OL Organic Letters

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Lewis Acid Catalyzed Ring-Opening 1,3-Aminothiolation of Donor–Acceptor Cyclopropanes Using Sulfenamides

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00483 Read Online

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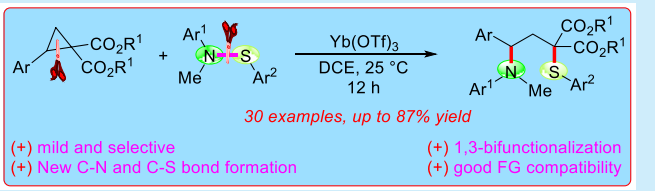
ABSTRACT: $Yb(OTf)_3$ catalyzed mild and regioselective ring-opening 1,3-aminothiolation of donor–acceptor (D–A) cyclopropanes using sulfenamides has been demonstrated. The insertion of the C–C σ-bond of D–A cyclopropanes into the S–N σ-bond of sulfenamides allows the synthesis of diverse γ-aminated α-thiolated malonic diesters in moderate to good yields (up to 87%) with good functional group compatibility. The stereospecificity of the reaction was demonstrated using enantiomerically pure D–A cyclopropane.



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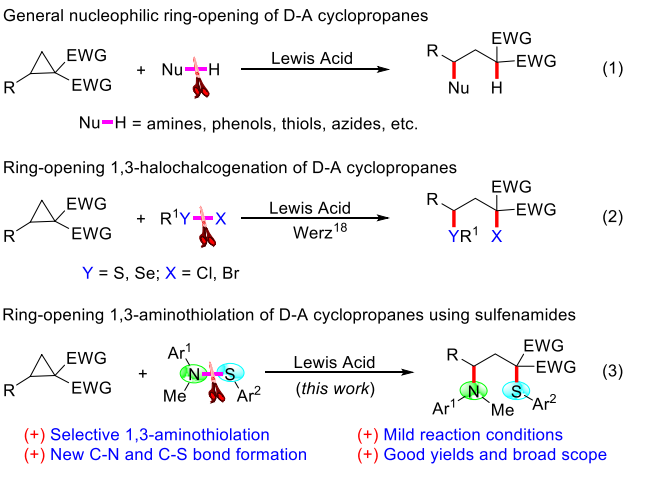
In recent years, donor–acceptor (D–A) cyclopropanes have emerged as one of the versatile polarized three-atom building blocks in organic synthesis.[1,2] The adjacent arrangement of the donor and the acceptor moieties combined with the exceptional reactivity of the strained cyclopropane ring system allows the facile cleavage of the ring under Lewis acid conditions.[3,4] The resultant 1,3-zwitterionic intermediate can be intercepted with compounds bearing carbon–carbon multiple bonds,[5] aldehydes,[6] imines,[7] nitrosoarenes,[8] etc. in a (3 + 2) annulation resulting in the formation of various carbocycles and heterocycles.[9] Moreover, a series of 1,3-dipoles can be added to Lewis acid activated D–A cyclopropanes in a formal (3 + 3) annulation leading to six-membered rings.[10] Further, employing (hetero)dienes to open D–A cyclopropanes could result in the synthesis of seven-membered rings following a (3 + 4) annulation.[11]

