michael addition may impart the overall excellent enantioselectivity.⁹ In addition, in the event where (*E*)-**4** and (*Z*)-**4** are generated during the course of the reaction, they could be incorporated back into the main catalytic process and ultimately lead to the formation of the desired products in high enantioselectivities.



Scheme 4. Proposed reaction pathways for the transformation.

Conclusion

In summary, the author have demonstrated the first net cycloaddition approach to 1,5-benzothiazepines, realizing a facile synthetic route to a number of benzothiazepine derivatives. The net cycloaddition procedure resulted in excellent regioselectivity and good stereoselectivity regardless of the steric and electronic characteristics of the substrates. Mechanistic studies suggested that the reversibility of the nucleophilic attack by sulfur-centered nucleophiles to α,β -unsaturated acylammonium intermediates imparts the high regio- and enantioselectivity of the transformation. This method is potentially useful for the construction of a library of optically active 1,5-benzothiazepines.

Experimental Section

Materials.

Unless otherwise noted, commercially available reagents were used without purification.

General procedure for asymmetric cycloaddition of α,β -unsaturated carbonic anhydrides with aminothiophenols

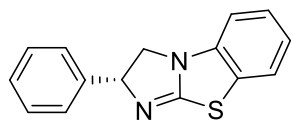
To a 5-mL vial were added sequentially α,β -unsaturated substrate **1** (0.15 mmol), CHCl_3 (0.3 mL), 4Å MS (75 mg), isothiurea catalyst **6a** (0.0075 mmol), and aminothiophenol **2** (0.15 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 5:1), passed through a short silica gel pad to remove **6a**, and concentrated in vacuo to give the crude 1,5-benzothiazepine **3** as a pale yellow solid. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent afforded the corresponding 1,5-benzothiazepines **3**. Racemic compounds were prepared using racemic isothiurea catalyst **6a**.

Procedure for preparation of benzotetramisole catalyst 6a

Benzotetramisole catalyst **6a** was prepared by the literature procedure.¹⁰ To the solution of (*R*)-(+)-phenylglycinol (1.4 g, 10 mmol) in *i*-Pr₂EtN (2.7 mL, 15 mmol) was added 2-chlorobenzothiazole (1.7 g, 10 mmol), and the mixture was heated at 135 °C for 24 h. After cooling the mixture to 40 °C, the viscous reaction mixture was treated with CH₂Cl₂ (5 mL), and left at ambient temperature overnight to dissolve the solid completely. The diluted reaction mixture was applied directly to a chromatographic column and eluted with CH₂Cl₂/*i*-PrOH (v/v = 20/1) to afford (*R*)-*N*-(triazolyl-2)-2-hydroxy-1-phenylethylamine (white solid, 2.4 g, 90% yield).

A solution of (*R*)-*N*-(triazolyl-2)-2-hydroxy-1-phenylethylamine (2.4 g, 9.0 mmol) in anhydrous CH₂Cl₂ (80 mL) was cooled to 0 °C under argon atmosphere and treated with NEt₃ (3.7 mL, 27 mmol) followed by MsCl (1.1 mL, 13.5 mmol). The mixture was stirred at 0 °C for 1 h and then warmed up to ambient temperature. Methanol (0.5 mL) was added to decompose the excess MsCl. NEt₃ (10 mL) was added, and the mixture was refluxed overnight. The cooled mixture was washed with water (10 mL), dried over Na₂SO₄, and evaporated in vacuo. The crude product was purified by column chromatography with hexane/*i*-PrOH/NEt₃ (v/v/v = 100/5/1) as an eluent to give a white solid. The compound was recrystallized from EtOAc/hexane to produce **6a** (white solid, 1.36 g, 60% yield).

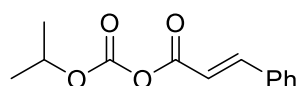
(*R*)-2,3-Dihydro-2-phenyl-imidazo[2,1-*b*]benzothiazole (6a): CAS RN [885051-07-0].



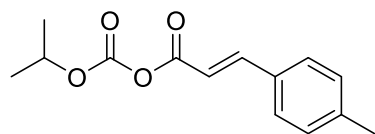
White solid. $[\alpha]_D^{18} +252.5$ (*c* 1.00, MeOH). ¹H NMR (CDCl₃) δ 7.38–7.37 (m, 4H), 7.34 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.30 (m, 1H), 7.22 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.01 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.72 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.70 (dd, *J* = 10.5, 8.0 Hz, 1H), 4.35 (dd, *J* = 10.5, 9.0 Hz, 1H), 3.78 (dd, *J* = 9.0, 8.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 167.2, 142.4, 136.7, 128.8, 127.8, 127.4, 126.7, 126.4, 123.3, 121.8, 108.8, 74.4, 52.6. Mp. 94.5–95.5 °C. TLC: R_f 0.30 (hexane/*i*-PrOH = 20:1). IR (KBr): 3024, 2871, 1596, 1574, 1452, 1376, 1217, 746 cm⁻¹. HRMS Calcd for C₁₅H₁₃N₂S: [M+H]⁺, 253.0794. Found: *m/z* 253.0788.

General procedure for preparation of α,β -unsaturated carbonic anhydrides 1a–1i

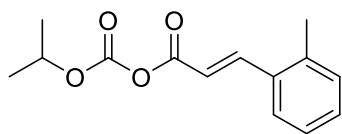
To a stirred solution of an α,β -unsaturated carboxylic acid (1.0 equiv) in CH_2Cl_2 (0.72 M) was slowly added *i*-Pr₂EtN (1.5 equiv) and isopropyl chloroformate (1.1 equiv) at 0 °C, and the mixture was stirred at 0 °C for 30 min. H_2O was added to the solution, and the mixture was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave the corresponding carbonic anhydride.

(*E*)-Cinnamic (isopropyl carbonic) anhydride ((*E*)-1a).

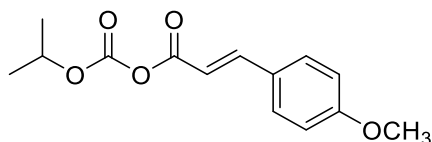
Colorless oil; 70% yield. ^1H NMR (CDCl_3) δ 7.82 (d, J = 16.0 Hz, 1H), 7.55 (m, 2H), 7.42 (m, 3H), 6.42 (d, J = 16.0 Hz, 1H), 5.05 (sept, J = 6.0 Hz, 1H), 1.39 (d, J = 6.0 Hz, 6H). ^{13}C NMR (CDCl_3) δ 161.1, 148.9, 148.6, 133.5, 131.3, 129.0, 128.5, 115.4, 74.2, 21.5. TLC: R_f 0.36 (hexane/EtOAc = 10:1). IR (neat): 2985, 1792, 1730, 1632, 1450, 1240, 1154, 1071, 903, 763, 697 cm^{-1} . HRMS Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 257.0784. Found: m/z 257.0778.

(*E*)-(Isopropyl carbonic) 3-(*p*-tolyl)acrylic anhydride (1b).

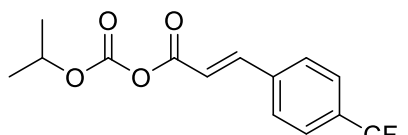
Colorless oil; 75% yield. ^1H NMR (CDCl_3) δ 7.80 (d, J = 16.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.36 (d, J = 16.0 Hz, 1H), 5.05 (sept, J = 6.0 Hz, 1H), 2.39 (s, 3H), 1.39 (d, J = 6.0 Hz, 6H). ^{13}C NMR (CDCl_3) δ 161.3, 149.0, 148.8, 142.0, 130.9, 129.8, 128.6, 114.3, 74.2, 21.6, 21.5. TLC: R_f 0.44 (hexane/EtOAc = 10:1). IR (neat): 2985, 1793, 1735, 1631, 1242, 1157, 1094, 1072, 906, 812 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 271.0941. Found: m/z 271.0943.

(*E*)-(Isopropyl carbonic) 3-(*o*-tolyl)acrylic anhydride (1c).

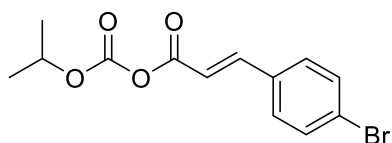
Colorless oil; 77% yield. ^1H NMR (CDCl_3) δ 8.12 (d, $J = 16.0$ Hz, 1H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.32 (t, $J = 7.5$ Hz, 1H), 7.26–7.22 (m, 2H), 6.34 (d, $J = 16.0$ Hz, 1H), 5.06 (sept, $J = 6.5$ Hz, 1H), 2.46 (s, 3H), 1.40 (d, $J = 6.5$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 162.3, 148.7, 146.5, 138.3, 132.5, 131.02, 131.99, 126.7, 126.5, 116.3, 71.3, 21.5, 19.8. TLC: R_f 0.44 (hexane/EtOAc = 10:1). IR (neat): 2985, 1797, 1735, 1628, 1466, 1240, 1160, 1075, 906, 761 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 271.0941. Found: m/z 271.0942.

(*E*)-(Isopropyl carbonic) 3-(4-methoxyphenyl)acrylic anhydride (1d).

Colorless oil; 38% yield. ^1H NMR (CDCl_3) δ 7.78 (d, $J = 16.0$ Hz, 1H), 7.51 (m, 2H), 6.92 (m, 2H), 6.28 (d, $J = 16.0$ Hz, 1H), 5.04 (sept, $J = 6.5$ Hz, 1H), 3.85 (s, 3H), 1.38 (d, $J = 6.5$ Hz, 6H). ^{13}C NMR (CDCl_3) δ 162.2, 161.4, 148.9, 148.7, 130.4, 126.3, 114.5, 112.7, 74.1, 55.4, 21.5. TLC: R_f 0.20 (hexane/EtOAc = 10:1). IR (neat): 2985, 1797, 1732, 1628, 1602, 1514, 1258, 1154, 1094, 906, 828 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_5\text{Na}$: $[\text{M}+\text{Na}]^+$, 287.0890. Found: m/z 287.0879.

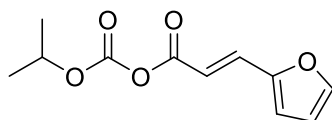
(*E*)-3-(4-(Trifluoromethyl)phenyl)acrylic (isopropyl carbonic) anhydride (1e).

White solid; 77% yield. ^1H NMR (CDCl_3) δ 7.82 ($J = 16.0$ Hz, 1H), 7.69–7.64 (m, 4H), 6.49 (d, $J = 16.0$ Hz, 1H), 5.05 (sept, $J = 6.0$ Hz, 1H), 1.38 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (CDCl_3) δ 160.6, 148.4, 146.7, 136.8, 132.2 (q, $J = 33.1$ Hz), 128.6, 126.0 (q, $J = 3.4$ Hz), 123.5 (q, $J = 272.6$ Hz), 118.1, 74.6, 21.4. ^{19}F NMR (CDCl_3) δ 98.8. TLC: R_f 0.33 (hexane/EtOAc = 10:1). IR (KBr): 2992, 1802, 1762, 1633, 1326, 1239, 1167, 1122, 1058, 907, 837, 823, 758 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{13}\text{F}_3\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 325.0658. Found: m/z 325.0644.

(E)-3-(4-Bromophenyl)acrylic (isopropyl carbonic) anhydride (1f).

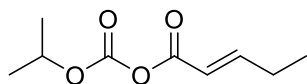
White solid; 36% yield. ^1H NMR (CDCl_3) δ 7.75 (d, $J = 15.5$ Hz, 1H), 7.55 (m, 2H), 7.41 (m, 2H), 6.40 (d, $J = 15.5$ Hz, 1H), 5.05 (sept, $J = 6.0$ Hz, 1H), 1.39 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR

(CDCl_3) δ 160.9, 148.5, 147.4, 132.5, 132.4, 129.8, 125.8, 116.2, 74.4, 21.5. TLC: R_f 0.36 (hexane/EtOAc = 10:1). IR (KBr): 2981, 1788, 1730, 1634, 1586, 1488, 1375, 1248, 1076, 1006, 910, 819 cm^{-1} . HRMS Calcd for $\text{C}_{13}\text{H}_{13}\text{BrO}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 334.9889. Found: m/z 334.9880.

(E)-3-(Furan-2-yl)acrylic (isopropyl carbonic) anhydride (1g).

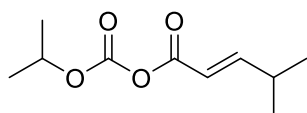
Colorless oil; 81% yield. ^1H NMR (CDCl_3) δ 7.53 (d, $J = 16.5$ Hz, 1H), 7.53 (m, 1H), 6.72 (d, $J = 3.5$ Hz, 1H), 6.51 (dd, $J = 3.5, 2.0$ Hz, 1H), 6.27 (d, $J = 16.5$ Hz, 1H), 5.03 (sept, $J = 6.5$ Hz, 1H), 1.37 (d, $J = 6.5$ Hz, 6H). ^{13}C NMR

(CDCl_3) δ 161.2, 150.2, 148.7, 145.9, 134.5, 117.1, 112.8, 112.7, 74.1, 21.5. TLC: R_f 0.21 (hexane/EtOAc = 10:1). IR (neat): 2986, 1793, 1734, 1634, 1469, 1244, 1163, 1084, 1019, 904, 754 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_5\text{Na}$: $[\text{M}+\text{Na}]^+$, 240.0577. Found: m/z 240.0570.

(E)-(Isopropyl carbonic) pent-2-enoic anhydride (1h).

Colorless oil; 70% yield. ^1H NMR (CDCl_3) δ 7.21 (dt, $J = 16.0, 6.0$ Hz, 1H), 5.82 (d, $J = 16.0$ Hz, 1H), 5.01 (sept, $J = 6.0$ Hz, 1H), 2.28 (m, 2H), 1.35 (d, $J = 6.0$ Hz, 6H), 1.09 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 160.8, 156.0, 148.8, 118.3,

74.1, 25.7, 21.5, 11.8. TLC: R_f 0.37 (hexane/EtOAc = 10:1). IR (neat): 2984, 1802, 1743, 1648, 1465, 1378, 1233, 1169, 1080, 1027, 904 cm^{-1} . HRMS Calcd for $\text{C}_9\text{H}_{14}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 209.0784. Found: m/z 209.0778.

(E)-(Isopropyl carbonic) 4-methylpent-2-enoic anhydride (1i).

Colorless oil; 71% yield. ^1H NMR (CDCl_3) δ 7.13 (dd, $J = 16.0, 7.0$ Hz, 1H), 6.78 (dd, $J = 16.0, 1.5$ Hz, 1H), 5.00 (sept, $J = 6.0$ Hz, 1H), 2.50

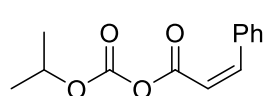
(m, 1H), 1.36 (d, $J = 6.0$ Hz, 6H), 1.08 (d, $J = 7.0$ Hz, 6H). ^{13}C NMR (CDCl_3) δ 161.0, 160.6, 148.8, 116.6, 74.1, 31.4, 21.5, 20.9. TLC: R_f 0.35 (hexane/EtOAc = 10:1). IR (neat): 2967, 1803, 1740, 1648, 1467, 1378, 1237, 1168, 1092, 902, 810 cm^{-1} . HRMS Calcd for $\text{C}_{10}\text{H}_{16}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 223.0941. Found: m/z 223.0933.

Procedure for preparation of (Z)- α,β -unsaturated carbonic anhydride 1a

A mixture of K_2PtCl_4 (103 mg, 0.25 mmol) and AgOTf (129 mg, 0.5 mmol) in trifluoroacetic acid (5 mL) was stirred at ambient temperature for 10 min. Benzene (5.3 mL, 60 mmol) and propionic acid (0.61 mL, 10 mmol) were added to the mixture. Then, the mixture was stirred at the 40 °C. After 3 days, the reaction mixture was poured into water (20 mL), neutralized with NaHCO_3 , and washed with Et_2O (30 mL). Subsequently, the ethereal layers were extracted with aqueous NaOH (20 mL $\times$ 3). The combined aqueous layers were washed with Et_2O (20 mL), acidified with 3 N aqueous HCl, and extracted with CH_2Cl_2 (35 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo, affording (Z)-cinnamic acid (810 mg, 55 % yield, $Z/E = 25/1$).

To a stirred solution of a (Z)-cinnamic acid (480 mg, 3.0 mmol) in CH_2Cl_2 (10 mL) was slowly added *i*- Pr_2EtN (1.2 mL, 6.0 mmol) and isopropyl chloroformate (0.45 mL, 4.5 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. H_2O was added to the solution, and the mixture was extracted with CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent gave (isopropyl carbonic) (Z)-3-phenylacrylic anhydride (159 mg, 23% yield, $Z/E = 25/1$).

(Z)-(Isopropyl carbonic) 3-phenylacrylic anhydride ((Z)-1a).



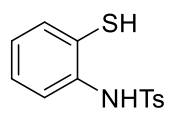
Colorless oil. ^1H NMR (CDCl_3) δ 7.70–7.67 (m, 2H), 7.39–7.37 (m, 3H), 7.16 (d, $J = 12.5$ Hz, 1H), 5.93 (d, $J = 12.5$ Hz, 1H), 4.99 (sept, $J = 6.0$ Hz, 1H), 1.34 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (CDCl_3) δ 159.9, 148.8, 148.6, 133.8, 130.3, 130.1,

128.2, 116.4, 74.2, 21.4. TLC: R_f 0.28 (hexane/EtOAc = 10:1). IR (neat): 2985, 1798, 1745, 1621, 1251, 1058, 901, 697 cm^{-1} . HRMS Calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 257.0784. Found: m/z 257.0777.

Procedure for preparation of aminothiophenol 2a

N-(2-Mercaptophenyl)-4-methylbenzenesulfonamide (**2a**) was prepared by literature procedure.^{11,12} The characterization results are as below.

***N*-(2-Mercaptophenyl)-4-methylbenzenesulfonamide (2a)**: CAS RN [55423-98-8].

 White solid. ^1H NMR (CDCl_3) δ 7.65 (m, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.24 (m, 3H), 7.02 (t, J = 6.0 Hz, 1H), 2.80 (s, 1H), 2.39 (s, 3H). ^{13}C NMR (CDCl_3) δ 144.2, 137.5, 136.1, 135.1, 129.7, 129.3, 127.2, 125.5, 122.3, 119.7, 21.6.

Procedure for preparation of aminothiophenol 2b

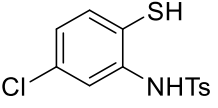
To the solution of 4-chloro-2-mercaptoaniline (1.6 g, 10 mmol) and NaI (15 mg, 0.1 mmol) in EtOAc (30 mL) was added aqueous H_2O_2 (30 wt%, 1.1 mL, 10 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at 0 $^\circ\text{C}$ for 30 min. The mixture was subsequently quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The crude product was used for the next step without further purification.

To the solution of 6,6'-disulfanediyldis(3-chloroaniline) (1.6 g, 5 mmol) in pyridine (20 mL) was added TsCl (3.8 g, 20 mmol), and the mixture was stirred at ambient temperature for 3 days. Then, the mixture was quenched with aqueous 4 N HCl and extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The crude product was used for the next step without further purification.

To the solution of *N,N'*-(disulfanediyldis(3-chloro-6,1-phenylene))bis(4-methylbenzenesulfonamide) (3.2 g, 5 mmol) in a mixture of H_2O and THF (v/v = 1/1, 20 mL) was

added triphenylphosphine (2.6 g, 10 mmol), and the mixture was stirred until the starting material disappeared. The mixture was then extracted with CH_2Cl_2 (20 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/ CH_2Cl_2 (v/v = 1/1) as an eluent gave *N*-(5-chloro-2-mercaptophenyl)-4-methylbenzenesulfonamide.

***N*-(5-Chloro-2-mercaptophenyl)-4-methylbenzenesulfonamide (2b).**

 White solid; 37% yield (1.2 g: for 3 steps). ^1H NMR (CDCl_3) δ 7.70–7.68 (m, 2H), 7.59 (d, J = 2.5 Hz, 1H), 7.35 (brs, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.27 (m, 2H), 6.99 (dd, J = 8.5, 2.5 Hz, 1H), 2.77 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (CDCl_3) δ 144.5, 138.9, 136.2, 135.8, 135.4, 129.9, 127.2, 125.3, 121.4, 116.9, 21.6. IR (KBr): 3268, 2577, 1566, 1476, 1377, 1332, 1166, 1090, 807, 675 cm^{-1} . Mp. 91.9–92.9 $^\circ\text{C}$. TLC: R_f 0.25 (hexane/EtOAc = 1:1). HRMS Calcd for $\text{C}_{13}\text{H}_{12}\text{ClINO}_2\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 335.9890. Found: m/z 335.9884.

General procedure for preparation of aminothiols 2c–e

A solution of 2-methylbenzothiazole derivative (10 mmol) in a mixture of aqueous 50% NaOH and ethylene glycol (v/v = 1/1, 20 mL) was refluxed under argon flux until the starting material disappeared. The mixture was then poured into ice-water, acidified to pH = 3 with 3 N aqueous HCl, and extracted several times with CH_2Cl_2 . The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 2/1 to 1/1) as an eluent gave the corresponding aminothiophenols (64–97% yield).

