Organic LETTERS

Letter

pubs.acs.org/OrgLett

Ring-Opening 1,3-Halochalcogenation of Cyclopropane Dicarboxylates

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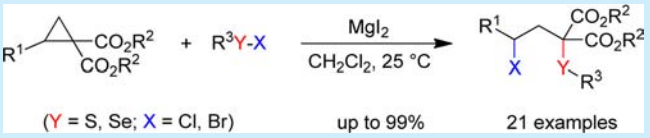
Supporting Information

ABSTRACT: Donor–acceptor cyclopropanes with two geminal carboxylic esters are reacted with chalcogenyl chlorides and bromides to afford ring-opened products bearing the halogen atoms in the 1-position, adjacent to the donor, and the chalcogenyl residue in the 3-position next to the two acceptor groups. A variety of different donors (e.g., aryl, N, and O) are used. The stereospecificity of the reaction is demonstrated by using a chiral starting material.

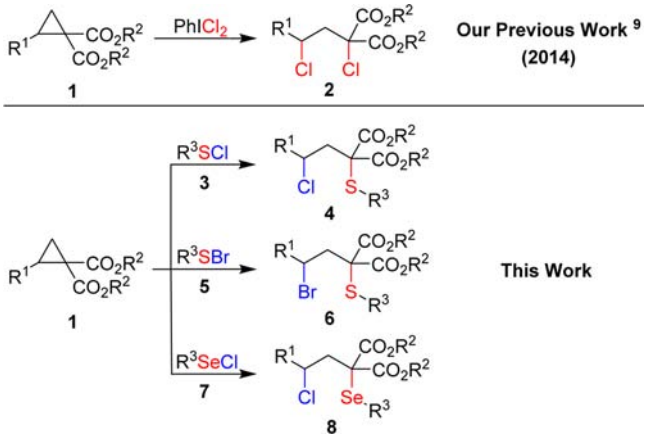


During the past decade, donor–acceptor (D–A) cyclopropanes have enjoyed a renaissance as easily available building blocks.[1] Although the basic chemistry in this field was developed by Wenkert and Reissig[2] in the 1970s and 1980s, many groups have recently utilized the unique features of this special class of three-membered rings. These highly polarized strained systems easily undergo cycloadditions,[3] rearrangements,[4,5] and ring-opening reactions. Thus, they are an ideal starting point for the synthesis of carbo- and heterocycles and have been used in the preparation of natural products.[6]

Cycloaddition and rearrangement reactions of D–A cyclopropanes commonly allow a rapid increase of complexity, whereas ring-opening reactions decrease the complexity by transforming the cyclopropane into an aliphatic chain. A variety of heteronucleophiles such as phenols, amines, azides, or indoles have been employed to open the ring.[7] As a result, the nucleophile is located next to the donor while the negative charge next to the acceptor is captured by a proton. To further weaken the bond between donor and acceptor and to promote the attack, Lewis acids are commonly applied. Whereas the transfer of a nucleophile to position 1 and a proton to position 3 has often been reported, only a few examples of ring-opening reactions exist in which two non-hydrogen substituents were attached to the 1- and 3-positions next to the donor and acceptor.[8] Recently, we found that cyclopropane dicarboxylates **1** react with Willgerodt's reagent ($PhICl_2$) to yield 1,3-dichlorinated compounds **2** (Scheme 1).[9] Sparr and Gilmour even performed enantioselective 1,3-dichlorinations of *meso*-cyclopropyl aldehydes using an organocatalytic approach.[10]

After our initial attempts with the ring-opening 1,3-dichlorination, we considered whether we might trigger other ring-opening 1,3-additions of cyclopropane dicarboxylates using strongly polarized bonds of the type RY–X. Prototypes of such species are provided by the sulfenyl and selenyl halides **3**, **5**, and **7**. The higher electronegativity of the halogen in comparison to that of the chalcogen efficiently polarizes the bond. Thus, we envisioned that the electrophilic part of the cyclopropane, the center next to the donor, might add the halide and that the nucleophilic part, next to the two acceptor moieties, would be captured by the positively polarized chalcogen. This assumption was corroborated by early work from Reissig and Reichelt that led to 2-chalcogenyl-substituted 4-oxoesters when TMSO-substituted cyclopropanes were treated with chalcogenyl chlorides.[11]

