



HAL
open science

**Designing Donor-Acceptor Cyclopropane for the
ThermalSynthesis of Carbocyclic Eight-Membered Rings
("Featured in Org. Chem. Highlights " /
<https://www.organic-chemistry.org/Highlights/2023/11December.shtm>)**

Kévin Masson, Maxime Dousset, Bohdan Biletskyi, Sara Chentouf,
Jean-valère Naubron, Jean-luc Parrain, Laurent Commeiras, Paola Nava,
Gaëlle Chouraqui

► **To cite this version:**

Kévin Masson, Maxime Dousset, Bohdan Biletskyi, Sara Chentouf, Jean-valère Naubron, et al.. Designing Donor-Acceptor Cyclopropane for the ThermalSynthesis of Carbocyclic Eight-Membered Rings ("Featured in Org. Chem. Highlights " / <https://www.organic-chemistry.org/Highlights/2023/11December.shtm>). *Advanced Synthesis and Catalysis*, 2023, 365 (7), pp.1002-1011. 10.1002/adsc.202300015 . hal-04153558

HAL Id: hal-04153558

<https://hal.science/hal-04153558v1>

Submitted on 11 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Designing Donor-Acceptor Cyclopropane for the Thermal Synthesis of Carbocyclic Eight-Membered Rings

Kévin Masson,^a Maxime Dousset,^a Bohdan Biletskyi,^a Sara Chentouf,^b Jean-Valère Naubron,^b Jean-Luc Parrain,^a Laurent Commeiras,^a Paola Nava,^{a,*} and Gaëlle Chouraqui^{a,*}

^a Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France

E-mail: paola.nava@univ-amu.fr; gaelle.chouraqui@univ-amu.fr

^b Aix Marseille Univ, CNRS, Centrale Marseille, Spectropole, FR1739 Marseille, France

Abstract: An access to functionalised eight-membered carbocyclic ring compounds was developed by simply stirring an unusual vinylogous Donor-Acceptor Cyclopropane (DAC) in boiling *o*-xylene. Both experimental and computational studies were performed to explain the diastereoselectivity/regioselectivity transfer observed and to provide an overall picture of the mechanism.

Keywords: Donor-Acceptor Cyclopropane; Rearrangement; Eight-membered ring; Mechanistic studies

Introduction

The development of efficient synthesis to access eight-membered carbocyclic ring systems represents an important area of research,^[1] given the number of biologically potent targets that incorporate such rings (the most famous one being, of course, the Taxol, Figure 1).^[2] However, owing to ring strain and transannular interactions,^[3] the formation of eight-membered carbocyclic derivatives has sometimes proven difficult.

To overcome the challenge of their synthesis, one strategy implies to take advantage of the ring strain relief of small cycles.^[4] Ring opening of activated cyclopropanes, the smallest carbocyclic systems, not only offers a thermodynamic driving force but also directs the selectivity of C–C bond cleavage. Therefore, high regio- and stereoselectivities can arise from rearrangement of small rings. Many strong methods are at disposal for the stereoselective synthesis of cyclopropanes.^[5] Consequently, this three-atom build-

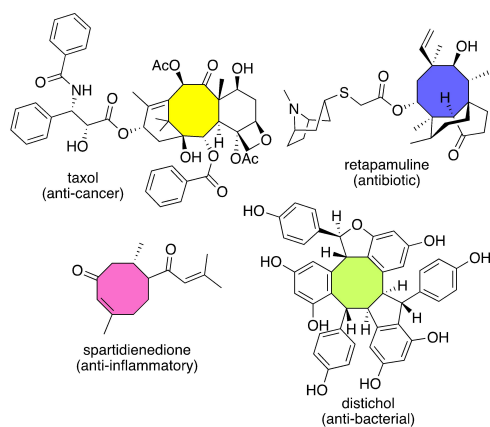
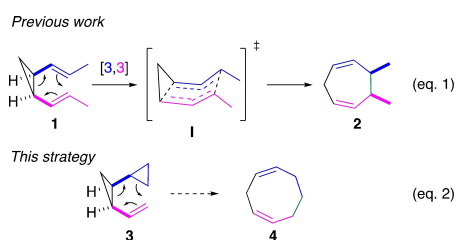


Figure 1. Biologically potent target incorporating an eight-membered ring.

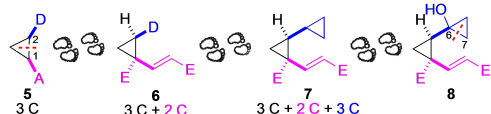
ing block is highly valuable in the controlled elaboration of carbon-carbon σ -bond of complex molecules.

