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Electrophilic Bromolactonization of Cyclopropyl Diesters Using Lewis Basic Chalcogenide Catalysts

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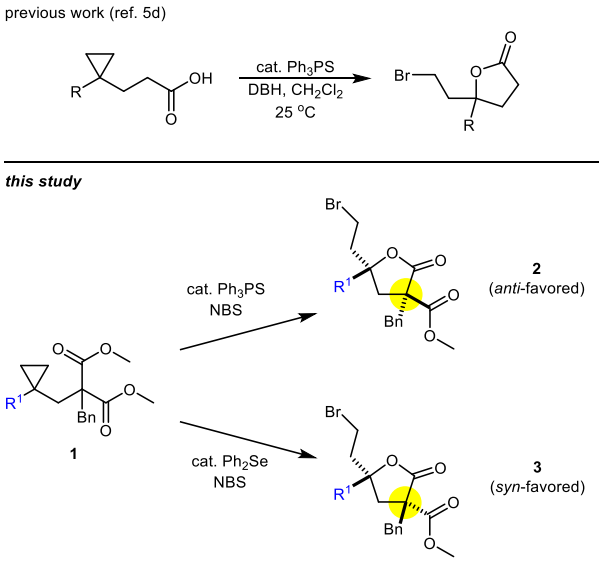
Abstract: An efficient and regioselective electrophilic bromolactonization of cyclopropylmethyl diesters using triphenylphosphine sulfide (Ph_3PS) or diphenyl selenide (Ph_2Se) as the Lewis basic chalcogenide catalyst has been developed. It was observed that Ph_3PS favored the formation of *anti*-diastereomer and yielded the multi-functional γ-lactones. Interestingly, the diastereoselectivity was reversed when using Ph_2Se as a catalyst where the *syn*-product instead of the *anti*-product was favored.

Keywords: Bromolactonization; Cyclopropane; Diastereoselectivity; Lactones; Lewis base

Cyclopropane is the fundamental core of many functional molecules and bioactive compounds.[1] It is featured with three bent σ-bonds and a high ring-strain system because of the inefficient orbital overlapping. The regions with the highest electron density in cyclopropane are off the C-C connecting lines. As a result, cyclopropanes have much resemblance in chemical behavior to olefins due to the significant π-character of their C-C bonds.[2] In the light of this aspect, significant research efforts have been devoted to exploiting the reactions using cyclopropanes in analogue to olefins. Among the efforts on the development of cyclopropane reactions, activated cyclopropanes such as donor-acceptor cyclopropanes have been frequently studied.[3] Radical initiated reactions are also common in the cyclopropane ring-opening reactions.[4]

While there are plentiful reports on ring-opening reactions of activated cyclopropanes, studies on their unactivated counterparts remain scarce. In 2011, Zyk and co-workers reported an electrophilic halogenation of unactivated cyclopropanes, in which they devised a $KICl_2$ mediated ring-opening reaction of arylcyclopropanes to yield a mixture of 1,3-dihalide products.[5a] Recently, Hennecke et al. reported a range of catalyst-free halocyclization of cyclopropanes with tosylamides, hydroxyl, and carboxyl substituents, yielding the corresponding pyrrolidines, tetrahydrofurans and lactones, respectively.[5b] An emerging research direction involves the oxidative ring-opening/functionalization of unactivated cyclopropanes using hypervalent iodine species.[6]

Based on our experience in Lewis base-catalyzed halocyclization of olefinic substrates,[7] we envisioned that using different nucleophilic partners, cyclopropane could be ring-opened to form various classes of compounds through electrophilic halocyclizations. We have shown that using 1,3-dibromo-5,5-dimethylhydantoin (DBH) as the bromine source and triphenylphosphine sulfide as the Lewis basic chalcogen catalyst, 1,1- and 1,2-disubstituted cyclopropylmethyl amides could be cyclized efficiently to give oxazolines and oxazines.[5c] Besides having amides as the nucleophilic partners, cyclopropylmethyl carboxylic acids, along with DBH and triphenylphosphine sulfide as the halogen source and the catalyst, respectively, could readily undergo the electrophilic bromolactonization in Markovnikov-fashion (Scheme 1).[5d] Very recently, we successfully developed a Lewis base-mediated ring-opening/1,3-difunctionalization of unactivated cyclopropanes using phenyliodane bis(trifluoroacetate).[8]



Scheme 1. Comparison of Previous and The Present Studies.