Scheme 1. Ring-Opening 1,3-Dichlorination of Cyclopropane Dicarboxylates and Our Extension to 1,3-Halochalcogenation



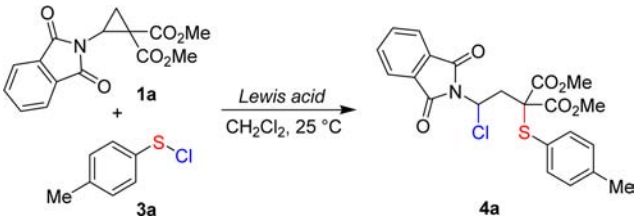
At the outset of our studies, D–A cyclopropane **1a** was chosen to explore suitable conditions for the expected process. As a component to be added, we chose *p*-tolylsulfenyl chloride **3a**, which is easily available from the respective thiophenol and *N*-chlorosuccinimide;[12] as donor, we employed phthalimide.

Initial experiments using $FeCl_2$, which is known to act as radical initiator in combination with sulfenyl chlorides,[13] showed no formation of the desired product (Table 1). Incorporation of stronger Lewis acids such as $Sc(OTf)_3$ (entry 2), $Yb(OTf)_3$, $BF_3{\cdot}OEt_2$, or $TiCl_4$ led to decomposition of the starting materials.

Received: November 11, 2016
Published: December 14, 2016

DOI: 10.1021/acs.orglett.6b03375
Org. Lett. 2017, 19, 98–101

Table 1. Optimization of the 1,3-Chlorosulfenylation[a]



entry	Lewis acid	**3a** (equiv)	*t* (h)	yield (%)
1	$FeCl_2$	1.1	24	–
2	$Sc(OTf)_3$	1.1	24	decomp
3	$FeCl_3$	1.1	24	complex mixture[b]
4	$ZnBr_2$	1.1	3	50 + byproducts
5	MgI_2	1.1	0.5	81
6	MgI_2	1.5	0.08	91

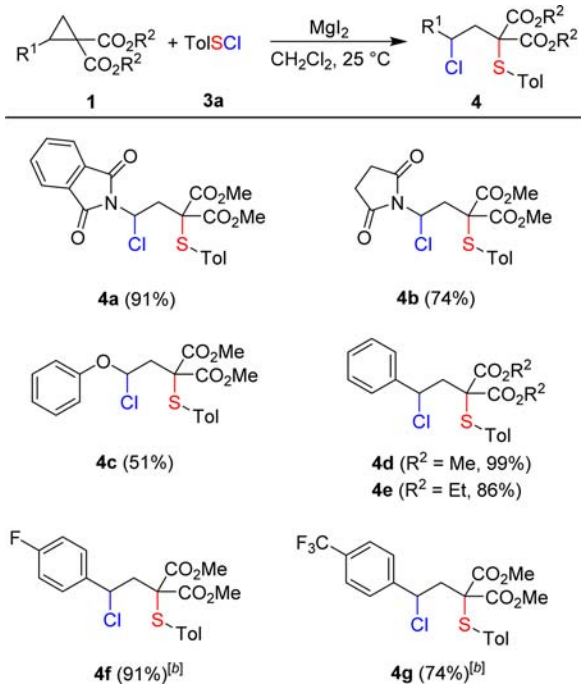
[a]Reaction conditions: **1a** (0.1 mmol), CH_2Cl_2 (0.1 M, with respect to the cyclopropane), 10 mol % of Lewis acid, ambient temperature. [b]Desired product was found in the mixture.

More promising results could be achieved with $FeCl_3$, indicating that the desired product is formed, and $ZnBr_2$, giving rise to 50% of **4a** in addition to some unspecified byproducts. Finally, utilization of 10 mol % of MgI_2 as Lewis acid, combined with an increase of the amount of sulfenyl chlorides to 1.5 equiv and a shortening of the reaction time to 5 min, yielded **4a** in 91% yield.

