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Electrophilic Bromolactonization of Cyclopropyl Carboxylic Acids Using Lewis Basic Sulfide Catalyst

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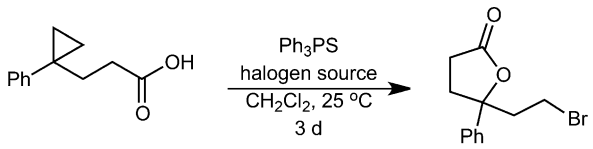
Abstract: A highly facile and efficient electrophilic bromolactonization of cyclopropylcarboxylic acids could be effected by a Lewis basic sulfide catalyst. Mechanistic studies performed revealed that the cyclopropane substrates could undergo radical bromination upon exposure to light, yielding a mixture of regioisomers. In stark contrast, the Lewis basic sulfide catalyst could promote the electrophilic bromolactonization and yield the Markovnikov product exclusively.

Keywords: bromolactonization; cyclization; cyclopropanes; lactones; Lewis bases

Cyclopropanes are known to possess a strained ring system. This is a consequence of inefficient orbital overlapping, leading to three strained σ-bonds (with interorbital angles of 105°) which carry significant π-character.[1] Thus, the reactivity of cyclopropane resembles that of the carbon-carbon double bond.[2] Recently, multiple research groups have invested considerable efforts in the development of Lewis base-catalyzed electrophilic bromocyclizations of olefinic substrates.[3] On the basis of the above explanation, it can be rationalized that cyclopropanes could substitute olefins in the same type of electrophilic bromocyclizations to give Markovnikov-type products.[4] Very recently Hennecke reported the cyclization of **1a** using 1,3-dibromo-5,5-dimethylhydantoin (DBH) in the absence of catalyst.[5] As part of the research interests in Lewis base-catalyzed halocyclization reactions in our team, we reported a Lewis basic sulfide-catalyzed electrophilic bromocyclization of cyclopropylmethyl amide very recently.[6] In a parallel research program, we are also studying the bromocyclization of cyclopropylcarboxylic acid **1**. However, after examining the reaction carefully it was found that such a reaction could not proceed in the absence of light (*vide infra*, Table 1). Under illuminated conditions, the cyclization could proceed to yield the lactone product, suggesting that, in the absence of a catalyst, cyclization of **1** might proceed through a radical mechanism triggered by light. Alternatively, we report herein the

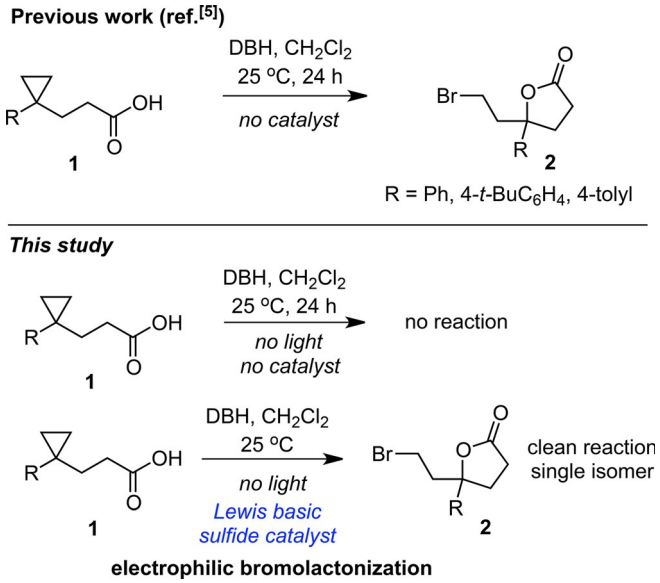
Table 1. Bromolactonization of cyclopropylcarboxylic acid **1a** with or without light.[a]



1a **2a**

Entry	Br source	Ph_3PS [mol%]	Light[b]	Yield [%]
1[c]	NBS	0	off	0
2[c]	DBH	0	off	0
3	NBS	0	on	53[e]
4	DBH	0	on	57[e]
5[d]	NBS	0	off	40[e]
6	NBS	10	off	56[f]
7	DBH	10	off	88[f]
8	NBS	10	on	58[f]
9	DBH	10	on	89[f]

