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Catalyst-Controlled Regio- and Stereoselective Bromolactonization with Chiral Bifunctional Sulfides

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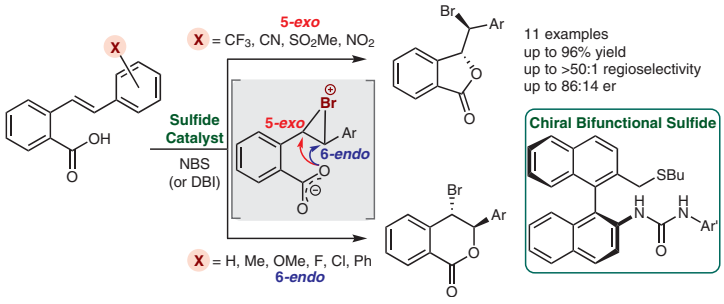

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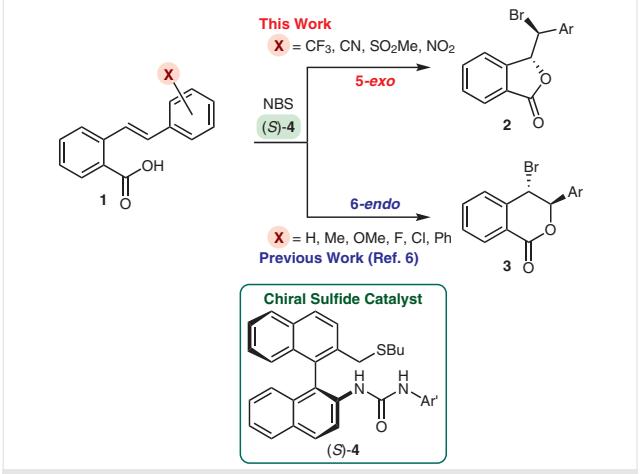
Abstract Highly regioselective 5-*exo* bromolactonizations of stilbene-type carboxylic acids bearing electron-withdrawing substituents are achieved for the first time via the use of chiral bifunctional sulfide catalysts possessing a urea moiety. The chiral phthalide products are obtained in moderate to good enantioselectivities as the result of 5-*exo* cyclizations.

Key words asymmetric synthesis, lactonization, organocatalysis, regioselectivity, sulfides

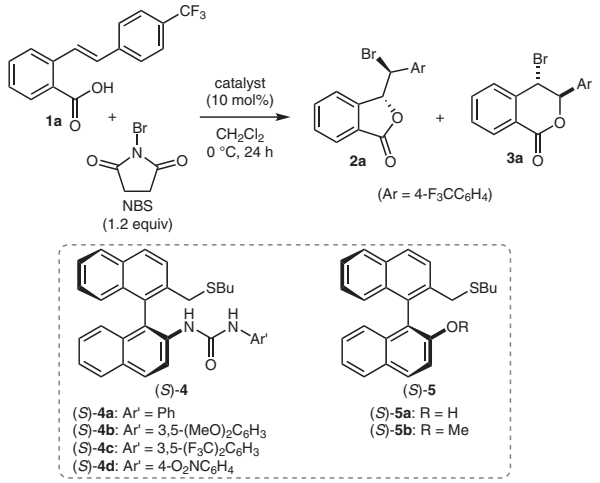
Catalytic asymmetric reactions with modularly designed organocatalysts are recognized as one of the most effective methods to produce important chiral molecules in highly enantioenriched form.[1] Various types of chiral organocatalysts have been designed and applied to highly stereoselective transformations over the past two decades. Among these organocatalysts, chiral amines and phosphines are some of the most widely utilized catalysts in catalytic asymmetric synthesis. By comparison with an inordinate number of reactions using chiral amine and phosphine catalysts, examples of efficient asymmetric reactions with chiral sulfide catalysts have remained limited and underdeveloped.[2,3] In this context, we became interested in the design of effective chiral sulfide catalysts and successfully developed bifunctional catalysts (*S*)-**4** for highly enantioselective bromolactonizations with stilbene-type carboxylic acids **1** (Scheme 1).[4–6] In previous work, we selectively synthesized 3,4-dihydroisocoumarin products **3** via 6-*endo* cyclization under optimized reaction conditions with selected substrates, and 5-*exo* products **2** were not formed.[6] During the course of an extension of the substrate scope for the asymmetric bromolactonization of **1**, we found that 5-*exo* cyclization products **2**, which possess a phthalide structure as an important structural motif,[7,8] could be selectively obtained in reactions with stilbene-type carboxylic acids **1** bearing electron-withdrawing substituents (Scheme 1). Herein, we report catalyst-controlled regio- and stereoselective 5-*exo* bromolactonizations of compounds **1** with bifunctional chiral sulfides (*S*)-**4**.