With optimized conditions in hand, the scope of this 1,3-chlorosulfenation reaction was examined. We started with a variation of the donor (R^1) at the three-membered ring (Scheme 2). Optimization was originally performed with the nitrogen donor phthalimide; thus, succinimide was also tested and provided a 74% yield of **4b**. Oxygens are other markedly electron-releasing donors, and a phenoxy-substituted cyclopropane afforded the desired product **4c** in 51% yield. Several arene units differing in their electron-donating ability were subjected to the reaction conditions. Transformations proceeded smoothly and furnished desired products **4d**–**4g** in yields of 74–99%. Cyclopropanes with very electron-rich arene units such as *p*-MeOPh underwent electrophilic aromatic substitution with a sulfenium ion, resulting in a mixture of products.

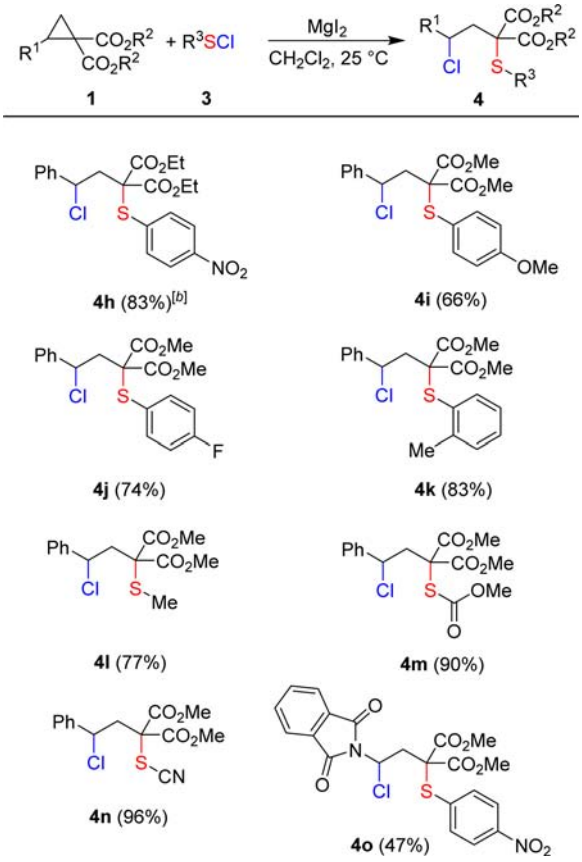
The scope of various sulfenyl chlorides was tested (Scheme 3). Electron-poor (**4h**, **4o**), electron-rich (**4i**), and fluoro-substituted (**4j**) aryl residues were compatible with the reaction. Use of bulky *o*-tolyl sulfenyl chloride provided **4k** in good yield of 83%. Aliphatic sulfenyl chlorides also participated in the reaction, and a similar yield was obtained (77%). Even a thiocarbonate was successfully introduced by the reaction of the cyclopropane with ClS(CO)OMe, affording the respective product **4m** in 90% yield. The pseudohalogen ClSCN is easily available from the reaction of lead(II) thiocyanate and sulfuryl chloride, and we therefore employed this reagent too to affect a ring-opening under our conditions; the transformation yielded the respective thiocyanate **4n** in 96% yield. Since sulfur is still positively polarized, thiocyanates were utilized as useful precursors for further

Scheme 2. 1,3-Chlorosulfenylation of D–A Cyclopropanes with *p*-Tolylsulfenyl Chloride[a]



[a]Reaction conditions: **1** (0.2 mmol), **3a** (1.5–2.0 equiv), MgI_2 (10 mol %), CH_2Cl_2 (0.1 M), reaction time: 5 min – 3 h. All yields represent isolated 1,3-functionalized products. [b]0.1 mmol of **1** was used.

