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Authors: Ryuichi Nishiyori, Ayano Tsuchihashi, Ayaka Mochizuki, Kazuma Kaneko, Masahiro Yamanaka, and Seiji Shirakawa

To be cited as: *Chem. Eur. J.* 10.1002/chem.201803703

Link to VoR: http://dx.doi.org/10.1002/chem.201803703

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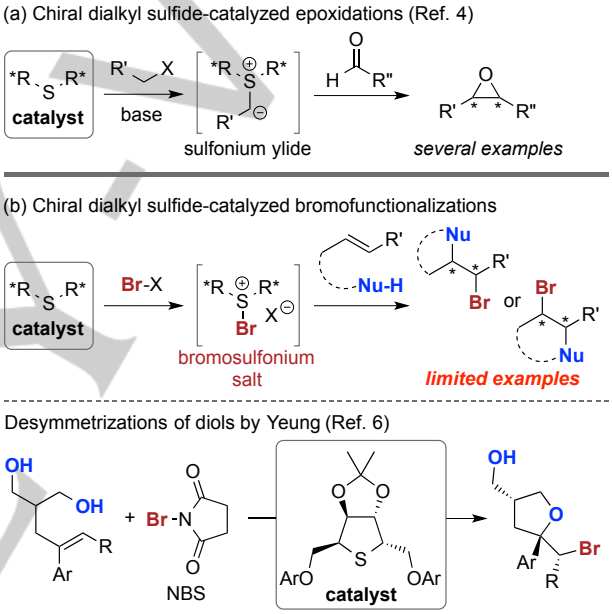
Design of Chiral Bifunctional Dialkyl Sulfide Catalysts for Regio-, Diastereo-, and Enantioselective Bromolactonization

Ryuichi Nishiyori,[a] Ayano Tsuchihashi,[a] Ayaka Mochizuki,[b] Kazuma Kaneko,[b] Masahiro Yamanaka,*[b] and Seiji Shirakawa*[a]

Abstract: Although a wide variety of chiral organocatalysts have been developed for asymmetric transformations, effective chiral dialkyl sulfide organocatalysts remain relatively rare and under-developed, despite the potential utility of dialkyl sulfide catalysts. Herein, we report the development of chiral bifunctional dialkyl sulfide catalysts possessing a urea moiety for regio-, diastereo-, and enantioselective bromolactonization. The importance of the bifunctional design of chiral sulfide catalysts was clearly demonstrated in the present work. The roles of both the sulfide and urea moieties of the catalyst were clarified based on the results of experimental and theoretical investigation.

Asymmetric organocatalysis using well-designed chiral catalysts is one of the most reliable methods to create important molecules in a highly stereoselective fashion.[1] A variety of chiral organocatalysts derived from both natural and synthetic scaffolds have been developed for asymmetric transformations, particularly over the past two decades. Among these, effective chiral dialkyl sulfide catalysts have remained relatively rare and under-developed, despite their potential.[2] Stoichiometric sulfonium ylide-mediated epoxidation is a well-known method in organic synthesis.[3] Based on the reaction, several examples of catalytic asymmetric epoxidation have been developed with chiral sulfide catalysts that generate sulfonium ylide intermediates (Scheme 1a).[4] Bromosulfonium salt-mediated asymmetric reactions are another form of chiral sulfide catalysis that seems to be attractive since bromosulfonium salts are common reagents for bromination (Scheme 1b).[5] Yeung and co-workers demonstrated the efficient catalysis of sugar-derived dialkyl sulfides in asymmetric bromoetherification via desymmetrization of diols.[6] Although this is an important achievement for chiral dialkyl sulfide-catalyzed bromofunctionalization, successful results have only been obtained in the desymmetrization of diols,[7] and a more general form of sulfide catalysis is highly desired.[8] In this context, we are interested in the design of new chiral dialkyl sulfide catalysts for asymmetric bromofunctionalization.[9] Herein, we report the development of 1,1'-bi-2-naphthol (BINOL)-derived bifunctional dialkyl sulfide catalysts possessing a urea moiety for highly regio-, diastereo-, and enantioselective bromolactonization.[10,11]



Scheme 1. Chiral dialkyl sulfide-catalyzed asymmetric reactions.

