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Reactive Cyclopropanes

Intriguing Electrophilic Reactivity of Donor–Acceptor Cyclopropanes: Experimental and Theoretical Studies

Maxime Dousset,^[a] Jean-Luc Parrain,^{*[a]} and Gaëlle Chouraqui^{*[a]}

Abstract: A new reactivity of donor–acceptor cyclopropanes (DACs) has been highlighted and, for the first time, we report that they could formally behave as nucleophiles and be functionalized at their C3 position. The donor–acceptor cyclopropane acts as a formal nucleophilic synthetic equivalent of a 1,2-zwitterion and could be described as an umpolung synthon.

A highly substituted lactone is reached, and even more impressive is the formation of four stereogenic centers with complete control of their relative configuration. Both experimental and computational studies were performed to provide an overall picture of the mechanism.

Introduction

Donor–acceptor cyclopropanes (DACs) represent a unique class of reactive molecules and have attracted continuous and growing interest in recent years.^[1,2] Ample evidence of this is the increasing number of publications related to this topic.

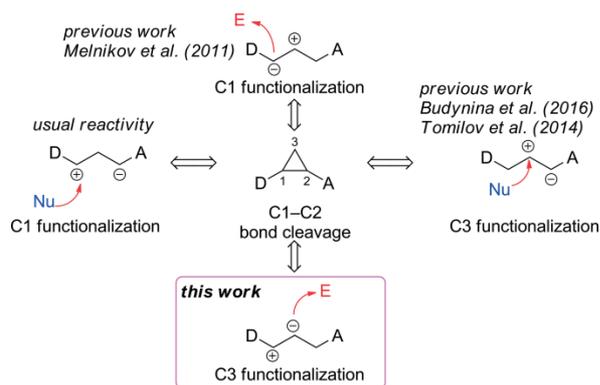
The presence of both antagonist partners on adjacent carbon atoms (C1 and C2) combined with the inherent ring strain of the cyclopropane (about 27.5 kcal mol⁻¹) provide a C1–C2 bond prone to heterolytic cleavage,^[3] and ring opening can therefore occur under mild conditions (usually under heating or Lewis acid activation). A valuable 1,3-dipole synthetic building block is thus delivered (Scheme 1, left) and has been utilized in plethora of reactions, for instance: nucleophilic trapping,^[4] [3+2],^[5] [3+3],^[6] and [3+4]^[7] cycloaddition reactions as

well as rearrangement.^[8] Some of the resulting molecules have been used as advanced materials in the construction of biologically relevant targets.^[9,2a,2c]

In 2011, Melnikov showed that DACs could behave as two carbon partners in a cyclodimerization process and provide a “normal” synthon, which is different to their typical behavior as umpolung synthons (Scheme 1, top).^[10] In 2014, Tomilov also reported that DACs could act as sources of formal 1,2- and 1,4-dipoles (positive charge migration from the benzyl ester), in the presence of anhydrous gallium trichloride (GaCl₃) (Scheme 1, right), in annulation processes.^[11] More recently, Budylnina described the reactivity of a synthetic equivalent of a 1,2-zwitterion which underwent a C3 nucleophilic addition in the presence of nitroalkanes.^[12]

With the aim to expand the reactivity scope of DACs, we hypothesized that the reactivity of the two distinct anionic and cationic parts could be disconnected by protonation of the anion to further exploit the pure cationic part. Moreover, depending on the stabilizing substituent at the cationic center, we were hoping to generate long living species potentially useful in synthetic transformations.

Herein, we disclose a new pathway of DAC reactions, where the DAC acts as a formal nucleophilic synthetic equivalent of a 1,2-zwitterion with a functionalization at the C3 position, which could be described as an umpolung synthon (Scheme 1, bottom).



Scheme 1. State of the art and objectives.

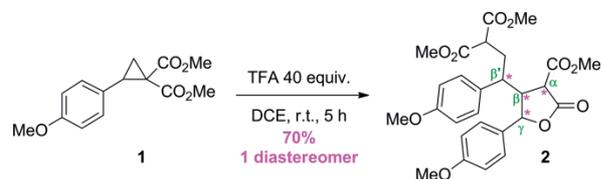
Results and Discussion

Preliminary Results

To get straight into the heart of the matter, when DAC **1** was mixed together with a large amount (40 equiv.) of trifluoroacetic acid (TFA) in 1,2-dichloroethane at room temperature for five hours, we observed the formation of the corresponding α,β,γ -trisubstituted lactone **2** in 70 % yield (Scheme 2), as the one and only product. It is worth noting that the latter exhibits

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four stereocenters and, satisfyingly, was isolated as a single diastereomer, which could not be assigned at the time.



Scheme 2. Preliminary result.

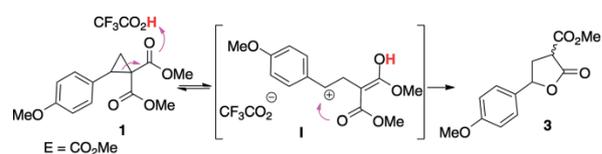
A bit puzzled by this unexpected result, we next devoted our efforts to optimizing and mainly to understanding the pathway taken by DAC **1** under Brønsted acidic conditions.