Scheme 3. 1,3-Chlorosulfenylation of Phenyl- and Imido-Substituted Cyclopropanes with Several Sulfenyl Chlorides, ClS(CO)OMe, and ClSCN[a]



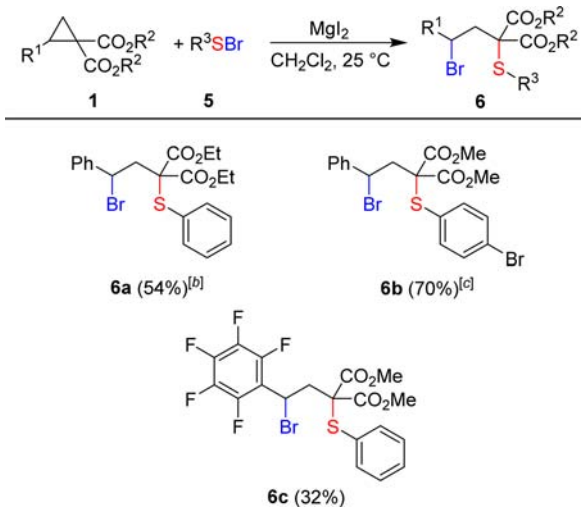
[a]Reaction conditions: **1** (0.1 mmol), **3** (1.5–5.0 equiv), MgI_2 (10 mol %), CH_2Cl_2 (0.1 M), 15 min to 20 h. All yields represent isolated 1,3-functionalized products. [b]0.2 mmol of **1** was used.

DOI: 10.1021/acs.orglett.6b03375
Org. Lett. 2017, 19, 98–101

reactions with carbon nucleophiles with loss of cyanide (e.g., leading to thioalkynes).[14]

We addressed the question whether sulfenyl bromides also react in an analogous way. These were obtained from the thiol and a solution of *N*-bromosuccinimide. To precipitate the resulting succinimide, the mixture was suspended with *n*-pentane and filtered. Removal of the solvent in vacuo gave sulfenyl bromide, which was used without further purification. Since sulfenyl bromides are more sensitive than sulfenyl chlorides, we employed only aryl sulfenyl bromides **5** and used more equivalents than in the experiments described before. Scheme 4 depicts three examples of 1,3-bromosulfenation. Much longer

Scheme 4. 1,3-Bromosulfenylation of D−A Cyclopropanes with Sulfenyl Bromide[a]



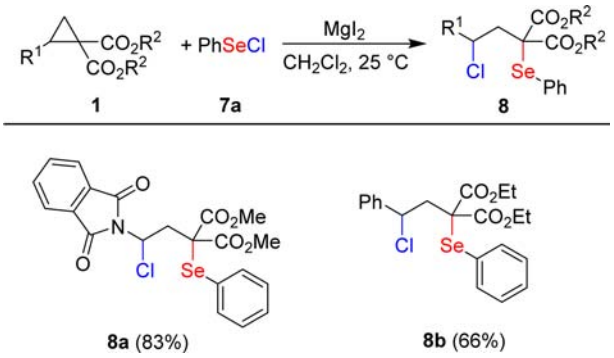
[a]Reaction conditions: **1** (0.1 mmol), **5** (3.0 equiv), MgI_2 (10 mol %), CH_2Cl_2 (0.1 M), 20−24 h. All yields represent isolated 1,3-functionalized products. [b]0.2 mmol of **1** used. [c]10 equiv of **5** used.

reactions times (20−24 h) were required for complete conversion, which might be attributed to the much less pronounced polarization of the S−Br bond. Yields of **6** ranging from 32 to 70% were much lower than for the lighter counterparts; nevertheless, even when the strongly electron-withdrawing pentafluorophenyl residue was used as a donor, it afforded **6c** in 32% yield.

Our reaction conditions were successfully extended to the synthesis of 1,3-chloroselenated products. Phthalimide- and phenyl-substituted three-membered rings were converted smoothly with commercially available phenylselenyl chloride (Scheme 5). The corresponding selenium-containing products were obtained in 66 and 83% yield. Formation of **8a** was much faster than **8b**. Because of the relative instability of corresponding aliphatic selenyl chlorides, we did not attempt transformations with these reagents. Analogous experiments with phenylselenyl bromide and thio- and selenocyanates showed no conversion, and the starting material was recovered.