Inspired by the elegant Cope rearrangement of divinylcyclopropane **1** into the corresponding seven-membered ring systems **2** (Scheme 1, eq. 1),^[6] and having in mind that the cyclopropane ring has a C=C double bond character,^[7] we hypothesized that replacing one of the double bonds by a cyclopropyl substituent could lead to the formation of the challenging eight-membered carbocyclic structure **4** (Scheme 1, eq. 2). It is worth noting that, for this divinylcyclopropane-cycloheptadiene rearrangement to occur at room temperature or even below, a *cis* relationship between the double bond partners is necessary (see transition state **I**, Scheme 1 eq. 1).^[8] Therefore, the relative stereochemistry between the double-bond (in pink) and the cyclopropane (in blue) of **3** must be considered.

This assumption made and the geometric parameters issues raised, we needed to find how to activate this framework **3**, to trigger the subsequent ring openings and final cyclization. Let us guide you carefully through the design of the cyclization precursor and take one step at a time. The central element lies in a Donor-Acceptor Cyclopropane (DAC) **5** (Scheme 2). The unique reactivity of DACs molecules has generated a great deal of interest in recent years.^[4d,9-10] The presence of antagonist electron-donating and electron-withdrawing partners on vicinal carbon atoms (C1 and C2) associated with the inherent ring strain of the cyclopropane (~ 27 kcal.mol⁻¹) leads to a high polarization of the C1-C2 bond, allowing ring cleavage, in mild conditions. A polarized three-carbon atom building block is thus at disposal for subsequent cyclizations, rearrangements, and so on. Regarding the structure of DACs, typical acceptor groups (A) are diesters, dinitriles or diketones. Having



Scheme 1. The concept.



Scheme 2. Design of the cyclisation precursor **8**.

in mind that a 2π partner is required, a *gem*-vinylester/ester group should be electron withdrawing enough to induce the cooperative C1-C2 bond breaking (see **6**). As for the donor component (D), a cyclopropyl element is necessary to bring the three last carbons needed **7**. This is strongly supported by several recent published works. The different groups demonstrated that a simple cyclopropyl group could act as an excellent donor in DACs.^[11] To favour the bond cleavage at C6-C7, an alkoxy substituent should be added **8**. This is largely inspired by the ability of vinyl cyclopropanol to rearrange.^[12] To summarize and looking at the overall picture of this precursor **8**, it is fully designed for the selective cyclopropyl bonds cleavage.

Herein, we report a simple, regio-, and diastereoselective route to functionalised carbocyclic eight-membered rings starting from an elaborated precursor, a vinylogous DAC.^[13,14] A computational study served not only to corroborate the experimental results but also to elucidate the reaction mechanism of this formal [3,3]-sigmatropic rearrangement.

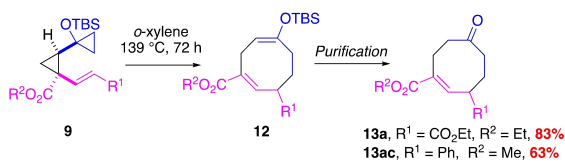
Results and Discussion

The strategy to synthesize the model bis-cyclopropane substrate **9a** relies on a classical Rh(II)-mediated cyclopropanation reaction of the described vinyl cyclopropane **10a**^[15] in presence of the di-acceptor diazo derivative **11a**,^[16] as carbenoid precursor (Scheme 3). A slow addition of the diazo derivative **11a** onto a mixture of olefin **10a** and rhodium catalyst provided the desired adduct **9a** in 81% yield with an excellent diastereoselectivity (95:5 dr). The *cis*-relationship^[17] between the alkene and cyclopropyl partners is in agreement with the diastereoselectivity usually observed with vinylcarbenoids.^[18]

With the availability of the benchmark substrate **9a**, the next issue to be addressed was its ability to undergo the planned cyclization to the eight-membered ring. We quickly found the optimal conditions. When bis-cyclopropane **9a** was stirred in *o*-xylene for 72 hours at 139 °C, very satisfactorily, the formation of the carbocyclic eight-membered ketone **13a** was observed in 83% yield, the enol ether **12a** being hydrolysed during the purification step (Scheme 4). It is worth underlining that the strategy could also deliver



Scheme 3. Synthesis of the model bis-cyclopropane **9a**.