Firstly, we could decrease the necessary amount of TFA (26 equiv.) without any loss in yield (70 %) and the reaction was complete within the same time scale (5 h) (Table 1, entry 2). Below this limit, things started to get a little bit messy; in the presence of 16 equiv. of TFA (Table 1, entry 3), 70 % of expected lactone **2** was again isolated but accompanied with 16 % of compound **3** (Scheme 3).

Table 1. Optimization of the necessary amount of TFA.

Entry	TFA [equiv.]	Time [h]	Yield of 2 [%]	Yield of 3 [%]
1	40	5	70	–
2	26	5	70	–
3	16	6	70	16
4	4	36	36	38 ^[a]

[a] Trace amount (4 %) of alkene **4** was also isolated and its presence will be explained in due course.



Scheme 3. Pathway to **3**.

The latter came from the intramolecular cyclization of **I** after ring opening of the starting cyclopropane **1** (Scheme 3).

With 4 equiv. of TFA, it became critical since the reaction requires 36 h to complete; the yield of the desired adduct **2** dropped to 36 % and the major product observed was lactone **3** (38 % yield) (Table 1, entry 4). We next turned our attention to the nature of the solvent. We initially thought, in order to stabilize the intermediate charges, that the reaction should be performed in a solvent with a higher dipole moment than that of 1,2-DCE ($\mu = 1.55$). However, nitromethane ($\mu = 3.57$) solely led to complete degradation of the starting material (Table 2, entry 2). We next examined chlorinated solvents. Chloroform gave a mixture of compounds **2/3/4/5** in a 52/14/22/12 ratio (determined by NMR spectroscopy) (Table 2, entry 3), whereas CH₂Cl₂ furnished the expected compound **2** but with a lower yield (58 %) than that observed in 1,2-DCE (Table 2, entry 4).

Table 2. Nature of solvent.

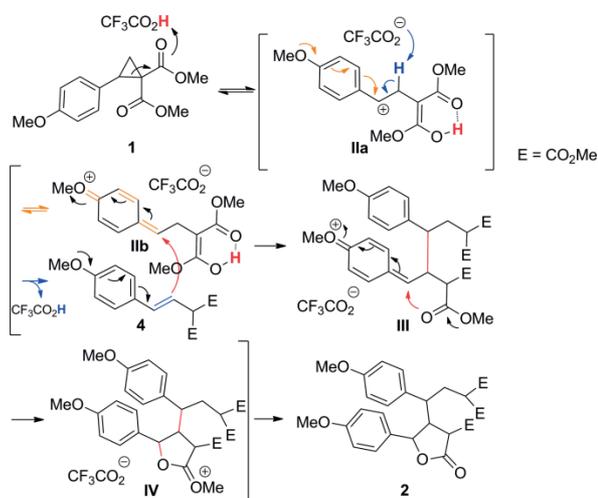
Entry	Solvent	Observations	Structure
1	1,2-DCE	70% of 2	
2	MeNO ₂	degradation	
3	CHCl ₃	2/3/4/5 52/14/22/12 ^[a]	
4	CH ₂ Cl ₂	58% of 2	

[a] NMR ratio.

To summarize, these different assays allowed us to lower down the amount of TFA (26 equiv. instead of 40 equiv.). Although the change of solvents did not lead to any improvement in yield and 1,2-DCE seemed to be the solvent of choice, it seemed like we dug crucial information. Accordingly, alkene **4** (Table 2) was repeatedly observed as a side product and we hypothesized that this species might be involved in the formation of the trisubstituted lactone **2**.

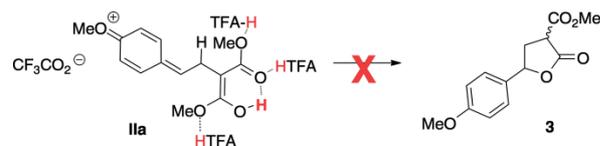
Insight into the Mechanism

In the light of the above preliminary results, the following mechanism was suggested. Note, that we decided to proceed step by step, and to initially put aside the stereoselectivity of the reaction. The Brønsted acidic medium could promote the ring opening of cyclopropane **1** towards intermediate **Ila**. On the one hand, **Ila** could be in equilibrium with the mesomeric form **Ilb** and, on the other hand, **Ila** could undergo an elimination reaction to give alkene **4**. It is worthy of note that such a compound has already been observed by Melnikov^[13] or Tomilov^[11a] in Lewis acidic conditions. A nucleophilic addition of olefin **4** onto intermediate **Ilb** could lead to the formation of the first carbon–carbon bond (cf. **III**). A further lactonization step could be responsible for the formation of the second simple bond (see **IV**). Finally, hydrolysis of the oxonium could deliver trisubstituted lactone **2** (Scheme 4).



Scheme 4. Hypothetical mechanism.

As stated earlier, increasing the amount of TFA from 16 to 26 equiv. led to complete disappearance of the lactone side product **3**, (Table 1) and this could provide valuable information about the mechanism. We indeed hypothesized that (i) the formation of olefin **4** could be kinetically favored in highly acidic conditions and (ii) that the formation of lactone **3** could be avoided by decreasing the nucleophilicity of the carbonyl function thanks to hydrogen bonds with the oxygen lone pairs (Scheme 5).