The design of new chiral dialkyl sulfide catalysts (*S*)-**1** and a working model of intramolecular bromofunctionalization appear in Scheme 2. When the sulfide catalyst is mixed with *N*-bromosuccinimide (NBS), bromosulfonium succinimide is formed. The position of the succinimide anion is fixed by the hydrogen-bonding interactions with a urea moiety of the catalyst. The double bond of an alkene substrate is then activated by the bromosulfonium moiety to form a cyclic bromonium ion intermediate. Simultaneously, an acidic pro-nucleophilic moiety is activated by the succinimide anion, which serves as a Brønsted base, to provide a well-organized transition-state (TS). Regio-, diastereo-, and enantioselective intramolecular cyclization then occurs to yield the bromofunctionalization product.

[a] R. Nishiyori, A. Tsuchihashi, Prof. Dr. S. Shirakawa
Department of Environmental Science, Graduate School of Fisheries and Environmental Sciences,
Nagasaki University
1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
E-mail: seijishirakawa@nagasaki-u.ac.jp
Homepage: http://seijishirakawa.wix.com/greenchemistry
[b] A. Mochizuki, K. Kaneko, Prof. Dr. M. Yamanaka
Department of Chemistry and Research Center for Smart Molecules, Faculty of Science,
Rikkyo University
3-34-1, Nishi-Ikebukuro, Toshima-ku, Tokyo 171-8501, Japan
E-mail: myamanak@rikkyo.ac.jp

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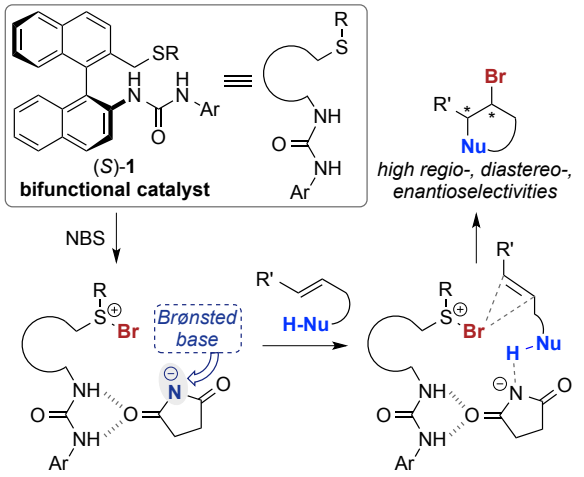
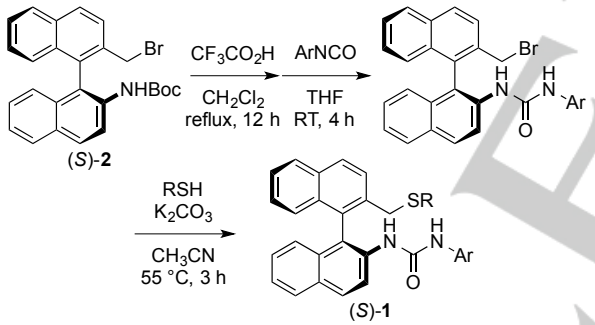


Scheme 2. Design and a possible working model of chiral bifunctional dialkyl sulfides (*S*)-**1**.

Target chiral bifunctional sulfides (*S*)-**1** were prepared from the reported compound (*S*)-**2** (Scheme 3).[12] Following deprotection of the *tert*-butoxycarbonyl (Boc) group on the nitrogen of (*S*)-**2**, the resultant primary amino group was treated with aryl isocyanates to obtain the corresponding aryl urea compounds. An arylmethyl bromide moiety of the resultant urea compounds was then treated with thiols to provide the target sulfide catalysts (*S*)-**1**.



Scheme 3. Synthesis of chiral bifunctional dialkyl sulfides (*S*)-**1**.

The absolute structure of a chiral dialkyl sulfide (*S*)-**1a** was unambiguously confirmed by X-ray diffraction analysis (Figure 1).[13] The positions of sulfide and urea moieties were suitable to create an effective reaction environment with the substrates, as shown in Scheme 2.