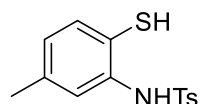
To the solution of the obtained aminothiophenol derivative (1.0 equiv) and NaI (5 mol %) in EtOAc (0.5 M) was added aqueous H_2O_2 (30 wt%, 1.0 equiv) at 0 $^\circ\text{C}$, and the mixture was stirred at 0 $^\circ\text{C}$ for 30 min. The reaction was subsequently quenched by saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$, and the mixture was extracted with EtOAc (15 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo. The crude product was used for the

next step without further purification.

To the solution of dithiodianiline derivative (1.0 equiv) in pyridine (0.2 M) was added TsCl (2.2 equiv), and the mixture was stirred at ambient temperature for 3 days. Then, the reaction was quenched with 4 N aqueous HCl, and the mixture was extracted with EtOAc (20 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude product was used for the next step without further purification.

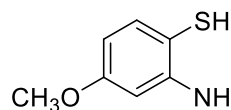
To the solution of tosylated disulfide (1.0 equiv) in a mixture of H₂O and THF (v/v = 1/1, 0.05 M) was added triphenylphosphine (2.1 equiv), and the mixture was stirred until the starting material disappeared. The mixture was then extracted with CH₂Cl₂ (20 mL $\times$ 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/CH₂Cl₂ (v/v = 1/1) as an eluent gave the corresponding *N*-(2-mercaptophenyl)-4-methylbenzenesulfonamides.

***N*-(2-Mercapto-5-methylphenyl)-4-methylbenzenesulfonamide (2c).**



Yellow solid; 13% yield (0.75 g: for 4 steps). ¹H NMR (CDCl₃) δ 7.64 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 2.0 Hz, 1H), 7.30 (brs, 1H), 7.27 (d, J = 8.5 Hz, 1H), 7.22 (m, 2H), 6.83 (dd, J = 8.0, 2.0 Hz, 1H), 2.62 (brs, 1H), 2.39 (s, 3H), 2.31 (s, 3H). ¹³C NMR (CDCl₃) δ 144.1, 140.1, 137.7, 136.2, 135.3, 129.7, 127.2, 126.3, 122.7, 115.3, 21.6, 21.4. IR (KBr): 3236, 2919, 2569, 1598, 1488, 1379, 1331, 1173, 1164, 899, 815, 679 cm⁻¹. Mp. 71.0–72.0 °C. TLC: R_f 0.21 (hexane/EtOAc = 2:1). HRMS Calcd for C₁₄H₁₅NO₂S₂Na: [M+Na]⁺, 316.0436. Found: m/z 316.0429.

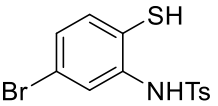
***N*-(2-Mercapto-5-methoxyphenyl)-4-methylbenzenesulfonamide (2d).**



Yellow solid; 14% yield (0.42 g: for 4 steps). ¹H NMR (CDCl₃) δ 7.68 (d, J = 8.0 Hz, 2H), 7.56 (brs, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 3.0 Hz, 1H), 6.56 (dd, J = 8.5, 3.0 Hz, 1H), 3.78 (s, 3H), 2.58 (brs, 1H), 2.38 (s, 3H). ¹³C NMR (CDCl₃) δ 160.9, 144.2, 139.8, 137.2, 136.0, 129.7, 127.2, 111.3, 107.5, 106.3,

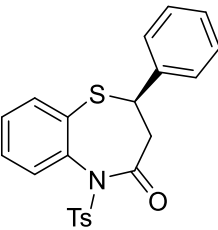
55.5, 21.6. IR (KBr): 3250, 2948, 2545, 1600, 1571, 1490, 1398, 1335, 1295, 1164, 891, 673 cm^{-1} . ¹H NMR (CDCl_3) δ 7.71–7.68 (m, 3H), 7.36 (brs, 1H), 7.30–7.24 (m, 3H), 7.15 (m, 1H), 2.83 (brs, 1H), 2.40 (s, 3H). ¹³C NMR (CDCl_3) δ 144.5, 138.6, 136.0, 135.7, 129.8, 128.3, 127.1, 124.6, 122.8, 118.3, 21.6. IR (KBr): 3235, 2551, 1573, 1468, 1378, 1336, 1164, 1089, 922, 808, 733, 679 cm^{-1} . Mp. 93.8–94.3 °C. TLC: R_f 0.25 (hexane/EtOAc = 2:1). HRMS Calcd for $\text{C}_{13}\text{H}_{12}\text{BrNO}_2\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 355.9420. Found: m/z 355.9425.

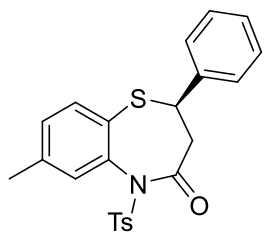
***N*-(5-Bromo-2-mercaptophenyl)-4-methylbenzenesulfonamide (2e).**

 White solid; 25% yield (0.88 g: for 4 steps). ¹H NMR (CDCl_3) δ 7.71–7.68 (m, 3H), 7.36 (brs, 1H), 7.30–7.24 (m, 3H), 7.15 (m, 1H), 2.83 (brs, 1H), 2.40 (s, 3H). ¹³C NMR (CDCl_3) δ 144.5, 138.6, 136.0, 135.7, 129.8, 128.3, 127.1, 124.6, 122.8, 118.3, 21.6. IR (KBr): 3235, 2551, 1573, 1468, 1378, 1336, 1164, 1089, 922, 808, 733, 679 cm^{-1} . Mp. 93.8–94.3 °C. TLC: R_f 0.25 (hexane/EtOAc = 2:1). HRMS Calcd for $\text{C}_{13}\text{H}_{12}\text{BrNO}_2\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 355.9420. Found: m/z 355.9425.

Characterization of Product

(*R*)-2-Phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3a).

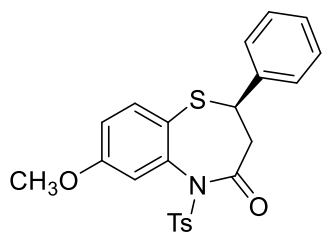
 From (*E*)-**1a**: 95% yield (58.1 mg), 97% *ee*.
From (*Z*)-**1a**: 75% yield (46.1 mg), 97% *ee*.
White solid. $[\alpha]_{\text{D}}^{18} -246.7$ (c 0.68, CH_2Cl_2). ¹H NMR (CDCl_3) δ 7.91 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.64–7.60 (m, 2H), 7.49 (d, J = 7.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.25–7.23 (m, 3H), 6.93 (d, J = 7.5 Hz, 1H), 6.92 (d, J = 5.5 Hz, 1H), 4.43 (dd, J = 11.0, 7.0 Hz, 1H), 2.76 (d, J = 11.0 Hz, 1H), 2.76 (d, J = 7.0 Hz, 1H), 2.48 (s, 3H). ¹³C NMR (CDCl_3) δ 169.2, 145.2, 142.2, 140.3, 136.9, 135.5, 130.5, 130.2, 130.0, 129.6, 129.1, 128.8, 127.9, 127.5, 125.9, 50.5, 42.4, 21.8. Mp. 144.5–145.5 °C. TLC: R_f 0.26 (hexane/EtOAc = 3:1). IR (KBr): 2363, 1712, 1366, 1286, 1172, 1129, 1086, 924, 843, 765 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{20}\text{NO}_3\text{S}_2$: $[\text{M}+\text{H}]^+$, 410.0879. Found: m/z 410.0877. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 15.5 min, t_{major} = 18.6 min.

7-Methyl-2-phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3b).

Yield: 94% (59.9 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -260.9$ (*c* 0.92, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.59 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 (m, 2H), 7.22–7.21 (m, 2H), 6.92 (m, 2H), 4.38 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.73 (d, *J* = 12.0 Hz, 1H), 2.72 (d, *J* =

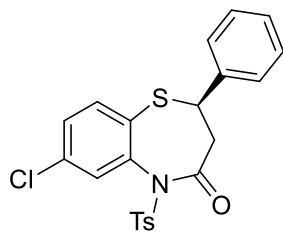
6.5 Hz, 1H), 2.51 (s, 3H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 169.4, 145.1, 142.6, 140.9, 140.0, 136.6, 131.2, 130.8, 130.5, 129.6, 129.0, 128.8, 127.8, 125.9, 123.9, 50.6, 42.5, 21.8, 21.3. Mp. 150.8–151.8 °C. TLC: *R*_f 0.36 (hexane/EtOAc = 3:1). IR (KBr): 3029, 2344, 1710, 1599, 1362, 1169, 1086, 829, 683 cm⁻¹. HRMS Calcd for C₂₃H₂₁NO₃S₂Na: [M+Na]⁺, 446.0855. Found: *m/z* 446.0848. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 8.5 min, *t*_{major} = 10.5 min.

7-Methoxy-2-phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3c).

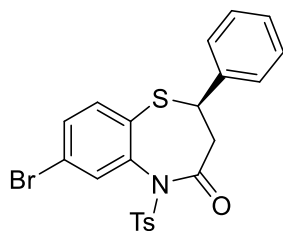
Yield: 79% (52.0 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -278.1$ (*c* 0.80, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.33–7.31 (m, 3H), 7.24–7.21 (m, 3H), 7.00 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.92–6.89 (m, 2H), 4.35 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.94

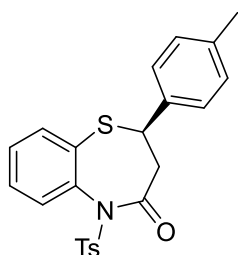
(s, 3H), 2.73 (d, *J* = 11.0 Hz, 1H), 2.72 (d, *J* = 7.0 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 169.4, 145.2, 142.2, 141.4, 137.6, 135.4, 129.6, 129.1, 128.8, 128.6, 127.8, 127.3, 125.9, 116.2, 116.0, 55.8, 50.9, 42.4, 21.8. Mp. 79.5–80.5 °C. TLC: *R*_f 0.36 (hexane/EtOAc = 3:1). IR (KBr): 3007, 2362, 1713, 1596, 1276, 1363, 1174, 1085, 1029, 814, 709 cm⁻¹. HRMS Calcd for C₂₃H₂₁NO₄S₂Na: [M+Na]⁺, 462.0804. Found: *m/z* 462.0783. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 11.3 min, *t*_{major} = 14.2 min.

7-Chloro-2-phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3d).

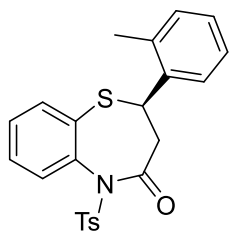
Yield: 85% (56.6 mg), 89% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -271.1$ (*c* 0.83, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.24–7.23 (m, 3H), 6.90 (m, 2H), 4.42 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.75 (d, *J* = 7.5 Hz, 1H), 2.75 (d, *J* = 10.5 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 168.8, 145.4, 142.0, 141.2, 137.5, 136.0, 135.3, 130.7, 130.1, 129.6, 129.2, 128.9, 128.1, 126.0, 125.8, 50.6, 42.2, 21.8. Mp. 210.1–210.8 °C. TLC: *R*_f 0.37 (hexane/EtOAc = 3:1). IR (KBr): 3084, 2362, 1711, 1356, 1166, 1128, 767, 698, 677, 652 cm⁻¹. HRMS Calcd for C₂₂H₁₈ClNO₃S₂Na: [M+Na]⁺, 466.0309. Found: *m/z* 466.0302. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 8.6 min, *t*_{major} = 9.8 min.

7-Bromo-2-phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3e).

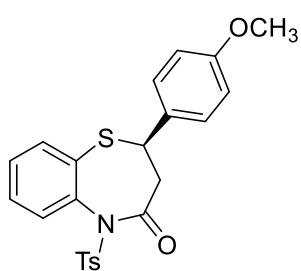
Yield: 87% (63.7 mg), 90% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -223.0$ (*c* 0.74, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.94 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.59 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.26–7.23 (m, 3H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.89 (d, *J* = 7.0 Hz, 1H), 4.44 (dd, *J* = 10.0, 8.0 Hz, 1H), 2.75 (d, *J* = 8.0 Hz, 1H), 2.74 (d, *J* = 10.0 Hz, 1H), 2.47 (s, 3H). ¹³C NMR (CDCl₃) δ 168.8, 145.4, 142.0, 141.2, 137.7, 135.2, 133.5, 133.0, 129.6, 129.1, 18.9, 128.1, 126.6, 125.8, 123.8, 50.5, 42.2, 21.8. Mp. 195.0–196.0 °C. TLC: *R*_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 3061, 2362, 1714, 1570, 1452, 1387, 1362, 1242, 1171, 1127, 1086, 814, 759, 707, 675 cm⁻¹. HRMS Calcd for C₂₂H₁₈BrNO₃S₂Na: [M+Na]⁺, 509.9804. Found: *m/z* 509.9795. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 8.9 min, *t*_{major} = 10.3 min.

2-(4-Methylphenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3f).

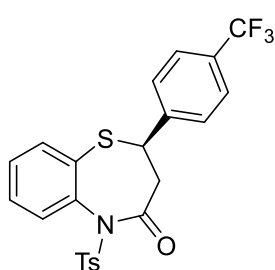
Yield: 82% (52.0 mg), 98% *ee*, white solid. $[\alpha]_D^{18} -264.5$ (*c* 0.86, CH₂Cl₂).
¹H NMR (CDCl₃) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.79 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.63–7.59 (m, 2H), 7.47 (dt, *J* = 8.5, 1.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 4.46 (dd, *J* = 12.0, 6.5 Hz, 1H), 2.75 (d, *J* = 12.0 Hz, 1H), 2.73 (d, *J* = 6.5 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H). ¹³C NMR (CDCl₃) δ 169.2, 145.1, 140.2, 139.5, 137.7, 136.9, 135.5, 130.5, 130.1, 129.9, 129.6, 129.4, 129.0, 127.5, 125.7, 50.3, 42.4, 21.7, 21.0. Mp. 84.7–85.2 °C. TLC: R_f 0.34 (hexane/EtOAc = 3:1). IR (KBr): 2967, 1712, 1596, 1465, 1437, 1363, 1170, 1086, 814, 669 cm⁻¹.
¹. HRMS Calcd for C₂₃H₂₁NO₃S₂Na: [M+Na]⁺, 446.0855. Found: *m/z* 446.0844. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 15.2 min, *t*_{major} = 17.4 min.

2-(2-Methylphenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3g).

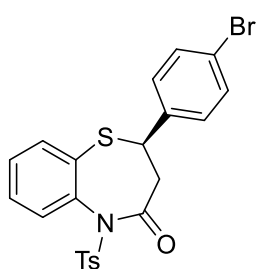
Yield: 76% (48.6 mg), 94% *ee*, white solid. $[\alpha]_D^{18} -280.0$ (*c* 1.00, CH₂Cl₂).
¹H NMR (CDCl₃) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.80 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.61 (dt, *J* = 7.5, 2.0 Hz, 1H), 7.49–7.42 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.13–7.09 (m, 2H), 7.02 (m, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 4.70 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.82 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.63 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.47 (s, 3H), 2.27 (s, 3H). ¹³C NMR (CDCl₃) δ 169.5, 145.1, 140.4, 139.7, 137.2, 135.6, 134.4, 130.7, 130.4, 130.2, 129.8, 129.5, 129.1, 127.6, 127.2, 126.2, 124.5, 46.1, 41.0, 21.8, 19.5. Mp. 175.1–176.1 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 2967, 1709, 1462, 1437, 1171, 1088, 760, 668 cm⁻¹.
 HRMS Calcd for C₂₃H₂₁NO₃S₂Na: [M+Na]⁺, 446.0855. Found: *m/z* 446.0845. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 6.2 min, *t*_{major} = 7.8 min.

2-(4-Methoxyphenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3h).

Yield: 78% (51.4 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -213.0$ (*c* 0.81, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.62–7.57 (m, 2H), 7.46 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.82 (m, 2H), 6.75 (m, 2H), 4.40 (dd, *J* = 11.0, 7.0 Hz, 1H), 3.75 (s, 3H), 2.71 (d, *J* = 11.0 Hz, 1H), 2.71 (d, *J* = 7.0 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 169.2, 159.1, 145.1, 140.2, 136.9, 135.5, 134.7, 130.5, 130.1, 129.9, 129.6, 129.0, 127.5, 127.0, 114.0, 55.2, 50.2, 42.6, 21.8. Mp. 79.5–80.5 °C. TLC: *R*_f 0.23 (hexane/EtOAc = 3:1). IR (KBr): 2960, 1713, 1596, 1512, 1363, 1254, 1170, 1030, 668 cm⁻¹. HRMS Calcd for C₂₃H₂₂NO₄S₂: [M+H]⁺, 440.0985. Found: *m/z* 440.0975. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 10.4 min, *t*_{major} = 16.2 min.

5-Tosyl-2-(4-(trifluoromethyl)phenyl)-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3i).

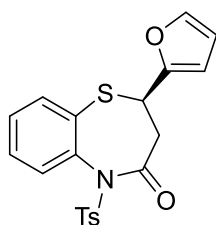
Yield: 86% (61.7 mg), 98% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -238.5$ (*c* 0.87, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.80 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.63 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.50–7.47 (m, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 7.5 Hz, 2H), 4.46 (dd, *J* = 9.5, 8.0 Hz, 1H), 2.73 (d, *J* = 8.0 Hz, 1H), 2.73 (d, *J* = 9.5 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 168.7, 146.1, 145.3, 140.3, 136.8, 135.8, 135.4, 130.7, 130.6, 130.4, 130.1 (q, *J* = 32.1 Hz), 129.6, 129.1, 126.3, 125.8 (q, *J* = 3.4 Hz), 123.7 (q, *J* = 272.1 Hz), 49.8, 42.0, 21.8. ¹⁹F NMR (CDCl₃) δ 99.1. Mp. 81.8–82.8 °C. TLC: *R*_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 2966, 1716, 1405, 1439, 1358, 1327, 1167, 1103, 1068, 834, 678 cm⁻¹. HRMS Calcd for C₂₃H₁₈F₃NO₃S₂Na: [M+Na]⁺, 500.0572. Found: *m/z* 500.0558. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 7.9 min, *t*_{major} = 14.6 min.

2-(4-Bromophenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3j).

Yield: 99% (77.5 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -236.8$ (*c* 0.76, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.78 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.62 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.56 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.47 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.77 (d, *J* = 8.0 Hz, 2H), 4.38 (dd, *J* = 11.0, 7.0 Hz, 1H), 2.70 (d, *J* = 7.0 Hz, 1H), 2.69

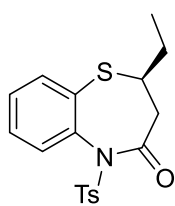
(d, *J* = 11.0 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 168.8, 145.2, 141.3, 140.2, 136.8, 131.9, 130.6, 130.43, 130.39, 130.0, 129.6, 129.1, 127.6, 127.0, 121.7, 49.8, 42.1, 21.8. Mp. 88.7–89.7 °C. TLC: *R*_f 0.31 (hexane/EtOAc = 3:1). IR (KBr): 2967, 1715, 1488, 1465, 1437, 1356, 1164, 1088, 1009, 824, 677 cm⁻¹. HRMS Calcd for C₂₂H₁₈BrNO₃S₂Na: [M+Na]⁺, 509.9804. Found: *m/z* 509.9794. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 9.6 min, *t*_{major} = 16.3 min.

2-(Furan-2-yl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3k).

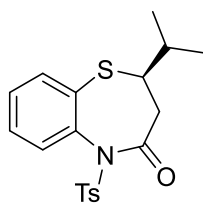
Yield: 78% (46.9 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -331.2$ (*c* 0.77, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.75 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.60–7.56 (m, 1H), 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.41 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.25 (dd, *J* = 2.0, 1.0 Hz, 1H), 6.21 (dd, *J* = 3.5, 2.0

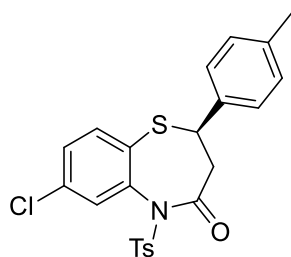
Hz, 1H), 5.83 (d, *J* = 3.5 Hz, 1H), 4.49 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.78 (dd, *J* = 8.0, 6.0 Hz, 1H), 2.65 (t, *J* = 12.0 Hz, 1H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 168.8, 153.3, 145.2, 142.4, 140.2, 137.3, 135.3, 130.4, 130.3, 129.8, 129.6, 129.1, 127.2, 110.3, 105.8, 43.8, 39.7, 21.8. Mp. decomposition. TLC: *R*_f 0.26 (hexane/EtOAc = 3:1). IR (KBr): 2967, 1714, 1596, 1465, 1439, 1363, 1289, 1170, 1086, 1010, 905, 732, 668 cm⁻¹. HRMS Calcd for C₂₀H₁₇NO₄S₂Na: [M+Na]⁺, 422.0991. Found: *m/z* 422.0980. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 12.0 min, *t*_{major} = 16.9 min.

2-Ethyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3l).

Yield: 96% (51.8 mg), 93% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -142.4$ (*c* 0.79, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.53 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.40 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 3.14 (m, 1H), 2.55 (dd, *J* = 12.0, 6.0 Hz, 1H), 2.43 (s, 3H), 2.06 (dd, *J* = 12.0, 12.0 Hz, 1H), 1.34 (m, 2H), 0.87 (t, *J* = 7.0 Hz, 3H). ¹³C NMR (CDCl₃) δ 170.0, 144.9, 140.5, 137.1, 135.5, 130.3, 129.9, 129.6, 129.5, 129.0, 127.2, 49.9, 41.6, 29.7, 21.7, 11.3. Mp. 36.8–37.8 °C. TLC: *R*_f 0.40 (hexane/EtOAc = 3:1). IR (KBr): 2955, 1718, 1598, 1467, 1440, 1366, 1166, 1141, 1085, 893, 761, 676 cm⁻¹. HRMS Calcd for C₁₈H₂₀NO₃S₂: [M+H]⁺, 362.0879. Found: *m/z* 362.0868. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 11.2 min, *t*_{major} = 15.3 min.

