COMMUNICATION

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

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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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 regio-selectivity.

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 NO_2, CF_3, 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.

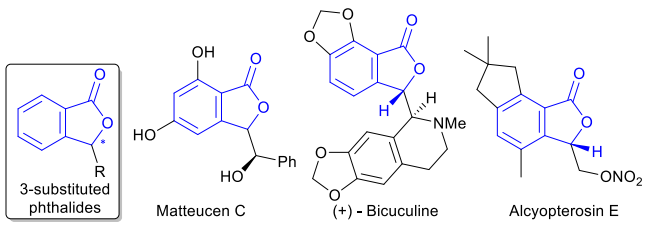
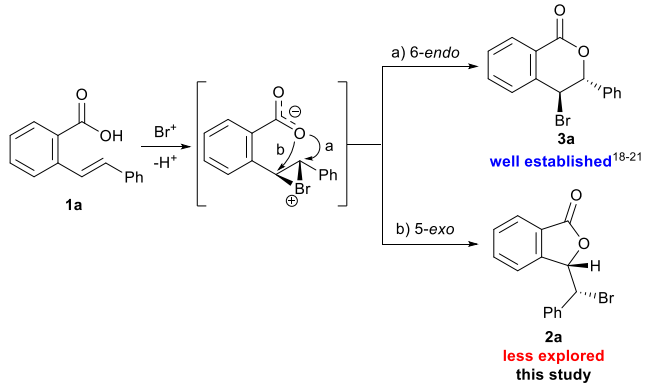


Figure 1. Selected examples of natural products containing chiral 3-substituted phthalide skeletons.



Scheme 1. Bromolactonization of Stilbenecarboxylic Acid.

Following Tang and coworkers' pionnering 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 amide[25] or urea;[26] guanidine with phenol;[27] sulfide with phenol[15] 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 stilbene-carboxylic 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]

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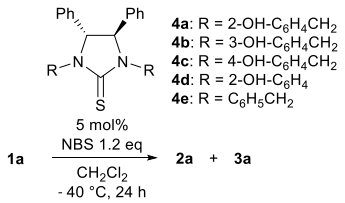
†*Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x*

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 °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), the decreased er should not be due to a background reaction. The results suggest that 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]



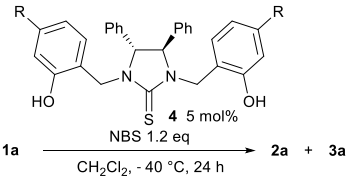
entry	4	yield[b]	2a:3a[c]	er of 2a[d]
1	**4a**	90%	4:1	82:18
2	**4b**	99%	<1:99	-
3	**4c**	82%	<1:99	-
4	**4d**	77%	<1:99	-
5	**4e**	86%	<1:99	-
6[e]	**4a**	92%	4:1	77:23
7[e]	none	trace	-	-

[a] Reaction was conducted using **1a** (0.1 mmol), NBS (0.12 mmol), and **4** (5 μmol) in CH_2Cl_2 (2 mL). Remaining bromine species were quenched by aq $Na_2S_2O_3$ after 24 h. Hyphens in the table denote "not determined." [b] Combined yield of **2a** and **3a**. [c] Determined by ^{1}H 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 °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]



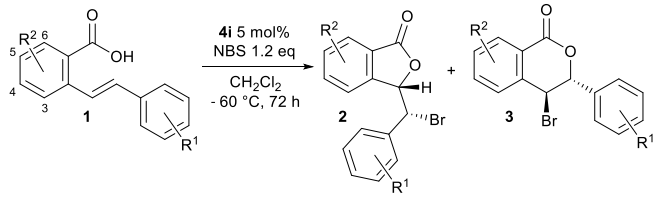
entry	4	R	yield[b]	2a:3a[c]	er of 2a[d]
1	**4a**	H	90%	4:1	82:18
2	**4f**	Me	99%	3:1	76:24
3	**4g**	Cl	78%	2:1	86:14
4	**4h**	F	77%	3:1	86:14
5	**4i**	Br	79%	2:1	92:8
6	**4j**	I	78%	2:1	87:13
7	**4k**	CF_3	71%	5:1	87:13
8[e]	**4i**	Br	76%	6:1	92:8
9[e,f]	**4i**	Br	70%	8:1	92:8
10[e,f,g]	**4i**	Br	90%	8:1	92:8