Scheme 1 Bifunctional-sulfide-catalyzed asymmetric bromolactonizations of stilbene-type carboxylic acids **1**

Asymmetric bromolactonization of **1a** possessing a trifluoromethyl group was selected as a model reaction in an attempt to develop an effective catalyst for the 5-*exo*-selective cyclization. Yeung reported that the 5-*exo* cyclization product **2a** was preferentially obtained in the bromolactonization of **1a**, with or without catalysts, in low to moderate regioselectivities (**2a**:**3a** = 2:1 to 4:1).[5] Our original aim was to improve the regioselectivity via the use of bifunctional sulfide catalysts (*S*)-**4** (Table 1). An attempted reaction of **1a** with *N*-bromosuccinimide (NBS) in CH_2Cl_2 under the influence of phenylurea-type bifunctional catalyst (*S*)-**4a** at 0 °C

Table 1 Catalyst Optimization[a]



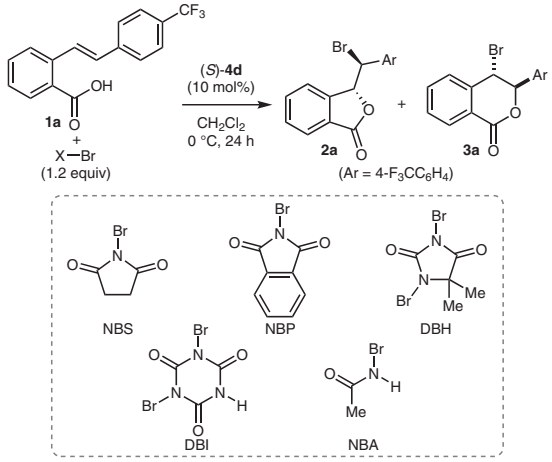
Entry	Cat.	Regioselectivity(**2a**:**3a**)[b]	Yield of **2a** (%)[c]	er of **2a**[d,e]
1	(*S*)-**4a**	5.3:1	76	76:24
2	(*S*)-**4b**	3.2:1	67	75:25
3	(*S*)-**4c**	7.1:1	84	82:18
4	(*S*)-**4d**	8.5:1	86	82:18
5	(*S*)-**5a**	2.3:1	59	49:51
6	(*S*)-**5b**	1.1:1	39	50:50
7	none[f]	1.8:1	7	(50:50)

[a] Reaction conditions: **1a** (0.10 mmol), NBS (0.12 mmol), catalyst (10 mol%, 0.010 mmol), CH_2Cl_2 (2.0 mL), 0 °C, 24 h.
[b] Regioselectivities were confirmed via ^{1}H NMR analysis of the crude reaction mixture.
[c] Yield of isolated product **2a**.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] Enantioselectivities of product **3a** were low (lower than 59:41 er).
[f] The reaction was performed without a catalyst.

