Cycloaddition

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# Donor–Acceptor Cyclopropanes as Three-Carbon Components in a [4+3] Cycloaddition Reaction with 1,3-Diphenylisobenzofuran

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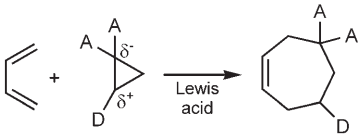
Substituted cyclopropanes have found broad application in modern organic synthesis owing to the unique reactivity of the cyclopropane moiety.[1] Cyclopropanes can often be considered as three-carbon analogues of C=C bonds.[1,2] For example, alkenes and cyclopropanes react with strong electrophiles and various radicals. Both undergo the addition of hydrogen and can be oxidized at the α position. The reactivity of cyclopropanes with electron-withdrawing substituents is similar to that of electron-deficient alkenes.[3] However, the cycloaddition reactions of alkenes and cyclopropanes are quite different. In particular, the thermal reactions of alkenes are represented mainly by [1+2], [3+2], and [4+2] cycloaddition processes; thermal [2+2] cycloaddition occurs in very specific cases only. In contrast, the most well known type of cyclopropane cycloaddition is the $[2\pi+2\sigma]$ reaction with alkenes.[4] As this reaction yields cyclopentanes, it can also be considered as a [2+3] cycloaddition. The scope of such [2+3] cycloaddition reactions has been expanded significantly through the use of donor–acceptor cyclopropanes.[5] The presence of both electron-donating and electron-withdrawing substituents on the cyclopropane ring enables cycloaddition to various multiple bonds, including[5] C=C,[6] C=O,[7] C=N,[8] and C≡N bonds.[9]

The [4+3] cycloaddition of cyclopropanes with dienes (Scheme 1) has not been reported previously, although this




A = electron-withdrawing group
D = electron-donating group

***Scheme 1.*** Schematic representation of the [4+3] cycloaddition reaction of dienes with donor–acceptor cyclopropanes.

$[4\pi+2\sigma]$ process is a formal analogue of the well-known Diels–Alder reaction. The formation of seven-membered rings in similar reactions between dienes and cyclopropanones has been reported.[10] However, the equivalent treatment of cyclopropanone dimethyl acetal failed to yield cycloaddition products under the same conditions.[11] Thus, it appears that the transformation of the cyclopropanone into an oxyallyl cation is required for this cycloaddition to proceed. Even so, cycloaddition reactions between dienes and cyclopropanes are not "forbidden" processes: Several examples of the reaction of vinylcyclopropanes with C=C or C=X bonds to afford cycloheptane derivatives have been described.[12] The cyclopropane ring participates in these processes in place of one double bond of a diene. Therefore, this type of reaction is analogous to the Diels–Alder cycloaddition. Owing to the importance of Diels–Alder-type reactions in modern organic synthesis, we investigated the possibility of a [4+3] cycloaddition between cyclopropane derivatives and appropriate dienes. Herein, we report a new route to substituted cycloheptenes through the [4+3] cycloaddition of dienes to cyclopropanes substituted with two electron-withdrawing groups at one carbon atom and an electron-donating group at a second carbon atom.

We selected 2-aryl 1,1-cyclopropane diesters **1** as substrates because of the previously reported smooth reactivity of such donor–acceptor cyclopropanes in $[2\pi+2\sigma]$ cycloaddition reactions with alkenes.[5] Moreover, substrates **1** are known to undergo [3+3] cycloaddition to 1,3-dipoles with the formation of six-membered rings.[13] Our selection of the diene 1,3-diphenylisobenzofuran (**2**) as the second substrate was based on the requirement for high reactivity in the Diels–Alder reaction and an inability to form [3+2] cycloaddition products. The latter limitation is related to the potential competition of [3+2] and [4+3] cycloaddition processes. We first screened reaction conditions for the model [4+3] cycloaddition between **2** and diethyl 2-phenylcyclopropane-1,1-dicarboxylate (**1a**; Table 1).