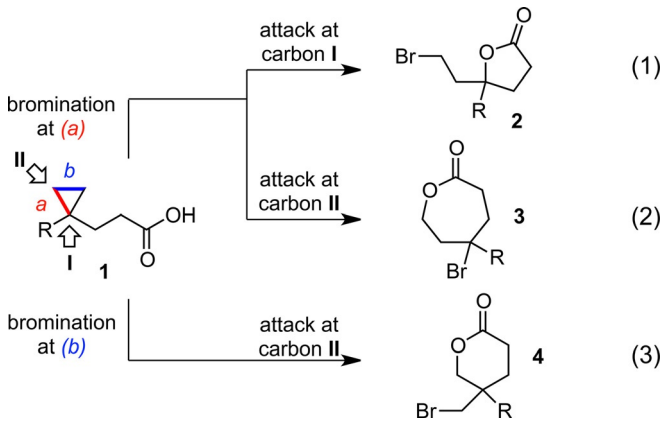
[a] Reactions were carried out with **1a** (0.05 mmol), freshly recrystallized halogen source (0.06 mmol), and Ph_3PS (0.005 mmol) in CH_2Cl_2 at 25 °C in the absence of light. The yields are of isolated products.
[b] Household 18 W fluorescent lamp.
[c] Starting material was recovered quantitatively.
[d] Aged bottle of NBS was used.
[e] The yield of the product mixture with **2a** as one of the products.
[f] **2a** was isolated exclusively as a clean product.



Scheme 1. Lewis basic sulfide-catalyzed electrophilic bromolactonization of cyclopropylcarboxylic acid **1**.

first example of a Lewis basic sulfide-catalyzed electrophilic bromolactonization of cyclopropylcarboxylic acids **1** (Scheme 1).

The cyclopropane in **1** contains two types of σ-bonds with π-character: the sterically hindered but electron-rich bond (a) which is more reactive towards electrophilic co-bromination; and the less substituted bond (b) which has reduced steric hindrance while being comparatively less electron-rich (Scheme 2). The bromolactonization of **1** can potentially proceed through multiple pathways: Eq. (1) – bromination at bond (*a*) and the subsequent attack of the carboxylate at the more substituted carbon **I** to give the five-membered lactone **2**; Eq. (2) – bromination at bond (*a*) followed by the attack of the carboxylate at the less hindered-carbon **II** to give the seven-membered lactone **3**; Eq. (3) – bromination at bond (*b*) followed by



Scheme 2. Possible pathways for the bromolactonization of cyclopropylcarboxylic acid **1**.

cyclization to yield the six-membered lactone **4**. The myriad of possibilities escalates the difficulty of the cyclopropane cyclization reaction as compared to the classical bromolactonization of olefinic acids.

The project was initiated with the use of cyclopropylcarboxylic acid **1a** as the substrate. It was noted that in the absence of light, a freshly recrystallized brominating agent such as *N*-bromosuccinimide (NBS) or 1,3-dibromo-5,5-dimethylhydantoin (DBH) alone could not promote the lactonization and the starting material **1a** was recovered quantitatively after 3 days (Table 1, entries 1 and 2). However, when the reaction was not shielded from light (standard household fluorescent lamp at the ceiling), the lactonization could proceed to give a mixture of cyclized products (Table 1, entry 3: *ca.* 53% yield when using NBS; entry 4: *ca.* 57% yield when using DBH) which could not be separated through column chromatography. In the mixture, **2a** was observed as one of the products (Figure 1a). From the empirical evidence garnered thus far, it was speculated that light might serve to catalyze the reaction, presumably through radical pathways,[7,8] to yield different isomers of lactones **2**–**4** (*vide infra*). Indeed, a similar product mixture could also be obtained in the absence of light when an aged bottle of NBS was used (Table 1, entry 5).

To our delight, the lactonization of **1a** proceeded smoothly when 10 mol% of triphenylphosphine sulfide was used as the Lewis base catalyst in the absence of light; **2a** was furnished in 56% yield (together with 40% of **1a** recovered) when NBS was used as the halogen source (Table 1, entry 6). Alternatively, an 88% yield of **2a** was achieved exclusively when the stronger brominating agent DBH was used (Table 1, entry 7). It is noteworthy that a clean product was obtained in both cases and **2a** was found to be the only constitutional isomer (Figure 1b and c). Unexpectedly, the cyclization could still proceed well in the presence of both light and the catalyst (10 mol% of triphenylphosphine sulfide). Reaction performance under Lewis base catalysis was noted to be identical in the presence or absence of light (Table 1, entries 6 and 7