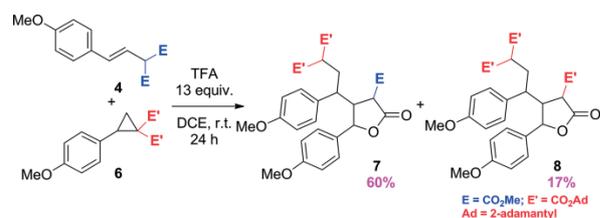


Scheme 5. About the disappearance of lactone **3**.

At this stage of the study, we decided to adopt both experimental and theoretical approaches in order to confirm the mechanism depicted above (Scheme 4) but mostly to rationalize the observed total diastereoselectivity.

Experimental Approach

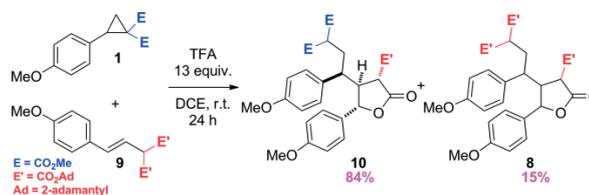
To shed the light on the role played by olefin **4** in the reaction mechanism, we ran a cross-reaction between the latter (**4**) and 2-adamantyl ester cyclopropane **6**. Alkene **4** was obtained from **1** by using a literature sequence of ring opening and elimination reactions promoted by tin(II) triflate.^[13] Pleasingly, cross-product **7** was isolated in 60 % yield together with an inseparable mixture of adamantyl-homodimer adduct **8** (17 %) and starting material **4** (14 % yield) (Scheme 6).



Scheme 6. Role of olefin **4**.

A similar experiment was next run with the adamantyl-alkene **9** and methyl ester cyclopropane **1**. Once again cross-product **10** was observed in very good yield (84 %), accompanied with adamantyl-homodimer adduct **8** (15 %) and traces of starting olefin **9** (Scheme 7). To our delight, we were able to grow crystals of compound **10** suitable for X-ray crystallographic analysis thus confirming the anticipated structure and its relative stereochemistry.^[14]

These results are in good agreement with the hypothesis that olefin **4** is an intermediate in the reaction mechanism (Scheme 4). Interestingly, in both cases, the starting olefin (**4** or **9**) is an integral part of the resulting five-membered ring itself (see products **7** and **10**, respectively). This chemoselectivity is valuable information and demonstrates that the olefin under-



Scheme 7. The other cross-reaction.

goes nucleophilic addition onto a compound which came from the ring opening of cyclopropane **6** or **1**, respectively, the latter being an integral part of the β substitution of the resulting lactone **7** or **10**. In addition, we wish to underline the fact that no homodimerization of the starting alkene **4** occurred, that the cross-compound is the main product in both cases, and the only homodimer obtained came from two subunits of adamantyl derivative **6** or **9**. We could draw the following conclusions: the reaction between the alkene and the cyclopropane must be faster than the reaction between cyclopropanes or alkenes since only 17 % of dimer **8** has been isolated in the first case and 15 % in the second one. The intermediate might be trapped as soon as it is formed and might not be able to perform the elimination step leading to the corresponding alkene. These results suggest that the alkene formation is certainly the rate-determining step of the title reaction.

Finally, it is worth noting that in situ IR studies also support the presence of alkene **4** as a reactive intermediate (see Supporting Information for further details).

Many studies have been performed on the homodimerization of donor-acceptor cyclopropanes;^[11c,15] however, to the best of our knowledge, such a behavior has never been reported. A highly substituted lactone is reached. We observed the substitution at the C3 position of the starting cyclopropane, and even more impressive is the formation of four stereogenic centers with complete control of their relative configuration.

Encouraged by those results and to provide an even clearer understanding of the reaction mechanism, notably, when it comes to provide an explanation for the relative stereochemistry observed, we carried out DFT calculations.^[16]

Theoretical Approach

To minimize calculation times, we constructed simplified diastereomeric transition-state structures shown schematically in Figure 1. Only the realistic cationic species involved in the formation of lactone **2** were taken into account and the counteranion was put aside. Initial geometry optimizations were performed with B3LYP/6-31G(d) and the polar continuum model (PCM), solvation model in Gaussian 09.^[17] However, the free-energy difference calculated by this method was nonsignificant ($\Delta\Delta G^\ddagger = 1.5 \text{ kcal mol}^{-1}$). On the other hand, the hybrid meta-GGA functional, M06-2X functional, which is described to give better performance in treating cation- π and π - π dispersion interactions and hydrogen bonding interactions,^[18] and is generally more robust than B3LYP in nonbonding interactions, was better suited to our system and produced a much better agree-

ment with the experimental data. As a matter of fact, this approach is routinely found in organocatalytic reactions.^[19] Thus, for the first step of this study, geometries were optimized with M06-2X and the 6-31G(d) basis set and single-point energies were calculated with M06-2X and the 6-311++G(d) basis set. Implicit solvation corrections were applied with use of the PCM,^[20] with dichloromethane as solvent.

