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Converting Strain Release into Aromaticity Loss for Activation of Donor−Acceptor Cyclopropanes: Generation of Quinone Methide Traps for C-Nucleophiles

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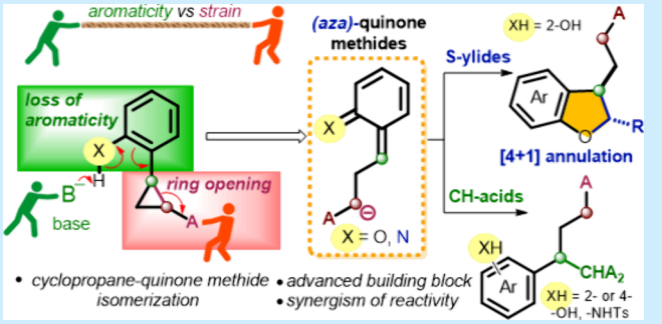
ABSTRACT: Here, we present a new approach for the activation of donor−acceptor cyclopropanes in ring-opening reactions, which does not require the use of a Lewis or Brønsted acid as a catalyst. Donor−acceptor cyclopropanes containing a phenolic group as the donor undergo deprotonation and isomerization to form the corresponding quinone methides. This innovative strategy was applied to achieve (4 + 1)-annulation of cyclopropanes with sulfur ylides, affording functionalized dihydrobenzofurans. Additionally, the generated *ortho*- and *para*-(aza)quinone methides can be trapped by various CH-acids.



Cyclopropane is an archetypical small carbocycle which is kinetically stable despite its high strain energy (*ca.* 27.6 kcal/mol).[1] The introduction of a donor and an acceptor to the vicinal positions of the cyclopropane ring polarizes the C−C bond between atoms bearing these groups. Such donor−acceptor (DA) cyclopropanes[2,3] are activated for wide range of ring-opening reactions. However, these compounds still need extra activation in most processes.

Thermal activation of DA cyclopropane ring opening is limited by low reaction selectivity under harsh conditions.[4] Alternative strategies, which do not alter the overall donor/acceptor framework, such as radical,[5] organocatalytic, and nucleophilic[6] activation are uncommon, with only a few of such ring openings reported.

Over the past two decades, the rapid expansion of DA cyclopropane research has been driven by the extensive use of Lewis acids (LA, Scheme 1a): the coordination of LA to acceptor substituent(s) enhances their electron-withdrawing ability that increases the polarization of the C(1)−C(2) bond facilitating its heterolysis.[2,3] Lewis acids have been widely used as effective ring cleavage initiators in various synthetic transformations of DA cyclopropanes, including nucleophilic ring openings, cycloadditions, annulations, rearrangements, ring expansions, dimerization, and 1,3-difunctionalizations.[2,3] Brønsted acids also catalyze DA cyclopropane reactions via a similar activation mechanism, but they are less commonly used now.[7] Our group contributed to this area of research by developing the protic ionic liquids as triplex reagents serving as (a) a regenerable solvent, (b) a source of Brønsted acid for DA cyclopropane activation, and (c) a source of a nucleophile.[7c,d]

For activation of DA cyclopropanes *via* acceptor group modification, diverse modes of organocatalysis are applied, depending on the nature of acceptor group(s).[8] For example, DA cyclopropanes with the aldehyde group as an acceptor were activated by the treatment with secondary amines, generating iminium ions with a higher electron-withdrawing ability than the starting aldehyde group.[8b,c] For the activation of nitrocyclopropanecarboxylates, ureas capable of forming H-bonds between their NH groups and both oxygens of the nitro group were applied.[8d]

In contrast to the activation of DA cyclopropanes through modifications to the acceptor, the activation of small ring opening by altering the electron-donating group has been less studied.[9] The pioneering work of Reissig,[9a] who introduced the concept of DA-substituted cyclopropanes, serves as an example of such a re-editing of donor structure. It has been known that the ease of ring opening of DA cyclopropane with siloxy substituents depends on the *in situ* release of the corresponding alkoxy anion (Scheme 1b). In recent years, other strategies

