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Intermolecular Electrophilic Bromoesterification and Bromoetherification of Unactivated Cyclopropanes

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Abstract. 1,3-difunctionalization of cyclopropane is a useful organic transformation. The corresponding 1,3-difunctionalized products are synthetic synthons and building blocks in many organic syntheses. Many existing ring-opening difunctionalization methodologies rely primarily on the use of donor–acceptor cyclopropanes, while the difunctionalization of unactivated cyclopropanes is less exploited. In this research, 1,3-bromoesterification and 1,3-bromoetherification of unactivated cyclopropanes were successfully achieved using *N*-bromosuccinimide as the brominating agent with high yields and regioselectivity.

Keywords: Cyclopropane; Haloether; Haloester; Halogenation; Mechanism

Introduction

Electrophilic halogenation of olefins in the difunctionalization of unsaturated carbon-carbon bonds appears in many organic transformations. It is an extremely useful methodology whereas halogen and another functionality can be introduced in a vicinal relationship simultaneously with good stereo- and regioselectivity.^[1] The halogen handles in the products can readily be manipulated using conventional methods. Both intramolecular and intermolecular electrophilic halogenation of olefins have been extensively studied.^[2,3]

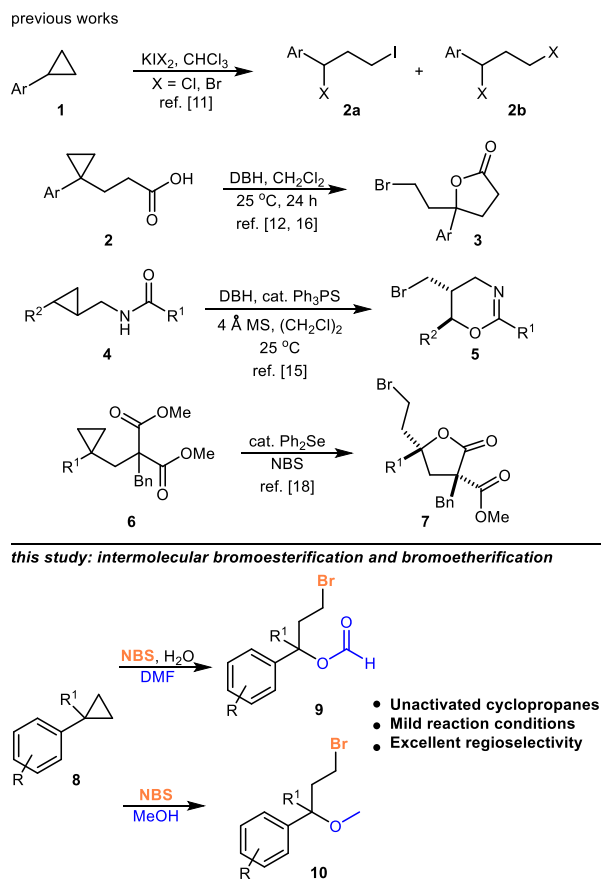
The complementary 1,3-difunctionalization reactions that involve highly ring-strained cyclopropanes also place great importance in synthetic organic chemistry. Cyclopropanes pose π -character σ -bonds and their reactivity resembles that of olefins in many situations.^[4] Most existing literature examples of ring-opening 1,3-difunctionalization of cyclopropanes rely on the use of activated cyclopropanes such as donor–acceptor cyclopropanes^[5] and transition metal mediated radical reactions.^[6–8] However, many cyclopropanes are unactivated.^[9,10]

Electrophilic halogenation of unactivated cyclopropanes opens a new opportunity to construct 1,3-halofunctionalized molecules. Zyk et al. reported a seminal work on the 1,3-dihalogenation of

cyclopropanes **1** using $KICl_2$ as the stoichiometric halogenating agent, giving a mixture of 1,3-halogenated products **2a** and **2b** (Scheme 1).^[11] Recently, Hennecke et al. described a catalyst-free halocyclization of cyclopropyl substrates **2** to give a range of halo-heterocyclic compounds **3**.^[12] Mechanistically relevant reactions that involve the use of hypervalent iodine species in the oxidative 1,3-difunctionalization of unactivated cyclopropanes have also been reported by Szabó^[13] and Jacobsen.^[14]