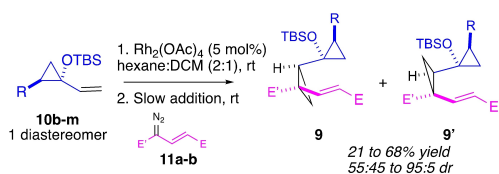
Scheme 4. Optimal conditions for the cyclisation.

the derivative **13 ac** ($R^1 = \text{Ph}$)^[19] in very good yield and in the same conditions.

In a single operation, thanks to a well-engineered design of the precursor, without the need of any kind of catalyst, solely under thermal conditions, we were able i) to selectively cleave two cyclopropane units in a constructive manner, ii) to relocate three pairs of bonding electrons and, finally, iii) to obtain the challenging all-carbon eight-membered rings **13** in an excellent yield.

Under the optimized conditions, the scope of the reaction was next investigated with respect to both donor and acceptor parts of the molecule. The strategy to form the starting material was identical, namely, the cyclopropanation reaction of an R substituted vinyl cyclopropane **10b–m** with diazo derivatives **11a–b**.^[20] The cyclopropanation process worked well and led to the diastereoselective formation of the corresponding three-membered rings in yields ranging from 21 to 68%. The target molecule presents four stereocentres and the main diastereomers usually observed **9** and **9'**, with the required *cis* relationship between the protected cyclopropanol and the α,β -unsaturated ester, are presented below (Scheme 5).

Having these novel substrates in hand, we were ready to explore the reaction scope, and we first studied the behaviour of aryl substituted bicyclop propane (**9b–i**; $R = \text{Ar}$) (Table 1). To make a long story short, all the precursors tested led to the corresponding eight-membered rings **14** at 100–120 °C this time. In these cases, the enol ethers happened to be stable and hydrolysis to the ketone was performed using Dowex H^+ cation-exchange resin. All these examples validated the catalyst free-cyclization leading to a medium-sized ring **14** with the control of two stereogenic centres. Aryl substituents were well tolerated; *o*-, *m*- or *p*-substituted aryls with different halogen atoms or



Scheme 5. Synthesis of a range of bicyclop propane **9** and **9'**.

Table 1. Scope of the cyclisation with aryl substituted bicyclop propane.

Entry	Bicyclop propane R = aryl, dr	Yield of 14 (over 2 steps)	dr (<i>cis</i> : <i>trans</i>)
1	Ph, 9b : 9b' , >95:5 E=E'=CO ₂ Et	88% 14b	70:30
2	<i>p</i> MeOPh, 9c : 9c' , >95:5 E=E'=CO ₂ Et	54% 14c	92:7
3	<i>p</i> FPh, 9d : 9d' , >95:5 E=E'=CO ₂ Et	54% 14d	62:38
4	<i>m</i> ClPh, 9e : 9e' , >95:5 E=E'=CO ₂ Et	70% 14e	62:38
5	<i>p</i> BrPh, 9f : 9f' , 90:10 E=E'=CO ₂ Et	58% 14f	65:35
6	<i>o</i> Tol, 9g : 9g' , 95:5 E=E'=CO ₂ Et	87% 14g	50:50
7	<i>o</i> FPh, 9h : 9h' , >95:5 E=E'=CO ₂ Et	92% 14h	64:36
8	<i>m</i> FPh, 9i : 9i' , >95:5 E < C=> E'=CO ₂ Et	57% 14i	62:38
9	Ph, 9bb : 9bb' , 90:10 E'=CO ₂ Et, E < C=> Ph	96% 14bb	>95:5

substituents of different electronic nature were all found to be suitable (yields ranging from 54 to 96%). In each case, sole the β -aryl-substituted ketone regioisomer was isolated as a mixture of two *cis*:*trans* diastereomers (Table 1). This first series of results indicated that the C6–C8 bond is broken during the cyclisation.

Alkyl substituents were next evaluated (Table 2). Interestingly, the reaction requires higher temperatures, and depends on the size of the R substituents and on the starting diastereomeric mixture of the bicyclop propane **9**:**9'**. Accordingly, when $R = i\text{Pr}$ or cyclohexyl (Cy) (Table 2, entries 1–3), the α -alkyl-substituted ketone regioisomer **15j**, **15k** and **15jb** were isolated in excellent yields (70, 87 and 99% yield respectively) and high diastereoselectivity, therefore meaning that the bond broken during the cyclization is, this time, the C6–C7 one. In presence of a primary alkyl group (entries 4–5), the regioselectivity dropped dramatically (either C6–C7 or C6–C8 bond could break) but the diastereoselectivity remains excellent. These two last results arose our curiosity and provided key information for the global understanding of the reaction. At that point and for the alkyl substituents (Table 2), we hypothesized that the regioselectivity of the reaction was strictly related to the nature of the starting

Table 2. Scope of the cyclisation with alkyl substituted bicyclopiperanes.