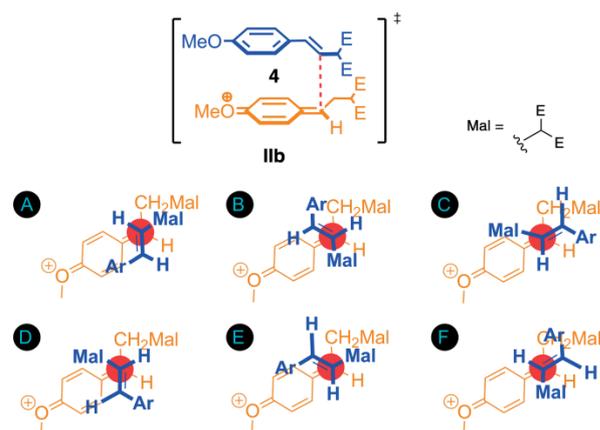


Figure 1. The six different staggered approaches.

We computed all intermediates, transition structures (TSs), and possible cationic complexes involved. To investigate the mechanism suggested in Scheme 4, exhaustive searches were performed to locate other pertinent conformations. Reported energies are computed as single-point energy calculations and include the zero-point energy (ZPE) correction. Each stationary point was adequately characterized by normal coordinate analysis (no imaginary frequencies for an equilibrium structure and one imaginary frequency for a transition-state structure).

According to the hypothetical mechanism, the creation and the control of the two first stereocenters, that is the β and β' substitutions of the resulting lactone **2**, occur during the nucleophilic addition of alkene **4** on cationic species **IIb** (Scheme 4). To gain insight into the mechanism pathway and the stereoselectivity of the reaction, six different staggered approaches **A-F** have been considered for calculations and are presented below (Figure 1).

Firstly, the reaction pathway starts with a mixture of **IIa** and **4** that was computed with a distance of 25 Å in order to examine the energetic requirements for the charge-transfer complex formation that we assigned to 0 kcal mol⁻¹. Computations are in accord with this structural assignment (Figure 2) and indicate that the enthalpy for the fragmentation of **IIa.4** to its two separate constituents is endothermic by 19.27 kcal mol⁻¹ at 298 K. The two aromatic cycles were cleanly superposed as seen in Figure 2 and the distance of the aromatic stacking is approximately 3.22 Å, which is consistent with prior literature.^[21]

Starting from this stabilized charge-transfer complex **IIa.4**, we searched all transition states (TSs) corresponding to the nucleophilic addition of alkene **4** onto cationic species **IIb** (re-

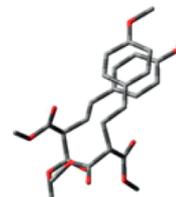


Figure 2. Charge-transfer complex **IIa.4**.

sulting from the ring opening of the DAC). The six possibilities are given in Figure 1. As expected, among the six transition states, those with lower energies (A and E) exhibit a π - π interaction that certainly stabilized the transition state. Thereafter and for each intermediate, the nucleophilic addition was found to be exothermic (more than 5.4 kcal mol⁻¹), with a transition state of at least 5.44 kcal mol⁻¹. A closer look at the values of the different TSs showed a preference for the formation of TS-**E**. All the other TSs were higher in energy, which could explain the experimentally observed trend. However, we found that transition state TS-**A** was indeed slightly higher in energy (difference of 2.52 kcal mol⁻¹), but not sufficiently high to justify the total stereoselectivity observed in favor of **III**.

To address this point, we performed more accurate calculations of starting material (**IIa.4**), TS-**A**, TS-**E**, and intermediates **III** and **IV** [geometry optimizations at M0-62X/6.31+g(d,p) and evaluation of energies M0-62X/6.311++g(d,p) taking into account solvent and ZPE correction]. In these cases the energies were higher from 0.6 to 1.1 kcal mol⁻¹ (Table 3) and the difference in energy (3.02 kcal mol⁻¹) was now consistent with the observed high diastereoselectivity.

Table 3. Comparative energies for TS-**A** and TS-**E** leading to *SS*-**III** and *RS*-**III**.

	M0-62X/6.31+g(d)// M0-62X/6.311++g(d,p) [kcal mol ⁻¹]	M0-62X/6.31+g(d,p)// M0-62X/6.311++g(d,p) [kcal mol ⁻¹]	C β -C β' distance [Å]
TS- A	7.40	8.48	2.306
TS- E	4.88	5.44	2.331

Finally, cation **III** having *RS* relative stereochemistry was found to be the thermodynamic product as well (Figure 3).

We next hypothesized an asynchronous concerted pathway leading directly to lactone **IV**. However, no TS was found to accredit this route. In fact, the observed cation *RS*-**III** exhibits a stabilizing intramolecular cation- π interaction (2.95 and 5.34 kcal mol⁻¹) and very large rotational barrier energies (14.95 and 12.72 kcal mol⁻¹) which was revealed through conformational analyses around the C β -C β' and C β -C γ carbon bonds, respectively (Scheme 8). Consequently, one of the faces of the cation would be completely inaccessible to the nucleophilic addition of the lone pair of the ester onto the benzylic cation. This could explain the total control of selectivity of the γ stereocenter.

