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COMMUNICATION

5-*exo*-Selective Asymmetric Bromolactonization of Stilbenecarboxylic Acids Catalyzed by Phenol-bearing Chiral Thiourea

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We developed a novel thiourea Lewis-base catalyst with phenol moieties for the enantioselective 5-*exo*-bromolactonization of stilbenecarboxylic acids to afford chiral 3-substituted phthalides. The phenol moieties are crucial for the enantio- and regioselectivity.

Chiral 3-substituted phthalides are core structures in numerous natural products with diverse biological activities (Figure 1).^{1,2} There is a sustained effort to formulate an efficient synthetic method for optically active 3-substituted phthalide derivatives.^{1,2} One attractive reaction is the halolactonization of alkenes,^{3–11} which creates two adjacent chiral centers and at the same time, installs a halogen atom, which enables various further transformations. Though catalytic enantioselective halocyclization of *o*-vinylbenzoic acid derivatives have been presented as an effective method for obtaining chiral 3-halomethylphthalide derivatives,^{12–17} halolactonization of stilbenecarboxylic acids exhibits issues with regioselectivity; the reaction of **1a** leads to phthalide **2a** and 3,4-dihydroisocoumarin **3a** via 5-*exo*- and 6-*endo*-cyclization pathways, respectively (Scheme 1). While many 6-*endo*-selective reactions have been documented,^{18–21} the 5-*exo* counterpart is primarily limited. Thus, Shirakawa reported that asymmetric bromolactonization of **1** bearing an electron-withdrawing group (EWG) such as NO₂, CF₃, or CN groups on the terminal aromatic ring proceeded 5-*exo*-selectively.²² Miura recently reported the first 5-*exo*-selective asymmetric bromolactonization of **1** without an EWG.²³ However, the regioselectivity in the reactions of those substrates was up to 2:1.

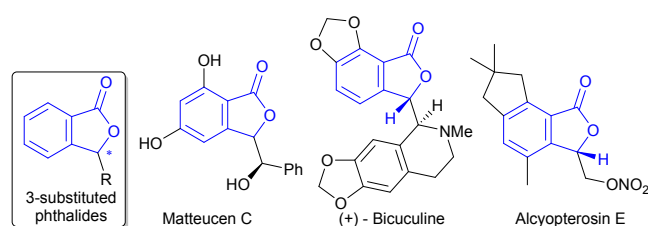
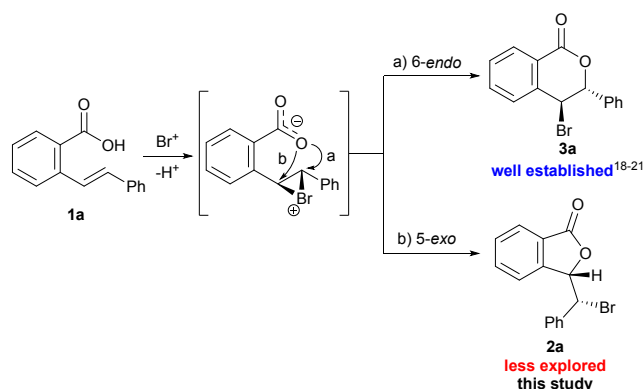


Figure 1. Selected examples of natural products containing chiral 3-substituted phthalide skeletons.



Scheme 1. Bromolactonization of Stilbenecarboxylic Acid.

Following Tang and coworkers' pioneering work on enantioselective bromolactonization of enynes using a quinine-derived urea catalyst,²⁴ a range of chiral Lewis base catalysts containing Brønsted acid or base functionalities, such as *tert*-amine with amide²⁵ or urea;²⁶ guanidine with phenol;²⁷ sulfide with phenol¹⁵ or urea;^{19,22} and carbamate,²⁸ thiocarbamate,²⁹ or thiourea^{30–32} with *tert*-amine have been reported as successful catalysts to achieve asymmetric halocyclization. These catalysts are thought to activate both a nucleophilic moiety and a halogenating reagent concurrently, which results in a reaction with high enantioselectivity. As part of our ongoing effort to develop organocatalyzed reactions,^{33–45} we have developed chiral thiourea catalysts with phenol moieties. Herein, we report our thiourea-catalyzed enantioselective 5-*exo*-bromolactonization of

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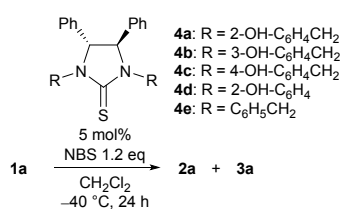
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stilbenecarboxylic acids. This is the first asymmetric reaction catalyzed by chiral thiourea Lewis base bearing a Brønsted acidic moiety to activate both nucleophile and electrophile concurrently.^{46,47}

