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The Cyclopropyl Group as a Neglected Donor in Donor−Acceptor Cyclopropane Chemistry

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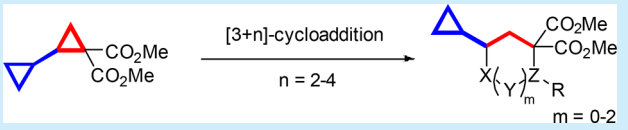
Supporting Information

ABSTRACT: D−A cyclopropanes bearing a simple cyclopropyl group as donor are shown to undergo a variety of [3+*n*]-cycloaddition reactions (*n* = 2−4). This behavior contrasts sharply with that of common D−A cyclopropanes with aliphatic donors. Kinetic experiments demonstrate that, in terms of donor ability, the cyclopropyl substituent lies between electron-rich and electron-neutral aryl donors.

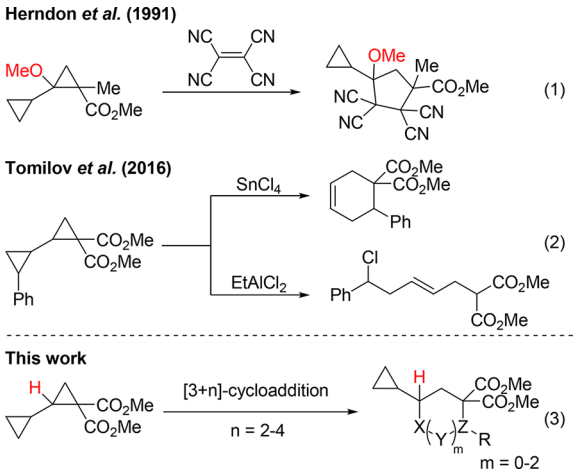


Donor−acceptor (D−A) cyclopropanes are one of the most versatile three-carbon-atom building blocks in organic synthesis.[1] These highly strained and, thus, "spring-loaded" molecules are substituted with an electron-donating and an electron-withdrawing group in vicinal positions, a substitution pattern that allows facile heterolytic cleavage of the corresponding bond in the cyclopropane by stabilizing a 1,3-zwitterionic structure. Consequently, these systems are easily able to undergo nucleophilic or electrophilic ring-opening,[2] rearrangement[3] and formal cycloaddition reactions.[4]

Whereas ring-opening reactions produce 1,3-bifunctionalized carbon chains, rearrangements and especially formal cycloaddition reactions allow fast and efficient access to complex (hetero)cyclic motifs. Nevertheless, established donor moieties generally involve aryl groups or heteroatoms (such as O and N); there are very few examples with aliphatic substituents. However, the cyclopropyl group itself is known to stabilize a positive charge in α-position because of an orbital overlap of the cyclopropane Walsh orbital with an emerging empty orbital.[5] Thus, we considered whether simple cyclopropyl moieties would allow a similar chemistry to that observed with common aryl-substituted D−A cyclopropanes. A scrutiny of the literature revealed that, as early as 1991, Herndon and co-workers had reported the synthesis and a formal cycloaddition reaction of a D−A cyclopropane bearing both a methoxy and a cyclopropyl group as donor on the same carbon (Scheme 1, eq 1).[6,7] However, in such experiments the effect of the cyclopropyl moiety alone could not be examined. In 2016, Tomilov et al. reported that a D−A cyclopropane possessing a phenyl-substituted cyclopropyl group as donor is able to undergo ring-opening reactions of both three-membered rings in the presence of strong Lewis acids, forming, e.g., either cyclohexene derivatives or open-chain products in an elegant way (Scheme 1, eq 2). In these transformations, the system acted as a formal six carbon synthon.[8]

Because of these observations, we were interested in establishing whether cycloaddition reactions could be triggered by the use of a simple biscyclopropyl dicarboxylate without incorporation of another donor (Scheme 1, eq 3) and whether

Scheme 1. Cyclopropyl Group in D−A Cyclopropane Chemistry



the cyclopropyl residue would stay intact under our selected reaction conditions. Finally, we wanted to compare the reactivity of this special D−A cyclopropane with that of aryl-substituted systems, which are widely used in this field of chemistry by our group and many others.

The desired starting material was readily available in a simple two-step synthesis beginning from commercially available cyclopropane carbaldehyde **1**. Knoevenagel condensation with dimethyl malonate and subsequent Johnson−Corey−Chaykovsky reaction with trimethylsulfoxonium iodide yielded the product **2** in an overall yield of 66% (Scheme 2).