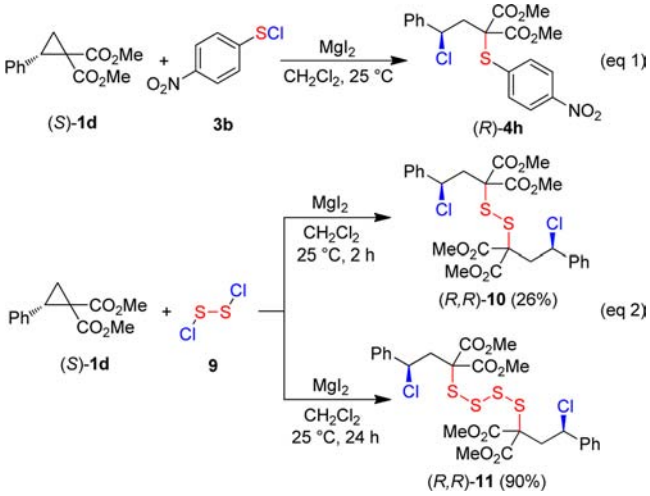
Finally, we explored the stereospecificity of the ring-opening 1,3-chlorosulfenation using enantioenriched (95% ee) phenyl-substituted cyclopropane (*S*)-**1d**. *p*-Nitrophenylsulfenyl chloride (**3b**) reacted with almost complete stereospecificity, giving (*R*)-**4h** in quantitative yield and 88% ee as revealed by chiral HPLC (Scheme 6, eq 1, and Supporting Information). Mechanistically, this process might be explained via S_N2-like attack of the chloride (from RSCl) to the cyclopropane, which then further reacts with

Scheme 5. 1,3-Chloroselenylation of D−A Cyclopropanes with Phenylselenyl Chloride[a]



[a]Reaction conditions: **1** (0.1 mmol), **7** (0.15 mmol), MgI_2 (10 mol %), CH_2Cl_2 (0.1 M), 15 min to 5 h. All yields represent isolated 1,3-functionalized products.

Scheme 6. Stereospecificity of the 1,3-Chlorosulfenylation (eq 1) and Transformation with S_2Cl_2 to Dimeric Structures (eq 2)



the sulfenium ion to give (*R*)-**4h**. We found that S_2Cl_2 was also able to undergo the reaction (Scheme 6, eq 2). Since both termini of the S_2 moiety react, we used (*S*)-**1d** to exclude the possibility of generating a diastereomeric mixture. The desired product **10** was obtained in poor yield of 26% after 2 h; longer reaction times furnished a product with an S_4 chain (**11**) in much higher yield (90%). For **10**, X-ray crystallographic analysis confirmed the expected structure and demonstrated the inversion of the stereocenter during the transformation. The molecular structure of this compound is depicted in Figure 1.

In conclusion, we have developed novel 1,3-halochalcogenation reactions of cyclopropane dicarboxylates. A variety of D−A cyclopropanes were converted with either readily available sulfenyl chlorides, sulfenyl bromides, or selenyl chlorides. Oxygen and nitrogen and even aromatic systems can be successfully employed as donors. Magnesium iodide proved to be the Lewis acid of choice. Further work with other highly polarized reagents to trigger other ring-opening 1,3-addition processes is in progress in our laboratory.

DOI: 10.1021/acs.orglett.6b03375
Org. Lett. 2017, 19, 98−101

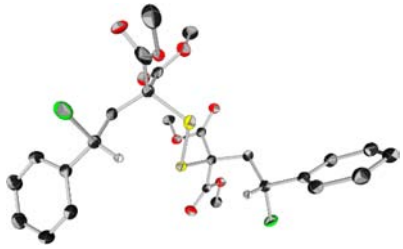


Figure 1. Molecular structure (50% ellipsoid probability) of **10** in the solid state. Oxygen atoms are shown in red, sulfur atoms in yellow, and chlorine atoms in green. Hydrogen atoms are omitted.[15,16]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03375.

Crystal data for **10** (CIF)

Detailed experimental procedures, analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the European Research Council (ERC Consolidator Grant "GAINBYSTRAIN" to D.B.W.). L.K.B.G. thanks the Studienstiftung des deutschen Volkes for a Ph.D. Fellowship.

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(16) The CIF file has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1507090 (**10**). Copies can be obtained via data_request@ccdc.cam.ac.uk.

DOI: 10.1021/acs.orglett.6b03375
Org. Lett. 2017, 19, 98−101