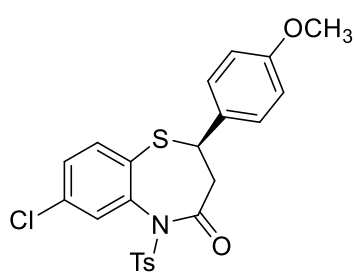
2-Isopropyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3m).

Yield: 99% (57.8 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -171.1$ (*c* 0.95, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.84 (d, *J* = 8.5 Hz, 2H), 7.68 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.64 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.51 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.39 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 3.06 (m, 1H), 2.53 (dd, *J* = 12.5, 5.0 Hz, 1H), 2.43 (s, 3H), 2.23 (dd, *J* = 12.5, 12.5 Hz, 1H), 1.57 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H). ¹³C NMR (CDCl₃) δ 170.4, 144.9, 140.3, 136.9, 135.5, 130.1, 129.65, 129.59, 129.54, 129.0, 128.1, 54.8, 39.5, 21.7, 19.5, 19.3. Mp. 106.8–107.8 °C. TLC: *R*_f 0.31 (hexane/EtOAc = 3:1). IR (KBr): 2962, 1714, 1596, 1465, 1438, 1363, 1171, 1087, 903, 668 cm⁻¹. HRMS Calcd for C₁₉H₂₂NO₃S₂: [M+H]⁺, 376.1036. Found: *m/z* 376.1024. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 9.8 min, *t*_{major} = 15.7 min.

7-Chloro-2-(*p*-tolyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3n).

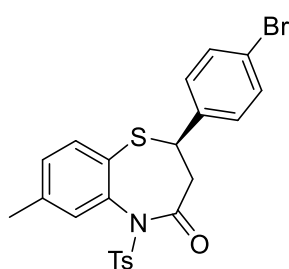
Yield: 74% (50.7 mg), 92% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -262.5$ (*c* 1.00, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 4.40 (t, *J* = 8.5 Hz, 1H), 2.73 (d, *J* = 8.5 Hz, 2H), 2.46 (s, 3H), 2.29 (s, 3H).

¹³C NMR (CDCl₃) δ 168.8, 145.4, 141.1, 139.1, 138.0, 137.5, 135.9, 135.2, 130.6, 130.0, 129.6, 129.5, 129.1, 126.1, 125.7, 50.5, 42.2, 21.8, 21.0. Mp. 88.8–89.8 °C. TLC: *R*_f 0.40 (hexane/EtOAc = 3:1). IR (KBr): 2968, 2921, 1717, 1576, 1457, 1394, 1363, 1260, 1171, 1127, 1086, 1000, 815, 677, 655 cm⁻¹. HRMS Calcd for C₂₃H₂₀ClNO₃S₂Na: [M+Na]⁺, 480.0465. Found: *m/z* 480.0455. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 8.5 min, *t*_{major} = 9.8 min.

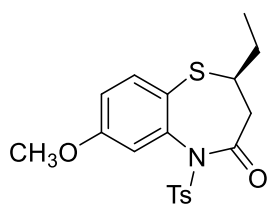
7-Chloro-2-(4-methoxyphenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3o).

Yield: 73% (52.1 mg), 91% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -254.7$ (*c* 1.06, CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.87 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 4.40 (dd, *J* = 10.5, 7.5 Hz, 1H), 3.75 (s, 3H), 2.72 (d, *J* = 10.5 Hz, 1H), 2.72 (d, *J* = 7.5 Hz, 1H), 2.46 (s, 3H).

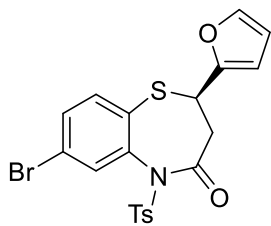
¹³C NMR (CDCl₃) δ 168.8, 159.2, 145.4, 141.1, 137.5, 135.9, 135.2, 134.2, 130.6, 130.0, 129.6, 129.1, 127.0, 126.1, 114.1, 55.2, 50.3, 42.3, 21.8. Mp. 80.0–80.5 °C. TLC: *R*_f 0.26 (hexane/EtOAc = 3:1). IR (KBr): 2967, 1717, 1576, 1512, 1457, 1394, 1362, 1252, 1171, 1128, 1032, 830, 814, 677, 656 cm⁻¹. HRMS Calcd for C₂₃H₂₀ClNO₄S₂Na: [M+Na]⁺, 496.0414. Found: *m/z* 496.0404. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 12.3 min, *t*_{major} = 13.7 min.

2-(4-Bromophenyl)-7-methyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3p).

Yield: 95% (71.5 mg), 97% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -302.6$ (*c* 0.95, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.59 (m, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.35 (m, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.26 (m, 2H), 7.18 (m, 2H), 4.33 (dd, *J* = 10.0, 9.0 Hz, 1H), 2.68 (d, *J* = 10.0 Hz, 1H), 2.68 (d, *J* = 9.0 Hz, 1H), 2.51 (s, 3H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 169.0, 145.1, 141.4, 141.2, 140.0, 136.5, 135.4, 131.8, 131.2, 130.9, 129.6, 129.0, 127.6, 123.4, 121.6, 49.8, 42.1, 21.7, 21.3. Mp. 93.2–94.2 °C. TLC: *R*_f 0.40 (hexane/EtOAc = 3:1). IR (KBr): 2921, 1715, 1599, 1487, 1359, 1254, 1166, 1088, 1008, 823, 812, 688, 656 cm⁻¹. HRMS Calcd for C₂₃H₂₀BrNO₃S₂Na: [M+Na]⁺, 523.9960. Found: *m/z* 523.9949. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 10.5 min, *t*_{major} = 12.4 min.

2-Ethyl-7-methoxy-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3q).

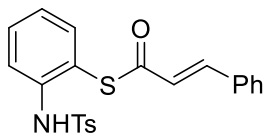
Yield: 94% (55.0 mg), 93% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -136.2$ (*c* 1.12, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.83 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 7.5, 2.5 Hz, 1H), 3.89 (s, 3H), 3.06 (m, 1H), 2.53 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.43 (s, 3H), 2.03 (dd, *J* = 7.0, 6.0 Hz, 1H), 1.31 (m, 2H), 0.85 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (CDCl₃) δ 170.2, 160.6, 144.9, 141.6, 137.6, 135.5, 129.6, 128.9, 118.0, 115.80, 115.76, 55.8, 50.2, 41.7, 29.4, 21.7, 11.3. Mp. 143.6–144.6 °C. TLC: *R*_f 0.29 (hexane/EtOAc = 3:1). IR (KBr): 2966, 2934, 1714, 1596, 1472, 1362, 1244, 1173, 1085, 1028, 895, 813, 711, 685, 654 cm⁻¹. HRMS Calcd for C₁₉H₂₁NO₄S₂Na: [M+Na]⁺, 414.0804. Found: *m/z* 414.0787. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 10.5 min, *t*_{major} = 11.3 min.

7-Bromo-2-(furan-2-yl)-5-tosyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (3r).

Yield: 70% (50.7 mg), 91% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -344.5$ (*c* 0.82, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.91 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.54 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.25 (m, 1H), 6.21 (dd, *J* = 3.0, 1.5 Hz, 1H), 5.86 (d, *J* = 3.0 Hz, 1H), 4.49

(dd, *J* = 12.5, 6.0 Hz, 1H), 2.80 (dd, *J* = 12.5, 6.0 Hz, 1H), 2.65 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 168.4, 152.9, 145.4, 142.5, 141.1, 138.1, 135.1, 133.2, 133.0, 129.6, 129.1, 126.1, 123.9, 110.3, 106.0, 43.8, 39.6, 21.8. Mp. 93.2–94.2 °C. TLC: *R*_f 0.51 (hexane/EtOAc = 3:1). IR (KBr): 1723, 1595, 1569, 1387, 1355, 1282, 1167, 1128, 1084, 1011, 992, 839, 740, 680, 655 cm⁻¹. HRMS Calcd for C₂₀H₁₆BrNO₄S₂Na: [M+Na]⁺, 499.9596. Found: *m/z* 499.9582. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 8.5 min, *t*_{major} = 9.8 min.

(*E*)-S-(2-(4-Methylphenylsulfonamido)phenyl) 3-phenylprop-2-enethioate (4a).

White solid. ¹H NMR (CDCl₃) δ 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.64–7.61 (m, 3H), 7.57 (m, 2H), 7.47–7.41 (m, 4H), 7.34 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.21–7.18 (m, 3H), 7.15 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H),

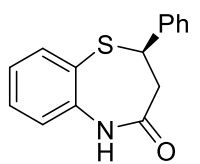
2.36 (s, 3H). ¹³C NMR (CDCl₃) δ 186.2, 144.0, 143.2, 138.8, 136.8, 136.0, 133.5, 131.6, 131.3, 129.6, 129.1, 128.7, 127.3, 125.5, 123.0, 121.9, 118.6, 21.6. Mp. 139.2–140.2 °C. TLC: *R*_f 0.31 (hexane/EtOAc = 3:1). IR (KBr): 3280, 1685, 1620, 1482, 1396, 1337, 1161, 1090, 1031, 911, 766, 667 cm⁻¹. HRMS Calcd for C₂₂H₂₀NO₃S₂: [M+H]⁺, 410.0879. Found: *m/z* 410.0877.

Procedure for synthesis of thiazesim

To a solution of SmI₂ (10 mL, 0.10 M, 1.0 mmol) in THF was added **3a** (69.6 mg, 0.17 mmol) followed by H₂O (54 μ L, 3.0 mmol) and triethylamine (0.28 mL, 2.0 mmol), and the mixture was stirred under argon atmosphere for 30 min. The resulting mixture was diluted with Et₂O (10 mL) and washed with saturated aqueous NaHCO₃ (10 mL $\times$ 3). The organic layers were washed with

brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 1/1) as an eluent gave the detosylated product **7**.

(R)-2-Phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (7) : CAS RN [119873-04-0].

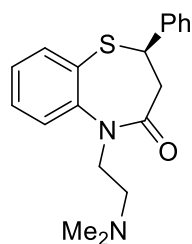


Yield: 64% yield (27.6 mg), 96% *ee*, white solid. $[\alpha]_D^{18} -448.4$ (*c* 0.63, CHCl₃).
¹H NMR (CDCl₃) δ 7.80 (brs, 1H), 7.67 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.43 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.34–7.23 (m, 6H), 7.16 (d, *J* = 7.5 Hz, 1H), 4.88 (dd, *J* = 11.5, 5.5 Hz, 1H), 2.89 (dd, *J* = 12.5, 11.5 Hz, 1H), 2.81 (dd, *J* = 12.5, 5.5 Hz, 1H). ¹³C NMR (CDCl₃) δ 171.9, 143.4, 141.2, 135.9, 130.2, 128.8, 127.8, 126.8, 126.6, 126.4, 123.2, 53.1, 41.4. TLC: R_f 0.38 (hexane/EtOAc = 1:1). HRMS Calcd for C₁₅H₁₄NOS: [M+H]⁺, 278.0610. Found: *m/z* 278.0606. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{major} = 5.9 min, *t*_{minor} = 8.5 min.

The absolute configuration of **7** was assigned as (*R*) by comparing the optical rotation with the literature value.¹⁴

$[\alpha]_D^{18} -448.4$ (*c* 0.63, CHCl₃) [lit.¹⁴ (*R*)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (98% *ee*): $[\alpha]_D^{25} -519.9$ (*c* 0.63, CHCl₃)].

To a solution of (*R*)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**7**, 30.6 mg, 0.12 mmol) in EtOAc (1.0 mL) was added 2-dimethylaminoethylchloride hydrochloride (34.6 mg, 0.24 mmol), followed by K₂CO₃ (66.3 mg, 0.48 mmol) and H₂O (10 μ L). After the mixture was stirred for 12 h under reflux, it was cooled to ambient temperature. The organic layers were washed with H₂O (5 mL $\times$ 2) and brine. The combined organic layers were dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using CHCl₃/MeOH (v/v = 10/1) as an eluent gave thiazesim (**8**).

(*R*)-5-(2-(Dimethylamino)ethyl)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(*5H*)-one (8).

Yield: 92% yield (35.9 mg), 97% *ee*, colorless oil. $[\alpha]_{\text{D}}^{18} -416.7$ (*c* 0.33, CHCl₃)

¹H NMR (CDCl₃) δ 7.62 (d, *J* = 7.5 Hz, 1H), 7.51–7.46 (m, 2H), 7.27–7.14 (m, 4H), 7.14–7.10 (m, 2H), 4.78 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.33–4.26 (m, 1H), 3.66 (m, 1H), 2.82–2.65 (m, 3H), 2.37 (m, 1H), 2.24 (s, 6H). ¹³C NMR (CDCl₃) δ

170.4, 146.4, 143.9, 136.3, 130.4, 128.7, 127.64, 127.58, 127.2, 126.1, 124.7, 56.3, 52.8, 47.5, 45.7, 41.9. TLC: *R*_f 0.36 (CHCl₃/MeOH = 10:1). HRMS Calcd for C₁₉H₂₃N₂OS: [M+H]⁺, 327.1526. Found: *m/z* 327.1521. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{major} = 8.0 min, *t*_{minor} = 9.8 min.

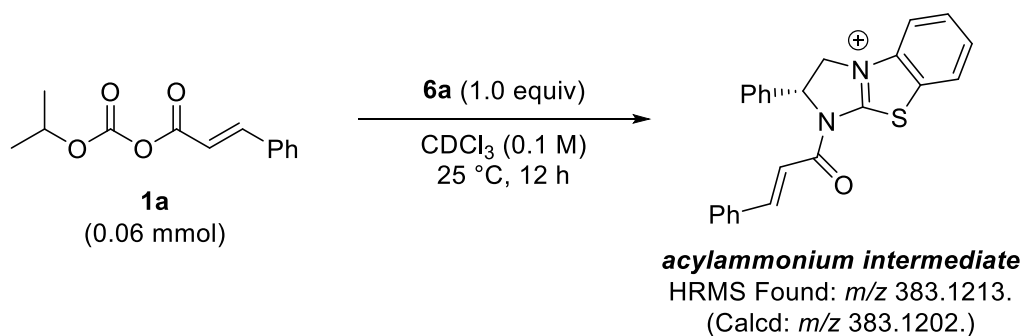
The absolute configuration of **8** was assigned as (*R*) by comparing the optical rotation with the literature value.¹⁴

$[\alpha]_{\text{D}}^{18} -416.7$ (*c* 0.33, CHCl₃) [lit.¹⁴ (*R*)-5-(2-(dimethylamino)ethyl)-2-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(*5H*)-one (99% *ee*): $[\alpha]_{\text{D}}^{18} -468.3$ (*c* 0.36, CHCl₃)].

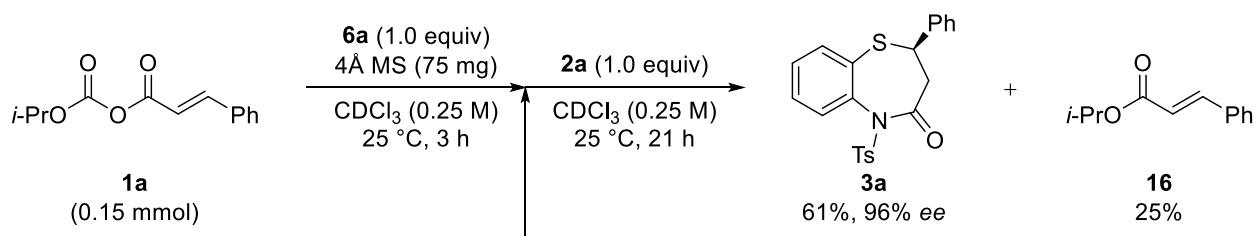
Supplemental Data**Table 3.** The Effects of Concentration^a

entry	conc. (M)	yield of 3a (%) ^b	ee of 3a (%)
1	0.5	59	97
2	1.0	57	97

^aReactions were run using **1a** (0.15 mmol), **2a** (0.15 mmol), and the catalyst (0.0075 mmol) in CHCl₃. ^bIsolated yields.

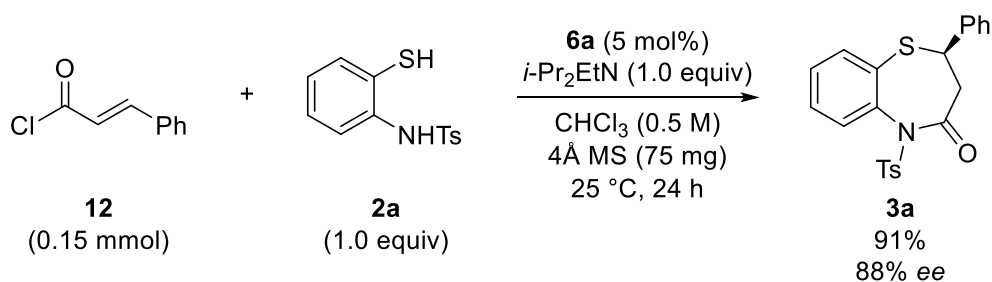


Scheme 5. HRMS analysis of the solution of **1a** in the presence of a stoichiometric amount of **6a**.

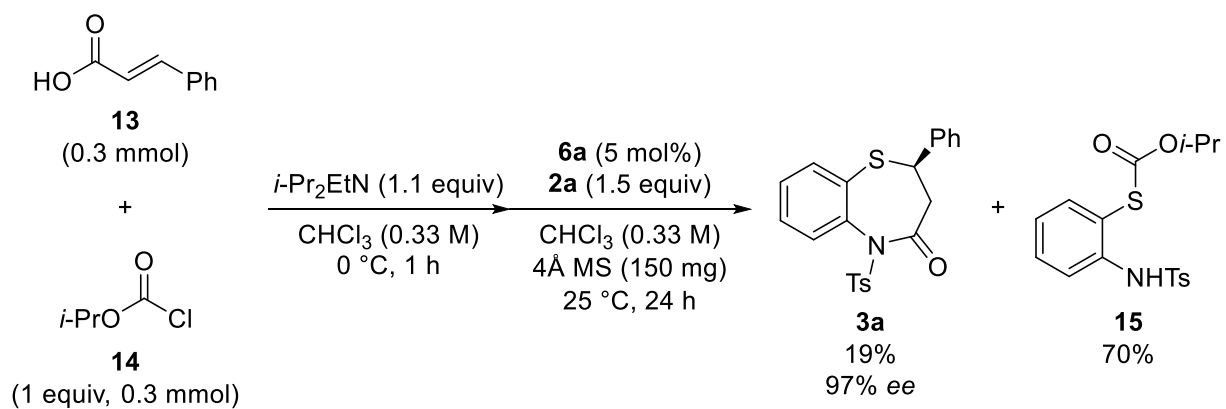


The formation of the acylammonium intermediate was confirmed by the NMR analyses (Figures 2 and 3).

Scheme 6. Reaction of the acylammonium intermediate prepared by stoichiometric reaction.



Scheme 8. Net [4+3] formal cycloaddition reaction using α,β -unsaturated carboxylic acid chloride.



Scheme 9. Net [4+3] formal cycloaddition reaction through the in-situ generation of carbonic anhydride using α,β -unsaturated carboxylic acid.