Our research group also reported Lewis basic chalcogen-catalyzed halocyclization of cyclopropyl amides **4** to give oxazines **5**.^[15] A similar system was found to be applicable to the halocyclization of cyclopropylmethyl carboxylic acids.^[16] Diastereoselective halocyclization of cyclopropyl diester compounds was also achieved with *N*-bromosuccinimide (NBS) as the halogen source.^[17] In addition, recently we reported a Lewis base-promoted 1,3-dioxygenation of unactivated cyclopropanes using hypervalent iodine reagents.^[18] Nonetheless, the difunctionalization of unactivated cyclopropanes via electrophilic halogenation remains less exploited and has been an attractive research area. Particularly, the intermolecular electrophilic halofunctionalization of unactivated cyclopropanes remain underexploited. Based on our previous experience on the electrophilic halogenation of unactivated olefins,^[19] we anticipated that unactivated cyclopropanes could undergo

intermolecular halogenation under mild conditions. Herein, we describe an intermolecular halofunctionalization of unactivated cyclopropanes **8** with *N,N*-dimethylformamide (DMF) and alcohols to give 1,3-haloesters **9** and 1,3-haloethers **10**, respectively.



Scheme 1. Comparison of The Previous and Present Studies.

Results and Discussion

At the beginning of experimentation, cyclopropylbenzene **8a** and NBS were used as the substrate and the halogen source, respectively. 1,3-halo-formyloxylation reaction was subjected to the investigation using DMF and water as the nucleophilic partners.^[20] To our delight, **8a** was converted to β -haloformate **9a** in 55% yield and excellent regioselectivity (Markovnikov product) at room temperature in the absence of any external promoter (Table 1, entry 1). Various reaction conditions were evaluated in order to optimize the reaction (Table 1). The choice of solvent and the composition of DMF were firstly investigated. The introduction of chlorinated solvents (dichloromethane, chloroform and 1,2-dichloroethane) gave higher yields (entries 2, 4-5). In contrast, using a solvent blend of DMF with THF (entry 6) or acetonitrile (entry 7) returned inferior reaction performance. Next, the brominating reagent and the reaction temperature

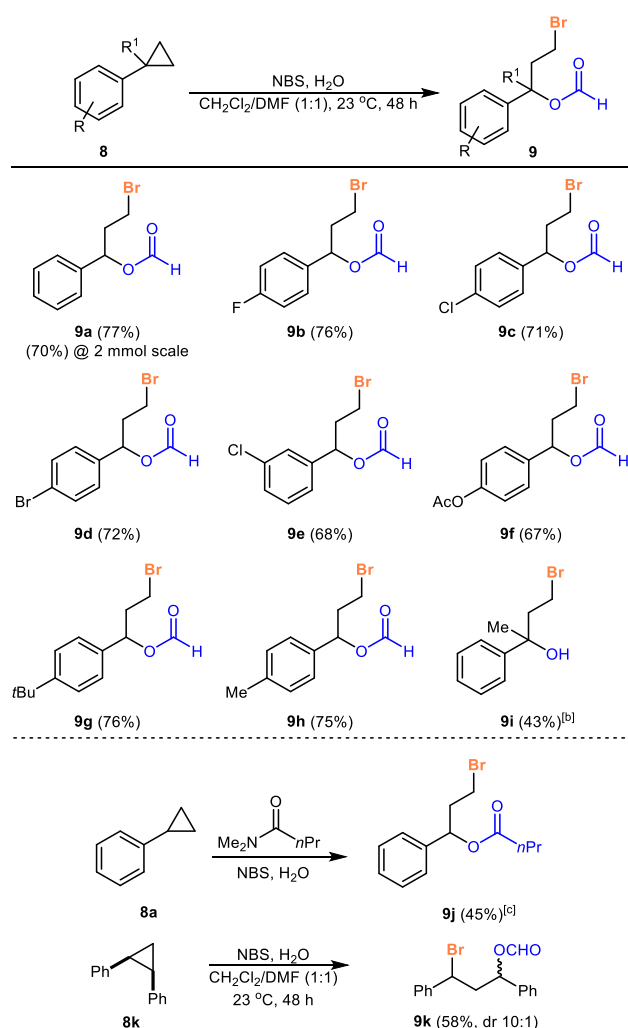
were also examined. Higher reaction yields were obtained using 1,3-dibromo-5,5-dimethylhydantoin (DBH) (entries 8 and 10). The reactions with *N*-bromophthalimide (NBP) resulted in lower yields (entries 9 and 11). However, the reactions using DBH and NBP gave significant amount of aromatic brominated side-products. Water was found to be crucial in which no desired product was detected when the reaction was carried out under anhydrous condition (entry 2 vs 3).