First, the reaction of **1a** with *N*-bromosuccinimide (NBS) as a bromine source was conducted in the presence of chiral thiourea **4a**, which bears phenol moieties, at $-40\text{ }^{\circ}\text{C}$ in dichloromethane (Table 1). Bromolactonization primarily proceeded through the 5-*exo* pathway to mainly produce **2a** with an enantiomer ratio (er) of 82:18 along with 6-*endo* product **3a** (4:1 regioselectivity) in a combined yield of 90% after 24 h (entry 1). In contrast, catalysts **4b** and **4c**, bearing hydroxy groups at the *meta*- and *para*-positions, respectively, and **4d**, which lacks a methylene linkage, predominantly produced racemic **3a** (entries 2–4). As predicted, thioureas **4e**, devoid of a hydroxy group, also yielded racemic **3a** in high yield (entry 5). These findings underscore the crucial role of the catalyst's phenol moiety for the enantio- and regioselectivity during the cyclization step.

When *N*-bromophthalimide (NBP) replaced NBS, the enantioselectivity of **2a** reduced to a 77:23 er (entry 6). Given that bromolactonization of **1a** using NBP does not progress without a catalyst (entry 7), it suggests that the decreased er was not due to a background reaction but the imide portions of NBS and NBP contribute to the enantio-determining cyclization step.

Table 1 Bromolactonization of **1a** to give **2a** and/or **3a**.^a



entry	4	yield ^b	2a:3a ^c	er of 2a ^d
1	4a	90%	4:1	82:18
2	4b	99%	<1:99	-
3	4c	82%	<1:99	-
4	4d	77%	<1:99	-
5	4e	86%	<1:99	-
6 ^e	4a	92%	4:1	77:23
7 ^e	none	trace	-	-

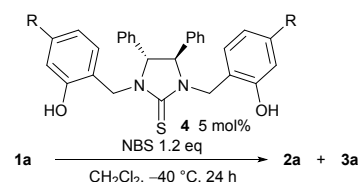
^a Reaction was conducted using **1a** (0.1 mmol), NBS (0.12 mmol), and **4** (5 μmol) in CH₂Cl₂ (2 mL). Remaining bromine species were quenched by aq Na₂S₂O₃ after 24 h. Hyphens in the table denote "not determined." ^b Combined yield of **2a** and **3a**. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC analysis. The enantiomer ratio of **3a** was generally low (50:50–55:45). ^e NBP was used instead of NBS.

We hypothesized the hydroxy groups to function as hydrogen bond donors. To enhance their hydrogen-bonding capability, we installed substituents at the phenol moieties of **4** (Table 2). As expected, the reaction with **4g**, bearing more acidic 2-hydroxy-4-chlorophenyl groups, gave **2a** with improved enantioselectivity (86:14 er, entry 3). Conversely, **4f**, with less acidic 2-hydroxy-4-methylphenyl groups, produced **2a** with diminished enantioselectivity (76:24 er, entry 2).

Following these outcomes, other EWGs were tested (entries 4–7). The optimal outcome was achieved with **4i**, hosting 2-hydroxy-4-bromophenyl groups (92:8 er, entry 5). The enantioselectivity did not improve when **4j** and **4k**, carrying iodine atoms and trifluoromethyl groups respectively, were employed (entries 6 and 7).

When the reaction was conducted at $-60\text{ }^{\circ}\text{C}$, the 5-*exo*-selectivity was significantly improved (**2a:3a** = 6:1, entry 8). A further improvement in 5-*exo*-selectivity was observed when the reaction was quenched by adding 2-methyl-2-butene, followed by an aqueous sodium thiosulfate solution (**2a:3a** = 8:1, entry 9). This could potentially be due to the inhibition of the background 6-*endo*-reaction induced by the rise in temperature from the added aqueous solution.⁴⁸ Finally, an excellent yield was achieved through extending the reaction time (90% yield, entry 10).

Table 2 Catalyst optimization.^a



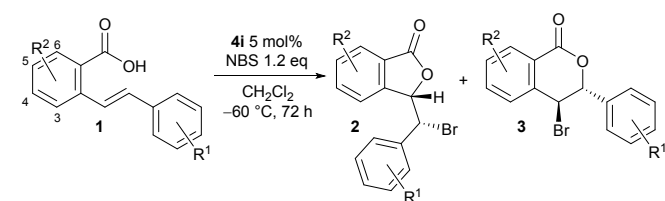
entry	4	R	yield ^b	2a:3a ^c	er of 2a ^d
1	4a	H	90%	4:1	82:18
2	4f	Me	99%	3:1	76:24
3	4g	Cl	78%	2:1	86:14
4	4h	F	77%	3:1	86:14
5	4i	Br	79%	2:1	92:8
6	4j	I	78%	2:1	87:13
7	4k	CF ₃	71%	5:1	87:13
8 ^e	4i	Br	76%	6:1	92:8
9 ^{e,f}	4i	Br	70%	8:1	92:8
10 ^{e,f,g}	4i	Br	90%	8:1	92:8

^a Reaction was conducted using **1a** (0.1 mmol), NBS (0.12 mmol), and **4** (5 μmol) in CH₂Cl₂ (2 mL). Remaining bromine species were quenched with aq Na₂S₂O₃ after 24 h, unless otherwise mentioned. ^b Combined yield of **2a** and **3a**. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC analysis. ^e Reaction at $-60\text{ }^{\circ}\text{C}$. ^f Remaining bromine species were quenched with amylene followed by aq Na₂S₂O₃. ^g Reaction for 72 h.