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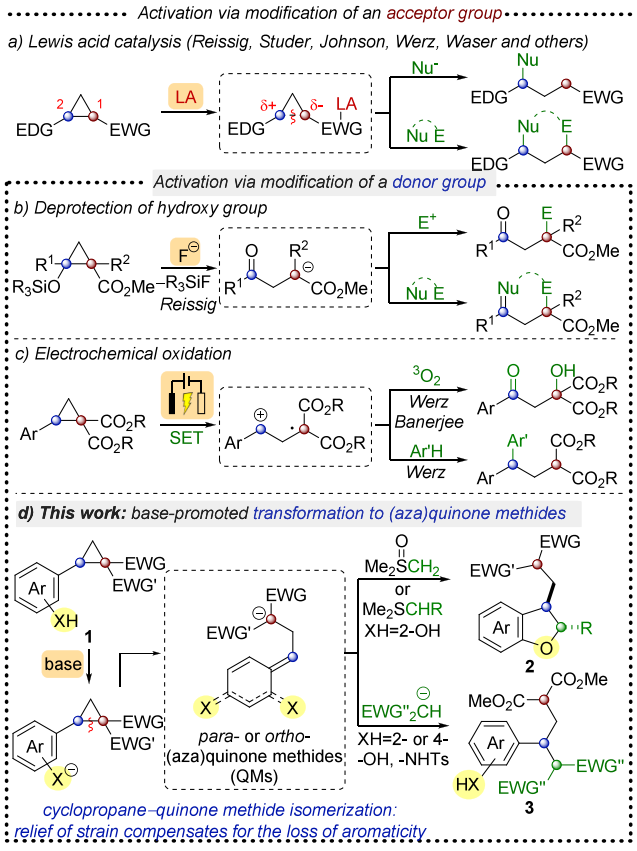
Scheme 1. Examples of Activating Modes of Donor–Acceptor Cyclopropanes



involving photocatalytic[9c,d] and electrochemical[9e,g] (Scheme 1c) conversions of DA cyclopropanes have attracted increased attention from mechanistic, theoretical, and synthetic viewpoints. Despite this, the activation modes utilized in the modifications of the donor group are relatively constrained, leaving considerable space for further studies.

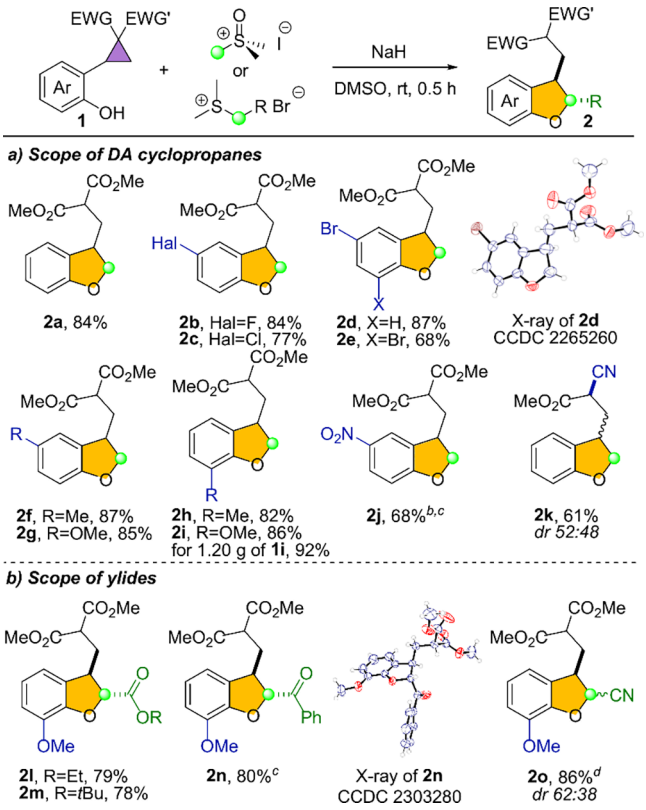
Intrigued by this scarcity, we focused on synthetically available (*ortho*-hydroxyaryl)-substituted cyclopropanes **1**, which have been previously used in LA-initiated (4 + 2)-annulation with alkenes[10a] and in intramolecular nucleophilic ring opening.[10b] We hypothesized that the deprotonation of the phenol group in cyclopropanes **1** could lead to the spontaneous three-membered ring opening to deliver an *ortho*-quinone methide (*o*-QM) based intermediate that can be trapped by suitable nucleophiles (Scheme 1d). In this study, we investigated reactions of cyclopropanes **1** with sulfur ylides as well as various C-nucleophiles, such as anions of selected CH-acids. We have shown that (4 + 1)-annulation of *o*-QMs, generated from DA cyclopropanes **1**, with sulfur ylides could lead to 2,3-dihydrobenzofurans, an important structural unit of some modern FDA-approved drugs.[11] Moreover, we found that not only *ortho*- but also *para*-quinone methides as well as their aza-analogs could be obtained by this method from the corresponding precursors as intermediates that can be trapped with CH-acids to give access to polyfunctional derivatives of γ-disubstituted butanoic acids.