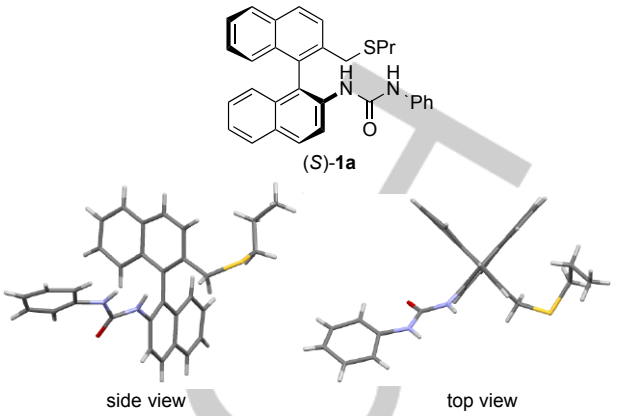


Figure 1. X-ray crystal structure of a chiral dialkyl sulfide (*S*)-**1a**.

Asymmetric bromolactonization with alkenes **3** was selected as a model reaction to examine the catalytic ability of chiral bifunctional sulfides (*S*)-**1** (Table 1).[14] The bromolactonization of alkenes **3** has produced 3,4-dihydroisocoumarin products **4** as a structural motif for important natural products and pharmaceuticals.[15] A bromo group of 3,4-dihydroisocoumarin products **4** easily transforms to other functional groups via S_N2-type reactions.[14] Although a highly enantioselective version of the bromolactonization of alkenes **3** with cinchona alkaloid-derived amino-thiocarbamate catalysts has already been reported by Yeung, several drawbacks exist in the catalytic system.[14a] First, the reaction with **3a** was efficiently promoted by a quinidine-derived catalyst to give (–)-**4a** (enantiomer of **4a** in Table 1). Surprisingly, however, the quinine-derived version of the catalyst, which was commonly recognized as a pseudo-enantiomer, did not promote the bromolactonization. That is to say, the reported catalytic system could not access product (+)-**4a** (absolute configuration of **4a** in Table 1). Second, the regioselectivities of the reactions were moderate, and 5-*exo*-cyclization products **5** were also produced. Our motivation was to solve these drawbacks by using bifunctional sulfides (*S*)-**1**, and the first issue was not a problem in our catalytic system since both enantiomers of BINOL-derived catalyst **1** were readily obtainable.

When a solution of substrate **3a** and NBS in CH_2Cl_2 was stirred at –78 °C for 24 h in the absence of a catalyst, only trace amounts of product **4a** were obtained (entry 1, Table 1). To our delight, chiral bifunctional sulfide (*S*)-**1a** efficiently promoted the reaction of **3a** with NBS to provide product **4a** in a high yield with good enantioselectivity (62% *ee*; entry 2). Fortunately, 5-*exo*-cyclization product **5a** was not formed in our catalytic system and the second issue of the reported method was also solved. Fine-tunings of sulfide and urea moieties [R and Ar in (*S*)-**1**] were performed (entries 2–8), and the best result was obtained with catalyst (*S*)-**1b** (68% *ee*; entry 3). Interestingly, phenyl sulfide catalyst (*S*)-**1e** showed a very low level of catalytic activity (entry 6). The reaction conditions were further optimized via the use of catalyst (*S*)-**1b**, and the enantioselectivity was improved to 83% with complete regio- and diastereoselectivities (entry 9). The enantiomer of **4a** [(–)-**4a**] could, of course, be obtained in the reaction using catalyst (*R*)-**1b** (entry 10).

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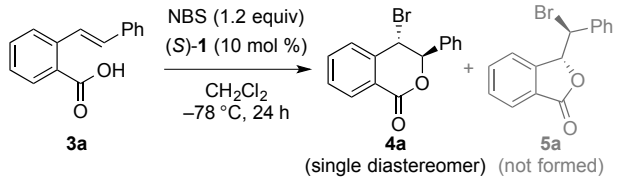
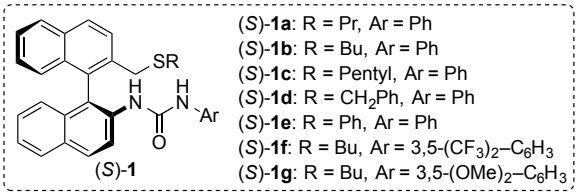
Table 1. Catalyst optimization.[a]