At the beginning of our studies, we chose various aromatic aldehydes as substrates for formal [3 + 2]-cycloadditions, yielding the corresponding tetrahydrofuran derivatives (Scheme 3). The reactions were carried out using conditions established

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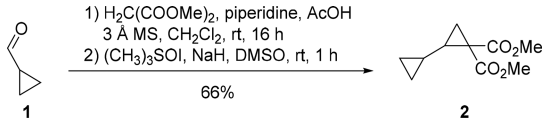
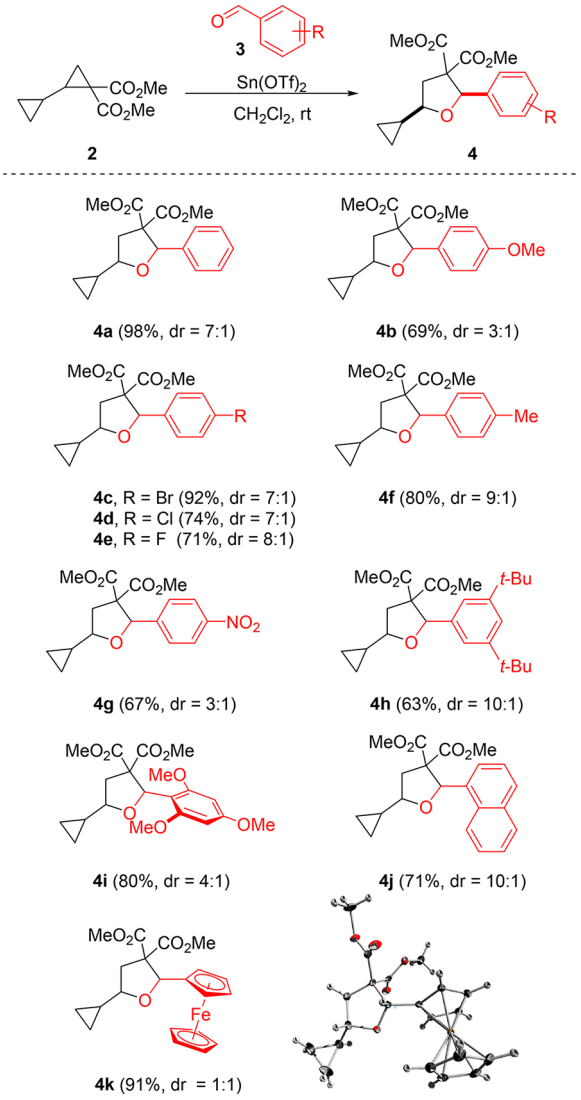
Scheme 2. Synthesis of Cyclopropyl Cyclopropane Dicarboxylate 2



by Johnson and co-workers; a catalytic amount of $Sn(OTf)_2$ as Lewis acid in CH_2Cl_2 at room temperature was employed.[9]

Scheme 3. Synthesis of Tetrahydrofurans[a]

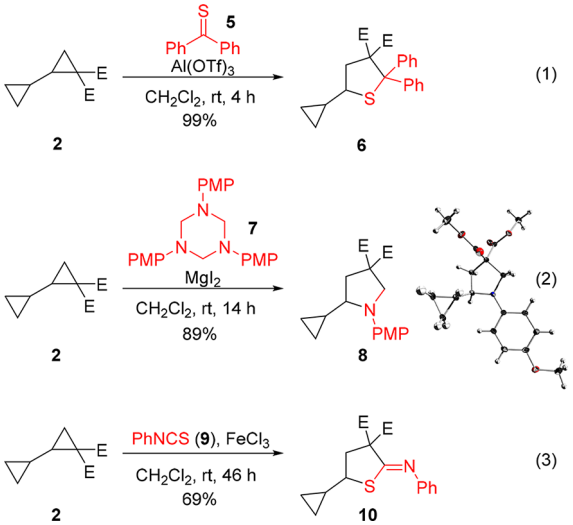


[a]Reaction conditions: **2** (0.2 mmol), **3** (1.2–3.0 equiv), $Sn(OTf)_2$ (0.1 equiv), CH_2Cl_2 (2 mL), rt. All yields represent isolated products.