Furthermore, this transformation is conceptually interesting as a new approach to highly reactive QMs[12] and their aza-analogs based on the cyclopropane–QM isomerization in which the release of energy strain during small ring opening compensates for the loss of aromaticity energy resulting from QM formation. Herein, we report the results of our investigation.

We started our study by optimization of model (4 + 1)-annulation of cyclopropane **1a** as a promising four-atom component with dimethylsulfoxonium methylide (DMSOM, Corey ylide). The main results of the screening of reaction conditions (solvent, type of base, and ratio of reagents) are presented in Supporting Information.[11] To summarize, the optimal conditions for carrying out the process under study are the reaction of a 0.1 M DMSO solution of cyclopropane **1a** with 2.1 equiv of Corey ylide at room temperature for 0.5 h.

With the optimized conditions in hand, the substrate scope of the disclosed (4 + 1)-annulation was evaluated, and the results were summarized in Scheme 2. Reaction of **1** with

Scheme 2. Substrate Scope for Synthesis of Dihydrobenzofurans 2[a]



[a]Reaction conditions: NaH (2.1 equiv), Me_3SOI or Me_2SCH_2RBr (2.1 equiv), DMSO (0.1 M for **1**); yields of isolated products are given. [b]3.0 equiv of Me_3SOI and 3.0 equiv of NaH were used. [c]Reaction time was 3 h. [d]Reaction time was 2 h.

DMSOM had good tolerance to halogen, methyl, and methoxy substituents in *ortho*- and *para*-positions relative to the OH moiety, affording the desired products **2b–d,f–i** in 77–87% yield (Scheme 2a). On the contrary, the presence of electron-withdrawing groups at the same positions decelerated the three-membered ring-opening stage (see the reaction mechanism below). For this reason, yield of substrate **2e**, bearing two bromine atoms, decreased to 68% compared to 87% for **2d**. For cyclopropane **1j** with a 5-NO_2 group in the benzene ring, this effect was revealed to a greater extent. To accelerate the annulation process, this reaction was performed with a 3-fold excess of Corey ylide. As a result, dihydrobenzofuran **2j** was

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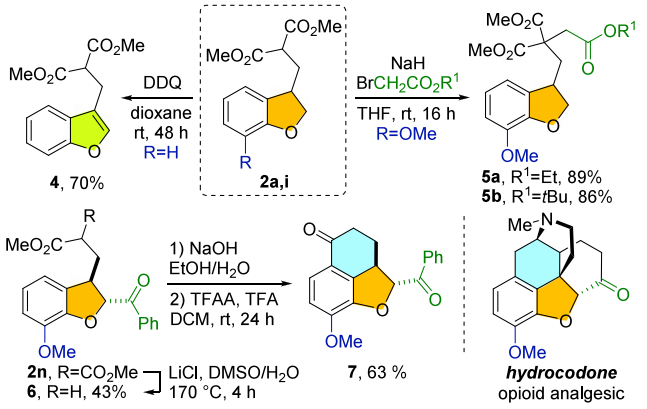
obtained in 68% yield after being stirred for 3 h. Next, compound **1k** with a nitrile group as an acceptor in ring was tested, and compound **2k** was isolated as the mixture of two diastereoisomers in a nearly equal ratio in 61% yield. The lower efficiency of (4 + 1)-annulation for this substrate presumably results from the realization of some side reactions with participation of the cyano group. Additionally, the structure of **2d** was unambiguously proven by single-crystal X-ray diffraction. The scalability was illustrated by converting 1.20 g of **1i** into 1.16 g of **2i** in 92% yield.

To better understand the scope and limitations of this protocol, we studied the reactivity of cyclopropane **1i** toward diverse stabilized sulfonium ylides (Scheme 2b). Reaction of substrate **1i** with bulky ylides, bearing CO_2Et, CO_2tBu, or COPh moieties, led to 2-substituted dihydrobenzofurans **2l–n** in 78–80% yield as single diastereomers. The *trans*-arrangement of substituents was proved by X-ray data for compound **2n**. In contrast, the reaction of the less hindered ylide $Me_2S{=}CHCN$ afforded dihydrobenzofuran **2o** in 86% yield as a mixture of diastereomers in a 62:38 ratio with a predominance of *trans*-isomer.