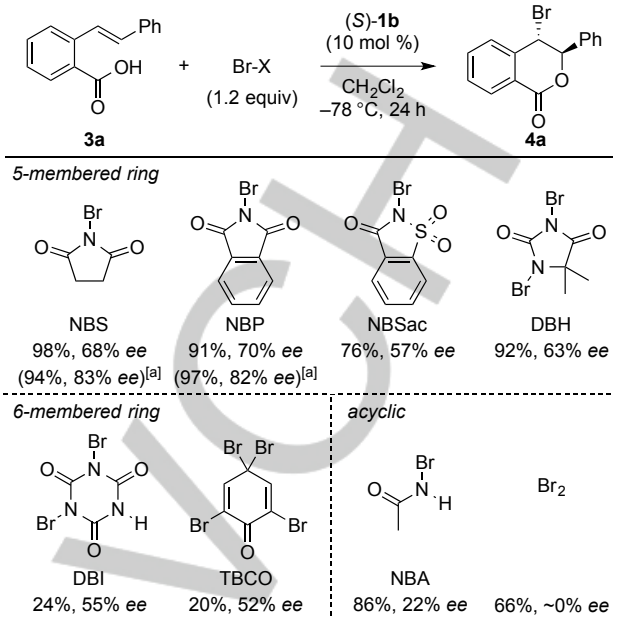




Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	none	trace	–
2	(*S*)-**1a**	95	62
3	(*S*)-**1b**	98	68
4	(*S*)-**1c**	92	66
5	(*S*)-**1d**	78	38
6	(*S*)-**1e**	<5	–
7	(*S*)-**1f**	99	53
8	(*S*)-**1g**	84	37
9[d]	(*S*)-**1b**	94	83
10[d]	(*R*)-**1b**	92	–83

[a] Reaction conditions: **3a** (0.10 mmol), NBS (0.12 mmol), catalyst (*S*)-**1** (10 mol %, 0.010 mmol), CH_2Cl_2 (2.0 mL), –78 °C, 24 h. Regio- and diastereoselectivities of product **4a** were confirmed via ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated product **4a**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed in CH_2Cl_2-methylcyclohexane (MeCy) (1.0 mL each) at –95 °C for 48 h.

To gain evidence for the proposed role of generated succinimide anion in Scheme 2, the effects of brominating reagents were examined with catalyst (*S*)-**1b** (Scheme 4). The enantioselectivities of product **4a** significantly depend on the structure of the brominating reagents. Reactions with brominating reagents possessing 5-membered ring structures gave product **4a** in similar levels of enantioselectivity (57–70% *ee*). Brominating reagents with 6-membered ring structures gave slightly lower enantioselectivities (52–55% *ee*) than 5-memberd ring structures. On the other hand, acyclic brominating reagents, such as *N*-bromoacetamide (NBA) and bromine, gave product **4a** in quite low enantioselectivities (0–22% *ee*). These results strongly suggested that corresponding (imide) anions generated from brominating reagents were involved in the stereochemistry-determining steps, as proposed in Scheme 2.



Scheme 4. Effect of brominating reagents. [a] Reactions in parentheses were performed in CH_2Cl_2-methylcyclohexane (MeCy) at –95 °C for 48 h.

Control experiments with several catalysts were performed to establish the importance of the bifunctional design of catalysts (*S*)-**1** (Table 2). When mono-functional sulfide catalyst (*S*)-**6a** was employed, the reaction of **3a** with NBS efficiently proceeded to give product **4a** in a high yield, but with no enantioselectivity (entry 2). A related bifunctional catalyst (*S*)-**6b**, that possesses a hydroxy group was also examined (entry 3). Although enantioselectivity of the obtained product **4a** was moderate (38% *ee*), chiral induction was observed. These results suggested that the bifunctional design of a sulfide catalyst is important for enantioselective bromofunctionalization. To clarify the role of the sulfide moiety in the (*S*)-**1**, chiral urea catalyst (*R*)-**7** was prepared and applied to the bromolactonization. As expected, the reaction was sluggish and product **4a** was obtained in only a low yield (entry 4). These results clearly indicated that the dialkyl sulfide moiety of the (*S*)-**1** is essential to promote the reaction. A dual catalyst system employing the (*R*)-**7** and dibutyl sulfide was also examined. Although the reaction proceeded to give product **4a**, the enantioselectivity was quite low (6% *ee*; entry 5). The results appear in Scheme 4 and in Table 2 fully support our proposed working model of catalysts (*S*)-**1** in Scheme 2.

