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[3+2] Cyclodimerization of 2-arylcyclopropane-1,1-diesters. Lewis acid induced reversion of cyclopropane umpolung

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ABSTRACT

A novel Lewis acid catalyzed [3+2] cyclodimerization of 2-arylcyclopropane-1,1-dicarboxylates is reported. It is the first example of a reaction wherein a donor–acceptor cyclopropane provides two carbons in a newly formed ring. The described cyclodimerization represents a general convenient approach to polyfunctionalized cyclopentanes.

In recent years, the diverse and often unexpected reactivity of donor–acceptor cyclopropanes (DACs) has attracted significant attention and stimulated research into new pathways for their synthetic utilization.[1–5] To date, the most studied DACs are 2-arylcyclopropane-1,1-dicarboxylates due to the simplicity of their synthesis and potential for variation of the aryl/heteroaryl groups. [3+*n*] Cycloadditions are among the most important reactions of DACs[6–17] wherein these compounds participate as a synthetic equivalent of 1,3-zwitterionic synthon **I** (path ***a***, Scheme 1). In these reactions all three carbon atoms of the cyclopropane ring are incorporated into a newly formed ring. An alternative reactivity of the DAC as a synthetic equivalent of synthon **II** (path ***b***) has recently been reported for cyclopropanes containing electron-rich (hetero)arene substituents.[18–21] In this case only one carbon atom of the three-membered ring is included in the new ring. Examples of reactions where the DAC provides two carbon atoms (path ***c***) have not been reported. In processes ***a*** and ***b*** the DAC reagents show umpolung,[22] while in ***c***, the cyclopropanes should react with normal reactivity.

Recently, we reported the Lewis acid induced cyclopropane-to-propene isomerization of 2-arylcyclopropane-1,1-dicarboxylates.[23] In the course of this research we found that under harsher conditions an unusual cyclodimerization of the parent cyclopropanes into cyclopentane derivatives occurred. In this process one DAC molecule participates as an equivalent of the common synthon **I** (umpolung), while another molecule reacts as an equivalent of synthon **III** (normal reactivity). Herein we report the results of our detailed research of this reactivity.

Our previous studies revealed that 2-arylcyclopropane-1,1-dicarboxylates containing an electron-rich aromatic substituent were more reactive than cyclopropanes with an electron-poor aryl group.[7,19–21] Therefore, we started our research using 2,4,6-trimethoxyphenyl-substituted cyclopropanes **1a**,**b** as well-proven reactive substrates (Scheme 2). The results obtained are summarized in Table 1.

During optimization of the [3+2] cyclodimerization of **1a**,**b**, we found that the best reaction conditions involved reflux of **1** in C_6H_5Cl in the presence of $Sn(OTf)_2$ or $Yb(OTf)_3$ (entries 6–8). These moderately activating Lewis acids have earlier been demonstrated to be efficient catalysts in various DAC reactions. A high temperature was crucial for this transformation as treatment of **1** with Lewis acids at lower temperature failed to give products **4** in good yields (entries 1–5). Instead, the reaction produced mixtures of alkenes **2**, and dimeric alkenes **3** and **4** in low yields under moderate heating. The use of strong Lewis acids, such as $BF_3{\cdot}OEt_2$, $AlCl_3$, $TiCl_4$ did not produce [3+2] cyclodimers of type **4** at all.

The concentration of cyclopropanes is another factor that influences the direction of the reaction. Thus, dimers **4** are formed when concentrated solutions of **1a**,**b** (0.1 M) are used, whereas the dilution of the reaction mixture leads to exclusive formation of products **2** even under the optimized reaction conditions.