The synthetic utility of obtained 2,3-dihydrobenzofurans **2** was further studied (Scheme 3). Compound **2a** was

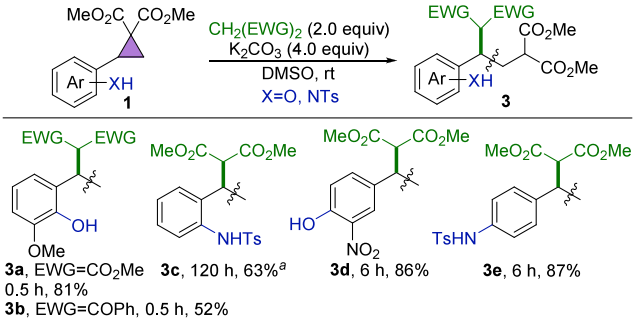
Scheme 3. Synthetic Applications of Dihydrobenzofurans 2



successfully aromatized with DDQ to form benzofuran **4** in 70% yield. In contrast to unsubstituted dihydrobenzofurans, the synthetic potential of substrates **2** is primarily conditioned by the carbon chain, implemented in their structures. This fragment can be used as a linker to bind the dihydrobenzofuran core with other moieties, which was demonstrated by alkylation of **2i** with ethyl and *tert*-butyl bromoacetates to afford products **5a,b** in 89% and 86% yield, respectively. Moreover, compounds **2** are preorganized for intramolecular annulation: Friedel–Crafts acylation of dealkoxycarbonylated product **6** (43% yield from **2n**) furnished tricyclic compound **7** in 63% yield. The latter is a structural analogue of *hydrocodone*—the main component of Vicodin analgesic.

To demonstrate the versatility of this DA cyclopropane activating mode, compound **1i** was introduced into the reaction with a series of typical CH-acids, such as dimethyl malonate and dibenzoylmethane. Under treatment with 2.0 equiv of carbonyl compound and 4.0 equiv of potassium carbonate, polyfunctional products **3a** and **3b** were obtained in 0.5 h in 81% and 52% yields, respectively (Scheme 4). Next, we applied the same strategy to DA cyclopropanes, whose anions are capable of undergoing isomerization to the *ortho*-

Scheme 4. Other Applications of the New DA Cyclopropane-Activating Mode



[a]$CH_2(CO_2Me)_2$ (5.0 equiv) and K_2CO_3 (6.0 equiv) were used.

azaquinone methide. For this purpose, we tested cyclopropane **1l**, bearing the NHTs moiety at the *ortho*-position of the donor aromatic substituent, in reaction with an excess of dimethyl malonate in the presence of potassium carbonate. To our delight, after stirring at room temperature for 3 h, the product of small ring opening **3c** was observed; however, a significant portion of starting material remained unreacted. We associate the reaction deceleration with the high stability of the anion of **1l** that results in a low concentration of the azaquinoid form in the reaction mixture. To achieve the full conversion, cyclopropane **1l** was stirred in the presence of a large excess of reagents for 5 days affording compound **3c** in 63% yield. Moreover, the strategy under investigation was applied to substrates **1m** and **1n**, bearing –OH and –NHTs groups in the *para*-position relative to the cyclopropane ring. Under mild conditions, products of ring opening with dimethyl malonate **3d** and **3e** were obtained after 6 h in 86% and 87% yields, respectively.

To better understand the mechanism of these transformations, we have analyzed the reaction between anion of **1a** and DMSOM with DFT calculations (Scheme 5a).[11,13] Unlike the parent phenol/dienone tautomerization, which is ~20 kcal/mol uphill, the anionic cyclopropane/quinone methide rearrangement is exergonic. Despite the loss of aromaticity, the isomerization of phenoxide **A** into *ortho*-quinone methide **B** is favorable both kinetically ($\Delta G^{\ddagger}_{AB}$ = 6.4 kcal/mol) and thermodynamically (ΔG_{AB} = −3.0 kcal/mol) and proceeds effectively at room temperature. Considering the similar stability of phenoxide and malonate anions, which can be evaluated from their basicity (pK_as of both conjugate acids are ~18–19 in DMSO),[14] the ~22–23 kcal/mol increase in exergonicity should largely stem from the strain stored in the cyclopropane moiety (~28 kcal/mol). Upon attack by the DMSOM molecule, the quinoid intermediate **B** restores aromaticity to form much more stable sulfoxonium salt **C**. Subsequent intramolecular 5-*exo*-*tet* nucleophilic substitution of DMSO by the phenolate anion results in a five-membered ring closure, leading to compound **D**. Finally, intermediate **D** is protonated to yield dihydrobenzofuran **2**. Annulation with the stabilized sulfonium ylides follows a similar path. However, in this case, intermediate **C′** is formed as a mixture of *syn*- and *anti*-isomers (Scheme 5b). As shown in the Newman projections, in the conformation favored for the 5-membered ring closure, the bulky substituents are pushed apart in *anti*-betaine, while in *syn*-betaine their proximity causes significant steric repulsion. This leads to a faster consumption of *anti*-betaine and the formation of predominantly *trans*-2,3-