The installation of the fourth stereocenter, that is the α substitution of lactone **2**, would also take place during the lacton-

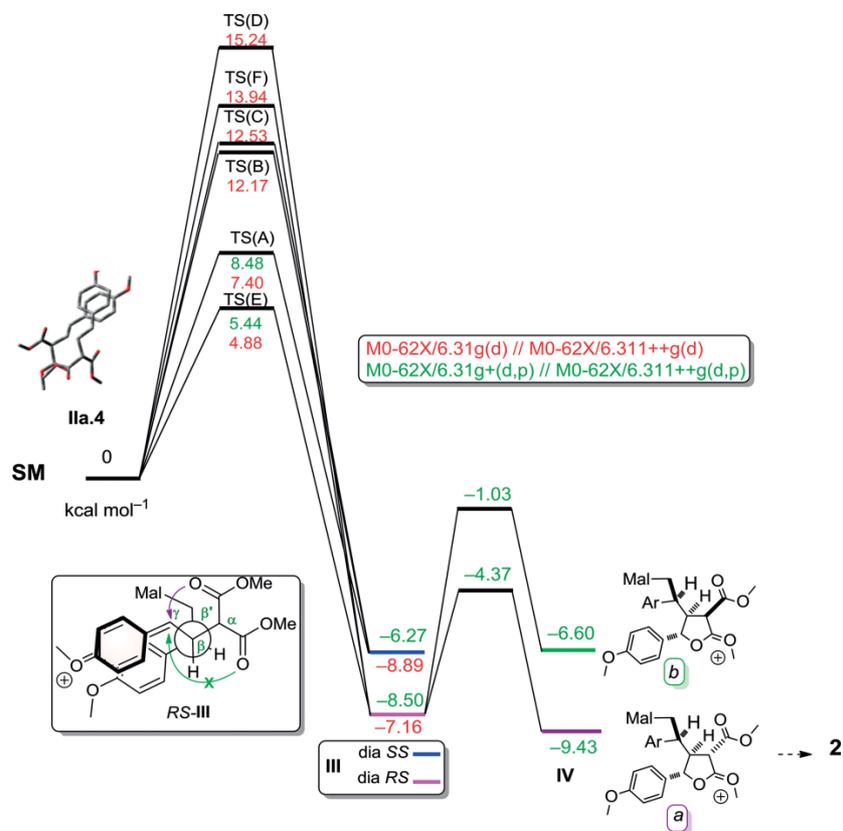
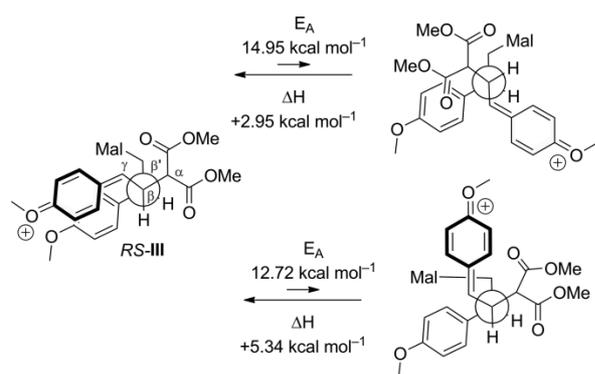
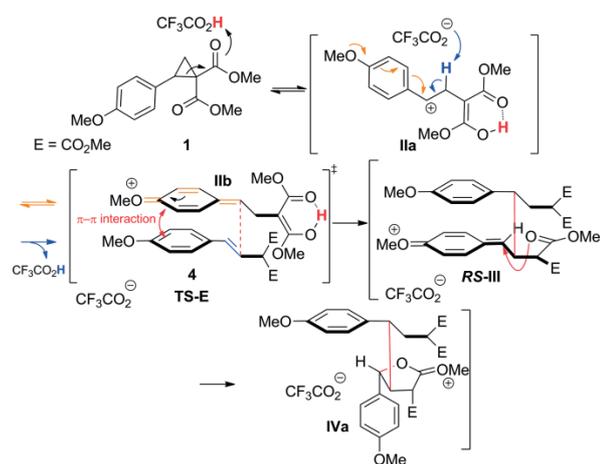


Figure 3. Energy profile.



Scheme 8. Control of selectivity of the γ stereocenter.



Scheme 9. Overall picture of the mechanism.

ization step of intermediate *RS-III* and would lead to formation of lactone *IVa* (Scheme 9). Once again, the energy difference between the calculated TSs ($3.34 \text{ kcal mol}^{-1}$) is sufficient to explain the total diastereoselectivity observed (Figure 3).

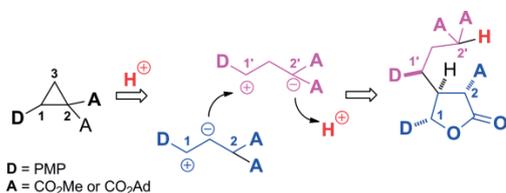
Experimental and *in silico* results allowed us to propose the mechanism given in Scheme 9. The relative stereochemistry of

each stereogenic center is quite well predicted by the calculations; the stereocenters in α , β , β' , and γ positions originated from both kinetic and thermodynamic parameters.