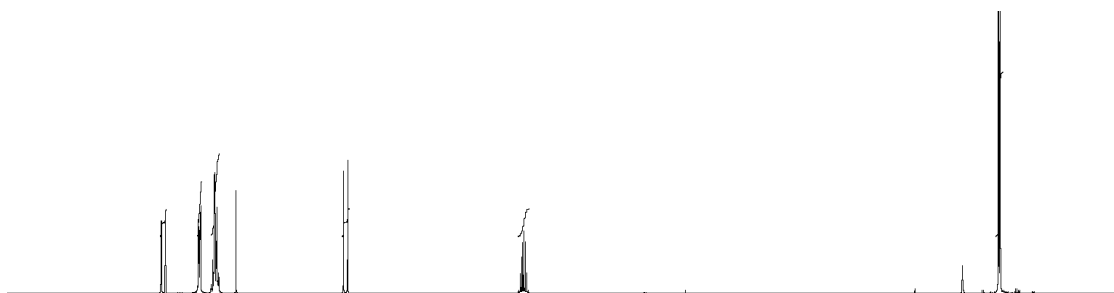
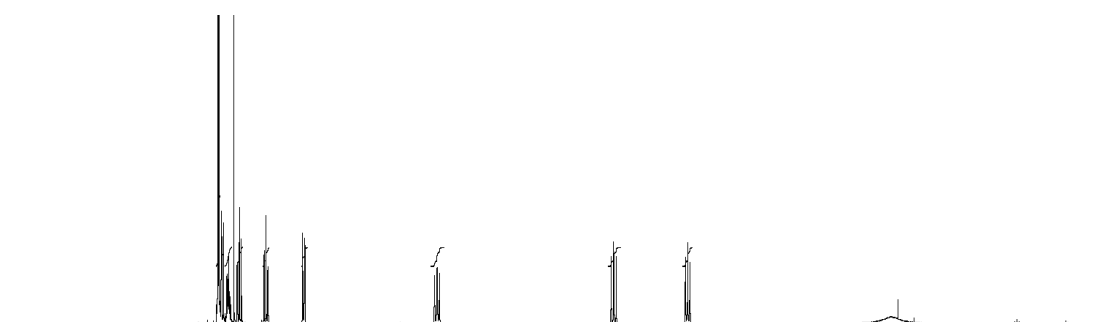
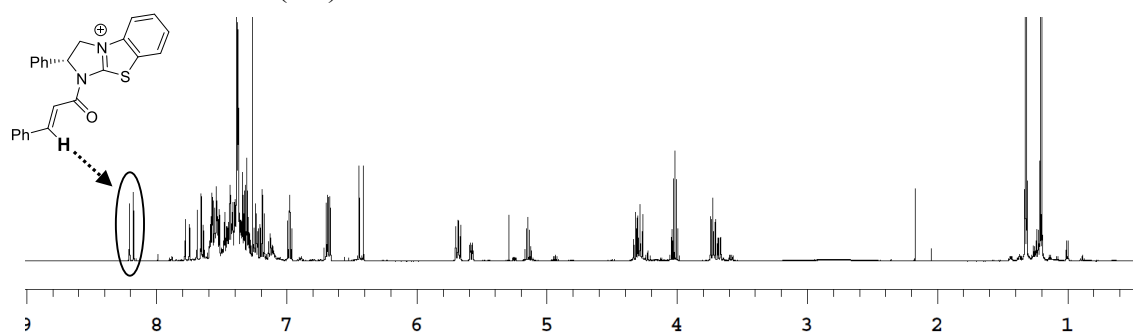
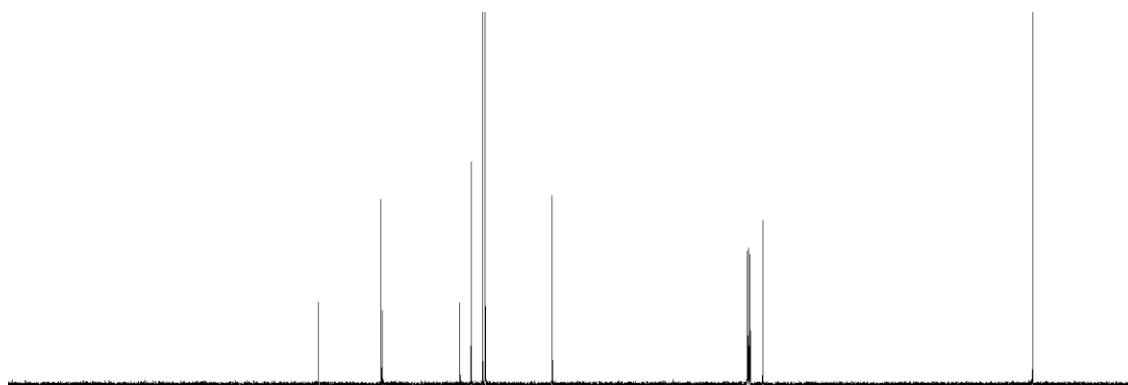
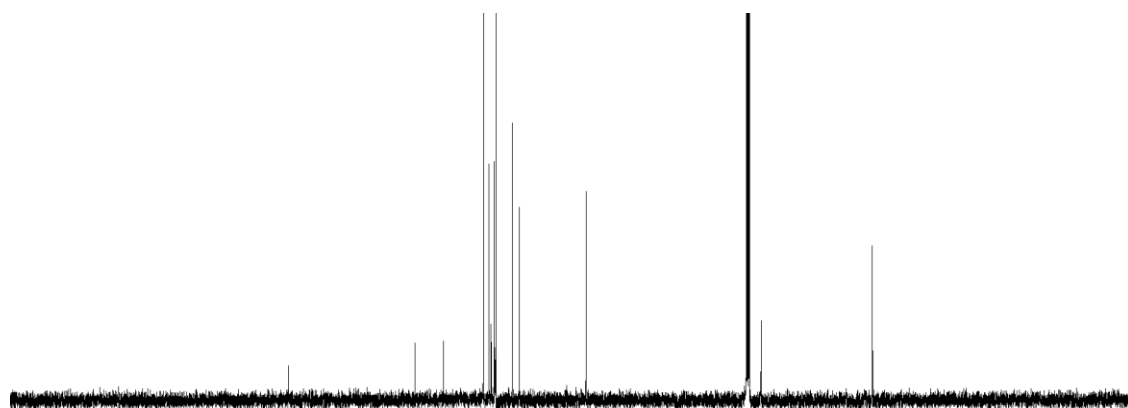
(a) α,β -unsaturated substrate **1a**(b) catalyst **6a**(c) mixture of **1a** and **6a** (1:1)

Figure 2. Independent ^1H NMR spectra of (a) α,β -unsaturated substrate **1a** and (b) catalyst **6a** and the spectra of (c) their 1:1 mixture (0.1 M, CDCl_3 , ambient temperature).

(a) α,β -unsaturated substrate **1a**



(b) catalyst **6a**



(c) mixture of **1a** and **6a** (1:1)

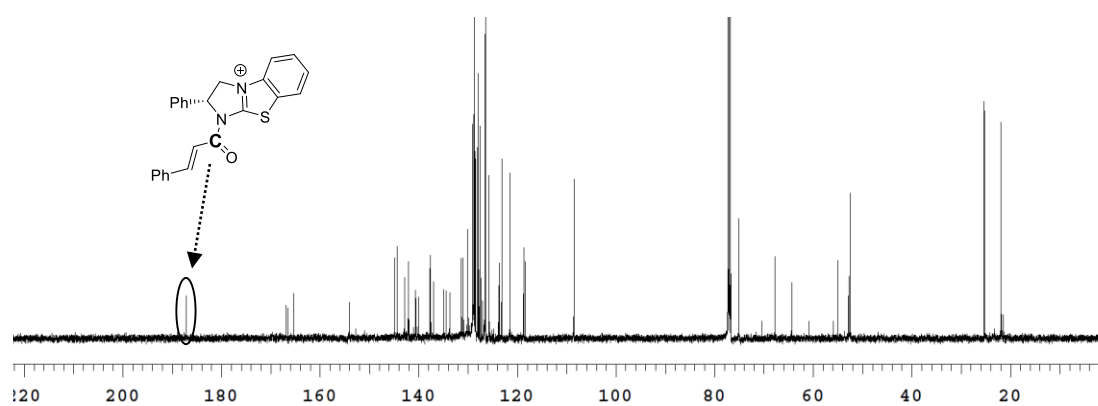
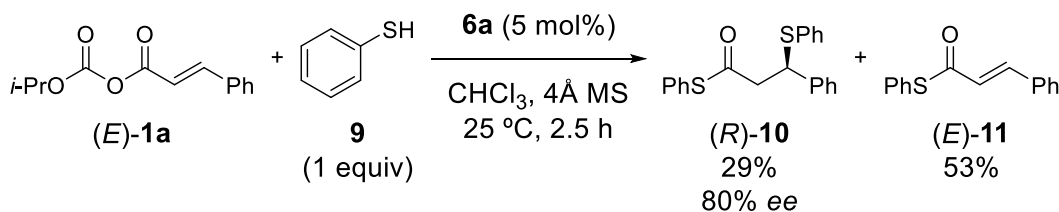
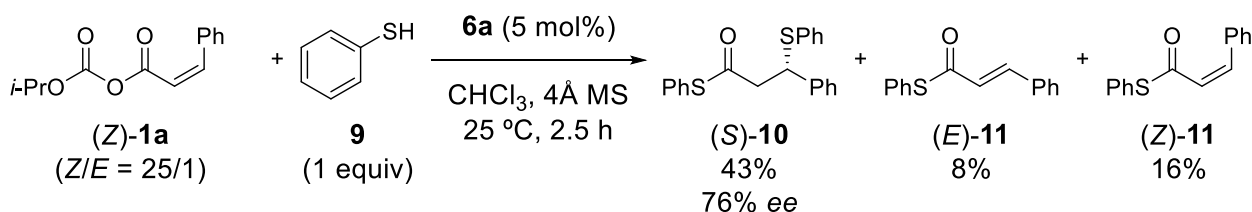


Figure 3. Independent ^{13}C NMR spectra of (a) α,β -unsaturated substrate **1a** and (b) catalyst **6a** and the spectra of (c) their 1:1 mixture (0.1 M, CDCl_3 , ambient temperature).

Scheme 7. Reactions of benzenethiol **9** with (*E*)- and (*Z*)-**1a** in the presence of **6a****a****b****Procedure for reactions of benzenethiol and α,β -unsaturated carbonic anhydrides**

To a 5-mL vial were added sequentially α,β -unsaturated carbonic anhydride **1a** (0.15 mmol), CHCl_3 (0.3 mL), 4Å MS (75 mg), benzotetramisole catalyst **6a** (0.0075 mmol), and benzenethiol **9** (0.15 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 2.5 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 20/1), passed through a short silica gel pad to remove **6a**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent afforded the mixture of **10** and **11**.

The absolute configuration of **10** obtained in the reaction of Scheme S2 (a) was assigned as (*R*), and that of Scheme S2 (b) was assigned as (*S*) by comparing the optical rotation with the literature value.

10 of Scheme S2 (a): $[\alpha]_{\text{D}}^{18} +19.9$ (*c* 3.40, CH_2Cl_2)

10 of Scheme S2 (b): $[\alpha]_{\text{D}}^{18} -21.6$ (*c* 3.41, CH_2Cl_2)

[lit.¹³ 73% ee, (*R*)-S-phenyl 3-phenyl-3-(phenylthio)propanethioate: $[\alpha]_{\text{D}}^{25} +43.5$ (*c* 3.47, CH_2Cl_2)].

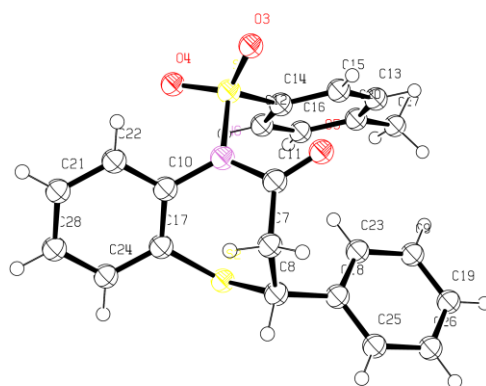


Figure 4. ORTEP drawing of **3a** ($\text{C}_{22}\text{H}_{19}\text{NO}_3\text{S}_2$, $M = 409.52$, $T = 293(0)$ K).

Wavelength	Mo-K α ($\lambda = 0.71075$ Å)
Crystal System	orthorhombic
Space Group	$P2_12_12$ (#18)
Crystal Dimensions	$0.460 \times 0.440 \times 0.200$ mm
Unit cell dimensions	$a = 12.4202(10)$ Å $\alpha = 90^\circ$ $b = 18.5765(15)$ Å $\beta = 90^\circ$ $c = 8.4080(7)$ Å $\gamma = 90^\circ$
Volume	$V = 1939.9(3)$ Å ³
Z value	4
D_{calc}	1.402 g/cm ³
$2\theta_{\text{max}}$	55.0°
Reflections collected	19465
Independent reflections	4431 [$R_{\text{int}} = 0.0154$]
No. Variables	253
Goodness of Fit Indicator	1.077
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0218$
R indices (all data)	$R_1 = 0.0221$, $wR_2 = 0.0609$
Flack Parameter	0.01(4)

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4. Fukata, Y.; Okamura, T.; Asano, K.; Matsubara, S. *Org. Lett.* **2014**, *16*, 2184.
5. For seminal works on isothioureia catalysts, see: (a) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (b) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (c) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347. For a review, see: Taylor, J. E.; Bull, S. D.; Williams, J. M. *J. Chem. Soc. Rev.* **2012**, *41*, 2109.
6. Although the corresponding acid chloride could be used as a substrate, the enantioselectivity was slightly lower in a preliminary study (91% yield, 88% ee, and see Scheme 8). In addition, the generation of the anhydride in situ from the corresponding carboxylic acid was also investigated, but the yield was much lower despite the comparable enantioselectivity (19% yield, 97% ee, and see Scheme 9).
7. The presence of intramolecular nonbonded S $\cdots$ O interaction has been recognized, see: (a) Minkin, V. I.; Minyaev, R. M. *Chem. Rev.* **2001**, *101*, 1247. (b) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104. (c) Brameld, K. A.; Kuhn, B.; Reuter, D. C.; Stahl, M. *J. Chem. Inf. Model.* **2008**, *48*, 1. For discussions on attractive no to $\sigma^*\text{C-S}$ interaction between the acylammonium oxygen and the sulfur atom of isothioureia catalysts, see refs 3b, d, e, and the following: (d) Birman, V. B.; Li, X.; Han, Z.

- Org. Lett.* **2007**, *9*, 37. (e) Leverett, C. A.; Purohit, V. C.; Romo, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 9479. (f) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. *Org. Lett.* **2012**, *14*, 3288.
8. The presence of cation- π interaction between the acylammonium cation generated by isothiurea catalysts and an aryl group in substrates was suggested in literature on the basis of computational and experimental studies, see ref 8f and the following: Belmessieri, D.; Joannesse, C.; Woods, P. A.; MacGregor, C.; Jones, C.; Campbell, C. D.; Johnston, C. P.; Duguet, N.; Concellón, C.; Bragg, R. A.; Smith, A. D. *Org. Biomol. Chem.* **2011**, *9*, 559.
 9. Since the reaction rate was not affected by the concentration (see Table 3), the intramolecular cyclization step is considered to be the rate-determining step.
 10. Birman, V. B.; Li, X. *Org. Lett.* **2008**, *10*, 1115.
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 13. Zhao, B.-L.; Du, D.-M. *Org. Biomol. Chem.* **2014**, *12*, 1585.
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Chapter 5

Isothiourea-Catalyzed Enantioselective Formal [4+3] Cycloaddition Affording 3-Substituted 1,5-Benzothiazepines

The organocatalytic enantioselective formal [4+3] cycloaddition of α -substituted α,β -unsaturated carboxylic acid anhydrides with 2-aminothiophenols was reported. Mechanistic studies suggest that this reaction proceeds via sulfa-Michael addition to α,β -unsaturated acylammonium intermediates followed by enantioselective cyclization, enabling the facile and divergent synthesis of optically active 3-substituted 1,5-benzothiazepines by formal cycloaddition. This process was demonstrated to be highly versatile, affording the corresponding products in excellent regioselectivities and high enantioselectivities. Furthermore, this process enabled the synthesis of chiral 2,3-disubstituted 1,5-benzothiazepine. Hence, this protocol can be applied for constructing a library of important pharmaceutical candidates.

Introduction

It is of significance to develop a novel synthetic method for constructing privileged heterocyclic scaffolds for drug discovery; several efforts have been devoted toward this goal in the past decade.¹ Currently, 1,5-benzothiazepines are known to be important skeletons, attributed to the fact that they exhibit several biological activities in the central nervous system as well as other therapeutic actions; furthermore, they are among the most widely used medicines for the treatment of cardiovascular disease (Figure 1).^{2,3} Hence, it is imperative to develop methods for the facile and divergent synthesis of these derivatives with the aim of supporting assay evaluation. Although a few catalytic asymmetric synthetic methods have been reported by the multi-step construction of such derivatives,⁴ a single-step approach has not been well established.

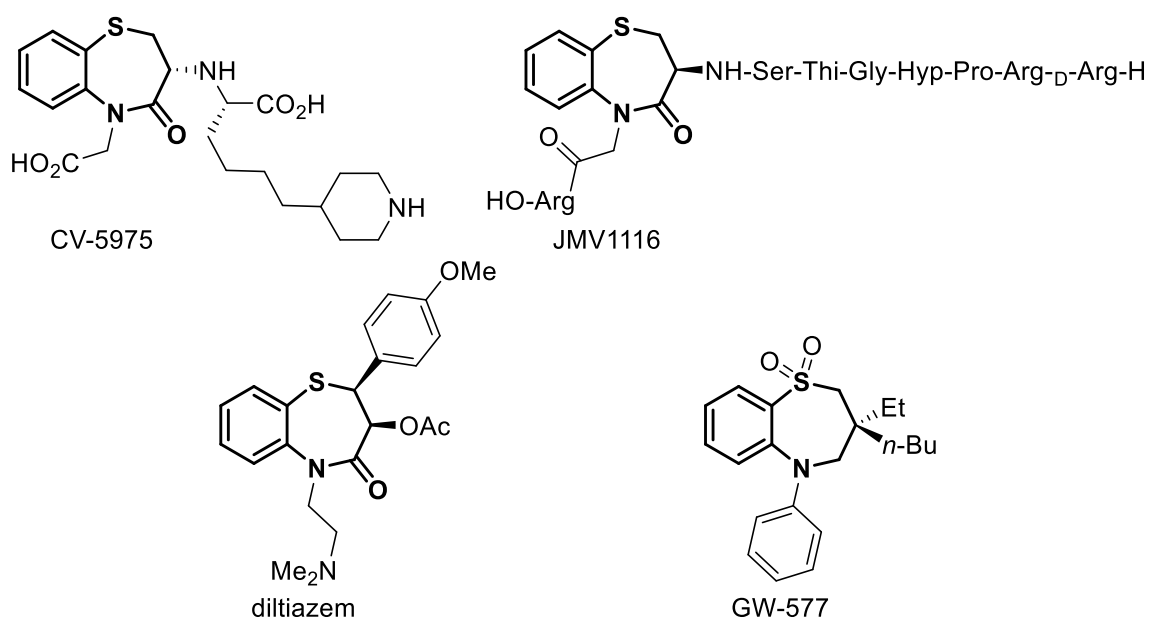
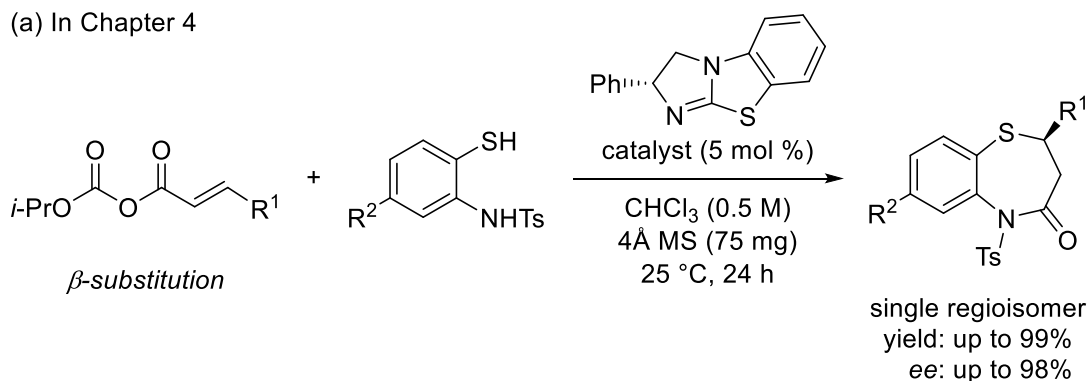


Figure 1. Representative pharmaceutical compounds containing the optically active 1,5-benzothiazepine moiety.

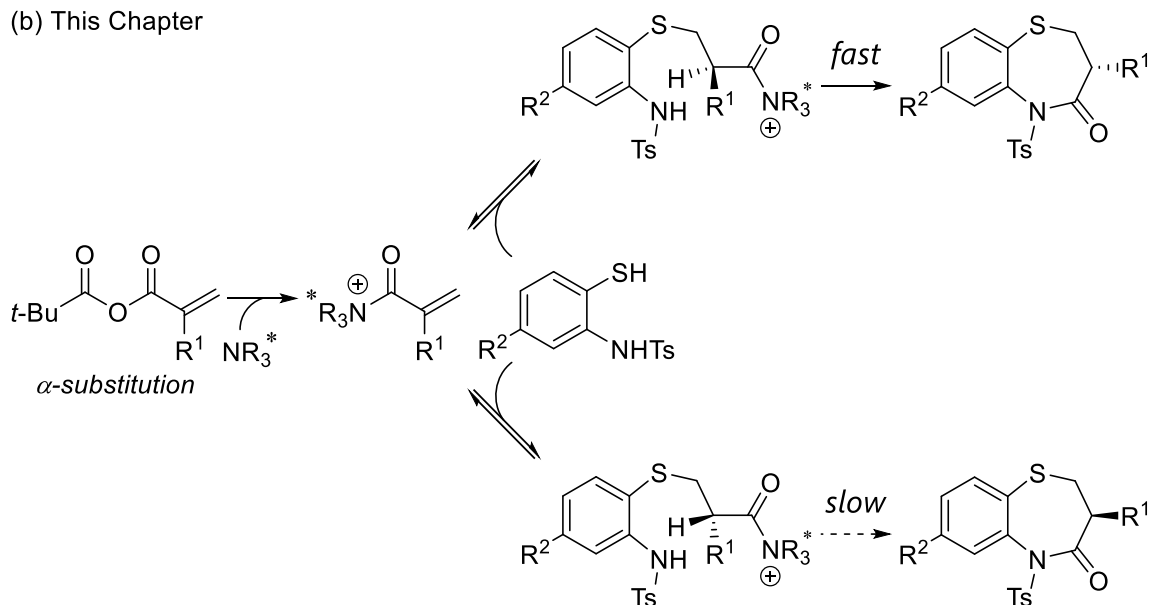
In Chapter 4, the author described a highly regio- and enantioselective net [4+3] cycloaddition approach for constructing optically active 2-substituted 1,5-benzothiazepines via α,β -unsaturated

acylammonium intermediates (Scheme 1, a).^{5,6} Mechanistic studies revealed the sulfa-Michael addition of 2-aminothiophenol to the acylammonium intermediate is reversible, and subsequent intramolecular amidation is the stereo-determining step. This process can be referred to as dynamic kinetic asymmetric transformation.⁷ The results obtained from that study have encouraged us to utilize this strategy despite the fact that a chiral center cannot be generated at the β -position by the Michael addition. Here, the author report a facile approach for net cycloaddition using a chiral isothiurea-catalyst for constructing optically active 3-substituted 1,5-benzothiazepines (Scheme 1, b).