[a] Reaction was conducted using **1a** (0.1 mmol), NBS (0.12 mmol), and **4** (5 μmol) in CH_2Cl_2 (2 mL). Remaining bromine species were quenched with aq $Na_2S_2O_3$ after 24 h, unless otherwise mentioned. [b] Combined yield of **2a** and **3a**. [c] Determined by ^{1}H NMR. [d] Determined by chiral HPLC analysis. [e] Reaction at –60 °C. [f] Remaining bromine species were quenched with amylene followed by aq $Na_2S_2O_3$. [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 **1d** with a strongly electron-donating methoxy group likely proceeded in a 6-*endo* manner via a carbocation intermediate (entry 3),[18,49,50] **1e** with a less electron-donating acetoxy group showed 5-*exo*-cyclization with moderate enantioselectivity (entry 4). Substrate **1f**, which carries an electron-withdrawing chlorine atom, was slowly converted to **2f** and **3f**, 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]

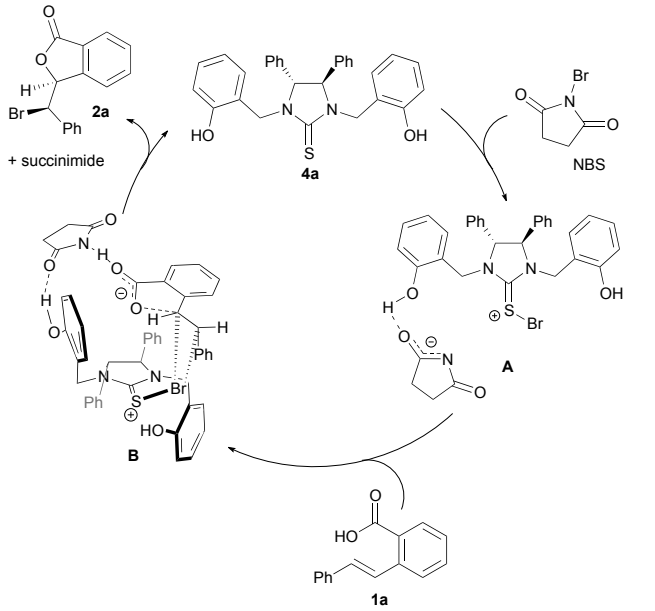


entry	1	R^1	R^2	yield[b]	2:3[c]	er of 2[d]
1	**1b**	4-Me	H	93%	5:2	94:6
2	**1c**	4-*t*-Bu	H	92%	1:1	91:9
3	**1d**	4-OMe	H	77%	<1:99	-
4	**1e**	4-OAc	H	84%	1:1	68:32
5[e]	**1f**	4-Cl	H	90%	7:2	86:14
6[f,g]	**1g**	4-NO_2	H	trace	-	-
7	**1h**	3-Me	H	88%	6:1	93:7
8	**1i**	3-OMe	H	71%	7:2	87:13
9[e]	**1j**	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 μmol) in CH_2Cl_2 (2 mL). Remaining bromine species were quenched with amylene followed by aq $Na_2S_2O_3$. Hyphens in the table denote "not determined." [b] Combined yield of **2** and **3**. [c] Determined by ^{1}H 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 **2a**. 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 ωB97X-D/6-311+G**/PCM:CH_2Cl_2//ωB97X-D/6-31G* theoretical level (Figure 2). Both TS involved C=S···Br^+ interactions and

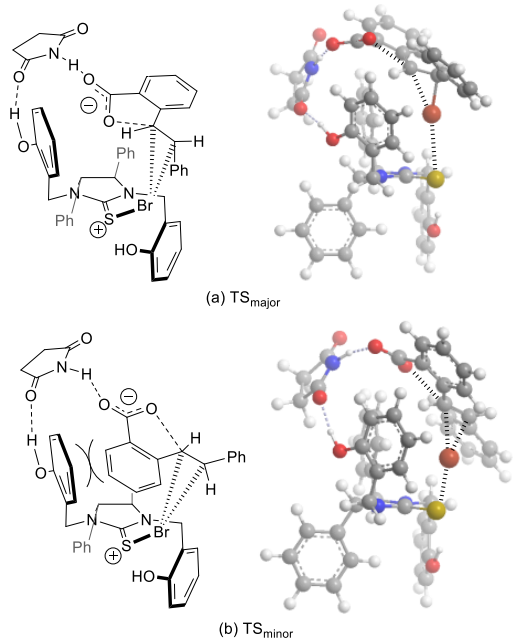


Figure 2 Transition state models for the reaction of **1a** with **4a**.

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. Inspite 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 restrain in the dual-activation of the substrates by the catalyst.

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

This research was supported in part by JSPS (KAKENHI JP22H05569), JST (JPMJFS2130), the Mochida Memorial Foundation for Medical and Pharmaceutical Research, Tokushima University (Research Clusters program No. 2201004), and the Japan Science Society (Sasakawa Scientific Research Grant)

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