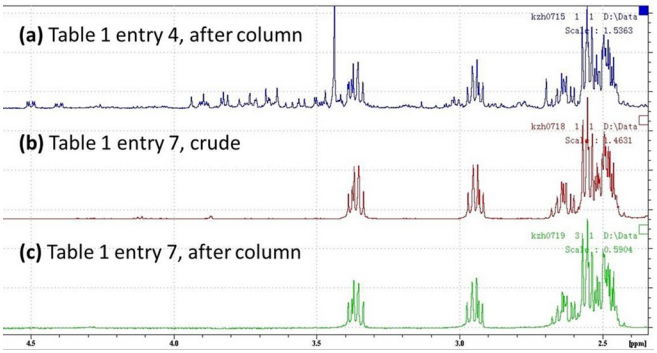


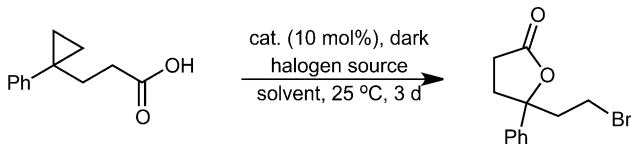
Figure 1. ^{1}H NMR study of product **2a** from the bromolactonization of **1a**.

vs. entries 8 and 9). This observation suggests that the Lewis basic sulfide-catalyzed electrophilic bromolactonization might predominate over the light-triggered pathway.

Subsequently, various catalysts were screened and the results are depicted in Table 2. The experimental outcomes revealed that tripheylphosphine selenide results in a much lower conversion as compared to triphenylphosphine sulfide (Table 2, entry 2). On the other hand, tetrahydrothiophene was found to be a potent Lewis basic catalyst which gave the desired lactone **2a** in 87% yield (Table 2, entry 3). We also attempted to utilize the organic amine base Et_3N or inorganic base K_2CO_3 aiming at generating the carboxylate anion as a better nucleophilic partner for the lactonization. However, the reaction turned out to be sluggish (Table 2, entries 4 and 5). We speculated that the electrophilic activation of the cyclopropane might be the main driving force of the bromolactonization of **1a**. Surprisingly, (±)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate, a good Brønsted acid activator for NBS, did not promote the bromolactonization of **1a** (Table 2, entry 6). Several bromine sources were also evaluated. As compared to NBS, it was realized that *N*-bromophthalimide (NBP) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCO) were inferior while DBH returned higher efficiency (Table 2, entries 1, 7–9). A brief solvent screening revealed that chlorinated solvents such as CH_2Cl_2 and 1,2-dichloroethane were suitable reaction media (Table 2, entries 9–13).

Next, the substrate scope was investigated (Table 3). The reactions were generally smooth when using electron-rich phenyl-substituted substrates including **1b** (*p*-methyl), **1c** (*m*-methyl), **1f** (*p*-methoxy), and **1g** (*p*-*tert*-butyl). Substrates with sterically bulky substituents (**1d**, **1e**, **1h**) also worked well under this catalytic protocol to give the corresponding products **2d**, **2e**, and **2h** in excellent yields. On the other hand, substrates **1i–l** bearing electron-deficient aryl substituents exhibited lower conversions. Cyclization of **1m**, a substrate with a methyl, and **1n**, a substrate with a cyclohexyl substituent, gave the desired products **2m** and **2n** in excellent yields. The reaction was also

Table 2. Optimization of the bromolactonization of **1a**.[a]