Fortunately, a first reaction with benzaldehyde as substrate yielded the desired product **4a** in 98% yield. Consequently, we subjected other aromatic aldehydes to these conditions. All of these transformations proceeded smoothly with yields up to 92%. Both electron-poor and electron-rich benzaldehydes were tolerated, but the diastereomeric ratios of the products were only moderate, with a preference for the *cis*-isomer (**4b**–**g**). Sterically more crowded substrates with two *tert*-butyl groups or three methoxy groups gave the products in reasonable yields of 63% or 80%, but with a somewhat better dr (**4h**, **4j**). An extension of the π-system by using 1-naphthaldehyde as starting material yielded the product **4j** in 71% yield. Single crystals of both diastereomers of the ferrocenyl-substituted tetrahydrofuran derivative **4k** were obtained, and X-ray crystallographic analysis confirmed the integrity of the intact cyclopropyl donor and the formation of the desired 5-membered heterocycle.

As the next step, further [3 + 2]-cycloaddition reactions were studied. The formal cycloaddition with thioketone **5** yielded the tetrahydrothiophene **6** in an excellent yield of 99% following a procedure recently established by our group (Scheme 4, eq 1).[10]

Scheme 4. Various Formal [3 + 2]-Cycloadditions[a]

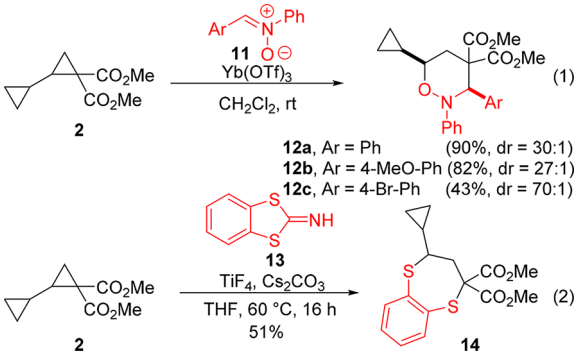


[a]All yields represent isolated products. E = CO_2Me, PMP = *p*-methoxyphenyl.

The transformation with triazinane **7** led to the pyrrolidine **8** in 89% (Scheme 4, eq 2; the structure was also elucidated by X-ray crystallography),[11] and the insertion of phenyl isothiocyanate **9** using a protocol of Stoltz and co-workers gave the corresponding thioimidate **10** in 69% yield (Scheme 4, eq 3).[12]

To examine potential syntheses of larger heterocycles, both a formal [3 + 3]- and a formal [3 + 4]-cycloaddition were studied. The reactions with various phenyl-substituted nitrones of type **11** yielded the tetrahydro-1,2-oxazines in very good yields of up to 90% (**12a**–**c**) following a procedure by Kerr (Scheme 5, eq 1).[13] The conversion of **2** with benzodithioloimine **13** promoted by TiF_4 as Lewis acid was more challenging and gave the

Scheme 5. Formal [3 + 3]- and [3 + 4]-Cycloaddition Reactions



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corresponding seven-membered ring **14** in a moderate yield of 51% (Scheme 5, eq 2).[14]

In order to quantify the donor ability of the cyclopropyl moiety with respect to phenyl-derived donors, the reaction rates of various D−A cyclopropanes for the formal cycloaddition with 4-fluorobenzaldehyde were measured by ^{19}F NMR spectroscopy. Previous studies of this cycloaddition showed a stepwise mechanism with an initial nucleophilic attack of the aldehyde at the positively polarized atom of the D−A cyclopropane ring together with simultaneous bond-breaking.[9] Taking into account these results, a more electron-rich donor should lower the energy of the transition state because of its better ability to polarize the bond that is broken during the reaction. If this step is the rate-determining step, a more electron-rich donor will lead to a faster transformation. As expected, the reaction of the electron-rich *p*-methoxyphenyl-substituted cyclopropane (Figure 1, pink dots)