(a) In Chapter 4



(b) This Chapter



Scheme 1. Organocatalytic enantioselective syntheses of optically active 1,5-benzothiazepines via net [4+3] cycloaddition reactions.

Results and Discussion

First, the author examined several leaving groups on the α -substituted α,β -unsaturated carboxylic acid derivatives for generating the α,β -unsaturated acylammonium intermediate in the presence of chiral isothioureia catalyst **5a**, and Table 1 shows the results.⁸ The reaction of α,β -unsaturated mixed anhydride **1a** with 2-aminothiophenol **2a**, catalyst **5a**, and 4Å molecular sieves in CHCl_3 at 25 °C afforded the desired 3-substituted 1,5-benzothiazepine **3a** in 80% yield with 76% *ee* (entry 1). Carbonic anhydride **1b** was also investigated; however, it did not work well even with increasing reaction temperature (entries 2 and 3). In addition, other leaving groups were not efficient (entry 4–6).

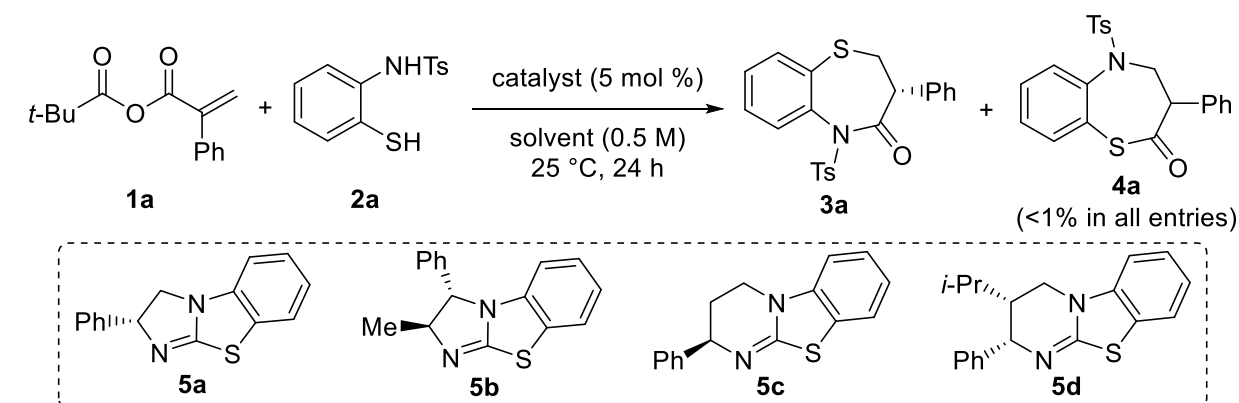
Table 1. Screening of leaving groups^a

entry	R (1)	yield of 3a (%) ^b	<i>ee</i> of 3a (%)
1	<i>t</i> -BuC(O) (1a)	80	76
2	<i>i</i> -PrOC(O) (1b)	trace	—
3 ^c	<i>i</i> -PrOC(O) (1b)	28	75
4	2,4,6-Me ₃ C ₆ H ₂ C(O) (1c)	23	55
5	2,6-Cl ₂ C ₆ H ₃ C(O) (1d)	17	22
6	(CF ₃) ₂ CH (1e)	<1	—

^aReactions were run using **1** (0.15 mmol), **2a** (0.15 mmol), **5a** (0.0075 mmol), 4Å MS (75 mg), and CHCl_3 (0.3 mL). ^bIsolated yields. ^cReaction was run at 40 °C.

With the optimized substrate **1a** in hand, the author next screened the reaction conditions. (Table 2). The addition of molecular sieves was detrimental for the success of cycloaddition, with respect to enantioselectivity (entries 1 and 2). While screening the catalyst in toluene at 25 °C, the use of 6-membered ring-fused isothiourea catalyst **5d** was crucial for accessing the practical chemical yield of **3a**, with only a slight decrease of the enantiomeric excess (entries 2–5).⁹ Among the solvents examined, less polar solvents such as benzene and toluene were more effective, affording high enantioselectivities (entries 5–9). The use of 1.2 equivalent of aminothiophenol **2a** further improved enantioselectivity (entry 10). Subsequently, the reaction temperature was optimized: the reaction performed better at 25 °C, which resulted in a practical yield with high enantioselectivity (entries 10–12).¹⁰

Table 2. Reaction Optimization^a



entry	catalyst	solvent	yield of 3a (%) ^b	ee of 3a (%)
1 ^c	5a	toluene	25	88
2	5a	toluene	25	88
3	5b	toluene	74	–33
4	5c	toluene	63	–84
5	5d	toluene	73	86
6	5d	benzene	59	86
7	5d	CH ₂ Cl ₂	69	77

Table2. (continued)

8	5d	CHCl ₃	67	73
9	5d	EtOAc	63	79
10 ^d	5d	toluene	69	90
11 ^{d,e}	5d	toluene	57	91
12 ^{d,f}	5d	toluene	15	82

^aReactions were run using **1a** (0.15 mmol), **2a** (0.15 mmol), the catalyst (0.0075 mmol), and the solvent (0.3 mL). ^bIsolated yields. ^cReaction was run in the presence of 4Å MS (75 mg).

^dReactions were run using 1.2 equivalent of **2a** (0.18 mmol). ^eReaction was run at 15 °C.

^fReaction was run at 0 °C.

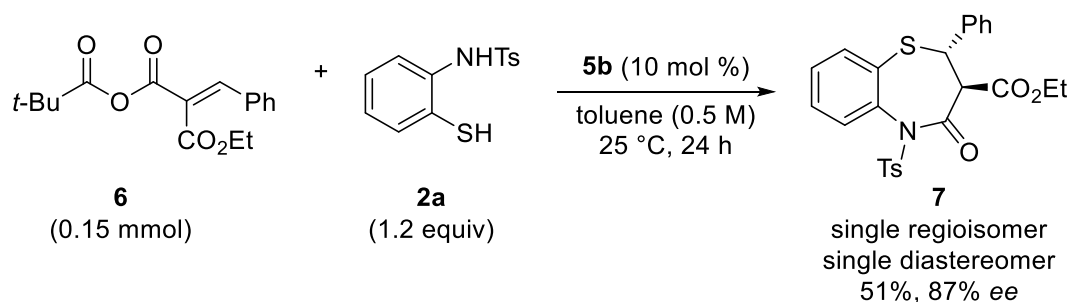
With these optimized conditions, the substrate scope of the asymmetric net [4+3] cycloaddition reactions was investigated (Table 3). Reactions using electron-rich aminothiophenols afforded the corresponding 1,5-benzothiazepines in high enantioselectivities (**3a–3e**). The reactions of various α -substituted α,β -unsaturated carboxylic acid mixed anhydrides **1** was also investigated. The electronic and steric characteristics of the aryl substituents of substrates **1** did not significantly affect the enantioselectivity, affording **3f–3k** in good yields. Substrates bearing aliphatic substituents were also tolerated, affording **3l–3n** in moderate yields and high enantioselectivities.¹¹ Moreover, other combinations of α,β -unsaturated carbonyl substrates **1** and 2-aminothiophenols **2** also afforded the corresponding products **3o–3q** in good yields and enantioselectivities.

Furthermore, in the presence of catalyst **5b**, the use of α,β -disubstituted conjugated mixed anhydride **6** afforded the corresponding 2,3-disubstituted 1,5-benzothiazepine **7** as a single regioisomer and diastereomer in 51% yield with 87% *ee* (Scheme 2).¹² These results, along with the Chapter 4,⁵ demonstrated that this cycloaddition protocol is potentially useful for constructing a library of optically active 1,5-benzothiazepines with various substitution patterns. X-ray analysis was employed for determining the absolute configurations of **3a** and **7** (see the Experimental Section for details), and the configurations of all other examples were assigned analogously.

Table 5-3. Substrate scope^a

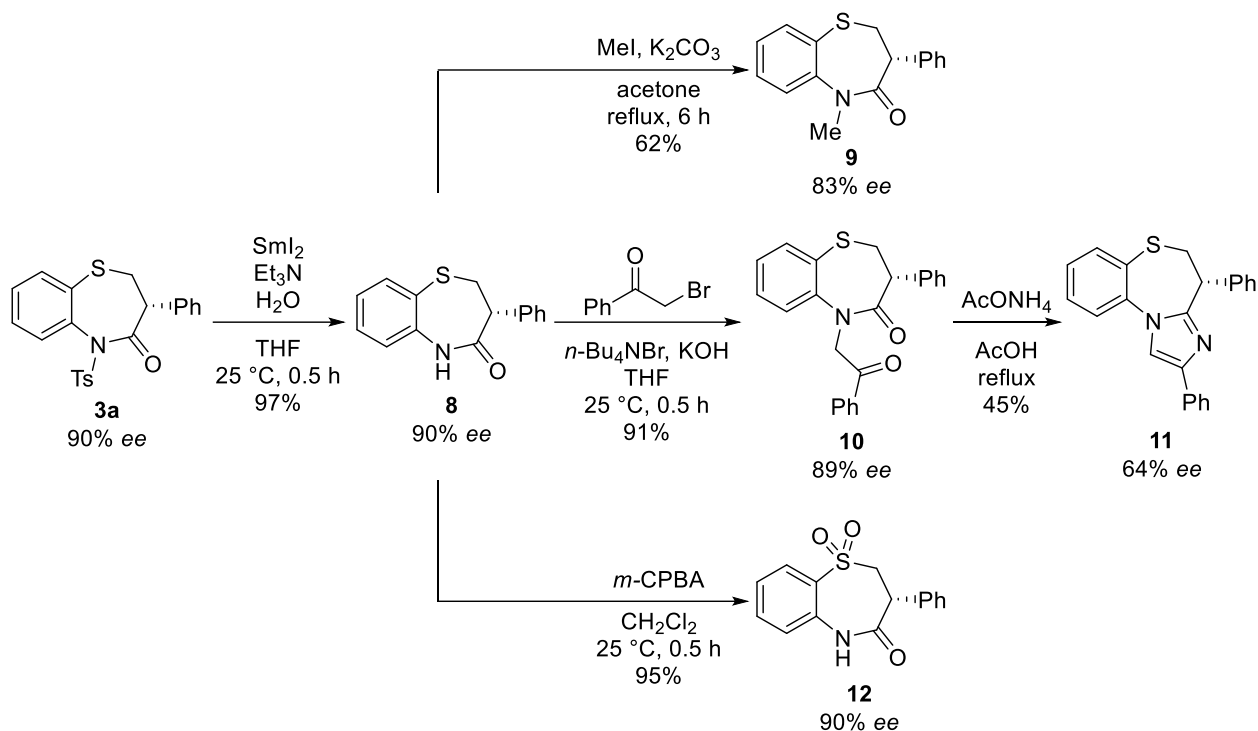
1	2
3	
Products^b	
R = H (3a): 69%, 90% <i>ee</i> R = Me (3b) ^c : 67%, 86% <i>ee</i> R = OCH ₃ (3c) ^c : 67%, 86% <i>ee</i> R = Cl (3d) ^c : 71%, 73% <i>ee</i> R = Br (3e) ^c : 90%, 65% <i>ee</i>	
R = Me (3f): 56%, 87% <i>ee</i> R = OCH ₃ (3g): 56%, 87% <i>ee</i> R = Cl (3h): 70%, 94% <i>ee</i> R = Br (3k): 94%, 95% <i>ee</i>	
3i	
76%, 94% <i>ee</i>	
3j	
60%, 87% <i>ee</i>	
3l	
39%, 90% <i>ee</i>	
3m	
56%, 81% <i>ee</i>	
3n	
49%, 84% <i>ee</i>	
3o^c	
61%, 96% <i>ee</i>	
3p^c	
91%, 95% <i>ee</i>	
3q^c	
88%, 86% <i>ee</i>	

^aReactions were run using **1** (0.15 mmol), **2** (0.18 mmol), and **5d** (0.0075 mmol), in CHCl₃ (0.3 mL). ^bYields represent material isolated after silica gel column chromatography. ^cReactions were run using **1** (0.10 mmol), **2** (0.12 mmol), **5d** (0.005 mmol), and toluene (0.2 mL).



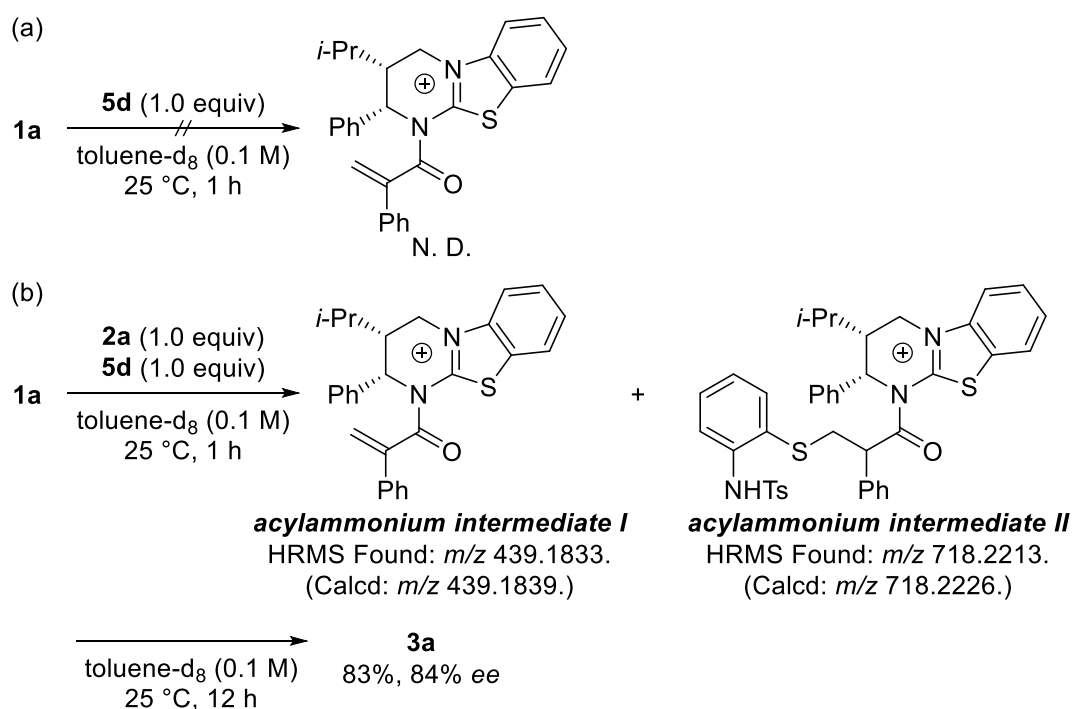
Scheme 2. Enantioselective synthesis of 2,3-disubstituted 1,5-benzothiazepine **7**.

For demonstrating the utility of the products obtained herein, derivatization of chiral 1,5-benzothiazepine **3a** was carried out (Scheme 3). The tosyl group was removed by treatment with samarium iodide,^{5,13} affording the corresponding unprotected 1,5-benzothiazepine **8** in 97% yield without the loss of optical purity. The subsequent methylation of **8** formed **9** in 62% yield, with a slight loss of optical purity. On the other hand, the alkylation of **8** with phenacyl bromide also formed the corresponding product **10** in 91% yield without the loss of enantiomeric purity. The alkylated product **10** was further transformed into chiral tricyclic compound **11**, the derivatives of which have attracted attention as bioactive compounds,^{2,14} in 45% yield, although the optical purity unfortunately decreased under the reaction conditions employed. In addition, under oxidative conditions, **8** was readily converted to corresponding sulfone **12** without the loss of enantiomeric purity, the derivatives of which are also observed in various bioactive compounds, in 95% yield.^{2,15}



Scheme 3. Synthetic transformations of **3a**.

For gaining insight into the reaction mechanism, a reaction between a 1:1 mixture of mixed anhydride **1a** and catalyst **5d** in toluene- d_8 was subjected to ^1H NMR analysis. The chemical shifts were unchanged under this condition (Scheme 4, a). On the other hand, after the addition of 1.0 equivalent of **2a** to this solution, the formation of α,β -unsaturated acylammonium intermediate **I** was clearly observed by HRMS (electrospray ionization in the positive mode). In addition, a signal corresponding to the presence of acylammonium intermediate **II** was also clearly observed.¹⁶ Furthermore, after stirring this mixture at 25 °C for an additional 12 h, chiral 1,5-benzothiazepine **3a** was obtained in 83% yield with 84% ee (Scheme 4, b). These results suggested that the generation of acylammonium intermediates **I** and **II** is induced by the addition of **2a**, and net cycloaddition occurs via these acylammonium intermediates.¹⁷



Scheme 4. Mechanistic studies.

Conclusion

In conclusion, the author developed the novel asymmetric net [4+3] cycloaddition of α,β -unsaturated mixed anhydrides with 2-aminothiophenols catalyzed by an isothioureia catalyst for synthesizing 3-substituted 1,5-benzothiazepines. This method could also be applied to the synthesis of 2,3-disubstituted 1,5-benzothiazepine. Along with the results obtained in Chapter 4,⁵ a wide range of 1,5-benzothiazepines were synthesized with excellent regioselectivities and good-to-excellent enantioselectivities by these cycloaddition reactions. Mechanistic studies suggested that the reaction proceeds by the Michael addition of sulfur-centered nucleophiles to chiral α,β -unsaturated acylammonium intermediates followed by intramolecular cyclization, which determines enantioselectivity. By this mechanism, this protocol can be applied for the divergent synthesis of 1,5-benzothiazepines with various substitution patterns; thus, this synthetic approach is expected to significantly contribute toward the construction of a library of 1,5-benzothiazepines.

Experimental Section

Materials.

Unless otherwise noted, commercially available reagents were used without purification. 2-amiothiophenols **2** were synthesized by method described in Chapter 4. The conjugated carboxylic acids were prepared by the literature procedure.¹⁸

General procedure for asymmetric cycloaddition of α,β -unsaturated carboxylic acid anhydrides with aminothiophenols

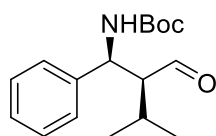
To a 5-mL vial were added sequentially α,β -unsaturated substrate **1** (0.15 mmol), toluene (0.3 mL), aminothiophenol **2** (0.18 mmol), and isothiourea catalyst **5d** (0.0075 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 24 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 3:1), passed through a short silica gel pad to remove **5d**, and concentrated in vacuo to give the crude 1,5-benzothiazepine **3** as a pale yellow solid. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent afforded the corresponding 1,5-benzothiazepines **3** as a white solid. Racemic compounds were prepared using racemic isothiourea catalyst **5a**.

Procedure for preparation of catalyst 5d^{9c}

Isothiourea catalyst **5d** was prepared by the literature procedure.^{9c} To a solution of 3-methylbutanal (1.6 mL, 15 mmol) in CH₃CN (65 mL) was added (*E*)-*tert*-butyl benzylidenecarbamate (1.5 g, 7.3 mmol). After the resulting solution was cooled to 0 °C, (*S*)-proline (0.17 g, 1.5 mmol) was added in one portion, and the solution was stirred overnight at 0 °C. The solution was treated with H₂O (25 mL) and allowed to warm to ambient temperature. The product was extracted with Et₂O (2 × 20 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to afford a colorless solid. The solid was then triturated with cold hexane to give *tert*-butyl (1*S*,2*S*)-2-formyl-3-methyl-1-

phenylbutylcarbamate (1.8 g, 86% yield).

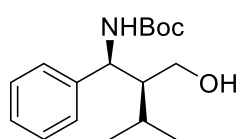
***tert*-Butyl (1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutylcarbamate:** CAS RN [926308-18-1].



Colorless solid. $[\alpha]_{\text{D}}^{18} -70.4$ (c 0.7, CHCl_3) [lit.^{9c} $[\alpha]_{\text{D}}^{20} -70.9$ (c 0.8, CHCl_3 , >99% *ee*)]. ^1H NMR (CDCl_3) δ 9.49 (d, $J = 4.5$ Hz, 1H), 7.33–7.22 (m, 5H), 5.10 (br s, 2H), 2.48 (m, 1H), 2.10 (m, 1H), 1.40 (s, 9H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.02 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 205.1, 154.9, 139.7, 128.8, 127.8, 127.2, 79.8, 62.0, 53.4, 28.3, 26.9, 21.1, 19.1.

To a solution of *tert*-butyl (1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutylcarbamate (1.8 g, 6.3 mmol) in methanol (50 mL) was added NaBH_4 (0.36 g, 9.5 mmol), and the mixture was stirred for 2 h. The reaction mixture was quenched with saturated aqueous NaHCO_3 (60 mL) and then concentrated in vacuo. The product was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give *tert*-butyl (1*S*,2*S*)-2-(hydroxymethyl)-3-methyl-1-phenylbutylcarbamate (1.6 g, 87% yield).