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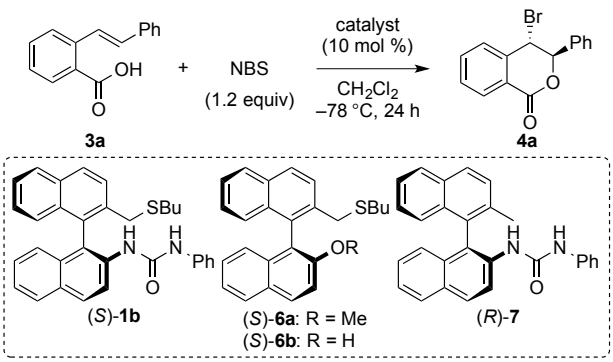
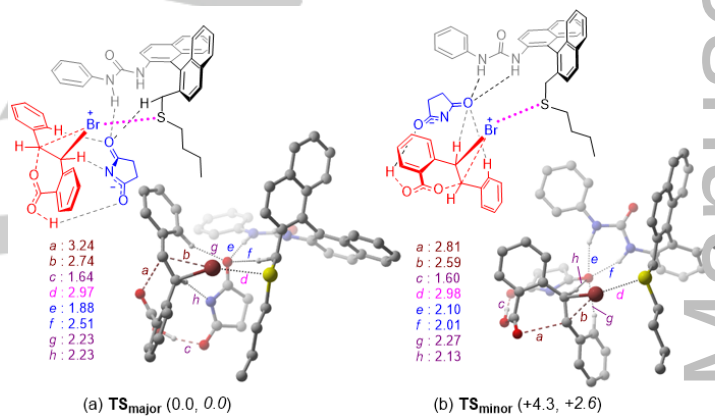
Table 2. Control experiments.[a]



Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	(*S*)-**1b**	98	68
2	(*S*)-**6a**	93	~0
3	(*S*)-**6b**	26	38
4	(*R*)-**7**	<5	–
5	(*R*)-**7** + Bu_2S[d]	64	6

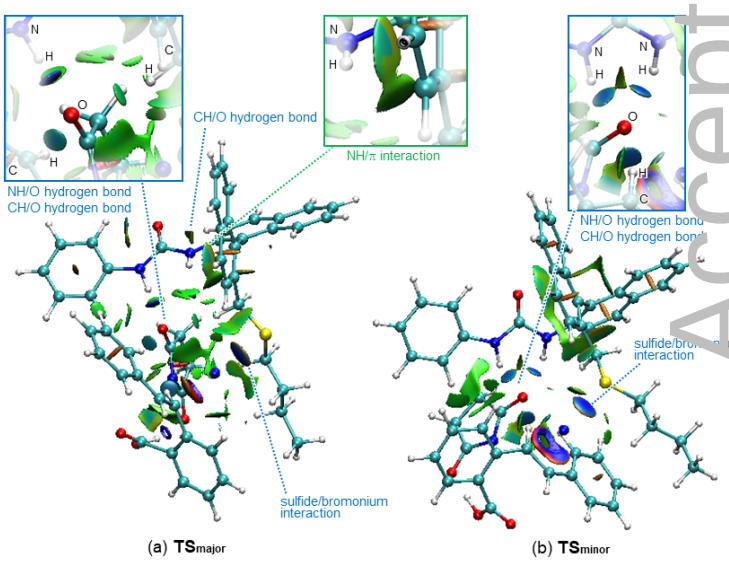
[a] Reaction conditions: **3a** (0.10 mmol), NBS (0.12 mmol), catalyst (10 mol %, 0.010 mmol), CH_2Cl_2 (2.0 mL), –78 °C, 24 h. Regio- and diastereoselectivities of product **4a** were confirmed by ^{1}H NMR analysis of the crude reaction mixture. [b] Yield of isolated product **4a**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed using a dual catalyst system [(*R*)-**7** (10 mol %, 0.010 mmol) + Bu_2S (10 mol %, 0.010 mmol)].