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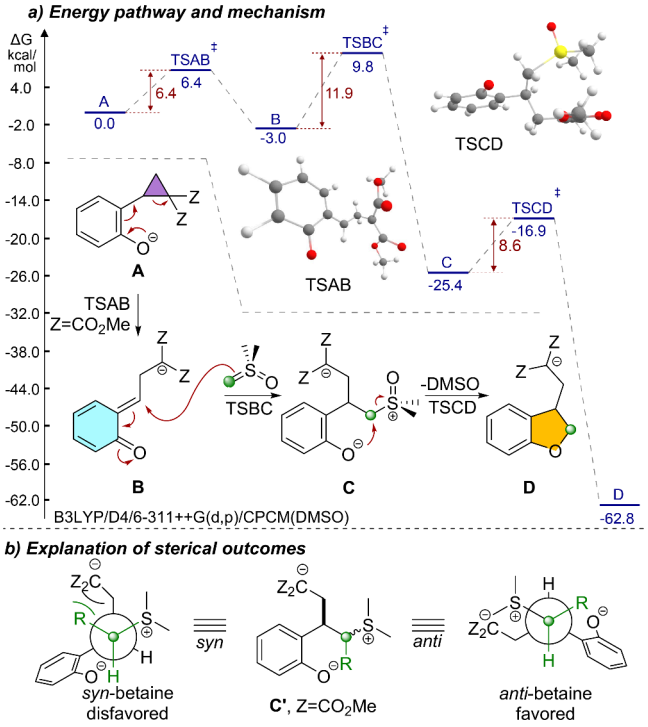
Scheme 5. (a) Energy Profile of (4 + 1)-Annulation of 1a with DMSOM and (b) Diastereoselectivity Explanation



dihydrobenzofurans **2l–o**. Moreover, stabilized sulfonium ylides are known to add reversibly,[15] which shifts the equilibrium completely toward the formation of the *trans*-isomer of **2l–o** when bulky sulfonium ylides were applied.

In conclusion, we have developed a conceptually new method for activation of DA cyclopropanes based on ring opening by rapid isomerization of deprotonated donor aromatic substituents into *ortho*- or *para*-(aza)quinone methide intermediates. The cyclopropanes, bearing a 2-hydroxyphenyl moiety, can be annulated with sulfur ylides, affording substituted dihydrobenzofurans in good yields. Computational analysis of the reaction path confirmed that spontaneous *in situ* isomerization of deprotonated substrate to *ortho*-quinone methide plays a crucial role in the small ring activation. Moreover, being applied to DA cyclopropanes, bearing appropriate phenolic or aniline substituents, this method allows the generation of *ortho*- or *para*-quinone methides and their aza-analogs and traps them with CH-acidic compounds as nucleophiles, providing an effective route toward acyclic polyfunctional derivatives of γ-disubstituted butanoic acids as promising building blocks. Having demonstrated this concept, studies are currently underway to exploit this activation in the design of other transformations.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c03106.

Text file of all computed molecule Cartesian coordinates in a format for convenient visualization (XYZ)

Details of experimental procedures, compound characterization data, X-ray crystallography, and NMR spectra of synthesized compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1f**, **1k**, **1l**, **1m**, **1n**, **2a–2o**, **3a–3e**, **4**, **5a**, **5b**, **6**, **7**, **S1a**, **S2a**, **S2b**, **S2c**, **S2d**, and **S3a** (ZIP)

Accession Codes

CCDC 2265260, 2294805, and 2303280 contain 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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Author Contributions

The manuscript was written through contributions of all authors.

Notes

A prior version of this work was previously published on ChemRxiv.[16]

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Professor Hans-Ulrich Reissig, on the occasion of his 75th birthday.

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