***tert*-Butyl (1*S*,2*S*)-2-(hydroxymethyl)-3-methyl-1-phenylbutylcarbamate:** CAS RN [1203506-99-3].



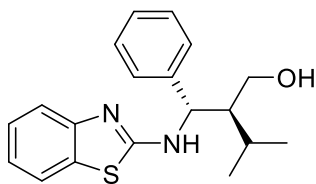
Colorless solid. $[\alpha]_{\text{D}}^{18} -28.6$ (c 0.7, CHCl_3) [lit.^{9c} $[\alpha]_{\text{D}}^{20} -26.7$ (c 0.7, CHCl_3)]. ^1H NMR (CDCl_3) δ 7.36–7.24 (m, 5H), 5.55 (d, $J = 8.5$ Hz, 1H), 5.03 (br s, 1H), 3.68 (br s, 1H), 3.48 (m, 1H), 2.19 (br s, 1H), 1.86 (br s, 1H), 1.68 (m, 1H), 1.42 (s, 9H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.85 (d, $J = 6.5$ Hz, 3H). ^{13}C NMR (CDCl_3) δ 155.8, 141.1, 128.5, 127.1, 126.8, 79.6, 60.9, 54.8, 51.3, 28.4, 26.3, 22.6, 19.0.

A solution of 4 M aqueous HCl in dioxane (15 mL, 60 mmol) was added to the *tert*-butyl (1*S*,2*S*)-2-(hydroxymethyl)-3-methyl-1-phenylbutylcarbamate (1.6 g, 5.5 mmol) and stirred at ambient temperature for 4 h. The reaction mixture was concentrated in vacuo to afford the crude product (1.4 g, 99% yield) as a colorless solid. It was used for the next step without further

purification.

To a solution of (*S*)-2-((*S*)-amino(phenyl)methyl)-3-methylbutan-1-ol hydrochloride (0.92 g, 4.0 mmol) in *i*-Pr₂EtN (1.3 mL, 7.5 mmol) was added 2-chlorobenzothiazole (0.5 mL, 4.0 mmol), and the mixture was heated at 135 °C for 3 d. After cooling, the reaction mixture was treated with CH₂Cl₂ (3.0 mL), and left at ambient temperature until the solid was dissolved completely. The diluted reaction mixture was applied directly to a chromatographic column and eluted with CH₂Cl₂/*i*-PrOH (v/v = 20:1) to afford (*S*)-2-((*S*)-benzothiazol-2-ylamino)(phenyl)methyl)-3-methylbutan-1-ol (1.1 g, 83% yield).

(*S*)-2-((*S*)-Benzothiazol-2-ylamino)(phenyl)methyl)-3-methylbutan-1-ol: CAS RN [1203507-01-1].

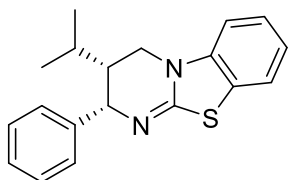


Orange solid. $[\alpha]_{\text{D}}^{18} -55.0$ (c 0.50, CHCl₃) [lit.^{9c} $[\alpha]_{\text{D}}^{20} -54.8$ (c 0.50, CHCl₃)]. ¹H NMR (CDCl₃) δ 8.19 (br s, 1H), 7.52–7.50 (m, 3H), 7.40 (d, $J = 7.5$ Hz, 1H), 7.33 (m, 2H), 7.28–7.22 (m, 2H), 7.02 (m, 1H), 5.30 (br s, 1H), 4.90 (m, 1H), 3.91 (dd, $J = 11.5, 4.0$ Hz, 1H), 3.66 (m, $J = 11.5$ Hz, 1H), 2.15 (m, 1H), 1.62 (sept, $J = 6.5$ Hz, 1H), 1.12 (d, $J = 6.5$ Hz, 3H), 0.78 (d, $J = 6.5$ Hz, 3H). ¹³C NMR (CDCl₃) δ 168.2, 151.4, 139.0, 129.8, 128.4, 128.1, 127.6, 125.9, 121.1, 120.8, 118.1, 61.9, 60.3, 50.8, 26.7, 22.6, 19.6.

Thionyl chloride (0.51 mL, 6.9 mmol) was added to the (*S*)-2-((*S*)-benzothiazol-2-ylamino)(phenyl)methyl)-3-methylbutan-1-ol (1.1 g, 3.3 mmol) in toluene (15 mL), and the reaction mixture was refluxed for 6 h. Then the mixture was cooled to ambient temperature and concentrated in vacuo to afford a brown solid. KOH (0.44 g, 7.8 mmol) and methanol (27 mL) were added to the resultant residue, and the solution was refluxed for 3 h. After cooling, the solution was poured into H₂O (10 mL) and extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude **5d**. Purification of the crude **5d** by flash silica gel column chromatography using

hexane/CH₂Cl₂ (v/v = 20:1) as an eluent afforded **5d** as a brown solid (0.44 g, 43% yield).

(2*S*,3*R*)-3-iso-Propyl-4-phenyl-3,4-dihydro-2*H*-pyrimido[2,1-*b*] benzothiazole (5d): CAS RN [1203507-02-1].

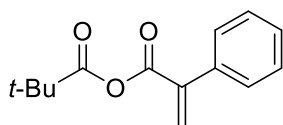


Enantiomeric excess was determined to be >99% *ee* by HPLC analysis (Daicel Chiralpak IA, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 6.1 min, t_{minor} = 7.5 min.

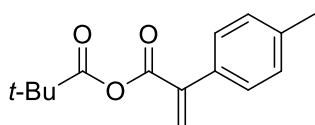
$[\alpha]_D^{18}$ +305.1 (*c* 0.68, CHCl₃) [lit.^{9c} $[\alpha]_D^{20}$ +288.4 (*c* 0.5, CHCl₃, >99% *ee*)]. ¹H NMR (CDCl₃) δ 7.35–7.30 (m, 3H), 7.27–7.22 (m, 4H), 7.05 (dt, *J* = 8.0, 0.5 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.94 (dd, *J* = 4.5, 1.5 Hz, 1H), 3.89 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 3.36 (t, *J* = 11.5 Hz, 1H), 1.96 (ddt, *J* = 11.0, 9.0, 5.0 Hz, 1H), 1.32 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (CDCl₃) δ 158.3, 140.6, 140.4, 128.3, 128.0, 127.1, 125.8, 123.0, 121.9, 121.8, 107.5, 61.2, 45.8, 40.8, 26.8, 21.9, 19.9. Mp. 156.5–158.0 °C. TLC: *R*_f 0.30 (hexane/*i*-PrOH = 20:1). IR (KBr): 2957, 2866, 1627, 1459, 1350, 1229, 1220, 766, 743, 708 cm⁻¹. HRMS Calcd for C₁₉H₂₁N₂S: [M+H]⁺, 309.1420. Found: *m/z* 309.1415.

General procedure for preparation of α,β -unsaturated mixed anhydrides **1 and **6****

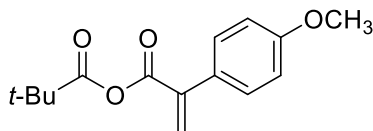
To a stirred solution of an α,β -unsaturated carboxylic acid (1.0 equiv) in CH₂Cl₂ (0.72 M) was slowly added *i*-Pr₂EtN (1.5 equiv) and pivaloyl chloride (1.0 equiv) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 5:1), passed through a short silica gel pad, and concentrated in vacuo to give the crude product. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 10:1) as an eluent gave the corresponding mixed anhydrides **1** and **6**.

2-phenylacrylic pivalic anhydride (1a): CAS RN [1396008-60-8].

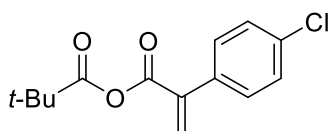
Colorless oil, 78% yield. ^1H NMR (CDCl_3) δ 7.44–7.42 (m, 2H), 7.38–7.37 (m, 3H), 6.45 (d, $J = 1.0$ Hz, 1H), 6.09 (d, $J = 1.0$ Hz, 1H), 1.26 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.9, 162.6, 140.9, 135.5, 129.9, 128.6, 128.3, 128.2, 40.0, 26.4.

2-(4-Methylphenyl)acrylic pivalic anhydride (1b).

Colorless oil, 33% yield. ^1H NMR (CDCl_3) δ 7.32 (m, 2H), 7.18 (m, 2H), 6.39 (d, $J = 0.5$ Hz, 1H), 6.06 (d, $J = 0.5$ Hz, 1H), 2.37 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.9, 162.7, 140.7, 138.6, 132.6, 129.2, 128.9, 128.2, 40.0, 26.5, 21.2. TLC: R_f 0.32 (hexane/EtOAc = 10:1). IR (KBr): 3431, 2977, 1805, 0735, 1479, 1367, 1041, 1008, 768, 731 cm^{-1} . HRMS Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na}$: $[\text{M}+\text{Na}]^+$, 269.1148. Found: m/z 269.1146.

2-(4-Methoxyphenyl)acrylic pivalic anhydride (1c).

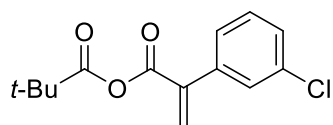
White solid, 84% yield. ^1H NMR (CDCl_3) δ 7.38 (m, 2H), 6.90 (m, 2H), 6.35 (d, $J = 1.0$ Hz, 1H), 6.03 (d, $J = 1.0$ Hz, 1H), 3.82 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (CDCl_3) δ 174.0, 162.9, 159.9, 140.2, 129.6, 128.4, 127.9, 113.6, 55.3, 40.0, 26.5. Mp. 35.4–36.0 $^\circ\text{C}$. TLC: R_f 0.21 (hexane/EtOAc = 10:1). IR (KBr): 2959, 1808, 1704, 1610, 1458, 1379, 1251, 1040, 1004 cm^{-1} . HRMS Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$: $[\text{M}+\text{Na}]^+$, 285.1097. Found: m/z 285.1094.

2-(4-Chlorophenyl)acrylic pivalic anhydride (1d).

Colorless oil, 59% yield. ^1H NMR (CDCl_3) δ 7.37 (m, 2H), 7.35 (m, 2H), 6.46 (d, $J = 0.5$ Hz, 1H), 6.09 (d, $J = 0.5$ Hz, 1H), 1.27 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.7, 162.2, 139.7, 134.7, 133.9, 130.2, 129.7, 128.4, 40.0, 26.4. TLC: R_f 0.28 (hexane/EtOAc = 10:1). IR (neat): 2978, 1805, 1735, 1492, 1397, 1088, 1040, 1018, 836 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{ClO}_3\text{Na}$: $[\text{M}+\text{Na}]^+$, 289.0602. Found:

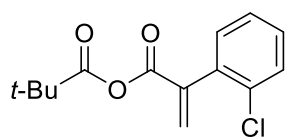
m/z 289.0597.

2-(3-Chlorophenyl)acrylic pivalic anhydride (1e).



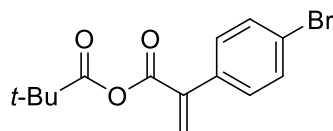
Colorless oil, 64% yield. ^1H NMR (CDCl_3) δ 7.43 (m, 1H), 7.34–7.30 (m, 3H), 6.94 (m, 1H), 6.11 (m, 1H), 1.26 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.6, 162.0, 139.6, 137.1, 134.1, 130.8, 129.5, 128.7, 128.5, 126.6, 40.0, 26.4. TLC: R_f 0.24 (hexane/EtOAc = 10:1). IR (neat): 3435, 2977, 1803, 1731, 1595, 1565, 1478, 1396, 1154, 1079, 1041, 1012, 794, 709 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{ClO}_3\text{Na}$: $[\text{M}+\text{Na}]^+$, 289.0602. Found: m/z 289.0597.

2-(2-Chlorophenyl)acrylic pivalic anhydride (1f).

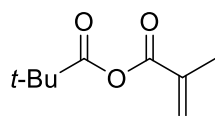


Colorless oil, 89% yield. ^1H NMR (CDCl_3) δ 7.40 (m, 1H), 7.32–7.28 (m, 3H), 6.66 (d, J = 1.0 Hz, 1H), 5.96 (d, J = 0.5 Hz, 1H), 1.11 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.3, 161.4, 139.6, 135.4, 133.4, 132.4, 131.0, 129.9, 129.2, 126.9, 39.9, 26.2. TLC: R_f 0.27 (hexane/EtOAc = 10:1). IR (neat): 2977, 1806, 1733, 1626, 1478, 1311, 1150, 1054, 1012, 908, 870, 767 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{ClO}_3\text{Na}$: $[\text{M}+\text{Na}]^+$, 289.0602. Found: m/z 289.0598.

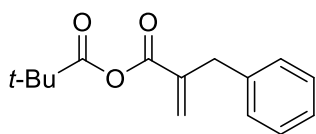
2-(4-Bromophenyl)acrylic pivalic anhydride (1g).



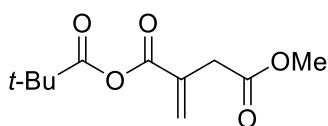
Colorless oil, 87% yield. ^1H NMR (CDCl_3) δ 7.50 (m, 2H), 7.31 (m, 2H), 6.47 (m, 1H), 6.10 (m, 1H), 1.27 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.7, 162.1, 139.8, 134.3, 131.4, 130.3, 130.0, 123.0, 40.0, 26.4. TLC: R_f 0.28 (hexane/EtOAc = 10:1). IR (neat): 2976, 1803, 1731, 1479, 1038, 1017, 833 cm^{-1} . HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{BrO}_3\text{Na}$: $[\text{M}+\text{Na}]^+$, 333.0097. Found: m/z 333.0091.

Methacrylic pivalic anhydride (1h): CAS RN [156491-92-8].

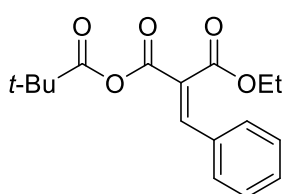
Colorless oil, 88% yield. ^1H NMR (CDCl_3) δ 6.17 (m, 1H), 5.79 (m, 1H), 1.98 (m, 3H), 1.29 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.9, 163.2, 136.0, 128.8, 40.0, 26.5, 17.9.

2-Benzylacrylic pivalic anhydride (1i).

Colorless oil, 98% yield. ^1H NMR (CDCl_3) δ 7.34 (m, 2H), 7.28–7.23 (m, 3H), 6.34 (m, 1H), 5.68 (m, 1H), 3.69 (m, 2H), 1.28 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.7, 162.7, 139.7, 137.7, 129.6, 128.9, 128.5, 126.5, 40.0, 37.4, 26.4. TLC: R_f 0.51 (hexane/EtOAc = 10:1). IR (neat): 2976, 1798, 1732, 1631, 1603, 1480, 1012, 739, 701 cm^{-1} . HRMS Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3\text{Na}$: $[\text{M}+\text{Na}]^+$, 269.1148. Found: m/z 269.1144.

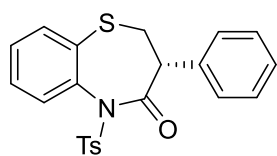
4-Methoxy-2-methylene-4-oxobutanoic pivalic anhydride (1j).

Colorless oil; 23% yield. ^1H NMR (CDCl_3) δ 6.40 (m, 1H), 5.92 (m, 1H), 3.69 (s, 3H), 3.36 (m, 2H), 1.27 (s, 9H). ^{13}C NMR (CDCl_3) δ 173.2, 170.5, 162.0, 133.3, 131.6, 52.2, 40.1, 36.9, 26.3. TLC: R_f 0.10 (hexane/EtOAc = 10:1). IR (neat): 2987, 1805, 1738, 1639, 1480, 1267, 1205, 1174, 1043, 1012, 736 cm^{-1} . HRMS Calcd for $\text{C}_{11}\text{H}_{16}\text{O}_5\text{Na}$: $[\text{M}+\text{Na}]^+$, 251.0890. Found: m/z 251.0887.

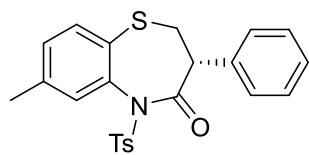
(E)-2-(ethoxycarbonyl)-3-phenylacrylic pivalic anhydride (6).

Colorless oil; 83% yield. ^1H NMR (CDCl_3) δ 7.83 (s, 1H), 7.49–7.41 (m, 5H), 4.34 (q, $J = 7.5$ Hz, 2H), 1.31 (t, $J = 7.5$ Hz, 3H), 1.30 (s, 9H). ^{13}C NMR (CDCl_3) δ 172.6, 165.7, 159.7, 145.8, 132.3, 131.4, 129.8, 125.1, 62.0, 40.2, 26.4, 13.9. TLC: R_f 0.37 (hexane/EtOAc = 5:1). IR (neat): 2979, 1805, 1733, 1622, 1480, 1380, 1219, 1174, 1055, 1012, 759, 690 cm^{-1} . HRMS Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_5\text{Na}$: $[\text{M}+\text{Na}]^+$, 327.1203. Found: m/z 327.1198.

Characterization Data of Products

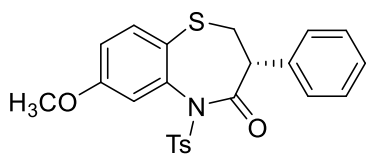
(R)-3-Phenyl-5-tosyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (3a).

Yield: 69% (42.5 mg), 90% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -212.3$ (*c* 0.53, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.87 (m, 2H), 7.78 (m, 1H), 7.71 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.60 (m, 1H), 7.48 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.31 (m, 2H), 7.27–7.25 (m, 3H), 7.21 (m, 2H), 3.70 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.30 (dd, *J* = 12.0, 6.5 Hz, 1H), 3.14 (dd, *J* = 12.5, 12.0 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 171.5, 144.9, 140.4, 136.0, 135.8, 134.9, 130.8, 130.2, 130.1, 129.7, 129.4, 129.1, 128.8, 128.4, 128.1, 46.7, 39.4, 21.8. Mp. 194.5–195.5 °C. TLC: *R*_f 0.47 (hexane/EtOAc = 2:1). IR (KBr): 2918, 1710, 1598, 1465, 1356, 1159, 1073, 917, 814, 758, 667 cm⁻¹. HRMS Calcd for C₂₂H₁₉NO₃S₂Na: [M+Na]⁺, 432.0699. Found: *m/z* 432.0688. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 14.1 min, *t*_{major} = 14.9 min.

7-Methyl-3-phenyl-5-tosyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (3b).

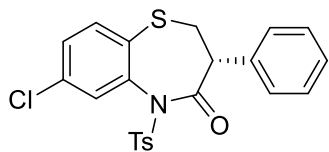
Yield: 67% (28.4 mg), 86% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -145.0$ (*c* 0.50, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.86 (m, 2H), 7.59–7.57 (m, 2H), 7.30 (m, 2H), 7.28–7.24 (m, 4H), 7.22–7.20 (m, 2H), 3.69 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.27 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.10 (dd, *J* = 12.0, 11.5 Hz, 1H), 2.51 (s, 3H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 171.7, 144.9, 140.7, 140.2, 135.8, 135.6, 135.0, 131.4, 131.0, 129.7, 129.4, 129.0, 128.3, 128.0, 125.2, 49.7, 39.6, 21.8, 21.3. Mp. 157.3–158.3 °C. TLC: *R*_f 0.51 (hexane/EtOAc = 2:1). IR (KBr): 2937, 2365, 1712, 1595, 1357, 1170, 1085, 917, 710, 692 cm⁻¹. HRMS Calcd for C₂₃H₂₁NO₃S₂Na: [M+Na]⁺, 446.0855. Found: *m/z* 446.0846. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 10.5 min, *t*_{major} = 12.1 min.

7-Methoxy-3-phenyl-5-tosyl-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one (3c).



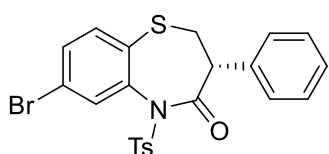
Yield: 67% (29.3 mg), 86% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -108.9$ (*c* 0.62, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.85 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.31–7.30 (m, 3H), 7.29–7.24 (m, 3H), 7.23 (m, 2H), 7.01 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.94 (s, 3H), 3.68 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.27 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.08 (dd, *J* = 12.0, 11.5 Hz, 1H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 171.8, 160.7, 144.9, 141.6, 136.5, 135.8, 135.0, 129.7, 129.4, 129.1, 128.4, 128.0, 119.5, 116.34, 116.26, 55.8, 49.8, 40.0, 21.8. Mp. decomp. TLC: *R*_f 0.46 (hexane/EtOAc = 2:1). IR (KBr): 2927, 1718, 1594, 1457, 1357, 1216, 1169, 827, 706, 675, 657 cm⁻¹. HRMS Calcd for C₂₃H₂₁NO₄S₂Na: [M+Na]⁺, 462.0804. Found: *m/z* 462.0793. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 13.5 min, *t*_{major} = 16.1 min.

7-Chloro-3-phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3d).