In addition to (3 + n) annulation reactions (where n = 2, 3, 4), a variety of nucleophiles can induce ring opening on activated D–A cyclopropanes. For instance, heteroatom nucleophiles of the type Nu-H such as amines,[12] phenols,[13] thiols,[14] azides,[15] etc. as well as carbon nucleophiles[16] can open the activated D–A cyclopropanes, where the nucleophile adds to the carbon next to the donor group and the emerging negative charge near the acceptor gets protonated thus leading to monofunctionalization of D–A cyclopropanes (Scheme 1, eq 1). If the ensuing anion is intercepted with an electrophile instead of the protonation, this could result in a valuable 1,3-bifunctionalization. Such ring-opening 1,3-bifunctionalization of D–A cyclopropanes can be achieved via three-component coupling as demonstrated by the Studer and Werz groups,[17] or by insertion of D–A cyclopropanes to heteroatom–heteroatom bonds. In 2017, Werz and co-workers reported an elegant 1,3-halochalcogenation of D–A cyclopropanes resulting in the synthesis of sulfenyl/selenyl halides (eq 2).[18,19] Interestingly, the introduction of both amino and sulfenyl groups at the 1,3-position of D–A cyclopropanes via the insertion to S–N bond, to the best of our knowledge, is unknown. Herein, we report the mild and regioselective ring opening of D–A cyclopropanes using sulfenamides, the 1,3-aminothiolation, allowing the synthesis of diverse γ-aminated α-thiolated malonic diesters in moderate to good yields (eq 3).[20]

Scheme 1. Lewis Acid Catalyzed Ring Opening of D–A Cyclopropanes



Received: February 6, 2020

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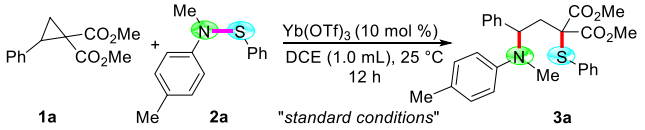
https://dx.doi.org/10.1021/acs.orglett.0c00483
Org. Lett. XXXX, XXX, XXX–XXX

We have recently demonstrated the insertion of sulfenamides to arynes resulting in the formation of versatile sulfanyl aniline derivatives.[21] Impressed by this and given the similarity in reactivity of arynes and D−A cyclopropanes,[22] the present studies were initiated by treating the cyclopropane **1a** with the sulfenamide **2a** in the presence of $Yb(OTf)_3$ (10 mol %) in dichloroethane (DCE) at 25 °C. Interestingly, under these conditions, a facile insertion reaction occurred leading to the formation of the γ-aminated α-thiolated malonic diester **3a** in 73% yield (Table 1, entry 1). Notably, the product **3a** was not

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

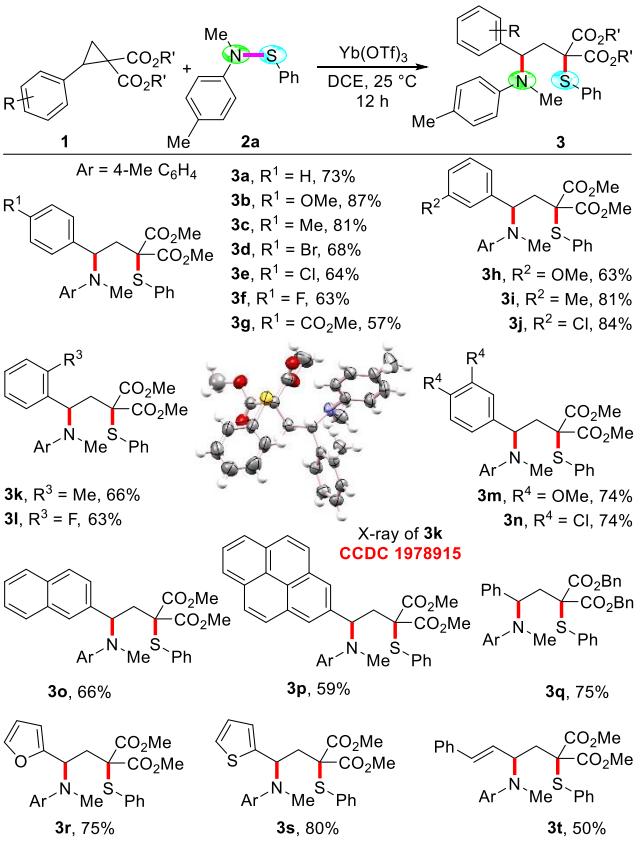
entry	variation of the standard conditions	yield of **3a** (%)[b]
1	*none*	73
2	no $Yb(OTf)_3$	<5
3	$Sc(OTf)_3$ instead of $Yb(OTf)_3$	15
4	$Sn(OTf)_2$ instead of $Yb(OTf)_3$	17
5	70 °C instead of 25 °C	43
6	0 °C instead of 25 °C	<5
7	CH_2Cl_2 instead of DCE	47
8	$CHCl_3$ instead of DCE	49
9	10 mol % TfOH instead of $Yb(OTf)_3$	<5
10	10 mol % PTSA instead of $Yb(OTf)_3$	<5
11	0.25 mmol of **1a** and 0.3 mmol of **2a**	68
12	5 mol % $Yb(OTf)_3$	61