for 24 hours provided bromolactonization product **2a** in a good yield but with moderate levels of regio- and enantioselectivity (Table 1, entry 1). Encouraged by this result, a fine-tuning of the urea moiety on catalyst (*S*)-**4** was performed to improve the regioselectivity. Although the introduction of an arylurea possessing electron-donating groups on the catalyst (**4b**) caused a reduction in regioselectivity (Table 1, entry 2), catalysts bearing electron-deficient arylureas (**4c** and **4d**) improved the levels of both the regio- and enantioselectivity (Table 1, entries 3 and 4). A higher level of regioselectivity was observed in the reaction with catalyst (*S*)-**4d** (Table 1, entry 4). To establish the importance of the urea moiety on catalysts (*S*)-**4**, we also examined the reactions with related BINOL-derived catalysts (*S*)-**5a** and **5b**. Although these catalysts promoted the bromolactonization of **1a**, the 5-*exo* cyclization product was obtained only in low levels of regio- and enantioselectivity (Table 1, entries 5 and 6). Additionally, the reaction without a catalyst proceeded slowly under the reaction conditions with low regioselectivity (Table 1, entry 7). These results clearly suggested that the urea moiety of catalysts (*S*)-**4** was essential for obtaining good levels of regio- and enantioselectivity in the present 5-*exo* bromolactonization.[9]

We also examined the effect of different brominating reagents under the influence of optimized catalyst (*S*)-**4d** (Table 2). The levels of regio- and enantioselectivity for product **2a** depend significantly on the structure of the brominating reagent. Reactions with brominating reagents possessing 5- and 6-membered ring structures generally gave the target 5-*exo* cyclization product **2a** in good to high levels of regioselectivity and with moderate to good levels of enantioselectivity (Table 2, entries 1–4). On the other hand, *N*-bromoacetamide (NBA), an acyclic brominating reagent, gave product **2a** with lower levels of regio- and enantioselectivity (Table 2, entry 5). Interestingly, the 6-*endo* cyclization product **3a** was obtained in good regioselectivity when the reaction was performed with bromine (Br_2) as the brominating reagent, although almost no enantioselectivity was observed (~50:50 er) (Table 2, entry 6).[10] Among these brominating reagents, the highest level of regioselectivity

Table 2 Effect of Different Brominating Reagents[a]