Discussion

As stated in the introduction, DACs are well known to undergo a ring opening through the C1–C2 single bond cleavage in the presence of Lewis acids and then react with a nucleophile at the C1 position. More recently, it was demonstrated that a selective C3 nucleophilic functionalization was also feasible.^[11,12]

In our case, it is quite different since the classical ring opening of DACs in the presence of a Brønsted acid was not observed. An unusual reactivity was instead witnessed. Accordingly, a nucleophilic addition occurred starting from the C3 pole of the latter onto another DAC unit. The second moiety behaved more classically as an electrophile and reacted at the C1' position. This unprecedented behavior allows an access to α,β,γ -trisubstituted butyrolactones in a highly diastereoselective manner. The isolated lactone presents four stereogenic centers, and only one diastereomer was observed (Scheme 10).



Scheme 10. Overall picture of the transformation.

We demonstrated that the reaction could also be rather selective in a cross-dimerization if the olefinic intermediate was directly used in the reaction pot (see Scheme 6 and Scheme 7).

The mechanism thus validated, we wanted to explore a bit further the reaction and develop a procedure where we could thoroughly diminish the amount of Brønsted acid needed. According to the demonstrated mechanism, the reaction theoretically requires only half an equivalent in the homodimerization process and one in the cross-dimerization one. We thought that running the reaction in the presence of a Lewis acid could do the trick and we would therefore be able to work in milder conditions. Satisfactorily, we rapidly obtained the proof of concept and after few assays, the following optimized set of conditions was obtained: in the presence of 0.4 equiv. of copper(II) triflate the reaction could be performed with 0.4 equiv. of TFA only. The desired lactone was obtained in four hours at room temperature and with 70 % yield as a single diastereomer once again (Scheme 11).



Scheme 11. A copper-catalyzed version.

Of course, it seemed obvious to study next the scope of this new reaction. However and despite all our attempts, we quickly realized that this reaction lacks of general application. Only the aromatic *p*-methoxy group was tolerated as the donor part. As

for the electron-withdrawing substituents, only methyl esters (for the copper/TFA and TFA approaches) or 2-adamantyl esters (for the TFA approach) were compatible with the transformation. The poor scope of this new reactivity can be explained by the major role of the *p*-methoxyaryl substituent. Firstly, the formation of a cationic charge-transfer complex certainly avoids the formation of lactone **3** and leads very rapidly to the formation of alkene **4** which, in turn, establishes a new charge-transfer complex. Alkene **4**, which was in the precedent step an electron-deficient species, acts now as a cation stabilizer. Under these conditions, it is interesting to note that the *p*-methoxyaryl substituent of the DAC plays efficiently and alternatively opposite roles. Subtle modifications by adding other donating substituents onto the aryl part or suppressing the methoxy substituent did not allow an efficient exchange role and led to numerous other by-products without any selectivity (results not shown here).

Conclusions

In this study, a new pathway of DAC reactions has been highlighted. Accordingly, we have shown that DACs could formally behave as nucleophiles and be functionalized at their C3 position to give α,β,γ -trisubstituted butyrolactones. Even if this reaction lacks a general scope, it is completely unprecedented and the impressive diastereoselectivity in such a cationic mechanism is worth to be brought to the scientific community. This could be seen as a step forward in the global understanding of these very interesting species.

Experimental Section

Lactone 2: To a stirred solution of cyclopropane **1** (500 mg, 0.94 mmol, 1 equiv.) in anhydrous 1,2-DCE (10 mL, *c* = 0.2 M) was added TFA (1.83 mL, 24.6 mmol, 26 equiv.) at 20 °C. The reaction mixture was stirred until completion (reaction was followed by TLC) and then quenched with the addition of water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried with Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/Et₂O 50:50) to give lactone **2** as a pale yellow oil. Yield: 70 % (342 mg). *R*_f = 0.20 (petroleum ether/Et₂O 60:40). ¹H NMR (400 MHz, CDCl₃): δ = 7.45 (d, *J* = 8.7 Hz, 2 H), 7.01 (d, *J* = 8.7 Hz, 2 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.11 (d, *J* = 8.1 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.68 (s, 3 H), 3.55 (s, 3 H), 3.51 (s, 3 H), 3.44–3.68 (m, 2 H), 3.05 (dd, *J* = 10.2 and 4.3 Hz, 1 H), 2.74 (ddd, *J* = 11.5, 7.4 and 3.8 Hz, 1 H), 2.27 (ddd, *J* = 14.0, 10.2 and 3.8 Hz, 1 H), 1.90 (ddd, *J* = 14.0, 11.7 and 4.5 Hz, 1 H) ppm. ¹³C NMR (75 MHz, CDCl₃): δ = 170.6 (C_q), 169.4 (C_q), 169.3 (C_q), 168.5 (C_q), 160.6 (C_q), 159.3 (C_q), 130.3 (C_q), 129.9 (CH), 129.5 (C_q), 129.4 (CH), 114.6 (CH), 85.0 (CH), 55.5 (CH₃), 55.5 (CH₃), 53.1 (CH₃), 53.0 (CH), 52.7 (CH₃), 52.7 (CH₃), 52.5 (CH), 49.5 (CH) 45.8 (CH), 32.9 (CH₂) ppm. IR (neat): $\tilde{\nu}_{\text{max}}$ = 2953, 2839, 1722, 1612, 1583, 1516, 1437, 1373, 1331, 1277, 1248, 1217, 1196, 1175, 1128, 1094, 1065, 1034, 987, 968, 922, 893, 835, 810, 775, 762, 708, 687, 565, 532 cm⁻¹. HRMS (ESI): calcd. for C₂₇H₃₀O₁₀ + NH₄⁺ [M + NH₄]⁺ 532.2177; found 532.2180.