[a]Standard conditions: **1a** (0.30 mmol), **2a** (0.25 mmol), $Yb(OTf)_3$ (10 mol %), DCE (1.0 mL), 25 °C for 12 h. [b]Given are yield of chromatographically purified **3a**.

formed in the absence of the Lewis acid catalyst (entry 2). Other Lewis acids such as $Sc(OTf)_3$ and $Sn(OTf)_2$ returned a reduced yield of **3a** under the present conditions (entries 3, 4). The performed reaction at 70 °C afforded a reduced yield of **3a**, and the reaction was sluggish at 0 °C (entries 5, 6). When the reaction was performed in other chlorinated solvents such as CH_2Cl_2 and $CHCl_3$, the desired product **3a** was formed in low yields (entries 7, 8). Only a trace of **3a** was formed when the reaction was carried out in the presence of TfOH and PTSA indicating that Brønsted acid activation is not operating in this case (entries 9, 10). When the stoichiometry of **1a** and **2a** are reversed, **3a** was formed in a slightly reduced yield of 68% (entry 11). Moreover, 10 mol % $Yb(OTf)_3$ was required for a good yield of **3a**, as the reaction carried out with 5 mol % catalyst provided only 61% of **3a** (entry 12).[23]

After having the optimized reaction conditions in hand (Table 1, entry 1), the substrate scope of this insertion reaction has been evaluated. First, we examined the scope of various D−A cyclopropanes in this insertion reaction (Scheme 2). A series of D−A cyclopropanes bearing electron-releasing, -neutral, and -withdrawing substituents at the 4-position of the benzene ring on the donor terminus underwent smooth insertion to sulfenamide **2a** to give the corresponding 1,3-bifunctionalized derivatives in good yields (**3a**−**3g**). Moreover, D−A cyclopropanes having substitution at the 3- and 2-position and disubstitution on the aryl ring are well tolerated under the present conditions leading to the formation of the desired products in good yields (**3h**−**3n**). In the case of the

Scheme 2. Substrate Scope of D−A Cyclopropanes[a]

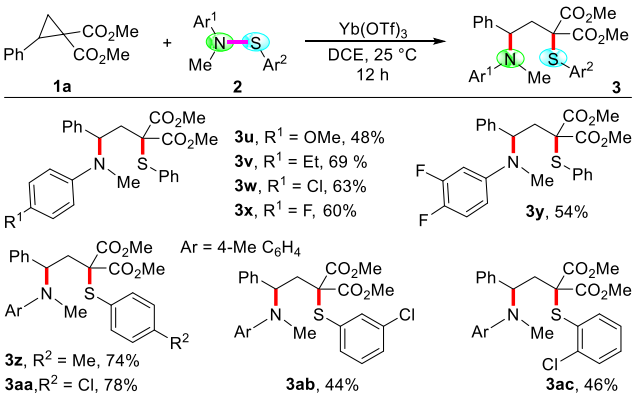


[a]General conditions: **1** (0.30 mmol), **2a** (0.25 mmol), $Yb(OTf)_3$ (10 mol %), DCE (1.0 mL), 25 °C for 12 h. Isolated yields are given.

methyl derivative **3k**, the structure was confirmed using X-ray analysis (CCDC 1978915). The naphthyl and pyrenyl groups worked well as donors (**3o**, **3p**), and the benzyl ester furnished the product **3q** in 75% yield. In addition, D−A cyclopropanes having heteroaryl groups such as furyl and thienyl could be used as donors and the use of a styrenyl moiety as the donor was also tolerated under the present conditions (**3r**−**3t**).