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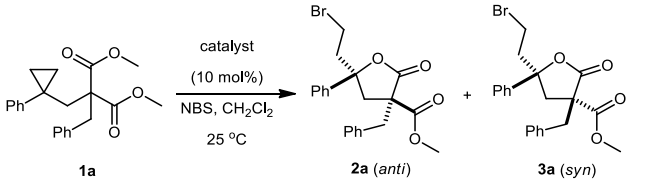
To further exploit the field of Lewis base-mediated functionalization of cyclopropyl compounds, we were in search of different nucleophilic partners. Herein, we are pleased to report an efficient and highly regioselective bromocyclization of cyclopropylmethyl diesters to give multi-functionalized lactones catalyzed by chalcogenide catalysts (Scheme 1). It is also interesting to realize that the diastereoselectivity could be dictated by the sulfide or selenide catalyst.

The study began with the cyclization of cyclopropylmethyl 1,3-diester **1a** using *N*-bromosuccinimide (NBS) as the halogen source and triphenylphosphine sulfide as the chalcogen catalyst under different conditions (Table 1).

Table 1. Electrophilic Bromolactonization of Cyclopropylmethyl Diester **1a**.[a]



1a **2a** (*anti*) **3a** (*syn*)

entry	catalyst	H_2O (equiv)	time (h)	yield (%)	dr (**2a**:**3a**)[b]
1	-	0	60	0	-
2[c]	-	0	18	0	-
3[c]	Ph_3PS	0	24	complex mixture	
4	Ph_3PS	0	168	77	2.5:1
5	Ph_3PS	1	12	92	2.2:1
6	-	1	16	0	-
7	Ph_3PSe	1	36	86	1:1.3
8	Ph_2Se	1	60	92	1:2.6
9	$(4\text{-}F_3C\text{-}C_6H_4)_2Se$	1	72	32	1:4.5
10	$(4\text{-}MeO\text{-}C_6H_4)_2Se$	1	48	99	1:1.7

[a] Reactions were carried out with **1a** (0.05 M), NBS (2 equiv), and catalyst (10 mol %) in CH_2Cl_2 (1 mL) at 25 °C in the absence of light. The yields are isolated yields. [b] Determined by ^1H NMR. [c] Reactions were conducted under household 18 W fluorescent lamp.

Bromolactonization of **1a** was sluggish in the absence of Ph_3PS in dark (Table 1, entry 1). Unlike the halocyclization of cyclopropylmethyl carboxylic acids that could be triggered by household fluorescence lamp (18 W),[5d] bromocyclization of **1a** remained sluggish in the presence of light (entry 2). In the presence of both light and a catalytic amount of Ph_3PS, a mixture of poly-brominated products was obtained (entry 3). In sharp contrast, halocyclization of **1a** underwent smoothly to give the desired cyclized products **2a** and **3a** in 77% isolated yield and 2.5:1 dr when the reaction was conducted with 10 mol % of Ph_3PS in the absence of light (entry 4). The structure of **2a** was confirmed by an X-ray crystallographic analysis on a single crystal sample (Figure 1).[9]

Interestingly, it was realized that water played an important role in the efficiency of the reaction; the reaction time was dramatically reduced from 7 days to 12 hours upon the addition of 1 equivalent of H_2O (Table 1, entry 4 vs 5). It was also shown that water alone could not promote the halocyclization (Table 1, entry 6). A brief survey on a series of solvents revealed the superior performance of CH_2Cl_2 in offering satisfactory reaction yield and diastereoselectivity (See Supporting Information Table S1 for details). Surprisingly, the diastereoselectivity could be dictated by the option of chalcogenide. It was observed that replacing Ph_3PS with Ph_3PSe as the catalyst in the bromocyclization of **1a** gave **3a** as the major diastereomeric product (Table 1, entry 7). The diastereoselectivity in favor of **3a** was further increased when using diphenyl selenide as the catalyst (Table 1, entry 8). The relatively more electron-deficient catalyst $(4\text{-}F_3C\text{-}C_6H_4)_2Se$ returned an even higher dr but with much lower reaction rate (Table 1, entry 9). On the other hand, the methoxy-substituted catalyst $(4\text{-}MeO\text{-}C_6H_4)_2Se$ gave excellent yield but with the significant diminishment of the dr (Table 1, entry 10).