To gain deeper insight into the origin of enantioselectivity, DFT calculation was conducted.[16] Based on the related studies,[10c,f,11b,c] the final cyclization step of our working model (Scheme 2) was investigated as the stereochemistry-determining step. After screening various cyclization TS models with and without a succinimide anion (Figure S1 in Supporting Information), an associative TS model involving monocoordinated succinimide anion proved to be the most promising model. This is consistent with the experimentally observed dependence of enantioselectivity on the counter anion of the brominating reagent (Scheme 4). Using the promising TS model, the origin of the high level of enantioselectivity was investigated in detail (**TS$_{major}$** and **TS$_{minor}$**, Figure 2). **TS$_{major}$** is 4.3 kcal mol^{-1} (2.6 kcal mol^{-1} in Gibbs free energy) more stable than **TS$_{minor}$** in qualitatively agreement with the experimental result. Both **TS$_{major}$** and **TS$_{minor}$** construct the well-organized structures via a hydrogen-bonding network around the succinimide anion and the sulfide/bromonium interaction (Figure 2). Non-covalent interaction (NCI) analysis[17] clearly revealed the differences in the hydrogen-bonding network between **TS$_{major}$** and **TS$_{minor}$** (Figure 3). The succinimide anion coordinated with both urea (e: 1.88 Å) and sulfide (f: 2.51 Å) moieties in **TS$_{major}$**, but only with the urea moiety (e: 2.10 Å, f: 2.01 Å) in **TS$_{minor}$**. A NH/π interaction exists between a portion of the NH residue of the urea moiety and naphthyl moiety in **TS$_{major}$** (Figure 3). The relative energy difference between **TS$_{major}$** and **TS$_{minor}$** is reduced to within 1 kcal/mol in the partially defected TS models (removing urea or sulfide moiety of (*S*)-**1b**, Figure S3 in Supporting Information). In the control experiments, the enantioselectivity was significantly decreased with the loss of either urea or sulfide moiety of (*S*)-**1b** (Table 2). Both urea and sulfide moieties of (*S*)-**1b** play key roles in the relative energy difference between **TS$_{major}$** and **TS$_{minor}$**.[18] Whereas **TS$_{major}$** has conjugation and a CH–O hydrogen bond between the urea and naphthyl moieties (Figure 3), the urea moiety is arranged nearly perpendicular to the naphthyl moiety to lose them in **TS$_{minor}$**. Therefore, the conformational requirements of a urea moiety, which are needed for keeping the hydrogen-bonding network, tend to destabilize the catalyst fragment in **TS$_{minor}$**. The CH–O hydrogen bond of the sulfide moiety along with sulfide/bromonium interaction stabilizes **TS$_{major}$**. These computational results clarified the importance of our bifunctional design in connecting the sulfide and urea units via a chiral scaffold (see, entries 1 and 5 in Table 2).



(a) **TS$_{major}$** (0.0, *0.0*) (b) **TS$_{minor}$** (+4.3, +*2.6*)

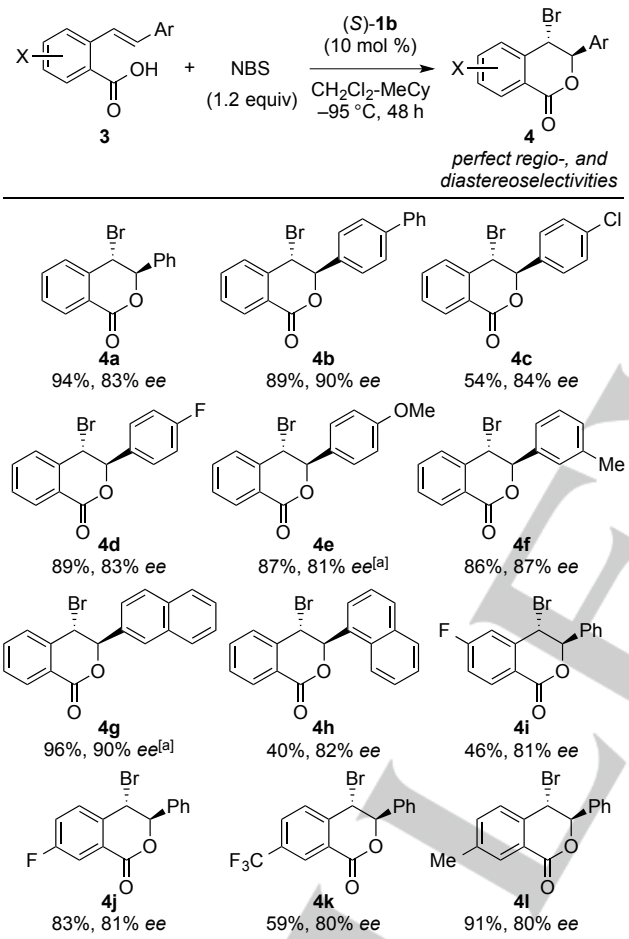
Figure 2. 3D structures and the relative Gibbs free energies (kcal mol^{-1}) of (a) **TS$_{major}$** and (b) **TS$_{minor}$**. Bond lengths are in Å.