Table 1. Reaction Optimization.^[a]

entry	Br source	solvent	yield (%) ^[b]
1	NBS	DMF	55
2	NBS	CH ₂ Cl ₂ /DMF (1:1)	77
3 ^[c]	NBS	CH ₂ Cl ₂ /DMF (1:1)	0
4	NBS	CHCl ₃ /DMF (1:1)	61
5	NBS	(CHCl ₃) ₂ /DMF (1:1)	63
6	NBS	THF/DMF (1:1)	53
7	NBS	MeCN/DMF (1:1)	51 ^[d,e]
8	DBH	CH ₂ Cl ₂ /DMF (1:1)	86 ^[e]
9	NBP	CH ₂ Cl ₂ /DMF (1:1)	35 ^[e]
10	DBH	CHCl ₃ /DMF (1:1)	85 ^[e]
11	NBP	CHCl ₃ /DMF (1:1)	73 ^[e]

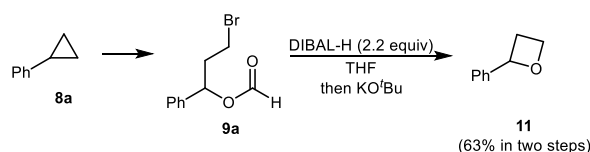
^[a] Reactions were carried out with cyclopropylbenzene **8a** (0.2 mmol), bromination source (0.4 mmol) and water (0.2 mmol) in various solvents (1.0 mL) at room temperature (except specified) in the absence of light for 48 h. ^[b] Isolated yield. ^[c] Water was not added. ^[d] Yield was measured by ¹H NMR. ^[e] Aromatic brominated product was observed in the NMR study on the crude product mixture and was inseparable by column chromatography.

With the optimized reaction conditions in hand, the substrate scope of the bromoesterification reaction was investigated (Table 2). Good conversion and regioselectivity were generally observed. The reaction (exemplified with **9a**) was found to be readily scalable with comparable performance. The reactions were also found to be compatible with substrates bearing various electron-withdrawing (**9b-9e**) and electron-donating (**9f-9h**) substituents. Apart from monosubstituted cyclopropanes, we also extended the substrate scope to a 1,1-disubstituted cyclopropane, (1-methylcyclopropyl)benzene (**8i**), giving **9i** in moderate yield.^[21] Instead of DMF, the use of *N,N*-dimethylbutyramide yielded the corresponding butyl ester product **9j** though the efficiency was moderate. The 1,2-disubstituted substrate *cis*-1,2-diphenylcyclopropane (**8k**) was also converted into 3-bromo-1,3-diphenylpropyl formate (**9k**) with a good diastereoselectivity.