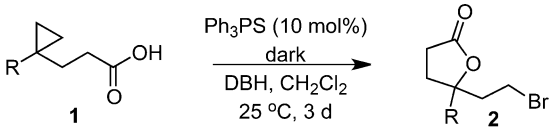


1a **2a**

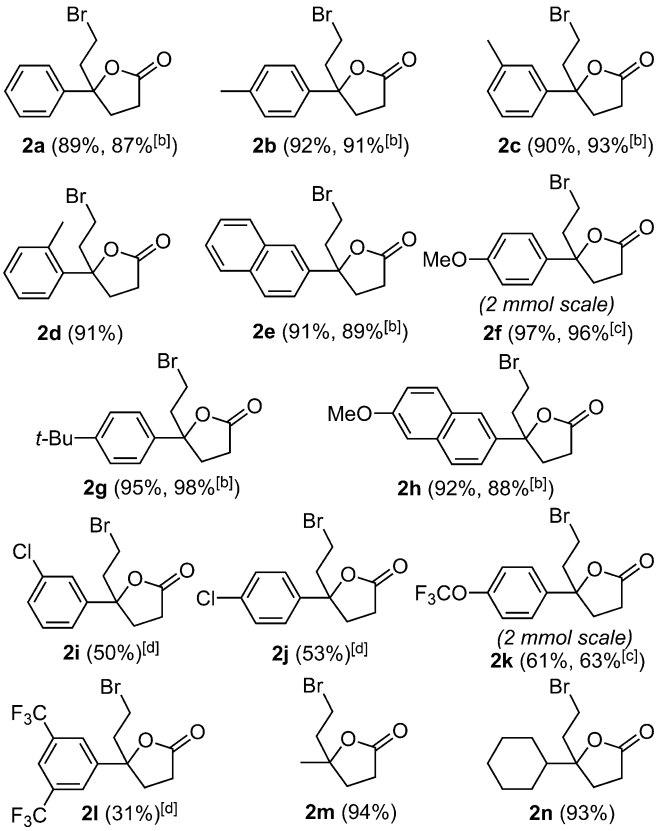
Entry	Br source	Catalyst	Solvent	Yield [%]
1	NBS	Ph_3PS	CH_2Cl_2	58
2	NBS	Ph_3PSe	CH_2Cl_2	trace
3	NBS	tetrahydrothiophene	CH_2Cl_2	87
4	NBS	Et_3N	CH_2Cl_2	0
5	NBS	K_2CO_3	CH_2Cl_2	0
6	NBS	(±)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate	CH_2Cl_2	0
7	NBP	Ph_3PS	CH_2Cl_2	52
8	TBCO	Ph_3PS	CH_2Cl_2	28
9	DBH	Ph_3PS	CH_2Cl_2	89
10	DBH	Ph_3PS	$(CH_2Cl)_2$	88
11	DBH	Ph_3PS	CH_3NO_2	62
12	DBH	Ph_3PS	$PhCH_3$	9
13	DBH	Ph_3PS	DMF	74

[a] Reactions were carried out with **1a** (0.05 mmol), freshly recrystallized halogen source (0.06 mmol), and Ph_3PS (0.005 mmol) in CH_2Cl_2 at 25 °C in the absence of light. The yields are of isolated products.

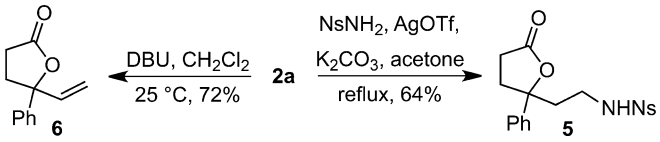
Table 3. Scope of the bromocyclization of **1**.[a]



1 **2**



[a] Reactions were conducted with **1** (0.05 mmol), DBH (0.06 mmol), and Ph_3PS (0.005 mmol) in CH_2Cl_2 (2.0 mL) at 25 °C in the absence of light.
[b] Yield when using tetrahydrothiophene and NBS instead of Ph_3PS and DBH.
[c] 2.0 mmol scale.
[d] TBCO was used instead of DBH.



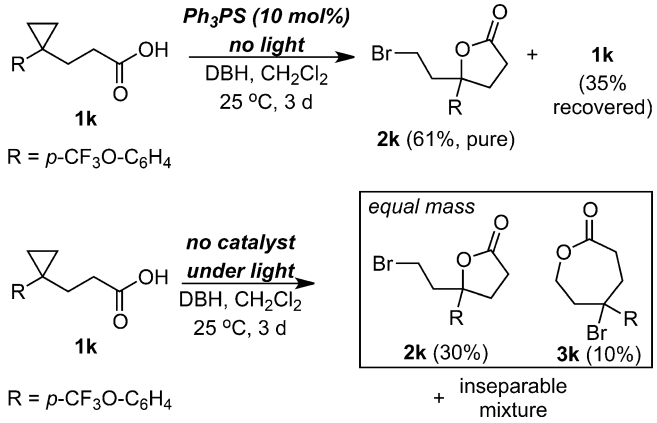
Scheme 3. Transformations using **2a**.

readily scalable without diminishing the reaction yields (**2f** and **2k**).