Entry	Bicyclopiperane R = alkyl, X, dr	Yield of 14/15 (over 2 steps)	dr (<i>cis</i> : <i>trans</i>)
1	<i>i</i> Pr, 9j : 9j' , > 95:5 E=E'=CO ₂ Et	70% 15j	> 95:5
2	Cy, 9k : 9k' , > 95:5 E=E'=CO ₂ Et	87% 15k	> 95:5
3	<i>i</i> Pr, 9jb : 9jb' , 92:8 E'=CO ₂ Et, E=Ph	99% 15jb	> 95:5
4	<i>n</i> -Hexyl, 9l : 9l' , 60:40 E=E'=CO ₂ Et	90% 15l : 14l (60:40)	> 95:5
5	Me, 9m : 9m' , 55:45 E=E'=CO ₂ Et	54% 15m : 14m (55:45)	> 95:5
6	Me, 9m ^[a] [^b] E=E'=CO ₂ Et	49% 15m	> 95:5
7	Me, 9m ^[a] [^c] E=E'=CO ₂ Et	60% 14m	90:10

[a] Pure diastereomer separated by chiral HPLC.

[b] Reaction ran at 160 °C.

[c] Reaction ran at 100 °C.

bicyclopiperane diastereomer **9** or **9'**. This assumption made, the reaction was repeated on pure separated diastereomers **9m**^[21] and **9m'** (entries 6–7 respectively). As suspected the reaction was completely regioselective. Namely, a pure diastereomer **9m** or **9m'** afforded a single regioisomer **15m** or **14m** respectively.

To summarize, the most significant feature of this methodology is the efficient catalyst-free regio- and stereoselective formation of the challenging eight-membered carbocyclic ring structure. The medium-size ring systems thus obtained contain useful functionalities for further synthetic elaboration from readily available components and is compatible with a wide range of different substituents. Interestingly, depending on a combination of the starting diastereomer and the nature of the R substituent, one or the other regioisomer can selectively be isolated (see schemes of Table 1 & 2). Intrigued by such a difference of reactivity and inspired by the total diastereoselectivity/regioselectivity transfer of the reaction, we embarked in a theoretical treatment to rationalize the empirical observations and to propose an overall picture of the mechanism.

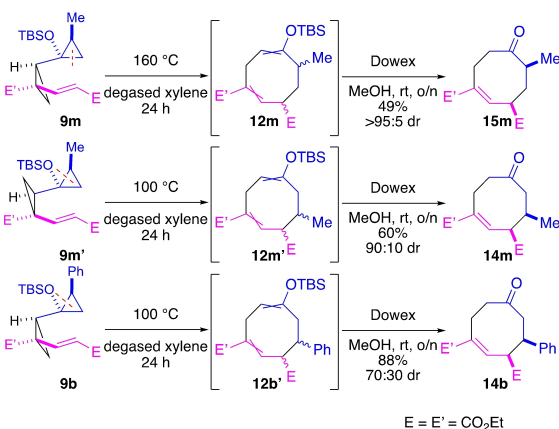
First and foremost, the 3D-structures of the direct products of the thermal reaction, namely the stereoisomers observed within the crude mixture of enol

ethers **12** (Scheme 6), required to be identified and assigned. From a practical point of view, this study was carried out using exclusively diastereopure bicyclopiperanes **9m** (R=Me), **9m'** (R=Me) that were separated by chiral HPLC, and **9b** (R=Ph) purified by selective crystallisation in pentane.

These three starting materials are reflective of the main paths undertaken by the title reaction.

For each material (**12m**, **12m'** and **12b'**), the *E* or *Z* stereochemistry of the 1,4-diene encompassed in the eight-membered ring required an elucidation. As for the *cis*-, *trans*-relationship between the ester and the Me (or Ph) substituents, a confirmation was also required. It is noteworthy that the regioselectivity of the reaction has already been devised thanks to the correlation NMR-experiments of the corresponding ketones **15m**, **14m** and **14b** (hydrolysis products of the enol ethers **12m**, **12m'** and **12b'** respectively). The same techniques were also employed on each mixture of enol ethers and the regioselectivity is indicated on the scheme above (Scheme 6). The 3D-structural elucidation of each compound was divided into different stages and understandably, the pieces of this intriguing puzzle fell into place.