We applied the optimized conditions to other stilbenecarboxylic acid derivatives (Table 3). When substrates with an electron-rich styryl group were used, the yields obtained were good to excellent (entries 1–4). Despite anticipating the 6-*endo* cyclization to primarily proceed when an electron-donating group resides at the *para*-position of the styryl group, the reaction of **1b**, which contains a methyl group, resulted in 5-*exo*-selectivity (entry 1). In the reaction of **1c** that has a more electron-donating *tert*-butyl group, the 5-*exo*-selectivity diminished, though the enantioselectivity remained favorable (entry 2). Although the reaction of **1c** with a strongly electron-donating methoxy group likely proceeded in a 6-*endo* manner via a carbocation intermediate (entry 3),^{18,49,50} **1d** with a less electron-donating acetoxy group showed 5-*exo*-cyclization with moderate enantioselectivity

(entry 4). Substrate **1e**, which carries an electron-withdrawing chlorine atom, was slowly converted to **2e** and **3e**, maintaining good 5-*exo*- and enantioselectivity (entry 5). However, with a more potent electron-withdrawing nitro group, the reaction failed to proceed even at 0 °C, likely due to the decreased π -electron-density on the C=C double bond (entry 6). Substrates carrying an electron-withdrawing chloro atom or a donating methyl group at the *ortho*- or *para*-position underwent reactions with satisfactory selectivity (entries 7–11).

Table 3. Substrate scope.^a



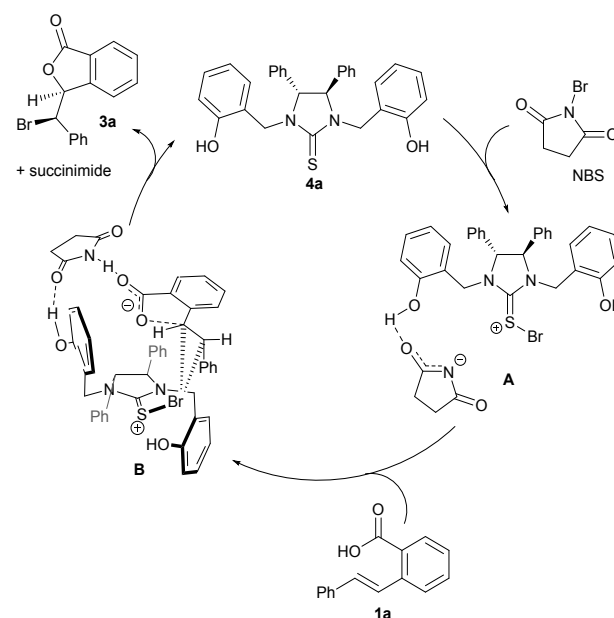
entry	1	R ¹	R ²	yield ^b	2:3 ^c	er of 2 ^d
1	1b	4-Me	H	93%	5:2	94:6
2	1c	4- <i>t</i> -Bu	H	92%	1:1	91:9
3	1d	4-OMe	H	77%	<1:99	-
4	1e	4-OAc	H	84%	1:1	68:32
5 ^e	1f	4-Cl	H	90%	7:2	86:14
6 ^{f,g}	1g	4-NO ₂	H	trace	-	-
7	1h	3-Me	H	88%	6:1	93:7
8	1i	3-OMe	H	71%	7:2	87:13
9 ^e	1j	3-Cl	H	24%	>20:1	78:22
10 ^e	1k	2-Me	H	77%	3:1	83:17
11 ^h	1l	2-Cl	H	72%	3:1	80:20
12	1m	H	6-Me	61%	1:2	61:39
13	1n	H	5-Me	82%	6:1	92:8
14	1o	H	5-Cl	79%	1:1	80:20
15 ^{h,i}	1p	H	4-Me	85%	1:1	86:14

^a Reaction was conducted using **1** (0.1 mmol), NBS (0.12 mmol), and **4i** (5 μ mol) in CH₂Cl₂ (2 mL). Remaining bromine species were quenched with amylene followed by aq Na₂S₂O₃. Hyphens in the table denote "not determined." ^b Combined yield of **2** and **3**. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC analysis. ^e Reaction for 120 h. ^f Reaction for 24 h. ^g Reaction at 0 °C. ^h Reaction at -40 °C. ⁱ NBP was used instead of NBS.