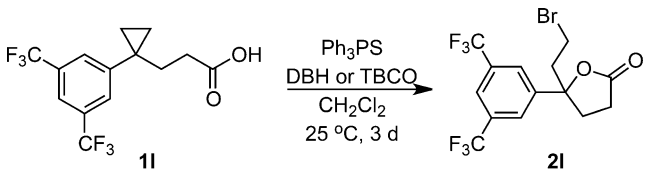
The bromide substituent in **2** could be further manipulated with ease. For instance, **2a** could react with *p*-nitrobenzenesulfonamide in the presence of AgOTf to give **5** in 64% yield (Scheme 3). The structure of **5** was confirmed unambiguously by an X-ray crystallographic study.[9] In addition, treatment of **2a** with DBU at 25 °C gave rise to the olefin **6**, a consequence of dehydrobromination, in 72% yield.

Several control experiments were performed with the objective of probing the reaction mechanism. Firstly, it was realized that no bromolactonization occurred for substrate **1k** in the absence of both light and catalyst. A 61% yield of **2k** was achieved (with 35% of **1k** recovered) when the reaction was conducted under the optimized conditions. However, a complex reaction mixture was obtained when the reaction was not shielded from light and no catalyst was applied. Three fractions (regioisomers **2k**, **3k**, and an inseparable mixture)[10] were isolated after extensive efforts (Scheme 4). The formation of regioisomers might be attributed to the uncontrolled radical bromination of cyclopropane.[4,7]

Secondly, it was discovered that bromolactonization of the highly electron-deficient substrate **1l** did not proceed in the absence of a Lewis basic catalyst, even after being subjected to illuminated conditions for 3 days (Scheme 5). In stark contrast, 31% of **2l** was isolated (together with 65% of **1l** recovered) when 10 mol% of triphenylphosphine sulfide was included in the reaction mixture in the absence of light.



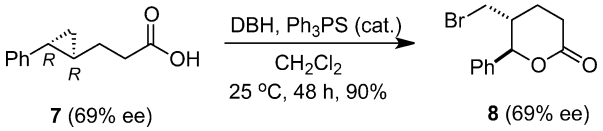
Scheme 4. Studies on the bromolactonization of **1k**.



Ph_3PS	light	yield of **2l**	recovery of **1l**
nil	off	0	95%
nil	on	0	96%
10 mol%	off	31%	65%

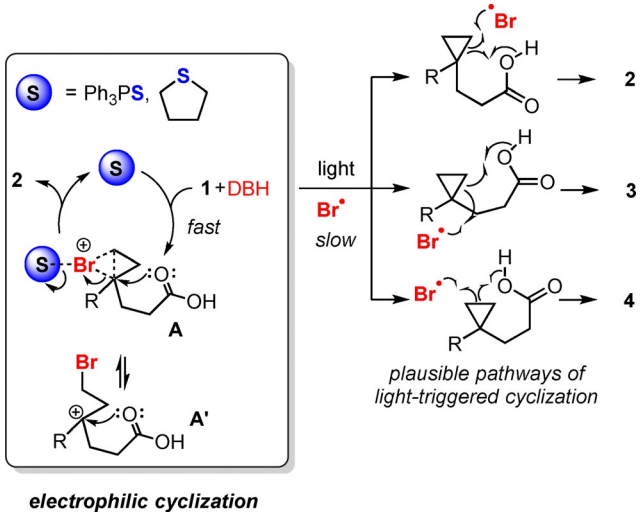
Scheme 5. Studies on the bromolactonization of **1l**.

Other than 1,1-disubstituted cyclopropanes **1**, we also investigated the bromocyclization of *trans*-1,2-disubstituted cyclopropyl acid **7**. To our delight, the desired δ-lactone **8** was obtained in high yield and diastereoselectivity. More importantly, the bromolactonization was also found to be enantiospecific (Scheme 6).



Scheme 6. Studies on the bromolactonization of **7**.