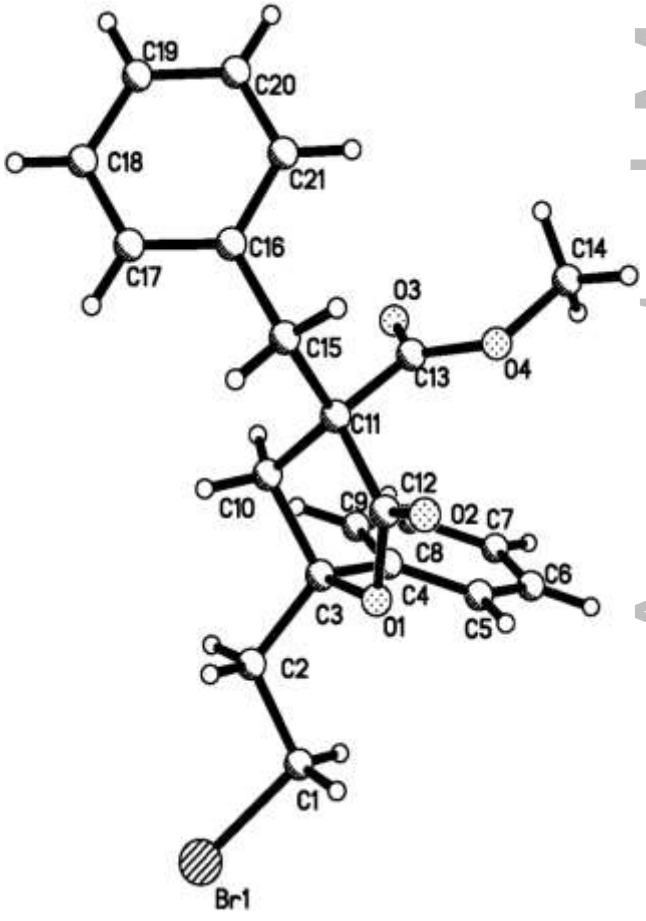


Figure 1. X-Ray Crystallographic Structure of **2a**.

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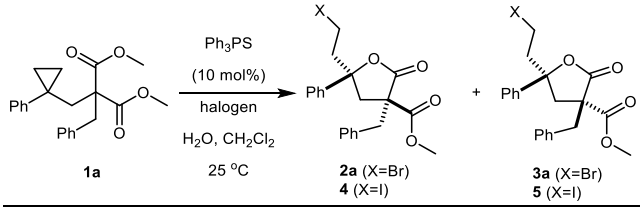
A systematic halogen source screening was also carried out and it was shown that NBS is still superior to other bromine sources such as DBH, *N*-bromoacetamide (NBA), *N*-bromophthalimide (NBP), 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) (Table 2, entries 1-5). The reaction could also proceed using NIS with satisfactory yield and diastereoselectivity (Table 2, entry 6).

Table 2. Electrophilic Lactonization of Cyclopropylmethyl Diester **1a** with Different Halogen Sources.[a]