The structural elucidation of the mixture of enol ethers **12m** was not straightforward since three main stereoisomers were observed (**A**, **A1** and **A2**) (Figure 2). Based on NOESY experiments run either on **12m** or on the corresponding ketone **15m** and on X-ray diffraction analysis of other analogous α -regioisomers (like **15j** or **15k**),^[22] we could conclude on a *cis* relationship between the Me and the ester groups. Next, experimental data gave us first insights on the geometry of the alkenes: **A1** and **A2** were unstable on silica gel or in the presence of any source of proton and evolved rapidly either to the more stable com-



Scheme 6. Structural elucidation of the enol ethers **12**, direct products of the cyclisation.

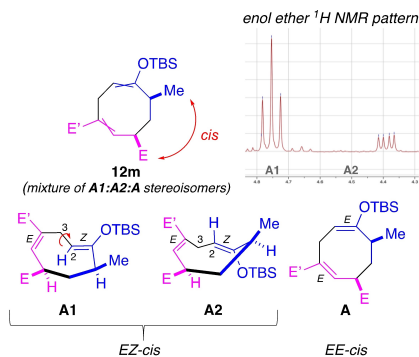
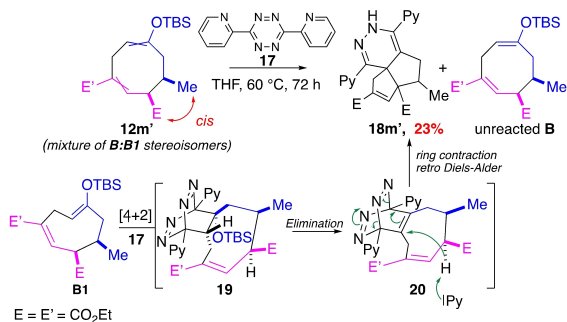


Figure 2. Structural elucidation for **12m**.

compound **A** and/or the corresponding ketone **15m**. We concluded that i) **A1** and **A2** were the direct products of the reaction and ii) their instability came from a strained *Z* alkene,^[23] which can easily isomerize to the corresponding *E* one (compound **A**, *EE-cis*). A combined NMR and computational study was performed to attribute the structures of **A1** and **A2**. Experimentally, the two isomers have very distinct patterns in proton NMR. The multiplicity of the silyl enol ether proton H_{A1} is an apparent triplet ($J_{exp} = 8.5$ Hz) whereas H_{A2} is a doublet of doublets ($J_{exp} = 10.2, 4.7$ Hz) (see spectrum Figure 2). Gratifyingly, the computed and measured *J* coupling constants were in very good agreement ($J_{comp, A1} = 8.1$ Hz, $J_{comp, A2} = 9.1, 3.6$ Hz, see Supporting Information) and allowed to undeniably assign **A**, **A1** and **A2**. **A1** and **A2** are in fact atropisomers of the same *EZ-cis* silyl enol ether and this chirality arises from a hindered rotation about the C2–C3 single bond. The barrier to atropimerisation is determined by the rigidity of the 1,4-cyclooctadiene. The ratio of the two stereoisomers is actually temperature dependent. At 160 °C, the major product formed is **A1** (75:25), whereas at 120 °C **A2** is observed predominantly (40:60). *Trans*-cyclooctenes are known to display atropisomerism,^[23d] however little is known on atropisomerism of (*E,Z*)-cycloocta-1,4-diene.^[24]

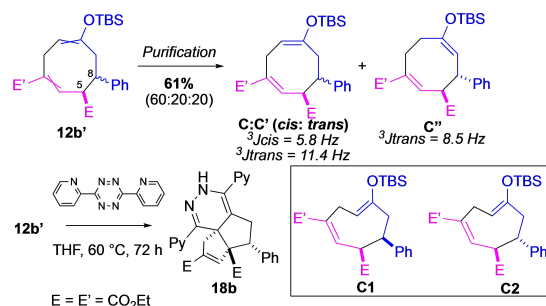
For compounds **12m'**, two main enol ethers **B1** and **B** were usually observed in the crude mixture (75:25). A first hint regarding their structures came from the corresponding ketone **14m**. The latter was transformed into a hydrazone derivative and its X-ray data,^[25] supported the *cis* relationship between the ester and the Me (Scheme 7). Secondly, the computed and measured NMR *Jcis* & *Jtrans* coupling constants for **B1**, were in good agreement ($J_{cis, exp} = 1.6$ Hz & $J_{cis, comp} = 1.5$ Hz, $J_{trans, comp} = 4.6$ Hz). In addition, an Inverse Electron Demand Diels Alder (IEDDA) reaction, in presence of tetrazine **17** under thermal conditions, was successfully carried out on the **B1** and **B** mixture. A fused tricyclic system **18m'**, was isolated in 23% yield together with



