

A New Type of Donor–Acceptor Cyclopropane Reactivity: The Generation of Formal 1,2- and 1,4-Dipoles**

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Abstract: A new type of donor–acceptor cyclopropane reactivity has been discovered. On treatment with anhydrous GaCl_3 , they react as sources of even-numbered 1,2- and 1,4-dipoles instead of the classical odd-numbered 1,3-dipoles due to migration of positive charge from the benzyl center. This type of reactivity has been demonstrated for new reactions, namely, cyclodimerizations of donor–acceptor cyclopropanes that occur as [2+2]-, [3+2]-, [4+2]-, [5+2]-, [4+3]-, and [5+4]-annulations. The [4+2]-annulation of 2-arylcyclopropane-1,1-dicarboxylates to give polysubstituted 2-aryltetralins has been developed in a preparative version that provides exceedingly high regio- and diastereoselectivity and high yields. The strategy for selective hetero-combination of donor–acceptor cyclopropanes was also been developed. The mechanisms of the discovered reactions involving the formation of a comparatively stable 1,2-ylide intermediate have been studied.

Donor–acceptor cyclopropanes (DAC) with donor and acceptor substituents at the vicinal position are nowadays popular in organic synthesis as sources of 1,3-dipoles generated from them in the presence of Lewis acids or heating.^[1,2] The capability of donor–acceptor cyclopropanes to undergo [2+3]-, [3+3]-, and [3+4]-dipolar cycloaddition with various substrates is used to construct five-, six-, and seven-membered carbo- and heterocycles,^[1,2] which makes them attractive for application in organic synthesis.

It was recently shown^[3] that, in the absence of unsaturated substrates or other compounds that trap the 1,3-dipoles being generated, DAC themselves can undergo dimerization upon treatment with Lewis acids and organocatalysts. Depending

on the reaction conditions and the nature of the aryl substituent, the reactions give dimers of various classes, such as arylidenemalonates,^[3a] diarylhexenes,^[3a,b] cyclohexanes,^[3b] tetralins,^[3b,c] dihydroanthracenes,^[3b] pentaleno[1,6-a,b]indoles,^[3d] cyclopentanes,^[3a,c] 2-oxabicyclo[3.3.0]octanes,^[3e] and indanes.^[3f]

Herein, we discuss a thorough study of DAC transformations in the presence of the anhydrous Lewis acid GaCl_3 ^[3c,e,g] under various conditions and the discovery of new reactivity types for these cyclopropanes. The new strategy uses DACs as the source of even-numbered 1,2- and 1,4-dipoles, instead of odd-numbered classical 1,3-dipoles (Figure 1). This is ach-

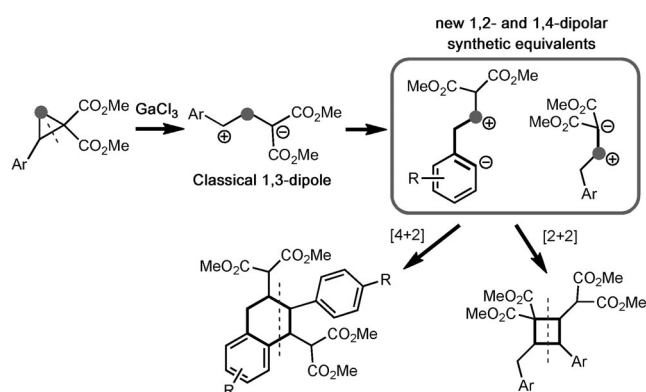


Figure 1. New Type of DAC Reactivity: generation of formal 1,2- and 1,4-dipoles.

ieved due to the positive charge shift along the alkyl chain at the stage of cyclopropane ring opening. This is an exclusive feature of reactions with GaCl_3 . Analysis of the entire diversity of DAC reactions described in the literature^[1–3] did not reveal similar reactions.

The discovered [4+2]-cyclodimerization of DAC is a synthetically valuable process that allows the one-stage assembly of polysubstituted tetralins from simple and readily available cyclopropanedicarboxylates with exceptionally high regio- and diastereoselectivity. The latter may be of interest as synthons in organic synthesis and as compounds possessing biological activity. In fact, the aryltetralin moiety occurs in the structures of a number of compounds that have been isolated from various natural sources and manifest a broad spectrum of biological activity,^[4] including antitumor activity.^[4e] (Figure 2).