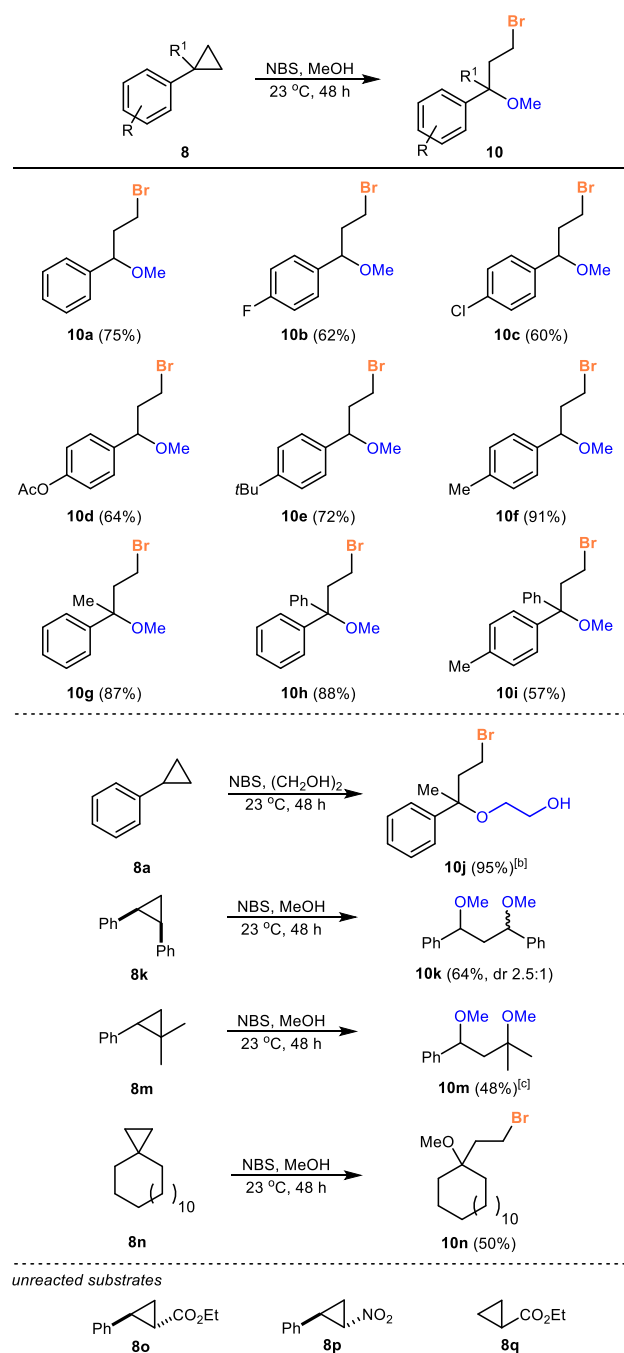
Table 2. Bromoesterification of Unactivated Cyclopropanes.^[a]

^[a] Reactions were carried out with aromatic substituted cyclopropylbenzene **8** (0.2 mmol), NBS (0.4 mmol) and water (0.2 mmol) in $\text{CH}_2\text{Cl}_2/\text{DMF}$ (1:1 v/v, 1.0 mL) at 23 °C in the absence of light for 48 h. The yields are isolated yields. ^[b] Isolated yield of **9i** for 2 steps: bromoesterification and hydrolysis. ^[c] *N,N*-dimethylbutyramide/ CH_2Cl_2 (1:1 v/v, 1 mL) was used.

The bromoester product **9a** was transformed into 2-phenyloxetane **11** (63%) using diisobutylaluminium hydride (DIBAL-H) followed by the addition of potassium *tert*-butoxide (Scheme 2). This approach can be considered as an oxygen-insertion/ring-expansion of cyclopropane **8a** in the synthesis of oxetane **11**.

**Scheme 2.** Transformation of Bromoester into Oxetane.

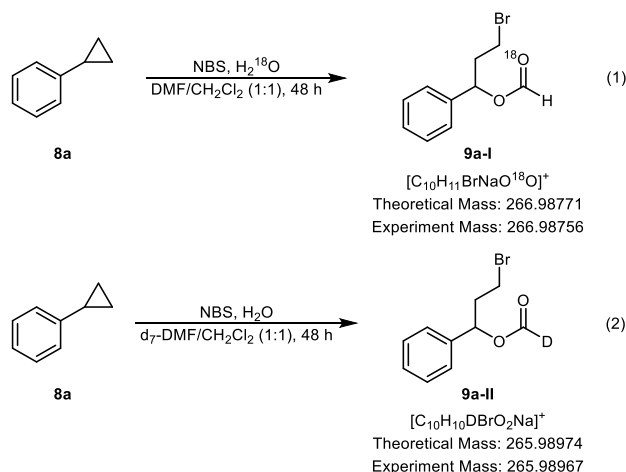
On the other hand, in the presence of NBS in methanol, **8a** was smoothly converted into bromoether **10a** (75%) at room temperature with high regioselectivity (Table 3). Substrates with various substituents were also compatible with the protocol to

Table 3. Bromoetherification of Unactivated Cyclopropanes.^[a]

^[a] Reactions were carried out with aromatic substituted cyclopropylbenzene **8** (0.2 mmol) and NBS (0.3 mmol) in MeOH (1.0 mL) at 23 °C in the absence of light for 48 h. The yields are isolated yields. ^[b] Ethylene glycol was used instead of MeOH. ^[c] NBS (0.2 mmol) was used. Aromatic bromination side-product was detected when more NBS was used.