We found that **1a** failed to react with **2** unless the reaction was promoted by a Lewis acid (Table 1, entry 1). Lewis acid catalysis was demonstrated previously for the reaction of **1a** with nitrones[13] and imines,[14] as well as in related [3+2][7d] and [3+1+1][15] cycloaddition reactions of cyclopropanes. We examined a variety of Lewis acids as catalysts for the [4+3] cycloaddition between **1a** and **2**. With $SnCl_4$ and other strong Lewis acids ($TiCl_4$, $BF_3{\cdot}OEt_2$, trimethylsilyl triflate), the desired cycloaddition product was formed in only small amounts, if at all. When $EtAlCl_2$ was used as the catalyst, the polymerization of the cyclopropane **1a** was the main process observed (Table 1, entry 2). After many attempts, we found that the target compound **3a** was formed under the catalysis of $Yb(OTf)_3$ (Table 1, entries 4–6).

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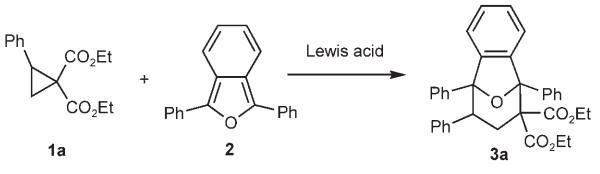
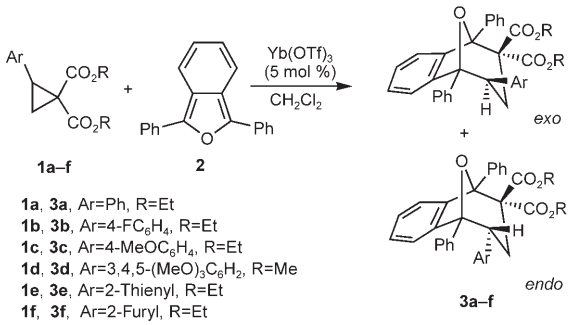
***Table 1:*** Optimization of the reaction conditions for the model [4+3] cycloaddition between **1a** and **2**.




| Entry | Solvent | Lewis acid | *T* [°C] | *t* [h] | Yield [%][a] | *exo*/*endo* |
|---|---|---|---|---|---|---|
| 1 | PhCl | – | reflux | 12 | –[b] | – |
| 2 | $CH_2Cl_2$ | $EtAlCl_2$ | −40→RT | 24 | –[c] | – |
| 3 | $CH_2Cl_2$ | $SnCl_4$ | −50→RT | 18 | –[d] | – |
| 4 | PhCl | $Yb(OTf)_3$[e] | reflux | 8 | 25[f] | <1:19 |
| 5 | PhCl | $Yb(OTf)_3$[e] | 80 | 26 | 50[g] | <1:19 |
| 6 | $CH_2Cl_2$ | $Yb(OTf)_3$[e] | reflux | 9 | 85 | 56:44 |

[a] Yield of the isolated product. [b] No conversion was observed. [c] The polymerization of **1a** was observed as the main process. [d] Only a small amount of the product of [4+3] cycloaddition was formed. [e] Catalyst loading: 5 mol%. [f] Compound **4a** was also isolated in 58% yield. [g] Compound **4a** was also isolated in 44% yield.

***Table 2:*** $Yb(OTf)_3$-catalyzed reaction of 2-aryl 1,1-cyclopropane diesters **1** with **2**.




**1a**, **3a**, Ar=Ph, R=Et
**1b**, **3b**, Ar=4-$FC_6H_4$, R=Et
**1c**, **3c**, Ar=4-$MeOC_6H_4$, R=Et
**1d**, **3d**, Ar=3,4,5-$(MeO)_3C_6H_2$, R=Me
**1e**, **3e**, Ar=2-Thienyl, R=Et
**1f**, **3f**, Ar=2-Furyl, R=Et

| Entry | **1** | *t* [h] | *T* [°C] | **3** | Yield [%][a] | *exo*/*endo* |
|---|---|---|---|---|---|---|
| 1 | **1a** | 9 | reflux | **3a** | 85 | 56:44 |
| 2 | **1b** | 3 | reflux | **3b** | 90 | 53:47 |
| 3 | **1c** | 24 | RT | **3c** | 86 | 86:14 |
| 4 | **1d** | 1 | RT | **3d** | 89 | 77:23 |
| 5 | **1e** | 3 | RT | **3e** | 92 | 74:26 |
| 6 | **1f** | 3 | RT | **3f** | 84 | 64:36 |

[a] Yield of the isolated product.