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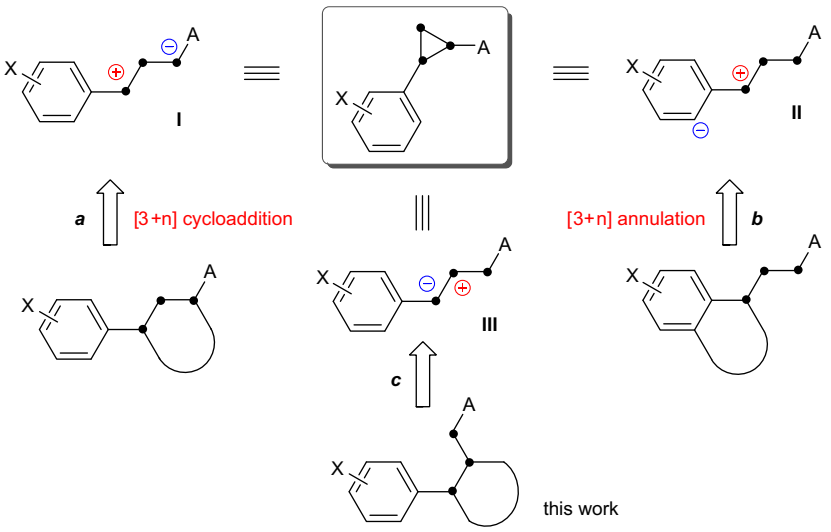


Scheme 1. DACs as a source of 1-, 2- and 3-carbon units for a new ring formation.

The formation of dimeric products was deduced unambiguously from mass spectrometry data. According to the ^{1}H and ^{13}C NMR spectra, cyclopentanes **4a**,**b** were formed as a single diastereomer. The complete assignments of the ^{1}H and ^{13}C NMR spectra of **4** were made with the aid of 2D COSY, HETCOR, HMBC and NOESY experiments. The results of the COSY and HMBC experiments revealed the presence of a five-membered cyclic fragment –(C–CH_2–CH–CH–C(CH)H)– in **4a**,**b**. Thus, one cyclopropane molecule is included in **4a**,**b** as a C–CH_2–CH fragment, while the other is transformed into a CH–CH–CH moiety. The strong cross-peaks between C(Ar‴) and H(3), C(Ar″) and H(4) in the HMBC spectrum allude to a Ar″C(3)H-C(4)HAr‴ fragment. The relative configurations of the chiral centers were assigned from NOESY data (Fig. 1).

The proposed mechanism for the formation of **4** is presented in Scheme 3. Among the possible retrosynthetic disconnections of **4** only one [3+2] disconnection corresponds to reaction of two DAC molecules. The first reacts as an equivalent of synthon **I** with reactivity umpolung, typical for the DAC. The second reacts as an equivalent of the 'normal' synthon **III** in which a negative charge is localized on the benzylic carbon atom and a positive charge is localized at the vicinal position. Such polarity can presumably occur in the enol form of propene **2** which was earlier postulated as an intermediate in the isomerization of **1** into styrylmalonates **2**.[23] Similar to a common diene, this dienol reacts with the electrophilic center of **A** (or the starting cyclopropane **1**) via an Ad_E reaction producing new dimeric zwitterion **C**. Further protonation of the malonyl anion in **C** leads to acyclic alkene **3** (path ***a***, Scheme 3), while intramolecular Michael-like reaction results in cyclic dimer **4** (path ***b***). Similar cyclizations were described for related substrates.[24,25]

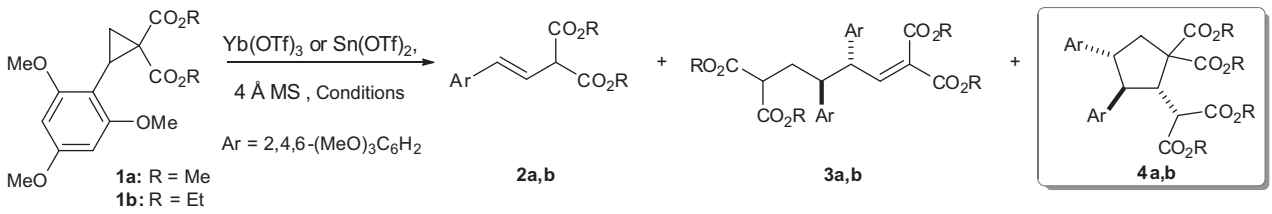
Therefore, this [3+2] cyclodimerization represents a very interesting example of reactions where transformation of reactivity umpolung into normal reactivity is required for the reaction with another 'umpolung reagent'.