The effects of substituents on the carboxylic acid side were also examined (entries 12–15). Both regio- and enantioselectivities declined in the reaction of **1m** with a methyl group at the 6-position, possibly due to interference with the interaction between the carboxylic acid and the catalyst (entry 12). Indeed, substrates **1n–p**, bearing a substituent at the 4- or 5-position, which likely has less steric interaction, reacted with superior 5-*exo*-selectivity and high enantioselectivity (entries 13–15). Interestingly, the reaction of **1p** with NBS preferentially proceeded in a 6-*endo* manner to yield a **3p**-rich product (**2p:3p** = 1:4). However, the use of NBP in place of NBS facilitated the 5-*exo*-cyclization to yield **2p** and **3p** in a 1:1 ratio (entry 15). The absolute configuration of **2b** was confirmed by X-ray crystallography,⁵¹ while those of other products were tentatively assigned by analogy.

A plausible catalytic cycle is depicted in Scheme 2.^{3–11} Initially, thiourea **4a** is brominated by NBS to form the reactive

brominating agent **A**, in which the resulting imide anion forms a hydrogen bond with the phenol moiety of **4a**. The alkene moiety and carboxy group of **1a** interact concurrently with the bromosulfonium and imide anion moieties of **A**, respectively, resulting in 5-*exo*-bromolactonization of **1a** to yield **3a**. As previously noted, the involvement of the imide anion in the enantio-determining transition state is corroborated by the experimental results (Table 1, entry 7 and Table 3, entry 15).



Scheme 2. Plausible catalytic cycle for the bromolactonization of **1a** with **4a**.

To further understand the origin of enantioselectivity, we carried out density functional theory (DFT) calculations for the transition-state (TS) of the cyclization step. The TS geometries of the reaction of **1a** with **4a**, resulting in the production of **3a** and *ent*-**3a** (TS_{major} and TS_{minor}), were optimized at the ω B97X-D/6-311+G**/PCM:CH₂Cl₂// ω B97X-D/6-31G* theoretical level (Figure 2). Both TS involved C=S \cdots Br⁺ interactions and H-bonding networks through the phenolic OH, succinimide, and the carboxylate anion. In TS_{minor}, a likely steric repulsion exists between the carboxy-attaching phenyl ring and the phenol moiety interacting with the succinimide, while the phenyl ring is located away from the phenol moiety in TS_{major}. Notably, the free energy of TS_{major} was 1.0 kcal/mol lower than TS_{minor}, which aligns with the experimental result (84:16 er). The TS where succinimide is not involved was found to be less stable by 1.5 kcal/mol compared to TS_{minor}. We next investigated the reason for the regioselectivity. In spite of intensive study, the TS to give 6-*endo* product, in which the thiourea moiety and the phenol moiety are both involved, was not located. This indicates that the 6-*endo* cyclization would proceed with mono-activation of bromine or the nucleophilic moiety, and that the observed 5-*exo*-preference is due to geometric restraint in the dual-activation of the substrates by the catalyst.

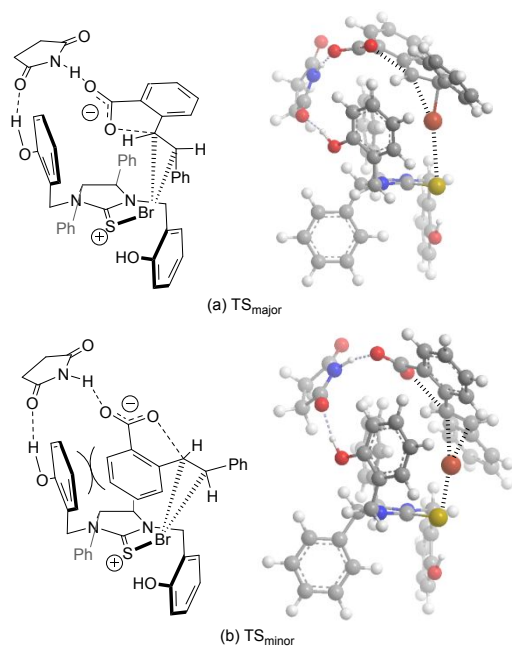


Figure 2 Transition state models for the reaction of **1a** with **4a**.

Conclusions

In conclusion, we have successfully developed the novel chiral thiourea bearing phenol moieties, which facilitates asymmetric 5-*exo*-bromolactonization of stilbenecarboxylic acid. Although the enantio- and regioselectivity have room for improvement, the higher regioselectivity was accomplished in the reaction of **1** without an EWG than the previous reports.^{22,23} Further applications of this catalyst to other asymmetric reactions are currently being explored by our group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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