The reaction temperature also influenced the efficiency of the cycloaddition. At reflux in chlorobenzene, the cycloadduct **3a** was formed in just 25% yield. The main product under these conditions was 1-(2-benzoylphenyl)-1,2-diphenylethene (**4a**), which was formed from **3a** through the elimination of diethyl methylenemalonate. The decomposition of **3a** decreased with decreasing reaction temperature. Unfortunately, the rate of formation of **3a** also decreased significantly as the reaction temperature was lowered. Thus, at room temperature only a trace amount of the desired cycloadduct **3a** was observed after 24 h. The best result for the [4+3] cycloaddition between **1a** and **2** was observed when the reaction mixture was heated at reflux in dichloromethane for 9 h in the presence of $Yb(OTf)_3$ (Table 1, entry 6).

To determine the scope of the [4+3] cycloaddition, we treated substrate **2** with a series of 2-aryl 1,1-cyclopropane diesters under similar reaction conditions (Table 2). We found the *para*-fluorophenyl-substituted cyclopropane **1b** to be more reactive than **1a**. Furthermore, the cycloadducts **3c–f** were formed efficiently from substrates **1c–f** with electron-donating aryl substituents even at room temperature: The reaction of the 3,4,5-trimethoxyphenyl-substituted cyclopropane **1d** was complete within 1 h.

According to the NMR spectroscopic data, products **3a–f** were formed as mixtures of two diastereomers in ratios of approximately 1.1:1 to 6.1:1. The data reveal a conformational distinction between the isomers caused by the orientation of the aryl group. The vicinal $J_{H,H}$ coupling constants for the $-C(Ar)H-CH_2-$ fragment of the six-membered ring differ significantly for the two isomers. The values of the $^3J$ coupling constants were approximately 6 and 1 Hz for the major isomers of **3a–f**; for the minor isomers these values were approximately 12 and 4 Hz. In agreement with the Karplus rule, these parameters show a clear-cut distinction in the HCCH dihedral angles of the diastereomers. The $H_{axial}$–$H_{axial}$ coupling ($^3J \approx 12$ Hz) was observed for one isomer only. From these data, one may conclude that the six-membered ring adopts a similar (chair or boat) conformation in both isomers of **3a–f**. Unfortunately, we were unable to determine whether the *endo* or *exo* product is the predominant isomer from the NMR spectroscopic data. To provide additional insight into the mechanism of the reaction and to determine the major isomer of the product, we performed ab initio quantum-chemical calculations of the geometries and relative stabilities of the two diastereomers of **3a** at the HF/6-31G level.[16] We found that the chair conformation is more stable for both diastereomers, and that the *endo* isomer is more stable than the *exo* isomer by 2.0 kcal mol$^{-1}$.

If the reaction proceeds by a stepwise mechanism, with the Lewis acid catalyzed electrophilic attack of cyclopropanes **1a–f** on the substrate **2**, followed by the cyclization of a zwitterionic intermediate, the predominant formation of the more stable *endo* isomer might be expected. However, the calculated values of the $^3J$ coupling constants for the less stable *exo* isomer were in full agreement with the experimental values for the major cycloadduct; the experimental *J* values for the minor isomer were in excellent agreement with the calculated data for the *endo* product. This conclusion was confirmed by single-crystal X-ray diffraction analysis, which proved unambiguously the structure of the major isomer. The diffraction data revealed the structure of the energetically less favorable *exo* isomer with a chair conformation of the six-membered ring.[16,17]

Comparison of the NMR spectroscopic data for **3b** with the data for the products formed in the other reactions showed that in all cases the major isomer was the less stable *exo* isomer. This phenomenon can be explained by a concerted cycloaddition mechanism that accounts for possible approaches of the reagents and orbital symmetry rules (Scheme 2).