Next, we examined the scope of the reaction using various sulfenamides (Scheme 3). Sulfenamides resulting from *N*-methyl aniline derivatives bearing electron-releasing and

Scheme 3. Substrate Scope: Variation of Sulfenamides[a]



[a]General conditions: **1a** (0.6 mmol), **2** (0.5 mmol), $Yb(OTf)_3$ (10 mol %), DCE (2.0 mL), 25 °C for 12 h. Isolated yields are given.

https://dx.doi.org/10.1021/acs.orglett.0c00483
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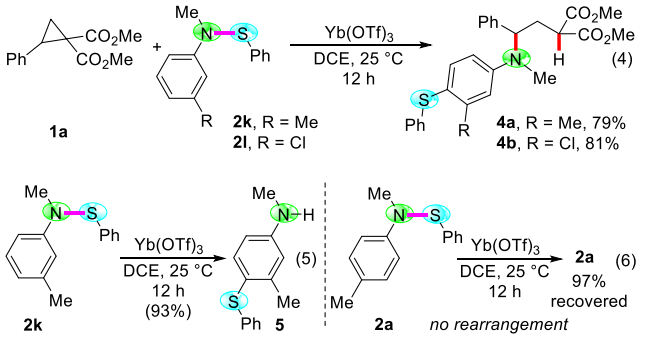
-neutral groups at the 4-position of the ring smoothly afforded the expected 1,3-aminothiolated products in moderate to good yields (**3u**−**3x**). Notably, the difluoro substituted aniline derivative afforded the product **3y** in 54% yield. Moreover, sulfenamides derived from substituted benzenethiols bearing substituents at various positions of the benzene ring were also well tolerated under optimized reaction conditions, and the desired products were formed in moderate to good yields (**3z**−**3ac**) thus demonstrating the versatile nature of the present insertion reaction. Disappointingly, *S*-alkyl sulfenamides did not furnish the desired insertion product under the optimized conditions.[24]

Interestingly, when the *N*,3-dimethylaniline-derived sulfenamide **2k** was subjected to the optimized reaction conditions, the desired 1,3-bifunctionalized product was not formed. Instead, the sulfenamide **2k** rearranges to *N*,3-dimethyl-4-(phenylthio) aniline **5** in the presence of $Yb(OTf)_3$ and then it adds to **1a** to give the N−H insertion product **4a** in 79% yield (Scheme 4, eq 4). A similar result was obtained with the 3-

Scheme 4. Reaction Using *N*-Methyl 3-Substituted Aniline-Derived Sulfenamides

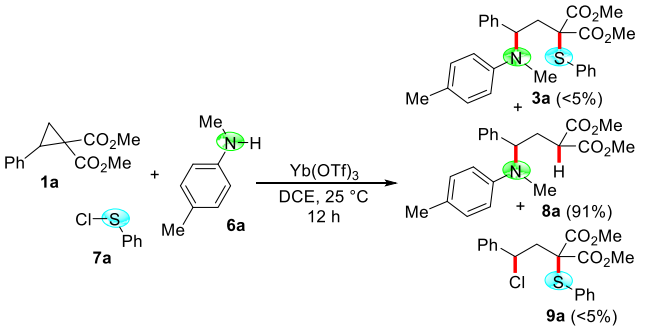


chloro derivative **2l** where the N−H insertion product **4b** was formed in 81% yield. To gain insight into this rearrangement, the sulfenamide **2k** was subjected to $Yb(OTf)_3$ in DCE resulting in the formation of the rearranged aniline **5** in 93% yield (eq 5).[25] Moreover, this rearrangement was not observed when **2a** was subjected to $Yb(OTf)_3$ without **1a**. Thus, it was concluded that 4-substitution on the *N*-methyl aniline moiety of **2** was required for the insertion of sulfenamide to D−A cyclopropanes.