It has been found that compound **1a** can undergo dimerization in the presence of GaCl_3 along four different pathways to give polysubstituted cyclopentane **2a**,^[3c] tetralin

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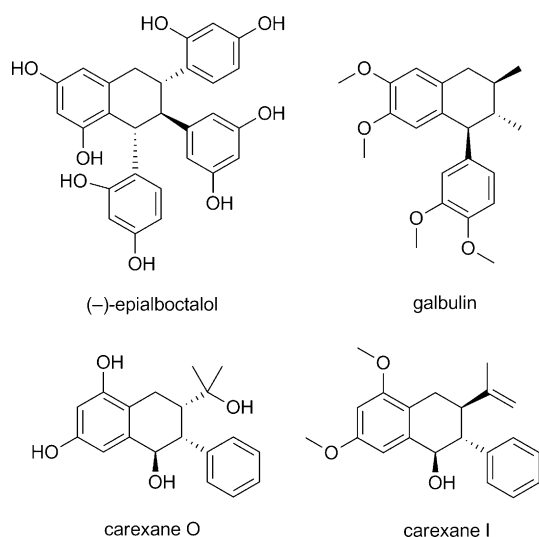
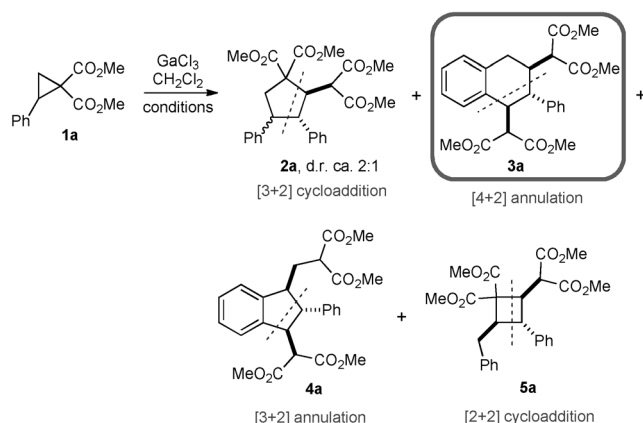


Figure 2. Examples of natural products with biological activity incorporating the 2-aryltetralin fragment.

3a, indane **4a**,^[3f] and cyclobutane **5a**. The fraction of each depends on the amount of GaCl₃ used and on the reaction temperature (Table 1). In this case, the formation of compounds **3a–5a** represents new types of DAC cyclodimerization

Table 1: GaCl₃-mediated dimerization of cyclopropane **1a** under different conditions.



Entry	GaCl ₃ [mol %]	T [°C]	t [min]	Yield ^[a,b,c] [%]			
				2a	3a	4a	5a
1	20	0	30	85			
2	20	20	30	73			
3	50	0	30	75	13		
4	50	20	30	35	44	9	
5	50	40	30	< 10	81		
6	100	0	30	70	16	< 3	< 3
7	100	20	30	35	39	11	9
8	100	40	30	10	79	< 2	< 2
9	100	40	90		34		
10	75	40	30	< 5	86		
11	75	80	30		10		

[a] Yield of isolated products. [b] ¹H NMR spectroscopic analysis was used in the case of unseparated mixtures. [c] Product yields can vary widely based on the quality of GaCl₃ used, and the amount of trace moisture present.

tion corresponding to [3+2]- and [4+2]-annulation and formal [2+2]-cycloaddition. All compounds, unlike cyclopentane **2a**, are formed as single diastereomers.

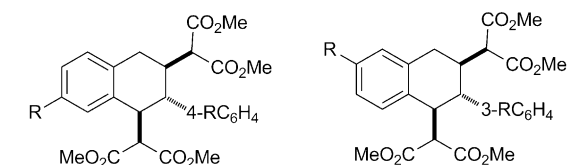
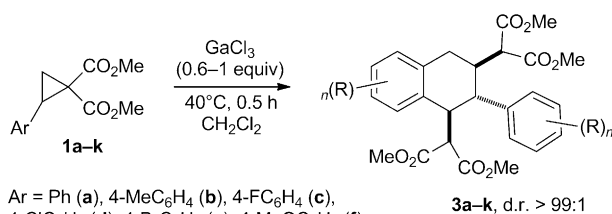
The dimerization of compound **1a** was found to be very sensitive to the reaction conditions (Table 1). In fact, cyclopropane **1a** underwent selective dimerization to cyclopentane **2a** at a temperature of about 0°C in the presence GaCl₃ (20 mol %), whereas other dimers were not formed.^[3c] If the temperature was increased to 40°C and the amount of GaCl₃ was increased, the regioselectivity of the process changed abruptly to give tetralin **3a** in high yield. The optimum results were obtained with 75 mol% of the Lewis acid. Under intermediate reaction conditions, a mixture of dimers **2a** and **3a** predominated, accompanied by indane **4a** and cyclobutane **5a**.