[3+2] Cyclodimerization of the DAC into cyclopentanes was found to be general for cyclopropanes with various aromatic or heteroaromatic substituents (Scheme 4, Table 2). Diaryl-substituted cyclopentane derivatives were formed with exceptional chemo- and regioselectivity in good yields. The moderate yield for pyrrolidine-substituted dimer **4f** was ascribed to the low stability of the parent cyclopropane **1f**.

The reactions of **1c**–**j** proceed with very high diastereoselectivity. Despite the formation of three stereogenic centers in **4c**–**j**, only two diastereomers with predominance of the *trans*–*trans*-2-[bis(alkoxycarbonyl)methyl]-3,4-diarylcyclopentane-1,1-diesters were formed. The relative configuration of the major isomers was determined from NOE experiments using **4c** as a reference model (Fig. 2). Unfortunately, due to partial overlapping of the signals in NMR spectra we could not determine the relative configuration of the minor isomers. However, according to our ab initio calculations at the HF/6-31G level, the second most stable isomer is the C(4) epimer of **4c** which is probably the minor isomer.[26]

In contrast to **4c**–**j**, the formation of **4a**,**b** as single diastereomers, is probably related to the high steric demands of 2,4,6-trimethoxyphenyl groups. As a result, the transition state leading to the *threo*-isomer of zwitterion **C** has much higher energy than that leading to the *erythro*-isomer.

As was mentioned above, under unoptimized reaction conditions, acyclic dimers of type **3** were formed in low yields. Screening of the reaction conditions for cyclopropane **1c** allowed the preparation of mainly **3c** in 60% yield as a mixture of two diastereomers (61:39). For this reaction to occur, **1c** was heated at 50–60 °C in nitroethane in the presence of MgI_2 (Scheme 5). Under these conditions styrylmalonate **2c** was also formed as a by-product in 30% yield. Analysis of mass spectrometric and NMR data allowed us to determine unambiguously the structure of **3c**. In particular, a characteristic signal in the ^{13}C NMR spectrum of **3c** was the resonance

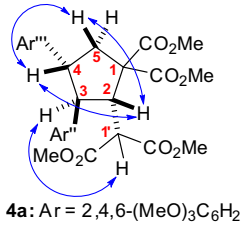


Scheme 2.

Table 1
Optimization of the reaction conditions for the cyclodimerization of **1a**,**b** into **4a**,**b**

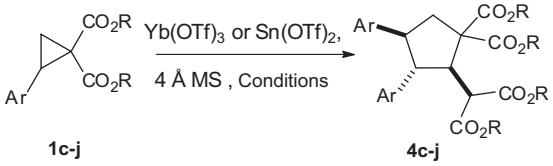
Entry	R	LA (mol %)	Conditions			Yield[a] (%)		
			Solvent	T (°C)	Reaction time (h)	**2**	**3**	**4**
1	Et	$Sn(OTf)_2$ (10)	CH_3NO_2	20	4	88[23]	–	–
2	Et	$Sn(OTf)_2$ (10)	C_6H_6 or CH_2Cl_2	20	23	13–18[b]	–	–
3	Me	$Sn(OTf)_2$ (10)	CH_2Cl_2	42	4	10[b,c]	15–20[c]	–
4	Et	$Yb(OTf)_3$ (5)	CH_2Cl_2	42	4	5 [c]	15 [c]	31 [c]
5	Et	$Sn(OTf)_2$ (10)	C_6H_6	80	6	15 [c]	25 [c]	38 [c]
6[d]	**Me**	**$Sn(OTf)_2$** (10)	**C_6H_5Cl**	**132**	**3**	–	–	**78**
7[d]	**Et**	**$Sn(OTf)_2$** (10)	**C_6H_5Cl**	**132**	**3**	–	–	**75**
8[d]	**Me**	**$Yb(OTf)_3$** (10)	**C_6H_5Cl**	**132**	**3**	–	–	**80**

[a] Isolated yields.
[b] Polymers and γ-aryl-α-(alkoxycarbonyl)butyrolactone were also detected in the reaction mixture.
[c] NMR yield.
[d] The most efficient reaction conditions are marked in bold font.