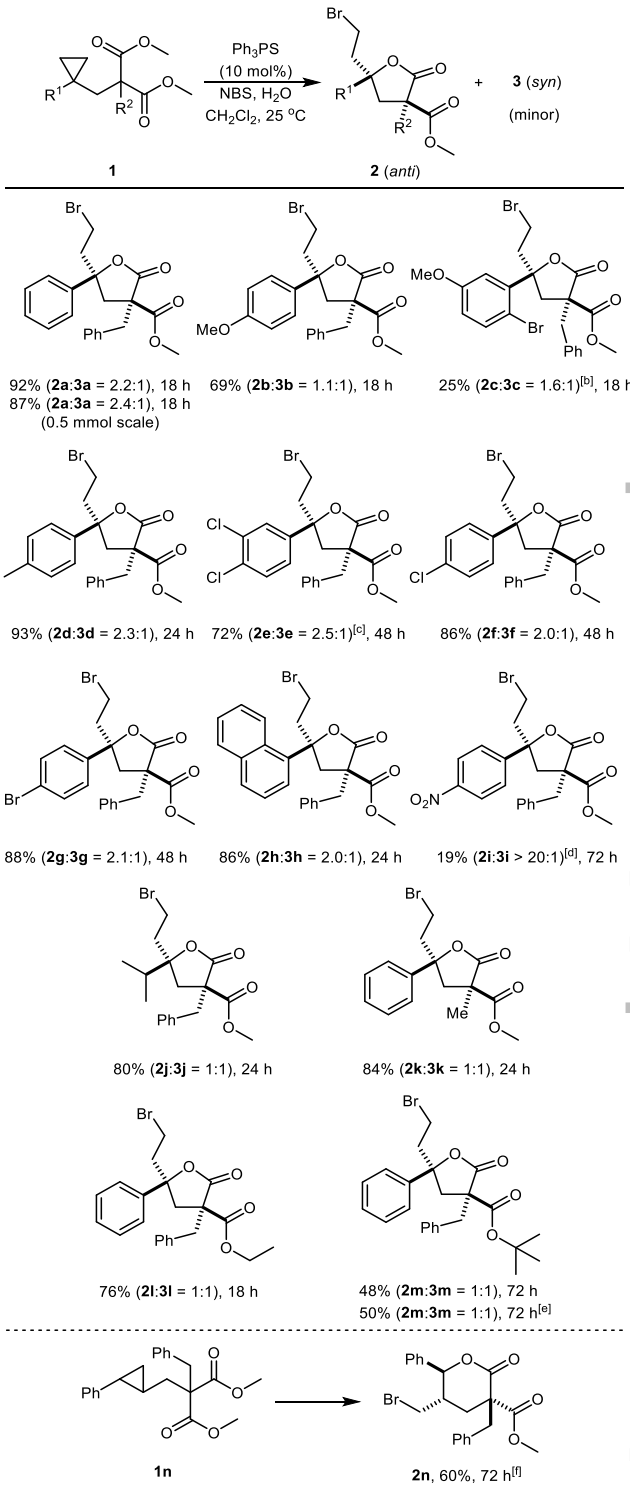


entry	halogen source (X)	time (h)	yield (%)	dr (**2a**:**3a**)[b]
1	NBS (Br)	12	92	2.2:1
2	DBH (Br)	24	82	2.0:1
3	NBA (Br)	24	79	1.5:1
4	NBP (Br)	24	78	2.1:1
5	TBCO (Br)	24	79	2.2:1
6[c]	NIS (I)	96	69	2.0:1

[a] Reactions were carried out with **1a** (0.05 M), halogen source (2 equiv), water (1 equiv), and Ph_3PS (10 mol %) in CH_2Cl_2 (1 mL) at 25 °C in the absence of light. The yields are isolated yields. [b] Determined by ^1H NMR. [c] NIS was used instead of NBS. The dr indicated is the ratio of the iodinated product **4**:**5**.

With the optimized conditions in hand, a variety of cyclopropylmethyl diesters **1** were subjected to the investigation (Table 3). In general, good reaction yields and diastereoselectivity in favor of the *anti*-products **2** were achieved. For **1c**, aromatic bromination was also taken place at the *para*-position to the methoxy group. For substrates with R^1 as electron-deficient substituents such as **1e** (3,4-Cl_2-C_6H_3), **1f** (4-Cl-C_6H_4) and **1g** (4-Br-C_6H_4), good yields and satisfactory diastereoselectivity were obtained. Excellent diastereoselectivity was observed with **1i** (4-NO_2-C_6H_4) although the reaction rate was relatively slow. Substrates with alkyl substituent at R^1 (**1j**) or R^2 (**1k**) were investigated as well. The corresponding cyclized products were obtained in satisfactory yields but the dr was significantly diminished. We suspect that the change in substituent might interrupt the diastero-determining step (vide infra, Scheme 2). Changing the alkyl malonate from methyl to ethyl (**1l**) or *tert*-butyl (**1m**) was also found to have a negative impact on the diastereoselectivity. For the case of *tert*-butyl ester substrate **1m**, the reaction rate was found to be insensitive to the amount of water. Apart from 1,1-disubstituted cyclopropylmethyl diesters, this protocol also worked well for *trans*-1,2-disubstituted cyclopropylmethyl

Table 3. Ph_3PS Catalyzed Bromolactonization of **1**.[a]



[a] Reactions were carried out with **1** (0.05 M), NBS (2 equiv), H_2O (1 equiv), Ph_3PS (10 mol %) in CH_2Cl_2 (1 mL) at 25 °C in the absence of light. The yields are isolated yields. [b] 38% of the starting material recovered. [c] 10% of starting material recovered. [d] 60% of starting material recovered. [e] Without 1 equiv. of H_2O, 30% of starting material recovered. [f] 15% of starting material recovered.