Scheme 7. Structural elucidation for **12m'**.

the unreacted starting enol ether **B** (12%). From a mechanistic point of view, the IEDDA on enol ether **B1** delivering **19**, could be followed by an elimination step leading to **20**. A ring contraction triggered by nitrogen extrusion could afford the observed polycyclic structure **18m**. The well-known remarkable selectivity of the IEDDA between tetrazines and *trans*-cyclooctenes^[26] in purely thermal conditions thus supported a “*trans*-enol ether” for **B1** (*i.e.* the *Z* enol ether in our case) and therefore the **B** one could be assigned as *E*. It is worth noting that the unstable nature of **B1** compared to **B** was also in agreement with a *Z* double bond configuration. Accordingly, **B1** decomposed quickly either to the more stable **B** enol ether or the ketone **14m**. To summarize, an experimental, theoretical and analytical approach allowed us to secure the 3D-structures of the mixture of enol ethers **B1** and **B** coming from the reaction of **9m'**.

The lower diastereoselectivity observed for the phenyl case combined with the instability of the *E* enol ethers led to a complex mixture of unstable and stable enol ethers **12b'**. Their purification by flash chromatography over silica gel led to the three stable compounds **C**, **C'** and **C''** in 61% yield and a 60:20:20 ratio (Scheme 8), identified thanks to NMR 2D experiments and the 3J coupling constant ($^3J_{cis, exp} =$



Scheme 8. Structural elucidation for **12b'**.

5.8 Hz, $^3J_{trans,exp} = 11.4$ Hz) between protons H5 & H8 (by analogy with the **B** observed coupling constants). At that stage, we could conclude that the major product of the reaction has a *cis* relationship, which is in agreement with the observed and isolated ketones **14b**. The IEDDA approach was then run on the mixture of crude enol ethers **12b'**, to identify the unstable enol ethers contained in the crude mixture. The expected fused tricyclic system **18b** was isolated and its structure was confirmed by X-ray diffraction analysis. The presence of *Z* enol ethers in the **12b'** mixture was

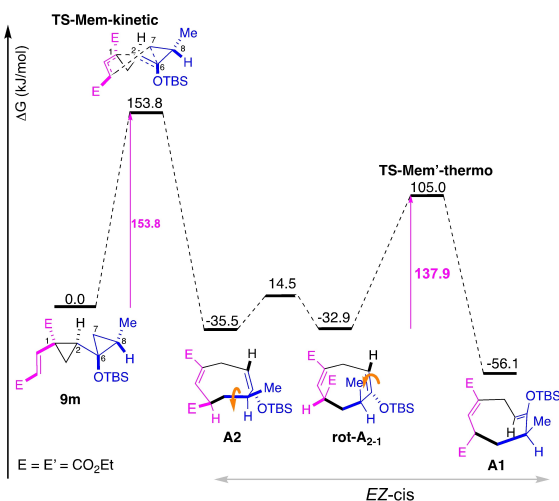


Figure 3. Computed ΔG profiles (PBE0-D3/def2-TZVP, $T = 100^\circ\text{C}$) for the concerted mechanism of the cyclisation reaction for **9m**.

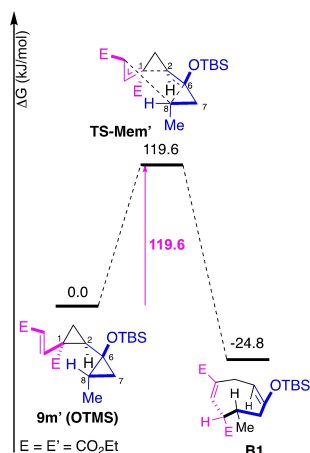


Figure 4. Computed ΔG profiles (PBE0-D3/def2-TZVP, $T = 100^\circ\text{C}$) for the concerted mechanism of the cyclisation reaction for modified **9m'**.

therefore not questionable, and the direct product of this thermal reaction are compounds **C1** and **C2**.