give **10b-10f** in good yields. Similar to the bromoesterification, bromoethers **10g**, **10h** and **10i** were obtained smoothly using the corresponding disubstituted substrates. When ethylene glycol was used in place of methanol in the bromoetherification of **8a**, **10j** was obtained in 95% yield and no dimerized product was observed. **8k** was transformed into 1,3-dimethoxy-1,3-diphenylpropane (**10k**), and (2,2-dimethylcyclopropyl)benzene (**8m**) was converted into (1,3-dimethoxy-3-methylbutyl)benzene (**10m**), presumably obtained from the substitution of the secondary benzyl/tertiary alkyl bromide intermediate by MeOH. Spiro substrate **8n** was also found to be compatible to the reaction, giving **10n** in moderate yield. For other cyclopropane substrates derived from cinnamates (**8o**), *trans*- β -nitrostyrene (**8p**), acrylates (**8q**), both electrophilic bromoesterification and bromoetherification were found to be sluggish.

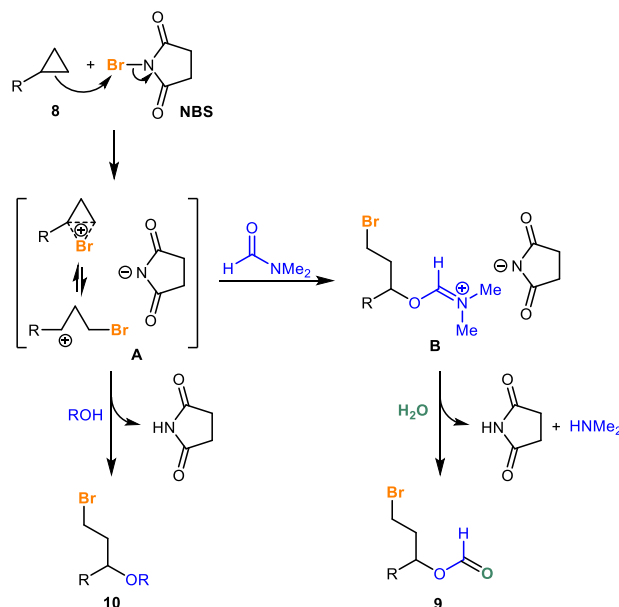
Isotopic labeling experiments were conducted in order to probe the reaction mechanism. Under optimized conditions, **8a** was subjected to the reaction using $H_2^{18}O$ instead of $H_2^{16}O$ as the nucleophilic partner (Scheme 3, eq. 1). The corresponding oxygen-labelled product **9a-I**, which was characterized by NMR and MS, was obtained in 70% yield with 90% deuterium purity. When the reaction was conducted using *N,N*-dimethylformamide- d_7 , the resultant deuterium-labelled product **9a-II** was obtained smoothly in 54% yield (Scheme 3, eq. 2). These results indicate that the carbonyl oxygen in the product **9** was contributed by water while the remaining ester moiety was originated from the DMF molecule.



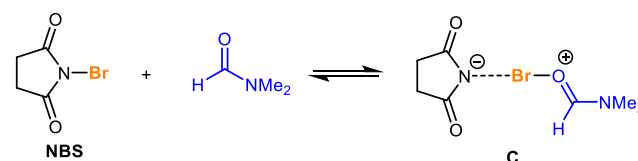
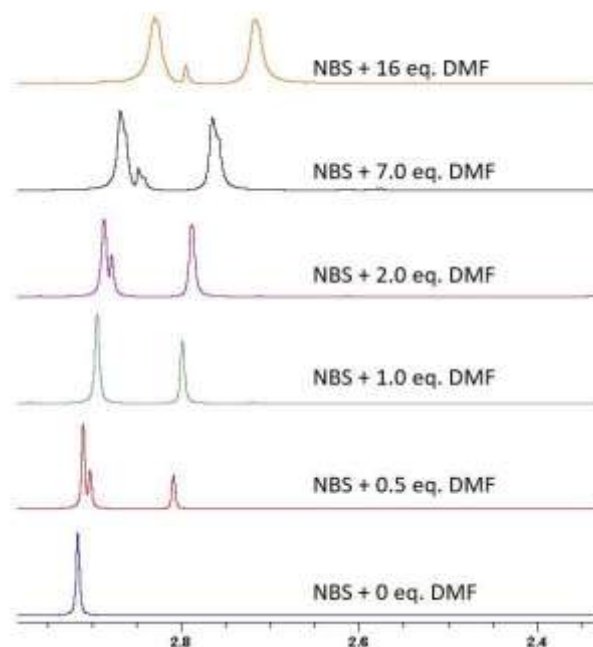
Scheme 3. Isotopic Labelling Experiments.