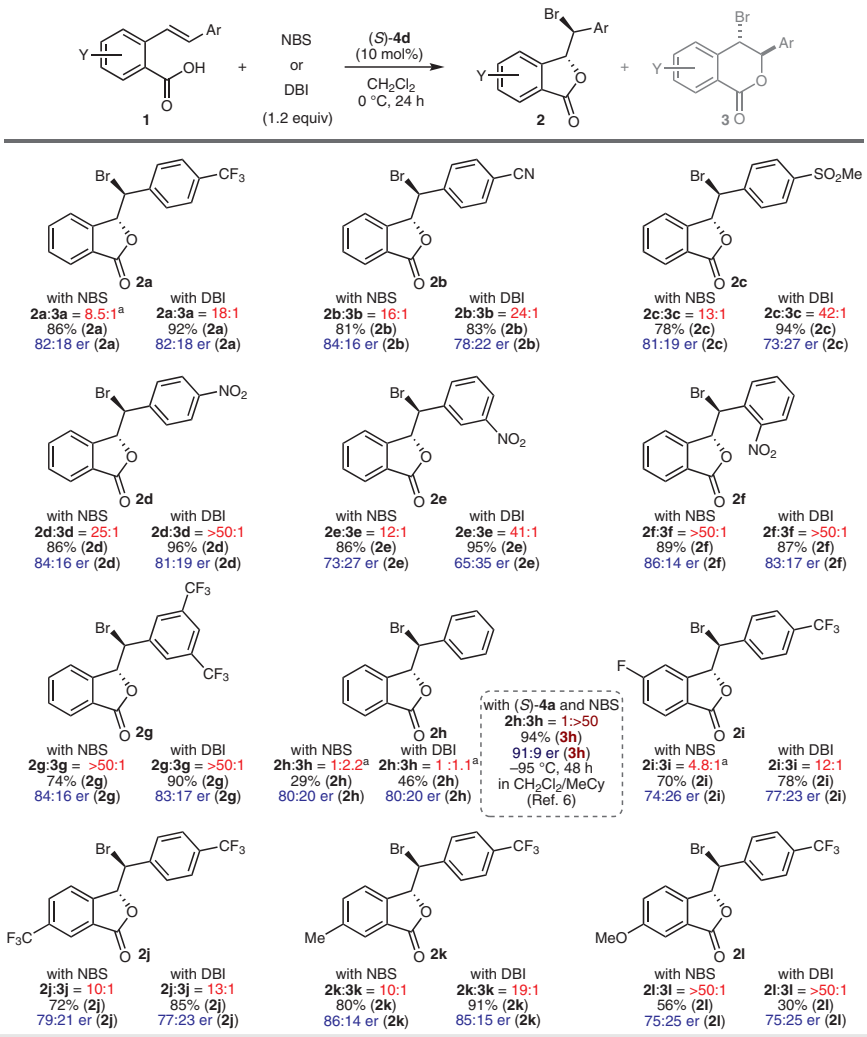


Entry	X–Br	Regioselectivity (**2a**:**3a**)[b]	Yield of **2a** (%)[c]	er of **2a**[d,e]
1	NBS	8.5:1	86	82:18
2	NBP	13:1	90	71:29
3	DBH	15:1	89	80:20
4	DBI	18:1	92	82:18
5	NBA	3.3:1	71	70:30
6	Br_2	1:11	8 (77)[f]	50:50

[a] Reaction conditions: **1a** (0.10 mmol), brominating reagent (0.12 mmol), catalyst (*S*)-**4d** (10 mol%, 0.010 mmol), CH_2Cl_2 (2.0 mL), 0 °C, 24 h.
[b] Regioselectivities were confirmed via ^{1}H NMR analysis of the crude reaction mixture.
[c] Yield of isolated product **2a**.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] Enantioselectivities of product **3a** were low (lower than 59:41 er).
[f] The yield in parentheses refers to the isolated yield of product **3a**.

for **2a** was observed with dibromoisocyanuric acid (DBI), and the highest levels of enantioselectivity were achieved with NBS and DBI (Table 2, entries 1 and 4).[11]

With the optimum catalyst (*S*)-**4d** and reaction conditions in hand, we next studied the substrate scope for the 5-*exo*-selective bromolactonization of **1** (Scheme 2).[12] Both NBS and DBI were examined as possible brominating reagents that could provide generality for each substrate. First, we investigated the effect that an electron-withdrawing group (EWG) at the *para*-position of **1** exerted on an aromatic ring (Ar). The application of stilbene-type carboxylic acids **1** bearing a variety of EWGs produced highly regioselective reactions and products **2a–d** in moderate to good levels of enantioselectivity. In general, the reactions with DBI provided higher levels of regioselectivity with slightly lower levels of enantioselectivity than those of the reactions with NBS. The reactions of compounds **1** possessing EWGs at the *meta*- and *ortho*-positions were also examined, and products **2e–g** were obtained with high levels of regioselectivity. On the other hand, the reactions with simple substrate **1h** (Ar = Ph), without an EWG, produced bromolactonization products **2h** and **3h** with low levels of regioselectivity, and 6-*endo* cyclization product **3h** was the major product even under the optimum reaction conditions for 5-*exo* cyclization. It should be noted that a completely regioselective reaction to produce **3h** in a highly enantioselective manner was achieved with catalyst (*S*)-**4a** under low reaction temperature conditions.[6] These opposite trends in regioselectivity can be explained by the nature of the substrates (Figure 1). When the reaction was performed with a simple substrate, **1h** (Ar = Ph), 6-*endo* cyclization was favored due to stabilization by the cationic nature of the benzylic carbon of the phenyl group (**A** in Figure 1). On the other hand, the introduction of an EWG on the aryl moiety (Ar) destabilized the cationic nature of the benzylic carbon. As a result, 5-*exo* cyclization was favored slightly more than 6-



Scheme 2 Substrate scope. [a] Enantioselectivities of products **3** were low (lower than 59:41 er).

endo cyclization (**B** in Figure 1). This trend for the production of 5-*exo* bromolactonization products **2** was enhanced by the reactions using urea-type bifunctional sulfide catalysts (*S*)-**4**, due to the formation of a well-organized intermediate (**C** in Figure 1).[6] The substituent effects on the other aromatic ring (Y) of **1** were also examined to produce **2i–l** (Scheme 2). Even with the introduction of EWGs to another aromatic ring (Y), the reactions proceeded with good levels of regioselectivity to give **2i** and **2j**. The products **2k** and **2l** possessed electron-donating groups and were obtained in good levels of regio- and enantioselectivity.