Yield: 71% (30.3 mg), 73% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -127.2$ (*c* 0.57, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.85 (m, 2H), 7.79 (m, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.46 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.31 (m, 2H), 7.27–7.24 (m, 2H), 7.21 (m, 2H), 3.67 (dd, *J* = 12.5, 6.5 Hz, 1H), 3.29 (dd, *J* = 11.5, 6.5 Hz, 1H), 3.14 (dd, *J* = 12.5, 11.5 Hz, 1H), 2.46 (s, 3H). ¹³C NMR (CDCl₃) δ 171.2, 145.2, 141.4, 136.6, 135.8, 135.5, 134.5, 130.9, 130.3, 129.7, 129.4, 129.2, 128.4, 128.2, 127.3, 49.7, 39.4, 21.8. Mp. 179.8–180.8 °C. TLC: *R*_f 0.52 (hexane/EtOAc = 2:1). IR (KBr): 2365, 1718, 1558, 1507, 1457, 1354, 1357, 1157, 1085, 944, 816, 672 cm⁻¹. HRMS Calcd for C₂₂H₁₈ClNO₃S₂Na: [M+Na]⁺, 466.0309. Found: *m/z* 466.0300. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 9.0 min, *t*_{major} = 11.8 min.

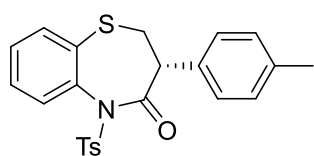
7-Bromo-3-phenyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3e).



Yield: 90% (44.1 mg), 65% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -78.9$ (*c* 0.57, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.93 (m, 1H), 7.85 (m, 2H), 7.61 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.31 (m, 2H), 7.30–7.26

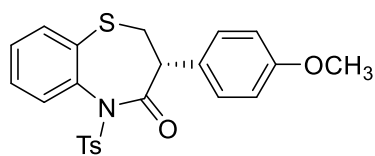
(m, 3H), 7.23–7.21 (m, 2H), 3.67 (dd, $J = 12.0, 7.0$ Hz, 1H), 3.29 (dd, $J = 12.5, 7.0$ Hz, 1H), 3.14 (dd, $J = 12.5, 12.0$ Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.2, 145.2, 141.4, 136.8, 135.5, 134.5, 133.7, 133.2, 129.7, 129.3, 129.2, 128.4, 128.2, 127.9, 123.6, 49.7, 39.4, 21.8. Mp. 214.9–215.9 °C. TLC: R_f 0.51 (hexane/EtOAc = 2:1). IR (KBr): 2917, 1717, 1593, 1555, 1457, 1357, 1157, 1085, 942, 816, 670 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{18}\text{BrNO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 509.9804. Found: m/z 509.9796. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 30 °C): $t_{\text{minor}} = 8.4$ min, $t_{\text{major}} = 11.1$ min.

3-(*p*-Tolyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3f).



Yield: 56% (35.7 mg), 87% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -114.3$ (*c* 0.70, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.86 (d, $J = 8.0$ Hz, 2H), 7.76 (m, 1H), 7.70 (m, 1H), 7.60 (m, 1H), 7.48 (m, 1H), 7.30 (d, $J = 8.0$ Hz, 2H), 7.10–7.06 (m, 4H), 3.66 (dd, $J = 12.0, 6.5$ Hz, 1H), 3.28 (dd, $J = 11.5, 6.5$ Hz, 1H), 3.12 (dd, $J = 12.0, 11.5$ Hz, 1H), 2.45 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.7, 144.9, 140.4, 137.9, 136.0, 135.8, 131.8, 130.8, 130.11, 130.08, 129.7, 129.2, 129.1, 128.8, 49.3, 39.4, 21.8, 21.0. Mp. decomp. TLC: R_f 0.32 (hexane/EtOAc = 3:1). IR (KBr): 2923, 1718, 1593, 1465, 1359, 1172, 1153, 1139, 1083, 932, 914, 710, 667 cm^{-1} . HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{NO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 446.0855. Found: m/z 446.0847. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 30 °C): $t_{\text{minor}} = 15.5$ min, $t_{\text{major}} = 17.4$ min.

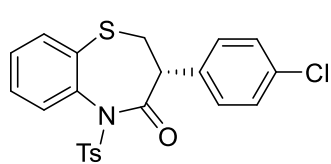
3-(4-Methoxyphenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3g).



Yield: 56% (36.6 mg), 87% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -175.9$ (*c* 0.54, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.85 (m, 2H), 7.76 (m, 1H), 7.70 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.59 (ddd, $J = 7.5, 7.5, 1.5$ Hz, 1H), 7.47 (ddd, $J = 7.5, 7.5, 1.5$ Hz, 1H), 7.31 (m, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), 6.79 (d, $J = 8.5$ Hz, 2H), 3.75 (s, 3H), 3.64 (dd, $J = 12.0, 7.0$ Hz, 1H), 3.26 (dd, $J = 11.5, 7.0$ Hz, 1H), 3.09 (dd, $J = 12.0, 11.5$ Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.8, 159.3, 144.9, 140.4, 136.0, 135.8, 130.8,

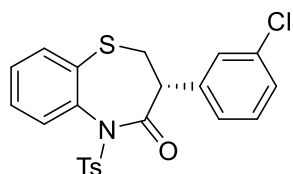
130.4, 130.11, 130.08, 129.7, 129.1, 128.8, 126.9, 113.8, 52.2, 48.9, 39.6, 21.8. Mp. 194.1–195.1 °C. TLC: R_f 0.20 (hexane/EtOAc = 3:1). IR (KBr): 1724, 1512, 1465, 1358, 1252, 1171, 1133, 1082, 827, 784, 667 cm^{-1} . HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{NO}_4\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 462.0804. Found: m/z 462.0793. HPLC (Daicel Chiralpak ID, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 17.8 min, t_{major} = 21.2 min.

3-(4-Chlorophenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3h).



Yield: 70% (46.4 mg), 94% *ee*, white solid. $[\alpha]_{\text{D}}^{18}$ –185.6 (*c* 0.66, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.86 (m, 2H), 7.76 (m, 1H), 7.71 (dd, J = 7.5, 1.5 Hz, 1H), 7.60 (m, 1H), 7.48 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.30 (m, 2H), 7.23 (m, 2H), 7.15 (m, 2H), 3.66 (dd, J = 12.5, 7.0 Hz, 1H), 3.28 (dd, J = 12.0, 7.0 Hz, 1H), 3.07 (dd, J = 12.5, 12.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.2, 145.1, 140.2, 136.0, 135.6, 134.0, 133.4, 130.8, 130.7, 130.25, 130.21, 129.7, 129.1, 128.6, 128.5, 49.0, 39.5, 21.8. Mp. 223.0–224.0 °C. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (KBr): 2358, 1714, 1653, 1559, 1490, 1465, 1363, 1173, 1139, 1083, 1016, 933, 904, 817, 765, 713, 668 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{18}\text{ClNO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 466.0309. Found: m/z 466.0300. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 13.3 min, t_{major} = 15.7 min.

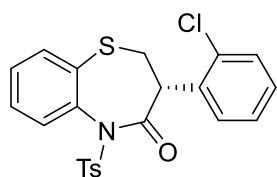
3-(3-Chlorophenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3i).



Yield: 76% (50.8 mg), 94% *ee*, white solid. $[\alpha]_{\text{D}}^{18}$ –200.0 (*c* 0.45, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.87 (d, J = 8.0 Hz, 2H), 7.77 (m, 1H), 7.71 (m, 1H), 7.61 (m, 1H), 7.49 (m, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.24–7.18 (m, 3H), 7.11 (m, 1H), 3.66 (dd, J = 12.0, 7.0 Hz, 1H), 3.29 (dd, J = 11.5, 7.0 Hz, 1H), 3.09 (dd, J = 12.0, 11.5 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.0, 145.1, 140.2, 136.8, 136.0, 135.6, 134.2, 130.8, 130.3, 129.7, 129.59, 129.56, 129.2, 128.5, 128.3, 127.6, 49.3, 39.4, 21.8. Mp. 164.0–164.7 °C. TLC: R_f 0.33 (hexane/EtOAc = 3:1). IR (KBr): 3067, 2921, 1711, 1595,

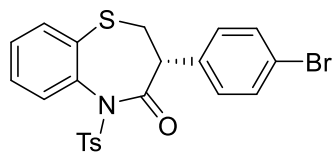
1465, 1437, 1363, 1175, 1154, 1086, 938, 910, 715, 666 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{18}\text{ClNO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 466.0309. Found: m/z 466.0304. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 11.4 min, t_{major} = 13.3 min.

3-(2-Chlorophenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3j).



Yield: 60% (40.2 mg), 87% *ee*, white solid. $[\alpha]_{\text{D}}^{18}$ -194.9 (*c* 0.59, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.87 (m, 2H), 7.83 (dd, J = 7.5, 1.5 Hz, 1H), 7.72 (dd, J = 7.5, 1.5 Hz, 1H), 7.61 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.47 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.33–7.28 (m, 4H), 7.24–7.17 (m, 2H), 4.18 (dd, J = 12.5, 6.5 Hz, 1H), 3.33 (dd, J = 11.0, 6.5 Hz, 1H), 3.23 (dd, J = 12.5, 11.0 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.2, 144.9, 140.3, 136.1, 135.8, 134.0, 133.4, 130.6, 130.3, 130.2, 129.6, 129.4, 129.3, 129.1, 128.3, 126.9, 46.0, 36.5, 21.7. Mp. 199.3–200.3 °C. TLC: R_f 0.27 (hexane/EtOAc = 3:1). IR (KBr): 2925, 1706, 1596, 1464, 1437, 1365, 1164, 1087, 934, 776, 746, 718, 666 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{18}\text{ClNO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 466.0309. Found: m/z 466.0308. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 20.1 min, t_{minor} = 23.0 min.

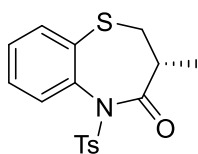
3-(4-Bromophenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3k).



Yield: 94% (69.0 mg), 95% *ee*, white solid. $[\alpha]_{\text{D}}^{18}$ -145.3 (*c* 0.86, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.85 (m, 2H), 7.76 (m, 1H), 7.70 (dd, J = 8.0, 1.5 Hz, 1H), 7.60 (m, 1H), 7.48 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.38 (m, 2H), 7.31 (m, 2H), 7.10 (m, 2H), 3.65 (dd, J = 12.5, 7.0 Hz, 1H), 3.27 (dd, J = 12.0, 7.0 Hz, 1H), 3.06 (dd, J = 12.5, 12.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.1, 145.1, 140.2, 136.0, 135.6, 133.9, 131.5, 131.1, 130.8, 130.3, 130.2, 129.7, 129.0, 128.6, 122.2, 49.1, 39.4, 21.8. Mp. decomp. TLC: R_f 0.30 (hexane/EtOAc = 3:1). IR (KBr): 1717, 1591, 1487, 1465, 1363, 1172, 1139, 1082, 1012, 816, 765, 712, 667 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{18}\text{BrNO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$,

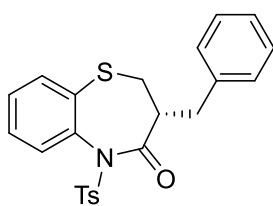
509.9804. Found: m/z 509.9795. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 14.6 min, t_{major} = 17.1 min.

3-Methyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3l).

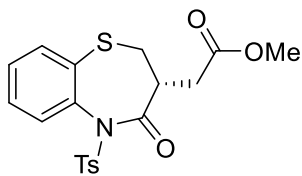


Yield: 39% (20.2 mg), 90% *ee*, white solid. $[\alpha]_D^{18}$ -86.5 (*c* 0.26, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.87 (m, 2H), 7.67 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.64 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.52 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.41 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.29 (m, 2H), 3.15 (dd, *J* = 10.0, 5.0 Hz, 1H), 2.60–2.47 (m, 2H), 2.43 (s, 3H), 1.09 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (CDCl₃) δ 173.5, 144.9, 139.9, 135.9, 135.8, 130.7, 129.9, 129.8, 129.6, 129.2, 129.0, 39.7, 38.6, 21.7, 14.8. Mp. 66.5–67.5 °C. TLC: *R*_f 0.44 (hexane/EtOAc = 2:1). IR (KBr): 2986, 2938, 1712, 1596, 1465, 1363, 1171, 1146, 1087, 817, 759, 717, 664 cm⁻¹. HRMS Calcd for C₁₇H₁₇NO₃S₂Na: [M+Na]⁺, 370.0542. Found: m/z 370.0534. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 8.7 min, t_{minor} = 11.7 min.

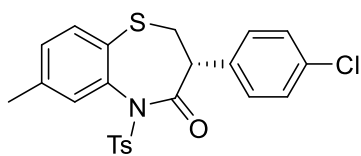
3-Benzyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3m).



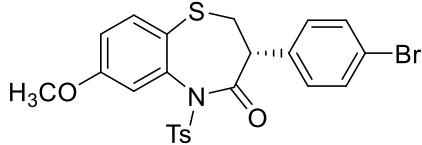
Yield: 56% (35.6 mg), 81% *ee*, white solid. $[\alpha]_D^{18}$ -108.5 (*c* 0.53, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.66 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.52 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.39 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.22–7.14 (m, 3H), 6.98 (m, 2H), 3.15 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.07 (dd, *J* = 11.0, 5.5 Hz, 1H), 2.70–2.59 (m, 3H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 172.9, 145.0, 139.7, 137.9, 135.8, 130.7, 130.0, 129.9, 129.6, 129.0, 128.9, 128.7, 128.5, 126.6, 45.8, 38.4, 36.0, 21.7. Mp. 206.2–207.2 °C. TLC: *R*_f 0.37 (hexane/EtOAc = 3:1). IR (KBr): 2547, 2365, 1709, 1594, 1465, 1381, 1359, 1173, 1153, 1085, 955, 809, 759, 717, 698 cm⁻¹. HRMS Calcd for C₂₃H₂₁NO₃S₂Na: [M+Na]⁺, 446.0855. Found: m/z 446.0846. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 95/5, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 11.5 min, t_{minor} = 14.6 min.

Methyl 2-(4-oxo-5-tosyl-2,3,4,5-dihydrobenzo[*b*][1,4]thiazepin-3-yl)acetate (3n).

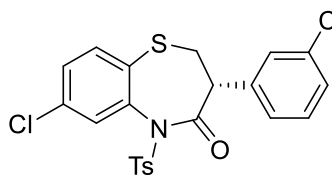
Yield: 49% (29.6 mg), 84% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -117.2$ (*c* 0.32, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.75 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.66 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.55 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.43 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.29 (d, *J* = 8.0, 2H), 3.61 (s, 3H), 3.19 (dd, *J* = 11.5, 6.0 Hz, 1H), 2.96–2.87 (m, 2H), 2.56 (dd, *J* = 11.5, 11.5 Hz, 1H), 2.43 (s, 3H), 2.27 (dd, *J* = 11.5, 4.0 Hz, 1H). ¹³C NMR (CDCl₃) δ 172.3, 171.2, 145.0, 139.8, 135.9, 135.8, 130.8, 130.2, 130.1, 129.5, 129.1, 128.6, 52.1, 40.4, 37.3, 34.2, 21.7. Mp. 56.5–57.5 °C. TLC: *R*_f 0.14 (hexane/EtOAc = 3:1). IR (KBr): 2360, 1740, 1714, 1654, 1559, 1465, 1433, 1367, 1175, 1152, 810, 713, 664 cm⁻¹. HRMS Calcd for C₁₉H₁₉NO₅S₂Na: [M+Na]⁺, 428.0597. Found: *m/z* 428.0588. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 11.0 min, *t*_{major} = 12.4 min.

3-(4-Chlorophenyl)-7-methyl-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3o).

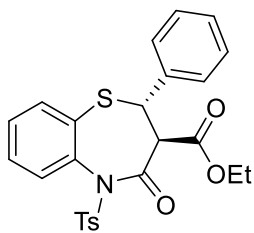
Yield: 61% (28.0 mg), 96% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -138.3$ (*c* 0.47, CH₂Cl₂). ¹H NMR (CDCl₃) δ 7.85 (m, 2H), 7.58 (m, 2H), 7.33 (m, 3H), 7.24 (m, 2H), 7.16 (m, 2H), 3.66 (dd, *J* = 12.5, 7.0 Hz, 1H), 3.25 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.03 (dd, *J* = 12.5, 12.0 Hz, 1H), 2.51 (s, 3H), 2.45 (s, 3H). ¹³C NMR (CDCl₃) δ 171.3, 145.0, 140.9, 140.0, 135.72, 135.69, 134.0, 133.5, 131.4, 131.1, 130.7, 129.7, 129.1, 128.5, 125.0, 49.1, 39.6, 21.8, 21.3. Mp. 212.9–213.6 °C. TLC: *R*_f 0.37 (hexane/EtOAc = 3:1). IR (KBr): 2917, 1717, 1597, 1492, 1357, 1171, 1158, 1086, 1011, 913, 820, 812, 736, 679 cm⁻¹. HRMS Calcd for C₂₃H₂₀ClNO₃S₂Na: [M+Na]⁺, 480.0465. Found: *m/z* 480.0462. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 9.5 min, *t*_{major} = 13.2 min.

3-(4-Bromophenyl)-7-methoxy-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3p).

Yield: 91% (45.7 mg), 95% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -175.9$ (*c* 0.54, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.84 (m, 2H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.38 (m, 2H), 7.31–7.29 (m, 3H), 7.11 (m, 2H), 7.01 (dd, *J* = 8.5, 2.5 Hz, 1H), 3.92 (s, 3H), 3.64 (dd, *J* = 12.0, 7.0 Hz, 1H), 3.24 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.00 (dd, *J* = 12.0, 11.5 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (CDCl_3) δ 171.3, 160.8, 145.0, 141.4, 136.6, 135.6, 134.0, 131.4, 131.1, 129.7, 129.1, 122.2, 119.2, 116.4, 116.3, 55.8, 49.3, 40.0, 21.8. Mp. 93.4–94.5 °C. TLC: R_f 0.31 (hexane/EtOAc = 3:1). IR (KBr): 2365, 1710, 1596, 1491, 1362, 1309, 1216, 1173, 1153, 1085, 1012, 904, 814, 705, 678, 657 cm^{-1} . HRMS Calcd for $\text{C}_{23}\text{H}_{20}\text{BrNO}_4\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 539.9909. Found: *m/z* 539.9906. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 13.0 min, t_{major} = 24.9 min.

7-Chloro-3-(3-chlorophenyl)-5-tosyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (3q).

Yield: 88% (41.9 mg), 86% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -84.5$ (*c* 0.71, CH_2Cl_2). ^1H NMR (CDCl_3) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.78 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.26–7.19 (m, 3H), 7.11 (m, 1H), 3.63 (dd, *J* = 12.5, 7.0 Hz, 1H), 3.28 (dd, *J* = 11.5, 7.0 Hz, 1H), 3.09 (dd, *J* = 12.5, 11.5 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (CDCl_3) δ 170.7, 145.4, 141.2, 136.7, 136.5, 136.0, 135.4, 134.2, 130.9, 130.4, 129.7, 129.63, 129.57, 129.2, 128.4, 127.6, 127.0, 49.3, 39.4, 21.8. Mp. 183.9–184.9 °C. TLC: R_f 0.44 (hexane/EtOAc = 3:1). IR (KBr): 2362, 1714, 1654, 1595, 1576, 1457, 1394, 1363, 1175, 1156, 1086, 992, 944, 814, 733, 668 cm^{-1} . HRMS Calcd for $\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{NO}_3\text{S}_2\text{Na}$: $[\text{M}+\text{Na}]^+$, 499.9919. Found: *m/z* 499.9912. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 7.6 min, t_{major} = 11.2 min.

Ethyl 4-oxo-2-phenyl-5-tosyl-2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine-3-carboxylate (7).

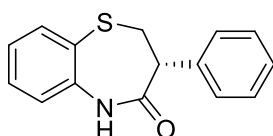
Yield: 51% (36.9 mg), 87% *ee*, white solid. $[\alpha]_{\text{D}}^{18} +270.0$ (*c* 0.50, CH₂Cl₂).

¹H NMR (CDCl₃) δ 7.88 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.67 (m, 1H), 7.48–7.45 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.20–7.17 (m, 3H), 6.78–6.76 (m, 2H), 4.67 (d, *J* = 11.5 Hz, 1H), 3.99 (m, 2H), 3.80 (d, *J* = 11.5

Hz, 1H), 2.46 (s, 3H), 1.06 (t, *J* = 7.5 Hz, 3H). ¹³C NMR (CDCl₃) δ 166.5, 165.4, 145.4, 140.9, 139.6, 137.1, 134.9, 131.0, 130.7, 130.1, 129.7, 129.2, 128.7, 128.0, 127.5, 126.1, 62.1, 56.4, 51.9, 21.8, 13.7. Mp. 171.1–172.1 °C. TLC: *R*_f 0.31 (hexane/EtOAc = 3:1). IR (KBr): 2981, 1734, 1713, 1596, 1464, 1354, 1275, 1260, 1173, 1165, 1152, 1085, 1035, 841, 812, 760, 710, 697, 672 cm⁻¹. HRMS Calcd for C₂₅H₂₄NO₅S₂: [M+H]⁺, 482.1090. Found: *m/z* 482.1082. HPLC (Daicel Chiralpak IA, hexane/*i*-PrOH = 90/10, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 9.1 min, *t*_{major} = 11.3 min.