Once the optimum conditions for the conversion of cyclopropane **1a** to tetralin **3a** were found, we studied other DACs in this process. It was found that [4+2]-cyclodimerization also occurred successfully for substituted cyclopropanes **1b–k**, in all cases to give 2-aryl-1,3-bis(malonyl)tetralins **3b–k** as the major products, in high yields and with exceptionally high diastereoselectivity (Scheme 1). The [4+2]-cyclodimerization of 3-substituted phenyl- (**1g,h**) and 2-naphthylcyclopropanedicarboxylates (**1k**) also occurred regioselectively. In fact, of the two possible directions of electrophilic substitution at the aromatic ring, the attack exclusively occurred at the less sterically hindered position, to give compounds **3g,h,k**. It was also found that the use of equimolar amounts of GaCl₃ and tetrahydrofuran as an additional ligand were the optimum conditions to improve the yield of dimers **3j,k**. In this case, tetrahydrofuran should be added after gallium trichloride. Tetrahydrofuran decreases the Lewis acidity of GaCl₃ but does not affect the overall pathway of the process. The composition of the target products was established by means of elemental analyses or HRMS. The structure and stereochemistry of the compounds obtained were determined by ¹H, ¹⁹F and ¹³C NMR, 1D and 2D COSY, TOCSY, NOESY, HSQC, and HMBC spectroscopy.

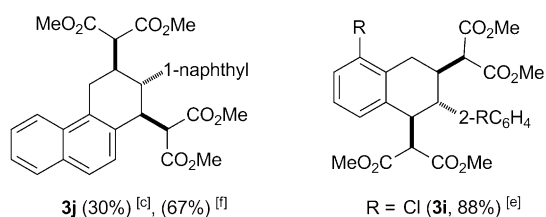
We detected cyclodimers **6–8** as admixtures upon [4+2]-cyclodimerization of 1-naphthylcyclopropane **1j** with GaCl₃ (Figure 3). The formation of these compounds also represents a new type of DAC dimerization involving [4+3]-, [5+2]-, and [5+4]-annulation on the naphthyl ring to give seven- and nine-membered rings.

We have recently synthesized and characterized hitherto unknown DAC complexes with Lewis acids, including GaCl₃.^[5] Considering the data on the detection of the dipolar intermediates formed, the mechanisms of the new processes of DAC cyclodimerization in the presence of GaCl₃ (Scheme 2) that we discovered can be proposed.

When GaCl₃ is added to cyclopropane **1**, it is instantly bound to give a relatively stable 1,2-dipole **II**,^[5] which is the key intermediate in DAC dimerization induced by GaCl₃ and exists in the reaction mixture for a rather long time. This intermediate exists in solution in equilibrium with minor amounts of much less stable intermediates **I** and **III**,^[5] which are continuously consumed in various processes due to their higher reactivity. The diversity of dimerization processes is limited to reactions of the three intermediates **I–III** with each



R = H (**3a**, 86%)^[a], Me (**3b**, ca. 50%)^[b], F (**3c**, 44%)^[b], Cl (**3d**, 51%)^[b], Br (**3e**, 51%)^[b], OMe (**3f**, <5%)^[c]
R = Cl (**3g**, 79%)^[d], Br (**3h**, 82%)^[d]



Scheme 1. GaCl₃-mediated [4+2]-cyclodimerization of DACs **1a-k** giving 2-aryltetralins **3a-k**. Reaction conditions: [a] GaCl₃ (0.75 equiv), 40°C, 30 min. [b] GaCl₃ (0.6 equiv), 40°C, 30 min. [c] GaCl₃ (0.75 equiv), 20°C, 30 min. [d] GaCl₃ (1 equiv), 40°C, 4 h. [e] GaCl₃ (1 equiv), 40°C, 6 h. [f] GaCl₃ (1 equiv), 0°C, then THF (1 equiv), 0→20°C, 6 h.