Thanks to further experiments and a combined reliable theoretical and analytical approach we were able to unambiguously identify and assign the mixture of the different enol ethers **12m**, **12m'** and **12b**. We even highlighted the presence of atropisomers in case of enol ethers **12m**. At that point, we were very pleased with the outcome of the reaction in terms of scope and selectivities. For a better understanding of the observed diastereoselectivity and intriguing regioselectivity, a theoretical treatment was carried out to propose cyclisation reaction pathways for **9m**, **9m'** and **9b**. Regarding **9m** and **9m'**, minimal free-energy profiles for concerted mechanisms were found and are shown in Figure 3 & Figure 4 respectively. In order to facilitate comparisons, ΔG values were all computed at $T = 100^\circ\text{C}$ at the PBE0-D3/def2-TZVP level.^[27] Solvent effects were taken into account by the implicit SMD continuum solvent model for benzene.^[28] The barrier in the case of **9m** (153.8 kJ/mol) is higher than for **9m'** (119.6 kJ/mol). This agrees with the experimental observations, suggesting that the reaction for **9m'** is easier (*i.e.*, ran at 100°C). The concerted mechanism for **9m** leads directly to **A2** via transition state **TS-Mem-kinetic**. **A2** exists in two conformations that differ by the equatorial or axial orientation of one ester group (see **rot-A2-1**). The thermodynamic product is **A1**, which can be formed from the axial conformer by crossing a non-negligible barrier of 137.9 kJ/mol: thus, **A2** could be identified at lower temperature (120°C), while **A1** is mostly observed at 160°C . Stepwise mechanisms through zwitterionic intermediates, presenting a charge separation, were ruled out, as any attempt to optimize the structures of such intermediates failed (see ESI for more details).

The mechanism reported for **9m** and **9m'** implies chair-like transition states, compatible with the stereochemistry of the predominant products in the crude. Transition states constructed from alternative conformations would lead to other isomers, with higher barriers (see Supplementary Information). The C1–C2 distances in the transition states are of 218.7 pm and 221.6 pm for **9m** and **9m'** respectively. They are longer than the C6–C7 & C6–C8 distances (204.2 and 210.0 pm for **9m** and **9m'**, respectively), suggesting that, although the mechanism is concerted, the opening of the central ring triggers the transformation, as expected due to its donor-acceptor properties.

In the Ph case, the concerted mechanism was ruled out on the basis of the following elements: i) the regioselectivity of the product is different than for **9m** (even though the diastereomers involved **9m** & **9b** are the same), ii) two major products could be identified in the crude, which differ by the *cis-trans* position of the Ph group with respect to the neighbouring ester, iii) preliminary calculations suggested that barriers for

concerted mechanisms leading to β,γ -regioselectivity are higher in energy than those for **9m** & **9m'**, as opposed to the milder conditions used in **9b** case (100°C for **9b** vs 160°C for **9m**) (see Supporting Information). For the phenyl case, gas phase calculations were performed at the PBE0-D3/def2-TZVP level on a model system, where the –OTBS was replaced by –OTMS substituent (see SI). This allows us to provide an overall global picture of the mechanism that leads to the *cis* product (Figure 5). We propose that the initial step is the opening of the two cyclopropane moieties, leading to a singlet biradical intermediate **I**, where C5 and C8 are distant. This is the rate-limiting step of the transformation, with a barrier estimated at 106 kJ/mol (within our model). Low-energy conformational changes are necessary to bring them closer: a rotation around C7–C8 (see intermediate **II**, Figure 4), followed by a rotation around C6–C7 (see intermediate **III**). The bond between C5 and C8 allowing the formation of the eight-membered ring *cis-12b'*, is created in the last step. The 6-*exo* C1–C8 ring closure is forbidden due to the *Z* geometry of the enol ether. Other conformational transformation patterns are possible, notably leading to the *trans* product, which is also present in the final product mixture (see Supporting Information for more details). Finally, it is worth underlining, that no approach leading to an *E* product regarding the silyl enol ether double bond was found, which agrees with the experiments and as also shown for **9m** and **9m'** cases.

The representation of the two SOMO orbitals are depicted in Figure 6: one orbital is localized on the ester side, notably on the carbon atom C5 implicated in the closure step; the other orbital reveals the existence

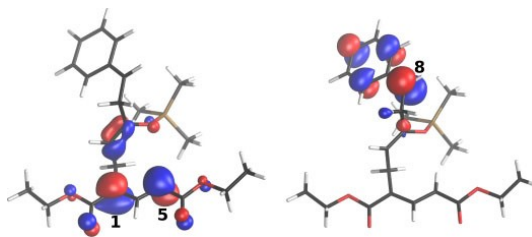


Figure 6. Representation of the SOMO orbitals (PBE0-D3/def2-TZVP) for the modified **9b** (–OTMS used instead of –OTBS)

of a benzyl radical on C8, accounting for the β -regioselectivity.