4a: Ar = 2,4,6-$(MeO)_3C_6H_2$

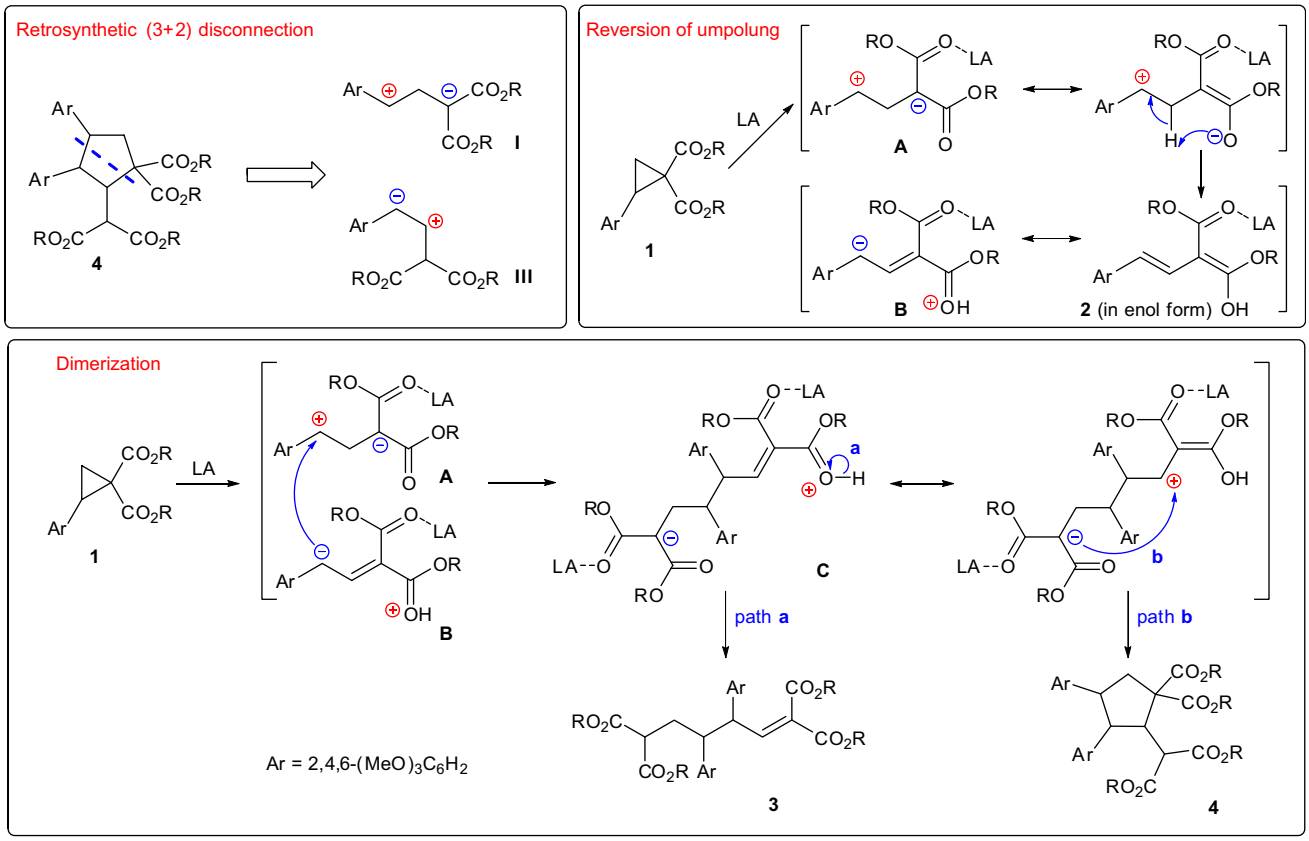
Figure 1. NOESY data for compound **4a**.