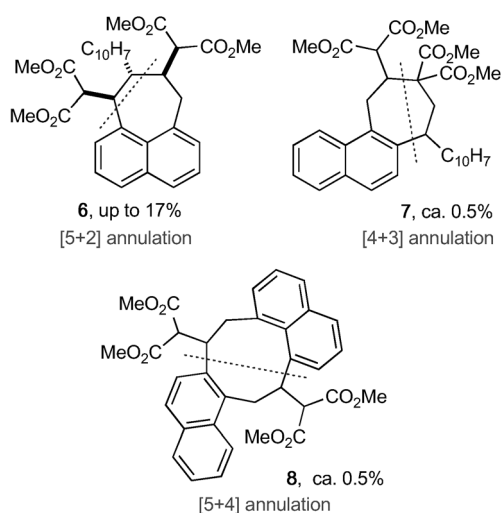
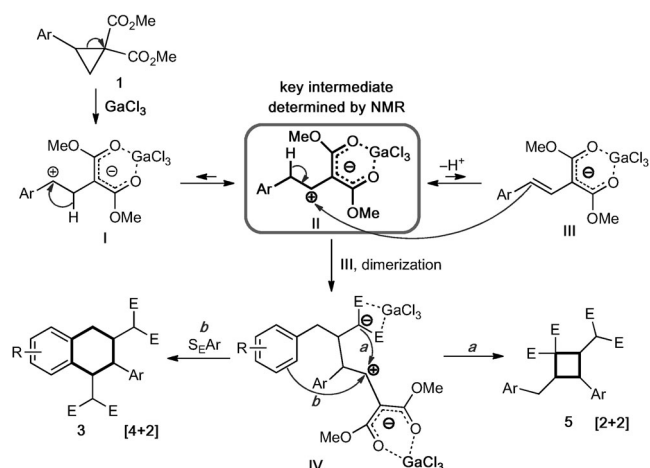


Figure 3. Minor products formed in the GaCl₃-mediated dimerization of cyclopropane **1j**.



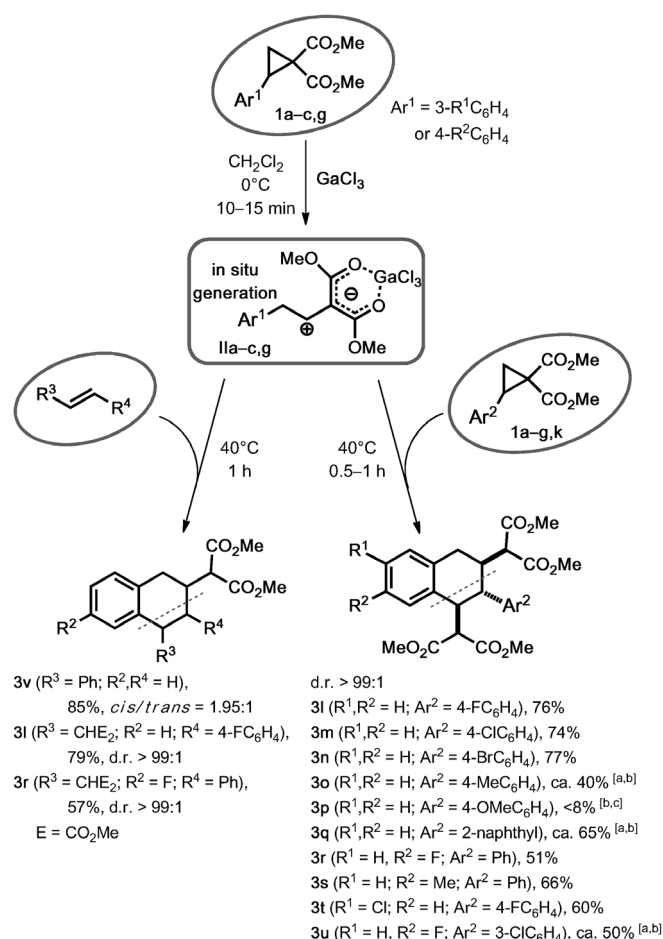
Scheme 2. Proposed mechanism of the GaCl₃-mediated cyclodimerization reactions of DACs.

other. Cyclobutanes **5** and tetralins **3** are formed in the reaction of intermediates **II** and **III**, which are initially coupled to give intermediate **IV**, then either 1,4-cyclization to compound **5** or electrophilic substitution at the aromatic ring to give compound **3** occurs (for detailed mechanisms, see the Supporting Information).