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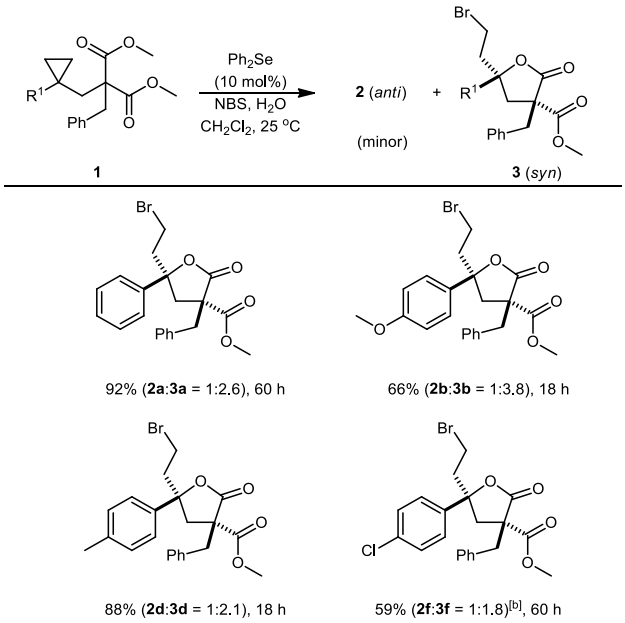
diester **1n**, where the major diastereomer **2n** was isolated in good yield and its relative configuration was confirmed by COSY and NOESY experiments.[10]

We have also investigated some entries using diphenyl selenide as the chalcogenide catalyst. In contrast to the reactions catalyzed by Ph_3PS, the formation of lactones **3** (*syn*-diastereomer) were favored instead of lactones **2** (*anti*-diastereomer) when Ph_2Se was used as the catalyst. In addition, the diastereoselectivity was reversed and the *syn*-products **3** were favored regardless of the electronic properties of the substrates (Table 4).

Since the diastereoselectivity could be dictated by the chalcogenide catalysts, we speculate that the Lewis bases might play a crucial role in controlling the diastereo-determining steps. NMR experiment on a mixture of 1,3-diester, NBS, and Ph_2Se was performed and a significant down-field shift of the Se signal was detected, attributed to the coordination of the ester's oxygen to the Se center of the Ph_2SeBr selenonium species.[11] On the other hand, there was no observable change in the signal from the ^{31}P NMR experiment on a mixture of 1,3-diester, NBS, and Ph_3PS.

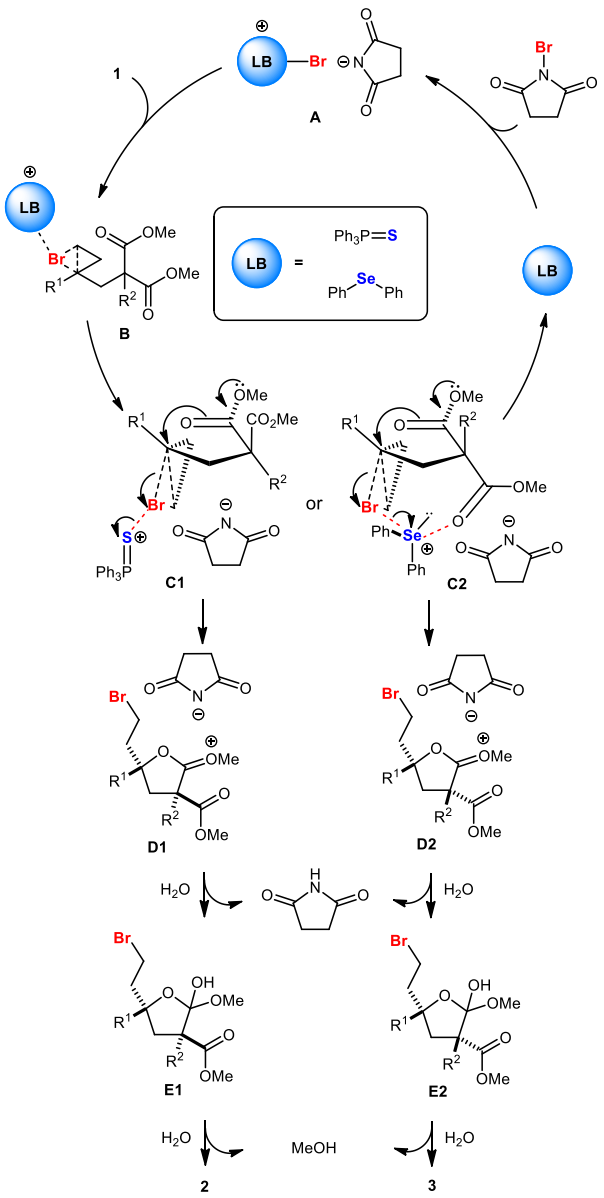
Table 4. Ph_2Se Catalyzed Bromolactonization of **1**.[a]



[a] Reactions were carried out with **1** (0.05 M), NBS (2 equiv), H_2O (1 equiv), Ph_2Se (10 mol %) in CH_2Cl_2 (1 mL) at 25 ºC in the absence of light. The yields are isolated yields. [b] 35% of the starting material was recovered.