(a) **TS$_{major}$** (b) **TS$_{minor}$**

Figure 3. NCI analysis of (a) TS_{major} and (b) TS_{minor}. Gradient surfaces correspond to $s = 0.25$ au and a color scale of $-0.05 < \rho < 0.05$ au (blue, strongly attractive; green, weakly attractive; red, strongly repulsive).

With important information of chiral bifunctional sulfide catalyst (*S*)-**1b** in hand, the substrate generality of the asymmetric bromolactonization of **3** was examined (Scheme 5). The introduction of various substituents on both of the aryl groups in **3** uniformly gave the target products (**4a**–**4l**) in high enantioselectivities (80–90% *ee*). It should be noted that all the reactions in Scheme 5 proceeded with complete regio- and diastereoselectivities.



Scheme 5. Substrate scope. [a] The reactions with **3e** and **3g** were performed with *N*-bromophthalimide (NBP) as a brominating reagent in CH_2Cl_2 at –78 °C for 48 h.

In summary, we have successfully developed chiral bifunctional dialkyl sulfides that possess a urea moiety, which functions as an effective catalyst for asymmetric bromolactonization. The importance of the bifunctional design of the catalysts was clearly demonstrated in the asymmetric bromolactonization, and the roles of both sulfide and urea moieties on the catalyst were discussed and clarified based on the results of experimental and theoretical investigation. Further applications of these bifunctional dialkyl sulfide catalysts to other asymmetric reactions as well as design of new chiral sulfide catalysts are currently underway by our group.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Numbers JP16K05780 (for S.S.), JP17KT0011 (for M.Y.), JP18H04660, (Hybrid Catalysis for M.Y.), and the Cooperative Research Program of "Network Joint Research Center for Materials and Devices" (20181268 for S.S.). We are grateful to Dr. Hiroyasu Sato (Rigaku Corporation) and Dr. Kazunobu Igawa (Kyushu University) for X-ray crystallographic analysis.

Keywords: asymmetric synthesis • lactonizations • organocatalysis • sulfides • transition states

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[18] The distortion/interaction analysis clarify the cooperative functions of urea and sulfide moieties. Details are shown in supporting information.

10.1002/chem.201803703

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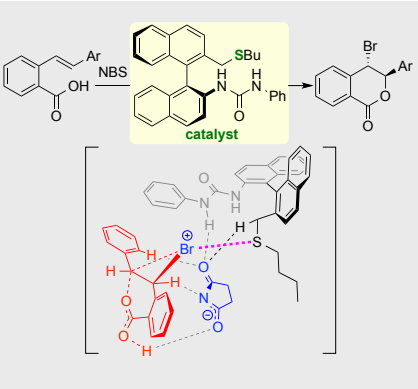
Layout 1:

COMMUNICATION

Chiral bifunctional dialkyl sulfide catalysts possessing a urea moiety were designed for enantioselective bromolactonization. The roles of both sulfide and urea moieties on the catalyst are discussed and clarified based on the results of both experimental and theoretical investigation.



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Design of Chiral Bifunctional Dialkyl Sulfide Catalysts for Regio-, Diastereo-, and Enantioselective Bromolactonization