A plausible mechanism is depicted in Scheme 4. Based on the previous studies,^[11,12,15-17] we believe that the π -character σ -bonds in the cyclopropane substrates **8** might interact with the electrophilic brominating agent NBS to give the corresponding bromiranium-like intermediate **A**, which might exist in equilibrium with the open-chain carbocation species. Subsequently, the oxygen of DMF might

attack species **A** via S_N1 or S_N2 mechanism to give the Markovnikov adduct **B**. Finally, species **B** might be hydrolyzed by water to give the desired product **9**. For the bromoetherification, a similar mechanism might be adopted whereas the alcohol might attack intermediate **A** to give the bromoether **10**.



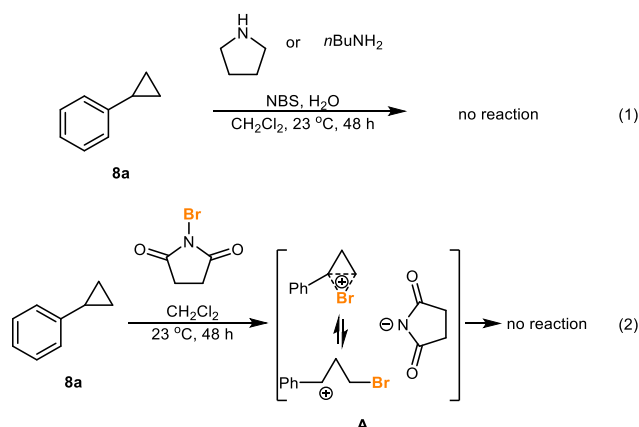
Scheme 4. Plausible Reaction Mechanism.



Scheme 5. 1H NMR Experiment of NBS and DMF.

Since the reaction proceeded smoothly without an external promoter, we suspected that the solvent might be involved in activating NBS. Indeed, it is known that DMF could activate NBS for aromatic halogenation.^[22] ¹H NMR experiment on a mixture of NBS (2.92 ppm) and DMF in CD₂Cl₂ was conducted (Scheme 5). It was found that the signals of succinimide's protons shifted up-field upon the addition of DMF. A possible explanation is that the Lewis basic DMF might coordinate to the Br of NBS to give activated brominating species **C**, which may increase the anionic character of the succinimide. We also performed a ¹H NMR experiment of NBS in CD₃OD. However, it appears that no adduct such as CD₃OBr was formed because no succinimide was detected (see SI for details). Thus, we suspect that the polar protic alcohol solvent might facilitate the reaction by stabilizing the charged species **A**.

When other nucleophiles such as pyrrolidine (secondary amine) or *n*-butylamine (primary amine) was used instead of methanol or DMF, no desired product was detected (Scheme 6, eq. 1). We also conducted the reaction in the absence of nucleophile and water in the hope of generating species **A** so that the succinimide might act as the nucleophile to attack the cationic species (Scheme 6, eq. 2). However, no reaction was observed and cyclopropylbenzene (**8a**) was recovered quantitatively.



Scheme 6. Attempts to use pyrrolidine and *n*-butylamine as the nucleophiles.

Conclusion

In summary, mild, efficient, and regioselective bromoesterification and bromoetherification of unactivated cyclopropanes have been developed. The methodology features advantages including broad substrate scope and products being possible 1,3-difunctionalized synthons to other biologically essential organic molecules.

Experimental Section

General procedure for the 1,3-bromo-formyloxylation reaction of cyclopropane **8**.

To a solution of cyclopropane **8** (0.2 mmol) in dichloromethane (0.5 mL) and *N,N*-dimethylformamide (0.5 mL) was added water (3.6 μ L, 0.2 mmol) and *N*-bromosuccinimide (71.2 mg, 0.4 mmol) into a vial. The reaction was shielded from light and then stirred at 23 °C for 48 h. The reaction was quenched with saturated aqueous Na₂SO₃ (0.5 mL) and H₂O (2 mL), and was then extracted with diethyl ether (3 \times 5 mL). The combined organic extract was washed with brine (5 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure with a rotary evaporator. The residue was purified by flash column chromatography to yield the desired methanoate **9**.

Acknowledgements

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FULL PAPER

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