Compound 3: *R*_f = 0.30 (petroleum ether/EtOAc 60:40). ¹H NMR (400 MHz, CDCl₃): δ = *cis* 7.33 (d, *J* = 8.6 Hz, 2 H), *trans* 7.27 (d, *J* =

8.7 Hz, 2 H) *cis* 6.94 (d, $J = 8.8$ Hz, 2 H), *trans* 6.93 (d, $J = 8.8$ Hz, 2 H), *trans* 5.68 (t, $J = 7.2$ Hz, 1 H) *cis* 5.41 (dd, $J = 10.4, 6.1$ Hz, 1 H), *trans* 3.84 (s, 3 H), *cis* 3.83 (s, 3 H) *cis* 3.82 (s, 3 H), *trans* 3.82 (s, 3 H), *cis* 3.80 (dd, $J = 11.9, 8.8$ Hz, 1 H), *trans* 3.75 (dd, $J = 9.3, 4.5$ Hz, 1 H) *trans* 3.01–2.95 (ddd, $J = 13.3, 6.8, 4.5$ Hz, 1 H), *cis* 2.85–2.68 (m, 2 H), *trans* 2.47 (ddd, $J = 13.3, 9.3, 7.8$ Hz, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 171.5$ (C_q), 171.4 (C_q), 168.2 (C_q), 168.1 (C_q), 160.2 (C_q), 160.0 (C_q), 130.3 (C_q), 128.7 (C_q), 127.6 (CH), 127.0 (CH), 114.3 (CH), 114.2 (CH), 80.7 (CH), 80.1 (CH), 55.3 (CH_3), 53.1 (CH_3), 53.0 (CH_3), 47.8 (CH), 47.1 (CH), 34.8 (CH_2), 34.6 (CH_2) ppm. IR (neat): $\tilde{\nu}_{\text{max}} = 2957, 2841, 1774, 1736, 1612, 1587, 1516, 1454, 1437, 1352, 1302, 1250, 1153, 1117, 1088, 1032$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_5 + \text{H}^+$ [M + H] $^+$ 250.0914; found 251.0912.

General Procedure for the Alkene–Cyclopropane Cross-Reactions: To a stirred solution of cyclopropane **6** (1 equiv.) and alkene **4** (1 equiv.) in anhydrous 1,2-DCE ($c = 0.2$ M) was added TFA (13 equiv.) at 20 °C. The reaction mixture was stirred until completion (reaction was followed by TLC) and then quenched with the addition of water. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried with Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel.

Compound 7: Colorless oil. Yield: 60 % (86 mg). $R_f = 0.60$ (petroleum ether/ Et_2O 50:50). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.45$ (d, $J = 8.7$ Hz, 2 H), 7.03 (d, $J = 8.7$ Hz, 2 H), 6.96 (d, $J = 8.7$ Hz, 2 H), 6.88 (d, $J = 8.7$ Hz, 2 H), 5.1 (d, $J = 8.3$ Hz, 1 H), 4.96 (br. s, 1 H), 4.77 (br. s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.56 (s, 3 H), 3.49–3.39 (m, 2 H), 3.02 (dd, $J = 11.3, 3.8$ Hz, 1 H), 2.79 (ddd, $J = 11.3, 5.5, 3.4$ Hz, 1 H), 2.29 (m, 1 H), 2.04–1.39 (m, 29 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 170.6$ (C_q), 168.5 (C_q), 168.3 (C_q), 167.3 (C_q), 160.6 (C_q), 159.3 (C_q), 130.3 (C_q), 129.9 (CH), 129.5 (C_q), 129.4 (CH), 114.6 (CH), 114.5 (CH), 84.9 (CH), 78.4 (CH), 55.4 (CH_3), 53.2 (CH), 52.9 (CH_3), 52.5 (CH), 50.6 (CH), 45.5 (CH), 37.3 (2 CH_2), 36.4 (2 CH_2), 36.3 (2 CH_2), 33.2 (CH_2), 32.1 (CH), 32.0 (CH), 31.8 (CH_2), 31.8 (CH), 31.7 (CH), 31.7 (2 CH_2), 27.2 (CH), 27.1 (CH), 27.0 (2CH) ppm. IR (neat): $\tilde{\nu}_{\text{max}} = 2908, 2856, 1778, 1738, 612, 1514, 1452, 1346, 1298, 1265, 1250, 1176, 1151, 1101, 1036$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{45}\text{H}_{54}\text{O}_{10} + \text{NH}_4^+$ [M + NH_4] $^+$ 772.4055; found 772.4063.