Scheme 4.

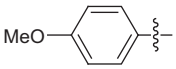
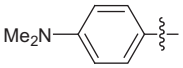
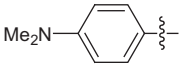
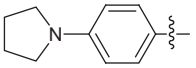
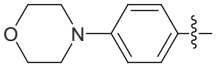
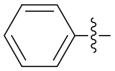
of the tertiary carbon atom at δ_C 149 indicating the presence of an alkylidenemalonate moiety. It is possible that the major isomers of **3c** and **4c** have the same relative configuration for the CHAr–CHAr fragment, as do the minor isomers. This is consistent with our theory that minor isomers of **4c**–**h** have a *cis*-relationship between the aryl groups.

In conclusion, we have described a novel [3+2] cyclodimerization of DACs. This atom-economic process represents a simple and convenient route to polysubstituted cyclopentanes which are useful substrates in both synthetic organic and medicinal

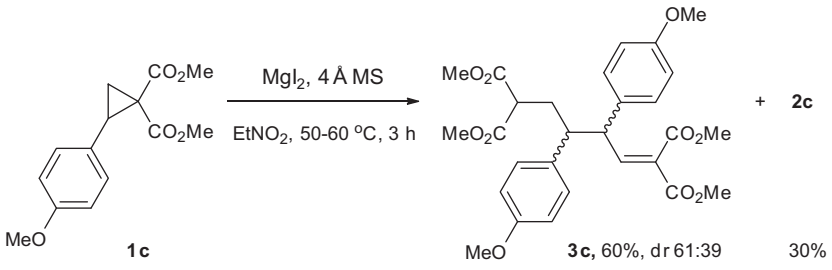


Scheme 3. Proposed mechanism for the [3+2] cyclodimerization of **1** into **4**.

Table 2
[3+2] Cyclodimerization of **1c–j** into cyclopentanes **4c–j**

1,4	R	Ar	LA (mol %)	Conditions			Yield of **4**[a] (%) (dr)[b]
				Solvent	T (°C)	Reaction time (h)	
c	Me		$Yb(OTf)_3$ (5)	C_6H_5Cl	132	5	79 (77:23)
d	Me		$Yb(OTf)_3$ (5)	C_6H_5Cl	132	5	80 (67:33)
e	Et		$Yb(OTf)_3$ (5)	CH_2Cl_2	42	5	75 (78:22)
f	Me		$Yb(OTf)_3$ (5)	CH_2Cl_2	42	5	50 (72:28)
g	Me		$Yb(OTf)_3$ (5)	$C_2H_4Cl_2$	84	4	73 (76:24)
h	Me		$Sn(OTf)_2$ (10)	C_6H_5Cl	132	3.5	67 (61:39)
i	Me		$Yb(OTf)_3$ (5)	C_6H_5Cl	132	7	75 (51:49)
j	Me		$Yb(OTf)_3$ (5)	C_6H_5Cl	132	11	70 (56:44)

[a] Isolated yields.
[b] According to NMR data.



Scheme 5.

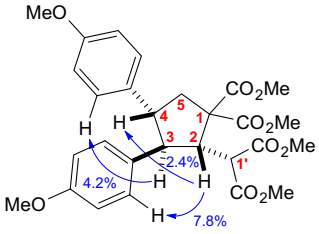


Figure 2. NOE data for the major isomer of **4c**.

chemistry. In this reaction the DAC demonstrates both typical reactivity umpolung acting as an equivalent of a 1,3-zwitterion, and unusual for cyclopropanes, 'normal' reactivity providing a two carbon unit for the newly formed ring. Presumably, normal reactivity is provided via double reactivity umpolung or, in other words, reversion of cyclopropane umpolung.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.059.

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26. See Supplementary data.