Procedure for synthesis of 8^{4,13}

To a solution of SmI₂ in THF (0.1 M, 17 mL, 10 equiv) was added **3a** (71 mg, 0.17 mmol) followed by H₂O (92 μ L, 5.1 mmol, 30 equiv) and triethylamine (0.47 mL, 3.4 mmol, 20 equiv), and the mixture was stirred under argon atmosphere for 0.5 h. The resulting mixture was diluted with Et₂O (10 mL) and washed with saturated aqueous NaHCO₃ (10 mL $\times$ 3). The organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 2/1) as an eluent gave the detosylated product **8**.

(*R*)-3-Phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (8): CAS RN [1346947-97-4].

Yield: 97% (43.0 mg), 90% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -117.1$ (*c* 0.47, CHCl₃).

¹H NMR (CDCl₃) δ 8.02 (br s, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.33 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.27–7.25 (m, 3H), 7.23 (m, 1H), 7.19 (dd, *J* = 7.5,

7.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 3.86 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.58 (dd, *J* = 12.0, 6.0 Hz,

1H), 3.50 (dd, $J = 12.5, 12.0$ Hz, 1H). ^{13}C NMR (CDCl_3) δ 173.6, 141.5, 136.5, 135.3, 130.0, 129.3, 128.3, 127.7, 127.1, 126.6, 123.5, 47.7, 40.9. Mp. 74.8–75.8 °C. TLC: R_f 0.27 (hexane/EtOAc = 2:1). IR (KBr): 3185, 3062, 2994, 1654, 1584, 1473, 1387, 1293, 1263, 1030, 906, 760, 694 cm^{-1} . HRMS Calcd for $\text{C}_{15}\text{H}_{13}\text{NOSNa}$: $[\text{M}+\text{Na}]^+$, 278.0610. Found: m/z 278.0603. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, $\lambda = 254$ nm, 30 °C): $t_{\text{major}} = 8.2$ min, $t_{\text{minor}} = 8.9$ min.

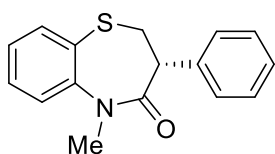
The absolute configuration of **8** was assigned as (*R*) by comparing the optical rotation with the literature value.^{4a}

$[\alpha]_{\text{D}}^{18} -117.1$ (c 0.47, CHCl_3) [lit.^{4a} (*R*)-3-Phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (86% *ee*): $[\alpha]_{\text{D}}^{25} -126.7$ (c 0.5, CHCl_3)].

Procedure for synthesis of **9**

To a solution of **8** (26 mg, 0.10 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in acetone (1.0 mL) was added MeI (7.6 μL , 0.12 mmol). After the mixture was stirred for 6 h under reflux, it was cooled to ambient temperature. The organic layers were washed with H_2O (5 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc ($v/v = 3:1$) as an eluent gave **9**.

5-Methyl-3-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**9**).



Yield: 62% (16 7mg), 83% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -71.9$ (c 1.67, CHCl_3).

^1H NMR (CDCl_3) δ 7.66 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.49 (m, 1H), 7.36–7.25 (m, 7H), 3.85 (dd, $J = 11.5, 7.0$ Hz, 1H), 3.53–3.50 (m, 2H), 3.38 (s, 3H).

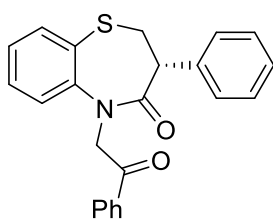
^{13}C NMR (CDCl_3) δ 172.5, 147.7, 136.8, 135.6, 130.3, 129.4, 128.2, 127.8, 127.6, 127.1, 124.5, 48.0, 41.0, 36.5. Mp. 143.4–144.4 °C. TLC: R_f 0.29 (hexane/EtOAc = 2:1). IR (KBr): 2927, 1662, 1584, 1477, 1387, 1291, 1128, 1075, 764 cm^{-1} . HRMS Calcd for $\text{C}_{16}\text{H}_{16}\text{NOS}$: $[\text{M}+\text{H}]^+$, 270.0947. Found: m/z 270.0942. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate

= 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 8.5 min, t_{minor} = 9.5 min.

Procedure for synthesis of **10**¹⁴

To a solution of **8** (31 mg, 0.12 mmol), tetrabutylammonium bromide (3.9 mg, 0.012 mmol), and phenacylbromide (35.8 mg, 0.18 mmol) in THF (2.0 mL), finely powdered KOH (13.5 mg, 0.24 mmol) was added, and the mixture was stirred for 1 h at ambient temperature. The resulting mixture was diluted with CH₂Cl₂ (10 mL), washed with H₂O (10 mL) and brine, dried over Na₂SO₄, and concentrated in vacuo. Purification by flash silica gel column chromatography using hexane/EtOAc (v/v = 3:1) as an eluent gave **10**.

5-(2-Oxo-2-phenylethyl)-3-phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one (**10**).



Yield: 91% yield (40.8 mg), 89% *ee*, yellow solid. $[\alpha]_D^{18}$ -241.4 (*c* 0.58, CHCl₃). ¹H NMR (CDCl₃) δ 7.98 (m, 2H), 7.69 (m, 1H), 7.58 (m, 1H), 7.48–7.42 (m, 3H), 7.35–7.24 (m, 7H), 5.87 (d, *J* = 17.0 Hz, 1H), 4.57 (d, *J* = 17.0 Hz, 1H), 4.05 (dd, *J* = 13.0, 6.5 Hz, 1H), 3.63–3.52 (m, 2H). ¹³C

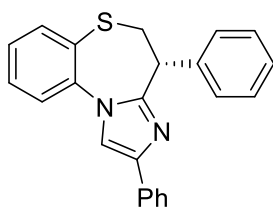
NMR (CDCl₃) δ 193.7, 172.5, 147.1, 136.7, 135.5, 134.9, 133.7, 130.5, 129.2, 128.7, 128.3, 128.1, 127.8, 127.6, 127.2, 124.0, 56.2, 47.8, 40.5. Mp. 61.9–63.1 °C. IR (KBr): 3060, 2924, 1700, 1671, 1597, 1580, 1474, 1448, 1383, 1225, 981, 757, 696 cm⁻¹. HRMS Calcd for C₂₃H₁₉NO₂SNa: [M+Na]⁺, 396.1029. Found: *m/z* 396.1024. HPLC (Daicel Chiralpak IF, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): t_{major} = 13.9 min, t_{minor} = 15.9 min.

Procedure for synthesis of **11**¹⁴

A mixture of **10** (24 mg, 0.065 mmol) and ammonium acetate (100 mg, 0.13 mmol) in acetic acid (3.0 mL) was refluxed for 1 h. After cooling, the solution was neutralized with 30% aqueous NH₃. The mixture was extracted with CHCl₃ (10 mL $\times$ 2) and washed with H₂O (10 mL) and brine. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Purification of the crude product by flash silica gel column chromatography using hexane/EtOAc

(v/v = 3:1) as an eluent afforded **11**.

2,4-Diphenyl-4,5-dihydrobenzo[*b*]imidazo[1,2-*d*][1,4]thiazepine (11**).**

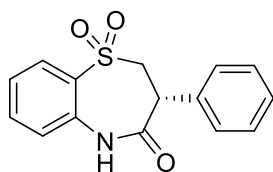


Yield: 45% (10.3 mg), 64% *ee*, brown solid. $[\alpha]_{\text{D}}^{18} +31.6$ (*c* 1.03, CHCl₃). ¹H NMR (CDCl₃) δ 7.82 (m, 2H), 7.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (m, 2H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.43–7.31 (m, 7H), 7.28–7.22 (m, 2H), 4.33 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.79 (dd, *J* = 11.5, 6.0 Hz, 1H), 3.69 (dd, *J* = 11.5, 10.5 Hz, 1H). ¹³C NMR (CDCl₃) δ 148.7, 141.4, 140.7, 138.1, 135.6, 133.8, 130.0, 129.1, 128.4, 128.2, 128.1, 127.3, 126.8, 124.9, 124.0, 115.4, 44.3, 43.5. Mp. 55.8–56.8 °C. TLC: *R*_f 0.36 (hexane/EtOAc = 2:1). IR (KBr): 3060, 3030, 2921, 1604, 1512, 1478, 1444, 1410, 1154, 751, 695 cm⁻¹. HRMS Calcd for C₂₃H₁₉N₂S: [M+H]⁺, 355.1263. Found: *m/z* 355.1259. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 80/20, flow rate = 2.0 mL/min, λ = 254 nm, 30 °C): *t*_{minor} = 5.8 min, *t*_{major} = 9.5 min.

Procedure for synthesis of **12**

To a solution of **8** (26 mg, 0.10 mmol) in CH₂Cl₂ (1.0 mL) was added *m*-CPBA (67 mg, 0.3 mmol), and the mixture was stirred for 1 h. The resulting mixture was diluted with CH₂Cl₂ (5 mL) and washed with 1N aqueous NaOH (5.0 mL) and aqueous Na₂S₂O₃ (5.0 mL). The organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo, and **12** was obtained.

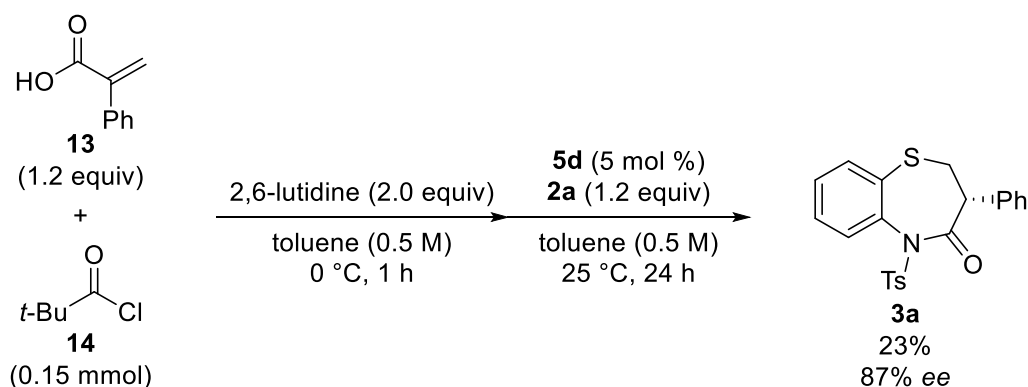
3-Phenyl-2,3-dihydrobenzo[*b*][1,4]thiazepin-4(5*H*)-one 1,1-dioxide (12**).**



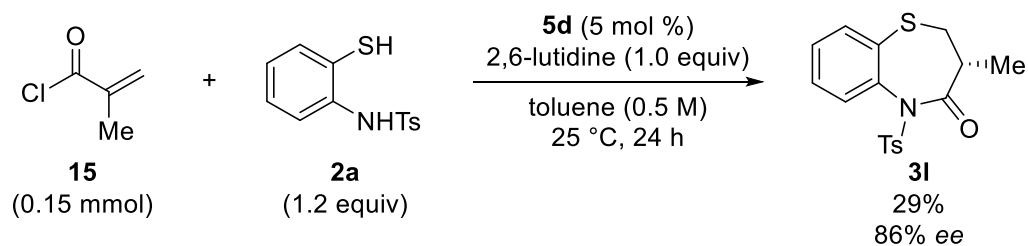
Yield: 95% (27.3 mg), 90% *ee*, white solid. $[\alpha]_{\text{D}}^{18} -147.7$ (*c* 0.22, CHCl₃). ¹H NMR (CDCl₃) δ 8.11 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.93 (br s, 1H), 7.72 (ddd, *J* = 8.0, 8.0, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 8.0, 0.5 Hz, 1H), 7.37–7.32 (m, 3H), 7.28–7.23 (m, 3H), 4.13–4.03 (m, 2H), 3.84 (dd, *J* = 12.5,

5.0 Hz, 1H). ^{13}C NMR (CDCl_3) δ 170.4, 136.5, 135.5, 134.2, 131.7, 129.12, 129.09, 128.7, 128.4, 126.5, 124.6, 63.9, 44.4. Mp. decomp. IR (KBr): 3195, 3055, 2924, 1684, 1591, 1478, 1374, 1321, 1265, 1243, 1155, 1125, 1068, 1025, 892, 767, 698 cm^{-1} . HRMS Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_3\text{SNa}$: $[\text{M}+\text{Na}]^+$, 310.0508. Found: m/z 310.0499. HPLC (Daicel Chiralpak IE, hexane/*i*-PrOH = 50/50, flow rate = 1.0 mL/min, λ = 254 nm, 30 °C): t_{minor} = 25.5 min, t_{major} = 40.8 min.

Supplemental Data



Scheme 5. Net [4+3] Formal Cycloaddition Reaction through the In-Situ Generation of Mixed Anhydride Using α,β -Unsaturated Carboxylic Acid

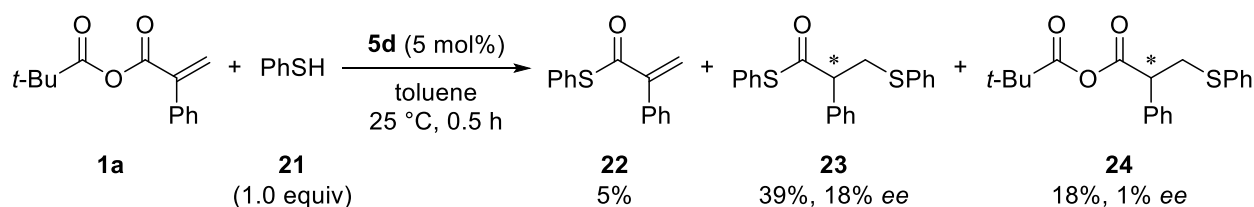


Scheme 6. Net [4+3] Formal Cycloaddition Reaction Using α,β -Unsaturated Carboxylic Acid Chloride

Table 4. Reaction of α,β -disubstituted conjugated mixed anhydride **6** with **2a**^a

entry	catalyst	yield of 7 (%) ^b	ee of 7 (%)	yield of 20 (%) ^c	yield of 21 (%) ^c
1	5b	51	87	8	22
2	5d	35	−40	27	31

^aReactions were run using **1a** (0.15 mmol), **2a** (0.18 mmol), and **5a** (0.015 mmol) in toluene (0.3 mL). ^bIsolated yields. ^cNMR yields.

Scheme 7. Reactions of benzenethiol **11** with **1a** in the presence of **5d**.

Procedure for reactions of benzenethiol and α,β -unsaturated carboxylic acid anhydride

To a 5-mL vial were added sequentially α,β -unsaturated carboxylic acid anhydride **1a** (0.15 mmol), toluene (0.3 mL), catalyst **5d** (0.0075 mmol), and benzenethiol (**21**, 0.15 mmol). The mixture was stirred in an oil bath maintained at 25 °C for 0.5 h. The reaction mixture was subsequently diluted with hexane/EtOAc (v/v = 20/1), passed through a short silica gel pad to remove **5c**, and concentrated in vacuo. Purification of the reaction mixture by flash silica gel column chromatography using hexane/EtOAc (v/v = 10/1) as an eluent afforded the mixture of **22**, **23**, and **24**.

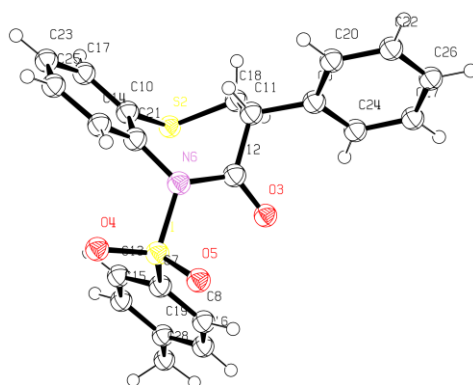


Figure 2. ORTEP drawing of **3a** ($\text{C}_{22}\text{H}_{19}\text{NO}_3\text{S}_2$, $M = 409.52$, $T = 293(2)$ K).

Crystal System	orthorhombic
Radiation	Mo-K α ($\lambda = 0.71075$ Å)
Space Group	$P2_12_12_1$ (#19)
Crystal Dimensions	$0.210 \times 0.210 \times 0.170$ mm
Unit cell dimensions	$a = 7.9922(8)$ Å $\alpha = 90^\circ$ $b = 11.596(2)$ Å $\beta = 90^\circ$ $c = 21.983(2)$ Å $\gamma = 90^\circ$
Volume	$2037.4(4)$ Å ³
Z value	4
D_{calc}	1.335 g/cm ³
$2\theta_{\text{max}}$	55.0°
Reflections collected	Total: 20533
Independent reflections	Unique: 4683 ($R_{\text{int}} = 0.0482$)
No. Variables	253
Goodness-of-fit on F^2	1.058
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0439$
R indices (all data)	$R_1 = 0.0593$, $wR_2 = 0.1008$
Flack Parameter	$-0.01(7)$

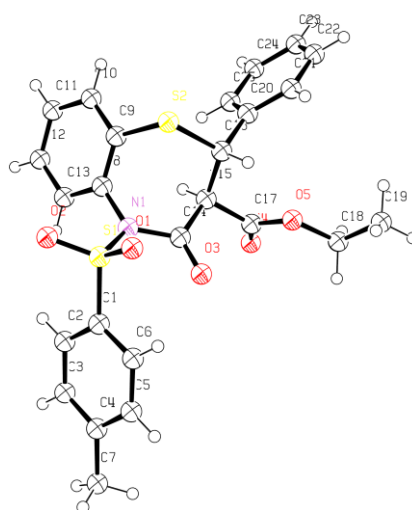


Figure 3. ORTEP drawing of **7** ($\text{C}_{25}\text{H}_{23}\text{NO}_5\text{S}_2$, $M = 481.58$, $T = 93(2)$ K).

Crystal System	orthorhombic
Radiation	CuK α ($\lambda = 1.54187 \text{ \AA}$)
Space group	Pca2 ₁ (#29)
Crystal Dimensions	$0.622 \times 0.020 \times 0.020 \text{ mm}$
Unit cell dimensions	$a = 16.4621(8) \text{ \AA}$ $\alpha = 90^\circ$ $b = 5.5190(3) \text{ \AA}$ $\beta = 90^\circ$ $c = 24.5110(13) \text{ \AA}$ $\gamma = 90^\circ$
Volume	$2226.9(2) \text{ \AA}^3$
Z	4
D _{calc}	1.436 g/cm^3
$2\theta_{\text{max}}$	136.5°
Reflections collected	14664
Independent reflections	3664 [$R_{\text{int}} = 0.0710$]
No. Variables	300
Goodness-of-fit on F^2	1.196
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0496$
R indices (all data)	$R_1 = 0.0705, wR_2 = 0.1386$
Flack parameter	0.042(14)

References and Notes

1. *Privileged Scaffolds in Medicinal Chemistry*, Brăce, S., Ed.; RSC Publication: Cambridge, U. K., 2015.
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10. The generation of the anhydride in situ from the corresponding carboxylic acid was also investigated; however, its yield was significantly lower despite the comparable enantioselectivity (23% yield, 87% *ee*, see the Scheme 5 for details)
11. Although methacryloyl chloride could be used as a substrate, both the yield and enantioselectivity of **3l** were slightly lower in the preliminary study (29% yield, 86% *ee*, see Scheme 6 for details).
12. With 10 mol% of **5d**, **7** was obtained as a single regioisomer and diastereomer; however, both the yield and *ee* were significantly lower (35%, –40% *ee*, respectively, see Table 4 for details).
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16. These results suggested that mixed anhydride **1a** is possibly converted to the corresponding thioester after the addition of **2a**, and the acylammonium intermediate is generated from the thioester. However, the possibility that thiol **2a** might activate mixed anhydride **1a** as a Brønsted acid cannot be excluded.
17. The reaction was conducted in the presence of benzenethiol instead of aminothiophenol **2a**; according to the chiral HPLC analysis of the products obtained, the enantiomeric excesses of the obtained products were very low (see Scheme 5 for details). The low enantioselectivities of the sulfa-Michael addition/protonation process implies that this process is reversible, and we believe that the enantioselectivity of net cycloaddition is determined by the intramolecular cyclization step via dynamic kinetic asymmetric transformation.
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Publication List

Parts of present Thesis have been or are to be published in the following journals.

- Chapter 1** Asymmetric Synthesis of 1,3-Oxazolidines via Intramolecular Aza-Michael Addition by Bifunctional Organocatalysts
Yukihiro Fukata, Keisuke Asano, and Seiji Matsubara
Chem. Lett. **2013**, 42, 355–357.
- Chapter 2** Procedure-Controlled Enantioselectivity Switch in Organocatalytic 2-Oxazolidinone Synthesis
Yukihiro Fukata, Keisuke Asano, and Seiji Matsubara
J. Am. Chem. Soc. **2013**, 135, 12160–12163.
- Chapter 3** Asymmetric Isomerization of ω -Hydroxy- α,β -Unsaturated Thioesters into β -Mercaptolactones by a Bifunctional Amino thiourea Catalyst
Yukihiro Fukata, Takaaki Okamura, Keisuke Asano, and Seiji Matsubara
Org. Lett. **2014**, 16, 2184–2187.
- Chapter 4** Facile Net Cycloaddition Approach to Optically Active 1,5-Benzothiazepines
Yukihiro Fukata, Keisuke Asano, and Seiji Matsubara
J. Am. Chem. Soc. **2015**, 137, 5320–5323.
- Chapter 5** Isothiourea-Catalyzed Enantioselective Formal [4+3] Cycloaddition Affording 3-Substituted 1,5-Benzothiazepines
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Yukihiro Fukata
Department of Material Chemistry
Graduate School of Engineering
Kyoto University