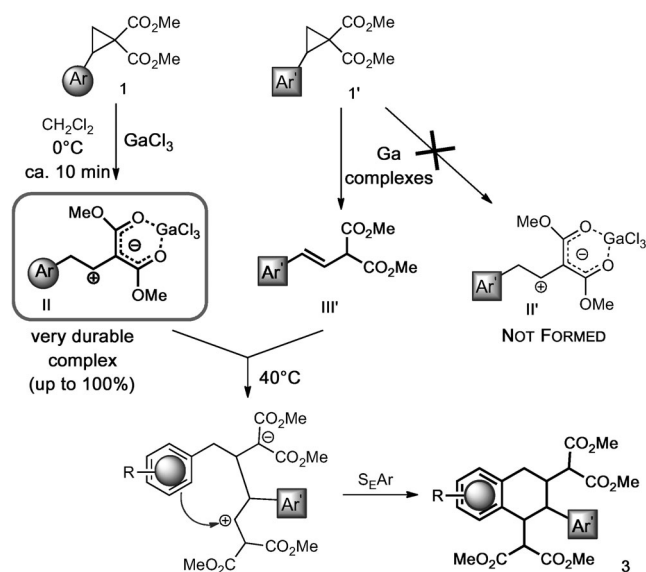
The regioselectivity of [4+2]-cyclodimerization reaction of DAC is anomalous. The fact is that styrylmalonate **III** is generated and reacts as a Ga complex (not in its free form). When its double C=C-bond is attacked by the carbocationic center generated from the second molecule of DAC, the alkyl carbocation **IV** is formed, which is highly stabilized by the negative or partial negative charge from the malonyl anion in coordination with the GaCl₃. The last carbocation is the analog of very stable 1,2-ylide **II**^[5] and turns out to be much more stable than the benzylic carbocation which had not formed (for details, see Supporting Information).

The high stability of 1,2-ylide Ga complex **II** makes it possible to develop an effective strategy for the [4+2]-annulation of DAC in a variant of strictly controlled hetero-combination of two different DAC molecules, or a combination of DAC with alkenes. This approach consists of the generation of the key dipolar intermediate from the necessary DAC molecule in situ, and its further introduction in the combination with the second substrate (DAC or alkene) under heating (Scheme 3). This preserves the diastereoselectivity of the reaction and each injected fragment gets into a strictly defined position in the final tetralin and the homodimerization products, whereas only a minor amount of random heterodimerization products are formed. In essence, this is the first example of selective DAC heterodimerization. This strategy significantly expands the possibilities of the DAC [4+2]-annulation reactions. In the future, we intend to develop this reactivity in order to include DAC reactions with various substituents and substrates.

The mechanism of the [4+2]-heterodimerization of DAC is similar to the homodimerization one. The key Ga intermediate that allows control of the cross-dimerization reaction is ylide **II**. It is a relatively stable complex in which Ga is strongly associated with the ester groups,^[5] and therefore this



Scheme 3. GaCl₃-mediated [4+2]-cross-dimerization and annulation with styrenes of DACs. [a] Isolated with 50–85% purity. [b] Yields determined by ¹H NMR spectroscopy. [c] Not isolated.



Scheme 4. Proposed mechanism of the GaCl₃-mediated selective [4+2]-cross-dimerization of DACs.

intermediate hardly exchanges gallium trichloride with other molecules and intermediates (for a detailed mechanism, see the Supporting Information). This allows high selectivity in the cross-dimerization reaction and makes this process possible. As almost all GaCl₃ is complexed in **II**, the second molecule of DAC cannot react with GaCl₃ to give corresponding ylide **III'**. Therefore, it isomerizes in styrylmalonate **III'** under the action of the Ga complexes (for example, **II**). Then reaction of intermediates **II** and **III'** takes place (Scheme 4).

In summary, we have discovered new DAC cyclodimerization processes initiated by anhydrous GaCl₃, which occur as [2+2]-, [3+2]-, [4+2]-, [5+2]-, [4+3]-, and [5+4]-annulation reactions and represent a new type of DAC reactivity wherein the latter serve as sources of even-numbered 1,2- and 1,4-dipoles instead of the classical odd-numbered 1,3-dipoles; this is due to migration of positive charge along the carbon chain from the benzyl center. A preparative version of regio- and diastereospecific DAC [4+2]-annulation to give tetralins has also been developed.

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