Given the fact that the sulfenamides **2** can be synthesized from the *N*-methyl aniline and sulfenyl chloride, and considering the three-component 1,3-aminothiolation of D−A cyclopropanes demonstrated by Werz and co-workers,[17a] we tried the three-component reaction involving **1a**, **6a**, and **7a** under the present conditions (Scheme 5). To our surprise, the desired 1,3-aminothiolated product **3a** was not formed under the present conditions and instead the N−H insertion of **6a** to **1a** took place leading to the formation of **8a** in 91% yield. Moreover, the insertion product **9a** derived from **7a** was not observed under this condition.[18] These studies indicate the role of preformed sulfenamides in this insertion reaction.

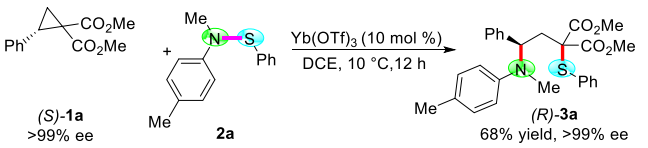
To gain insight into the mode of addition of sulfenamide to D−A cyclopropanes, we have performed the reaction using enantiomerically pure D−A cyclopropanes. When the reaction of (*S*)-**1a** (>99% ee) was performed with **2a** under the optimized conditions, the product (*R*)-**3a** was formed in 72% yield and 52% ee. Moreover, treatment of (*S*)-**1a** under the Lewis acid conditions (without **2a**) resulted in the complete

Scheme 5. Envisioned Three-Component Approach



recovery of (*S*)-**1a** without loss of enantiopurity. This allowed us to perform the reaction at a low temperature. Gratifyingly, when the reaction of (*S*)-**1a** with **2a** was carried out at 10 °C, the desired product (*R*)-**3a** was formed in 68% yield and >99% ee (Scheme 6).[26] These results indicate that the nucleophilic attack of the sulfenamide proceeds in an S_N2-like fashion with complete stereospecificity.[23,27]

Scheme 6. Enantiospecific 1,3-Aminothiolation



In conclusion, we have demonstrated the $Yb(OTf)_3$ catalyzed regioselective ring opening 1,3-aminothiolation of D−A cyclopropanes using sulfenamides resulting in the synthesis of γ-aminated α-thiolated malonic diesters in moderate to good yields. Mild conditions, selective product formation, and good functional group compatibility with broad scope are the notable features of the present reaction. The reaction performed using enantiopure D−A cyclopropane indicated that the ring opening is stereospecific and proceeds in an S_N2-like pathway. Further studies on related ring-opening reactions of D−A cyclopropanes are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00483.

Details on experimental procedures, characterization, and NMR spectra of γ-aminated α-thiolated malonic diesters (PDF)

Accession Codes

CCDC 1978915 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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https://dx.doi.org/10.1021/acs.orglett.0c00483
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous financial support by Science and Engineering Research Board (SERB), Government of India (File Number: EMR/2016/007021) is gratefully acknowledged. A.G. thanks CSIR, and T.R. and R.N.G. thank IISc respectively for the research fellowship. We thank Ms. Rekha Kumari (SSCU, IISc) for the X-ray data.

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(27) Cross-over experiments performed using differently substituted sulfenamides indicated the formation of four γ-aminated α-thiolated malonic diester products shedding light on the stepwise mode of insertion and the intermolecular nature of the sulfur group migration.

https://dx.doi.org/10.1021/acs.orglett.0c00483
Org. Lett. XXXX, XXX, XXX−XXX