Although a detailed mechanism has yet to be determined, a plausible mechanistic picture is depicted in Scheme 2 based on the acquired data and our experience in the chalcogenide-catalyzed halocyclization reactions.[7] Since the chalcogenides exhibited appreciable catalytic property in the reactions, we speculate that the Lewis basic chalcogenides could activate the Br in NBS to give the active halogenating species **A**.[12] The π-characted σ-bond in cyclopropyl substrate **1** might then interact with the electrophilic brominating species **A** to form the putative bromiranium-like intermediate **B**. We suspect that the diastereo-determining step **C1** with Ph_3PS as the catalyst might follow a steric control mechanism in which the bulky substituent R^2 might sit at the pseudo-equatorial position. This model could also explain the poor dr in the reaction with **1k** [the steric effect of the substituent (R^2 = Me) might be less significant] and **1m** (the bulky *tert*-butyl ester group sitting at the pseudo-axial position might be disfavored). The subsequent intramolecular nucleophilic attack on the bromiranium-like ion in **C1** by the carboxylate group in substrate **1** could then be executed in Markovnikov-fashion to furnish the cyclized species **D1**. We believe that demethylation of the methyl group at the oxonium ion of species **D1** by the succinimide counter-anion might not be the dominated pathway in giving the cyclized product **2** because *N*-methylsuccinimide was not detected in the reaction. Since the reaction rate was relatively low when water was not added (Table 1, entry 4 vs 5) but water itself could not promote the reaction (Table 1, entry 7), a possible dominated reaction pathway from species **D1** to lactone **2** might go through intermediate **E1** as a result of the water attack at the carbonyl carbon of the oxonium moiety.[13] Since water was found to be not necessary for the cyclization of *tert*-butyl ester substrate **1m** (Table 3), we suspect the *tert*-butyl group might be eliminated in the form of isobutene through the E1 or E2 mechanism. In the case with Ph_2Se as the catalyst, the ester moiety might interact with the species **A** (**LB** = Ph_2Se) as evidenced by the ^{77}Se NMR experiment. The Se-O interaction might direct the bromination through transition state **C2** and the higher dr dictated by the more electron-deficient catalyst $(4\text{-}F_3C\text{-}C_6H_4)_2Se$ (Table 1, entry 9) could be attributed to the stronger Se-O interaction. Subsequently, product **3** could be accomplished through the cyclization-demethylation sequence **C2→D2→E2**. A more detailed study is required in order to elucidate the sole origin of the diastereoselectivity.

In summary, we have devised an efficient catalytic protocol to synthesize multi-functionalized lactones **2** and **3** by the electrophilic bromolactonization of cyclopropylmethyl diesters **1**. In most cases, both **2** (*anti*-diastereomer) and **3** (*syn*-diastereomer) could be preferentially synthesized using Ph_3PS or Ph_2Se as the catalyst, respectively. The synthetic application and more sophisticated mechanistic studies are underway.



Scheme 2. A Plausible Mechanism of Bromolactonization of **1**.

Experimental Section

General Procedure for the Bromolactonization of Cyclopropylmethyl Diester 1.

Cyclopropylmethyl diester **1** (0.05 mmol, 1.0 equiv), the chalcogenide catalyst (0.005 mmol, 0.1 equiv) and H_2O (0.9 μL, 0.05 mmol) were added to dichloromethane (1 mL) at 25 °C. Subsequently, NBS (0.1 mmol, 2.0 equiv) was added into the reaction mixture. The reaction was then stirred at 25 °C in the absence of light. Upon completion, saturated aqueous solution of Na_2SO_3 (0.5 mL) was added to quench the reaction. The mixture was further diluted with DI water (2 mL) and extracted with CH_2Cl_2 (3 × 5 ml). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified over silica gel chromatography with eluent *n*-hexane/diethyl ether (3:1) to yield the corresponding cyclized product **2** or **3**.

Acknowledgements

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[9] CCDC 1847912 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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