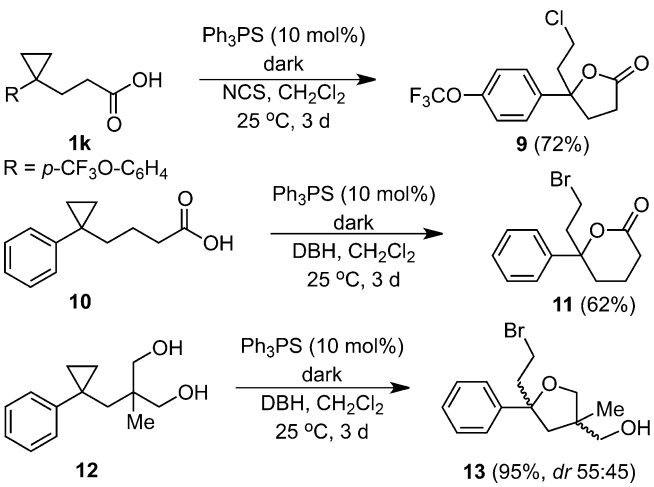
We speculated that the Lewis basic sulfide catalyst could activate the brominating agent and promote the electrophilic bromination[11] of the cyclopropane moiety in **1** to yield bromiranium-like species **A** (Scheme 7). Subsequent cyclization following the



Scheme 7. A plausible mechanism of the lewis base-catalyzed electrophilic bromolactonization of cyclopropylcarboxylic acid **1**.

Markovnikov rule could give the observed product **2**. On the other hand, the light-triggered conditions might lead to the radical bromination of the cyclopropane in **1** followed by cyclization to yield lactone products **2**–**4** through some plausible pathways as depicted in Scheme 7. On the basis of the results in Table 1 and Scheme 5, it appears that the Lewis basic sulfide-catalyzed electrophilic bromination of **1** is more efficient than the light-triggered radical pathway. However, we could not rule out the possibility that a carbocation **A′** (the ring-opened species of **A**) might be involved in the reaction and a more detailed mechanistic study is required in order to elucidate the mechanistic picture.

We also attempted to apply the catalytic protocol in other reactions (Scheme 8). Preliminary results show that *N*-chlorosuccinimide (NCS) could be utilized in this catalytic protocol to give the chlorinated compound **9**. In addition, other than the synthesis of γ-lactone, δ-lactone **11** could be furnished using cyclopropylcarboxylic acid **10** as the substrate. When using cyclopropyl 1,3-diol **12** as the substrate, the multifunctionalized THF **13** could be furnished in good conversion.



Scheme 8. Halocyclization of **1k**, **10**, and **12**.

In summary, we have developed a facile and highly efficient electrophilic bromolactonization of cyclopropylcarboxylic acids using a Lewis basic sulfide as the catalyst. Although light could trigger the reaction to give a mixture of constitutional isomers, the Lewis basic sulfide-catalyzed reaction was found to be the prevailing pathway which led to the desired lactone as the exclusive isomer. Further studies on the applications and mechanism of this reaction are underway.

Experimental Section

General Procedure for the Bromolactonization of Cyclopropylcarboxylic Acids 1

The cyclopropylcarboxylic acid **1** (0.05 mmol, 1.0 equiv.) and Ph_3PS (0.005 mmol, 0.1 equiv.) were dissolved in dichloromethane (2 mL) and stirred at 25 °C. Subsequently, DBH (0.06 mmol, 1.2 equiv.) was added into the reaction mixture. The mixture was then stirred at 25 °C in the absence or presence of light. For the reaction without light, the flask was wrapped with aluminum foil tightly. For the reaction run in the presence of light, the flask was exposed under household florescent lamp (18 W). Upon completion, a saturated aqueous solution of Na_2SO_3 (1 mL) was added to quench the reaction. The mixture was further diluted with DI water (3 mL) and extracted with CH_2Cl_2 (3×5 mL). The organic extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified over silica gel chromatography with eluent *n*-hexane/ethyl acetate (20:1) to yield the corresponding cyclized product.

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[8] For the light-triggered reaction of **1a**, the lactonization could still proceed but gives a mixture of cyclized products when the light is removed after the reaction is initiated.

[9] CCDC 1410272 (**5**) 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.

[10] MS studies on the inseparable mixture revealed the existence of a major species having an equal mass to **2k** and **3k**. We speculated that the species might be the δ-lactone generated through the cyclization indicated in Scheme 2 Eq. (3). A more detailed study is underway to clarify this aspect.

[11] a) S. E. Denmark, M. T. Burk, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20655; b) D. W. L. Tay, I. T. Tsoi, J. C. Er, G. Y. C. Leung, Y.-Y. Yeung, *Org. Lett.* **2013**, *15*, 1310; c) F. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2013**, *135*, 1232; d) Z. Ke, C. K. Tan, F. Chen, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2014**, *136*, 5627.