Compound 8: Colorless oil. $R_f = 0.80$ (petroleum ether/ Et_2O 60:40). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.45$ (d, $J = 8.5$ Hz, 2 H), 7.05 (d, $J = 8.5$ Hz, 2 H), 6.95 (d, $J = 8.5$ Hz, 2 H), 6.87 (d, $J = 8.5$ Hz, 2 H), 5.17–5.06 (m, 1 H), 4.97 (br. s, 1 H), 4.78 (br. s, 2 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.51–3.36 (m, 2 H), 3.03 (dd, $J = 11.1, 3.2$ Hz, 1 H), 2.80–2.69 (m, 1 H), 2.34 (br. ddd, $J = 14.2, 11.3, 3.0$ Hz, 1 H), 2.09–1.39 (br. m, 43 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 170.9$ (C_q), 168.5 (C_q), 168.3 (C_q), 167.3 (C_q), 160.6 (C_q), 159.3 (C_q), 130.5 (C_q), 130.0 (C_q), 129.9 (2CH), 129.3 (2CH), 114.6 (2CH), 114.5 (2CH), 84.9 (2CH), 79.3 (CH), 78.4 (2CH), 55.4 (CH_3), 55.3 (CH_3), 52.9 (2CH), 50.7 (CH), 45.8 (CH), 37.5 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 36.5 (2 CH_2), 36.4 (2 CH_2), 36.3 (CH_2), 36.3 (CH_2), 33.4 (CH_2), 32.1 (CH), 32.0 (CH), 31.8 (4 CH_2), 31.8 (2CH), 31.7 (2CH), 31.7 (2 CH_2), 27.3 (2CH), 27.2 (CH), 27.1 (2CH), 26.9 (CH) ppm. IR (neat): $\tilde{\nu}_{\text{max}} = 2908, 2856, 1776, 1724, 1612, 1514, 1452, 1346, 1254, 1155, 1099, 1038$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{54}\text{H}_{66}\text{O}_{10} + \text{NH}_4^+$ [M + NH_4] $^+$ 892.4994; found 892.4996.

Compound 10: White crystals (recrystallized from MeOH). Yield: 84 % (37 mg). M.p. 126 °C. $R_f = 0.20$ (petroleum ether/ EtOAc 60:40). ^1H NMR (400 MHz, CDCl_3): $\delta = 7.45$ (d, $J = 8.7$ Hz, 2 H), 7.02 (d, $J = 8.7$ Hz, 2 H), 6.98 (d, $J = 8.7$ Hz, 2 H), 6.86 (d, $J = 8.7$ Hz, 2 H), 5.12–5.09 (m, 1 H), 4.79 (br. s, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.53 (s, 3 H), 3.47–3.67 (m, 2 H), 3.06 (dd, $J = 10.4$ and 4.2 Hz, 1 H), 2.74 (br. ddd, $J = 11.2, 7.2, 3.4$ Hz, 1 H), 2.27 (ddd, $J = 14.0, 10.4, 3.4$ Hz, 1 H), 2.08–1.97 (m, 2 H), 1.94 (ddd, $J = 14.0, 11.7, 4.2$ Hz, 1

H), 1.94–1.66 (m, 10 H), 1.61–1.48 (m, 2 H) ppm. ^{13}C NMR (75 MHz, CDCl_3): $\delta = 170.9$ (C_q), 169.4 (C_q), 169.3 (C_q), 167.3 (C_q), 160.6 (C_q), 159.3 (C_q), 130.5 (C_q), 130.1 (C_q), 129.9 (CH), 129.2 (CH), 114.6 (CH), 84.8 (CH), 79.3 (CH), 55.5 (CH_3), 55.4 (CH_3), 52.9 (CH), 52.7 (CH_3), 52.6 (CH), 49.6 (CH) 46.0 (CH), 37.5 (CH_2), 36.5 (CH_2), 36.4 (CH $_2$), 33.2 (CH_2), 31.9 (CH_2), 31.8 (CH_2), 31.7 (2CH) 27.3 (CH), 27.0 (CH) ppm. IR (neat): $\tilde{\nu}_{\text{max}} = 2910, 2856, 1776, 1729, 1612, 1585, 1513, 1436, 1346, 1301, 1247, 1153, 1101, 1033$ cm^{-1} . HRMS (ESI): calcd. for $\text{C}_{36}\text{H}_{42}\text{O}_{10} + \text{NH}_4^+$ [M + NH_4] $^+$ 652.3116; found 652.3121.

Procedure for the Copper-Catalyzed Version: To a stirred solution of cyclopropane **1** (50 mg, 0.188 mmol, 1 equiv.) in anhydrous 1,2-DCE (1 mL, $c = 0.2$ M) were consecutively added TFA (5.7 μL , 0.075 mmol, 0.4 equiv.) and $\text{Cu}(\text{OTf})_2$ (27.1 mg, 0.075 mmol, 0.4 equiv.) at 20 °C. The reaction mixture was stirred until completion (reaction followed by TLC) and then quenched with the addition of water. The layers were partitioned. The aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried with Na_2SO_4 , filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ Et_2O 50:50) to give lactone **2** as a pale yellow oil. Yield: 70 % (34 mg).

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Keywords: Donor–acceptor systems · Cyclopropanes · Zwitterions · Reaction mechanisms · Density functional calculations

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