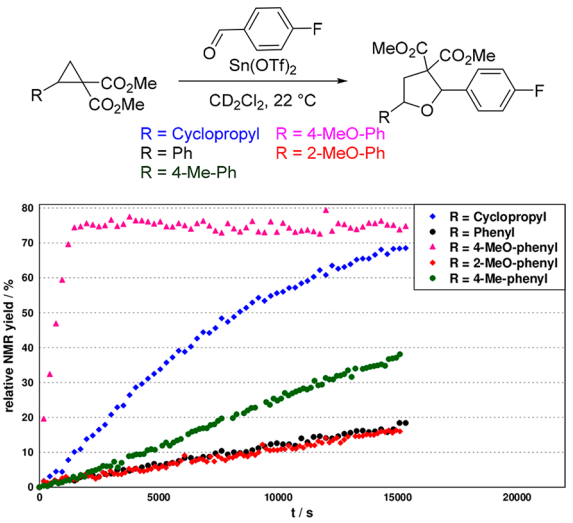

Figure 1. Measurement of the relative reaction rate of 4-fluorobenzaldehyde with different D−A cyclopropanes. The reaction progress was monitored by ^{19}F NMR spectroscopy. Reaction conditions: D−A cyclopropane (1.00 equiv), 4-fluorobenzaldehyde (1.00 equiv), $Sn(OTf)_2$ (8 mol %), CD_2Cl_2 (0.10 M).

was significantly faster than the same reaction with a phenyl-substituted derivative (Figure 1, black dots), which showed after 4 h an NMR yield of the desired product of only about 20%. The D−A cyclopropane with a cyclopropyl group as donor showed after 4 h an NMR yield of ∼69%, about 10 times slower than the *p*-methoxyphenyl-substituted cyclopropane (Figure 1, blue dots). While the reaction rate with an *o*-methoxyphenyl-substituted cyclopropane lay in the same range as that of the unsubstituted starting material (Figure 1, red dots), the reaction with the *p*-methylphenyl cyclopropane was about twice as fast as the phenyl cyclopropane and thus nearly half as fast as the cyclopropyl-substituted D−A cyclopropane (Figure 1, green dots).

Finally, we sought to compare the cyclopropyl donor to π-system-derived donors by computational means (Figure 2). However, instead of looking into transition-state structures, we simply calculated the energy difference of the hypothetical isomeric cations **C1** and **C2** on the basis of density functional theory for various residues R. Although these results represent thermodynamic data, the trend of the kinetic data is roughly mirrored. Thus, we were able to rank the ability to stabilize a positive charge in α-position. In a first-order approximation, this

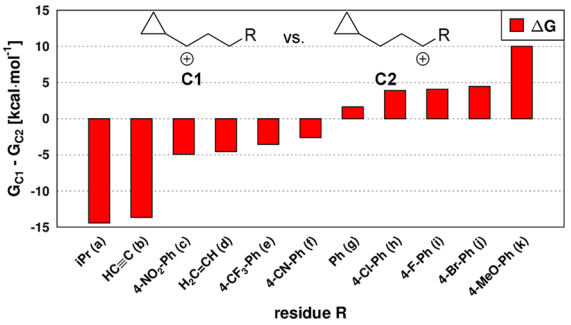

Figure 2. Energy difference of the hypothetical isomeric cations **C1** and **C2** for different residues R. A negative value indicates a better stabilization of the cation next to the three-membered ring; a positive value shows a better stabilization next to the residue R. All calculations were performed on the DFT level of theory using the PW6B95 functional and the triple-ζ basis def2-TZVP together with the dispersion correction D3BJ.[15]

can give an indication as to which of the two compared groups is the better donor in D−A cyclopropane chemistry with respect to the formal zwitterionic structure of these substrates. As estimated, a positive charge is much better stabilized by a cyclopropyl group than by an isopropyl residue (ΔG = −14.4 kcal·mol^{-1}, Figure 2a) or an alkyne residue (ΔG = −13.7 kcal·mol^{-1}, Figure 2b). Furthermore, a better stabilization of the cationic structure **C1** is observed in comparison to electron-poor aromatic residues and surprisingly even to an alkene residue (Figure 2c−f). If the residue is changed to a simple phenyl- or halide-substituted phenyl group, the cation is slightly favored at the benzylic position (Figure 2g−j). In the case of the very electron-rich *p*-methoxyphenyl, the cationic structure **C2** is the most stable (ΔG = 10.0 kcal·mol^{-1}, Figure 2k).

In summary, we have shown that the cyclopropyl group is able to act as an excellent donor in D−A cyclopropane chemistry. Various [3+*n*]-cycloaddition reactions catalyzed by Lewis acids were accomplished, thereby generating a variety of heterocycles bearing an intact cyclopropyl group. Moreover, kinetic studies revealed that the donor ability of the cyclopropyl group ranges between that of a phenyl residue and a *p*-methoxyphenyl group. Simple computational studies comparing the stabilization of positive charge either adjacent to cyclopropyl or adjacent to various aryls confirm this view qualitatively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00603.

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

Accession Codes

CCDC 1823935−1823937 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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Notes

The authors declare no competing financial interest.

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