The formation of the less stable *exo* isomer **3a** as the main product is also supported by the results of the reaction between **1a** and **2** at higher temperatures (Table 1, entries 4–6). We found that the major isomer *exo*-**3a** decomposed during prolonged heating in the presence of the catalyst with

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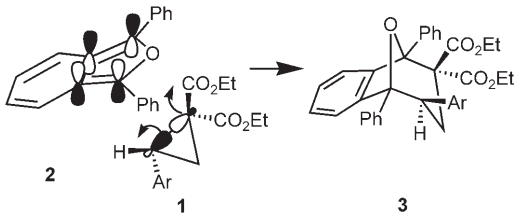
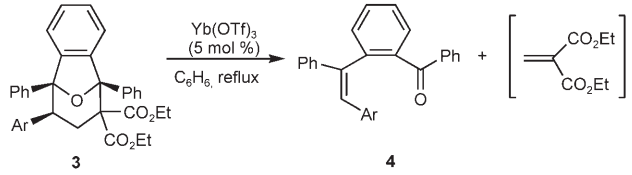


***Scheme 2.*** Proposed mechanism of the [4+3] cycloaddition between **1** and **2**, and configuration of the main product **3**.

the elimination of diethyl methylenemalonate to form **4a**. In contrast, the minor isomer *endo*-**3a** was stable under these conditions. Similar results were observed for other cyclopropane substrates. These observations are consistent with the higher stability of the minor *endo* isomer. The decomposition product **4** can exist as the *E* or the *Z* isomer. However, the *exo* adducts **3a**,**b**,**e** decomposed to form a single isomer of **4** at reflux in benzene in the presence of $Yb(OTf)_3$ (Table 3). Unfortunately, the differentiation of the two

***Table 3:*** $Yb(OTf)_3$-catalyzed decomposition of cycloadducts **3**.



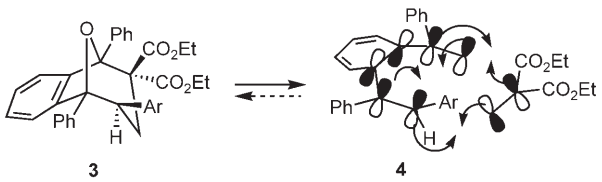
**3a**, **4a**, Ar = Ph  **3b**, **4b**, Ar = 4-$FC_6H_4$  **3e**, **4c**, Ar = 2-Thienyl

| Entry | 3 | *t* [h] | 4 | Yield [%][a] |
|---|---|---|---|---|
| 1 | **3a** | 10 | **4a** | 85 |
| 2 | **3b** | 10 | **4b** | 81 |
| 3 | **3e** | 4 | **4c** | 86 |

[a] Yield of the isolated product.

isomers by NMR spectroscopy was not possible. Therefore, we grew crystals of **4b** and determined the molecular structure of this compound by single-crystal X-ray diffraction analysis.[16,17] The data obtained demonstrated unambiguously that products **4** of cycloreversion have a double bond with *Z* geometry.[16,17]

The formation of the *Z* product **4** may appear unusual. However, the results of quantum-chemical calculations (HF/6-31G) of the two isomers showed that the *Z* isomer is more stable than the *E* alkene by 2.2 kcal mol$^{-1}$. Moreover, the *Z* geometry is predicted by orbital symmetry rules for the product of the concerted cycloreversion process (Scheme 3).



***Scheme 3.*** Disrotatory mechanism of ring opening (closure) for the transformation of **3** into **4** (and the reverse reaction).

In conclusion, we have developed an analogue of the Diels–Alder reaction with donor–acceptor cyclopropanes as dienophiles. This formal [4+3] cycloaddition between 2-aryl cyclopropane diesters and 1,3-diphenylisobenzofuran (**2**) proceeds under mild reaction conditions to yield two isomeric cycloadducts in a combined yield of 84–92%. The predominant formation of the less stable *exo* isomer suggests a concerted mechanism with orbital control of the stereochemical course of the reaction. We are investigating the extension of this reaction to other dienes.

## Experimental Section

General procedure for the cycloaddition: 1,3-Diphenylisobenzofuran (**2**; 284 mg, 1.05 mmol), **1** (1 mmol), and $Yb(OTf)_3$ (31 mg, 0.05 mmol) were dissolved in dry $CH_2Cl_2$ (4 mL), and the resulting mixture was stirred with activated 4-Å molecular sieves under argon at the appropriate temperature (Table 2) until TLC and $^1$H NMR spectroscopy indicated the complete consumption of the cyclopropane diester. The reaction mixture was then filtered, the solvent was evaporated under vacuum, and the residue was purified by column chromatography ($SiO_2$, eluent: hexane–$CHCl_3$ 1:1) to yield **3**.[16]

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[16] For details, see the Supporting Information.
[17] CCDC 654178 (**3b**) and 654179 (**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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