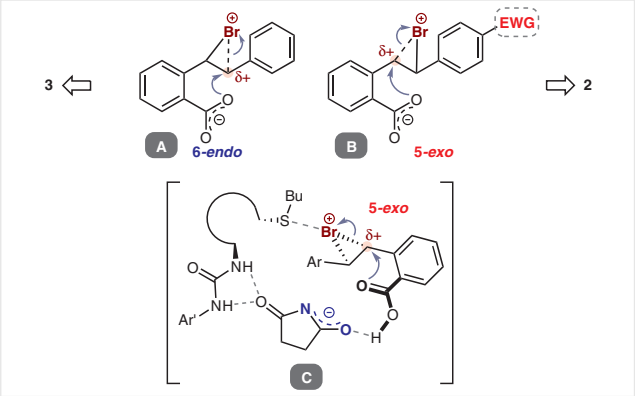


Figure 1 Cyclization steps

In summary, we have successfully achieved hitherto unknown, highly regioselective 5-*exo* bromolactonizations of stilbene-type carboxylic acids **1** bearing EWGs under the influence of urea-type chiral bifunctional sulfide catalysts (*S*)-**4**. The target chiral phthalide products **2** were obtained with moderate to good levels of enantioselectivity. The bifunctional design of catalysts (*S*)-**4** with a urea moiety was essential in obtaining good levels of regio- and enantioselectivity for the reported 5-*exo* bromolactonization.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610716.

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(9) For the reaction with catalyst (*S*)-**4d** at low temperature and the reaction with another different catalyst, see Schemes S1 and S2 in the Supporting Information.

(10) The reaction with bromine (Br_2) may proceed via a non-catalyzed reaction pathway (background reaction pathway). For a reaction using another reactive brominating reagent, see Scheme S3 in the Supporting Information.

(11) For other control experiments, see Scheme S4 in the Supporting Information.

(12) **Asymmetric Bromolactonizations; General Procedure**
A solution of substrate **1** (0.10 mmol) and catalyst (*S*)-**4d** (10 mol%, 0.010 mmol) in CH_2Cl_2 (2 mL) was cooled to 0 °C. After stirring for 10 min, *N*-bromosuccinimide (NBS) (0.12 mmol) was added and the resulting mixture was stirred for 24 h at 0 °C. The mixture was quenched with saturated aqueous Na_2SO_3 (4.0 mL) at 0 °C, stirred for 10 min at 0 °C, diluted with CH_2Cl_2 (2 mL) and H_2O (2 mL) and then warmed to room temperature. The organic materials were extracted with CH_2Cl_2 (3 × 5 mL) and the combined extracts dried over Na_2SO_4 and concentrated. (The ^1H NMR analysis of the crude reaction mixture was performed at this stage to determine the regioselectivity of the bromolactonization products.) The residue was purified by flash column chromatography on silica gel (hexane/EtOAc as eluent) to give product **2**. The enantioselectivity of the product **2** was determined by HPLC analysis on a chiral stationary phase.

Compound 2a[5]
Yield: 31.9 mg (86%); colorless oil; $[\alpha]_D^{21}$ +4.4 (*c* = 0.87, $CHCl_3$); 82:18 er; HPLC (Daicel Chiralpak IC-3, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, 230 nm): t_R = 59.3 min (major) and 68.8 min (minor). IR (neat): 1769, 1324, 1286, 1167, 1124, 1114, 1067, 1018 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.2 Hz, 1 H), 7.67–7.71 (m, 2 H), 7.53–7.60 (m, 5 H), 5.96 (d, *J* = 6.4 Hz, 1 H), 5.16 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 146.0, 140.1, 134.1, 131.1 (q, *J* = 32.1 Hz), 130.2, 129.0, 126.5, 126.0 (q, *J* = 2.5 Hz), 125.7 (m), 123.7, 123.6 (q, *J* = 272 Hz), 82.1, 51.8.