Finally, the different regio- and stereoselectivity of the cyclisation reactions are rationalized by two kinds of mechanisms, a concerted one for the Me cases **9m** and **9m'**, and a stepwise radical mechanism for the Ph substituent **9b**. We were not able to find a mechanism to a product that possesses an *E* conformation on the enol ether. Thus, the direct products of the reaction are of type *EZ*, which is right in line with the different experiments.

Conclusion

In conclusion, this paper devises the reactivity of an original donor-acceptor cyclopropane capable of undergoing a rearrangement to generate numerous functionalized cyclooctanoid ring systems. The conditions of the reaction allow the formation of the challenging eight-membered all carbon ring by simple heating, without any catalyst or reagent and in a single

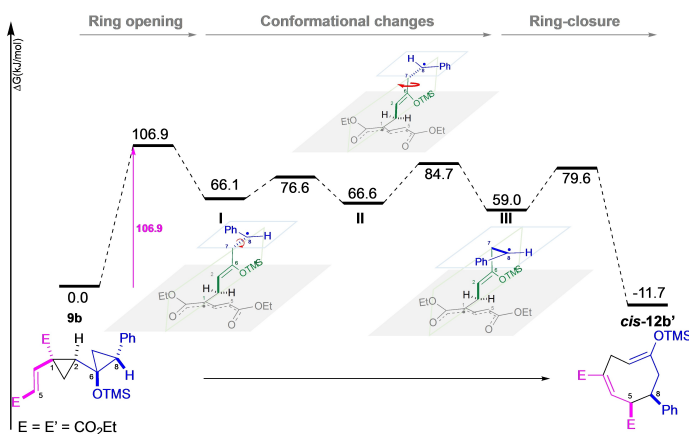


Figure 5. Computed ΔG profiles (PBE0-D3/def2-TZVP, T=100°C) for the radical mechanism of the cyclisation reaction for modified **9b** (–OTMS used instead of –OTBS).

step. The subsequent hydrolysis under mild conditions leads to the corresponding cyclooctenones in good overall yields.

Three classes of donor-acceptor cyclopropanes have been identified exhibiting a particular regio- and diastereo-selectivity. Especially, the link between the geometry of the starting material and the observed regioselectivity has been unambiguously established and supported by DFT calculations. Two mechanisms are at work and rely either on a concerted or a stepwise radical path depending on the nature of the substituent on the donor part of the bicyclic cyclopropane. More importantly thanks to a careful design of the initial donor-acceptor cyclopropane, we were able to selectively break the carbon-carbon bond of the central three-membered ring.

Experimental Section

General Procedure for the Conversion of Vinyl-Bicyclic Cyclopropanes to Cyclooctenones

A Schlenk tube was charged with a vinylbicyclic cyclopropane **9** and/or **9'** and *o*-xylene (20 mL/mmol). The resulting solution was degassed thanks to a freeze-pump-thaw procedure. The reaction was heated overnight at temperatures ranging from 100 to 160 °C. After cooling down, the xylene was evaporated under reduced pressure and the crude product was directly dissolved in MeOH (20 mL/mmol). To this solution was added Dowex 50WX8 (hydrogen form) resin (1 : 1%w VBCP) and the mixture was stirred for 12 h at room temperature. Volatiles were then removed under reduced pressure and the crude material was purified by silica gel flash chromatography (PE/EtOAc=9 : 1-6 : 4) to afford pure cyclooctenones **13**, **14** and/or **15**. All the cyclooctenones presented in this section have exhibited a retention factor of approximately 0.2–0.4 in PE/AcOEt = 8 : 2.

diethyl (E)-6-oxocyclooct-1-ene-1,3-dicarboxylate (**13a**)

Reagents used according to the general procedure: vinylbicyclic cyclopropane **9a** (50 mg, 0.13 mmol), 2.6 mL of *o*-xylene. Temperature: 160 °C. The cyclooctenone was isolated as a colourless oil (27.8 mg, 80%).

¹H NMR (300 MHz, Benzene-*d*₆): δ = 7.32 (dd, *J* = 9.0, 1.0 Hz, 1H), 4.02–3.80 (m, 4H), 3.09 (ddd, *J* = 12.4, 9.0, 3.1 Hz, 1H), 2.72 (dt, *J* = 13.6, 4.3 Hz, 1H), 2.47 (ddd, *J* = 13.4, 12.4, 4.4 Hz, 1H), 2.17 (dt, *J* = 12.5, 4.1 Hz, 1H), 2.05 (ddd, *J* = 13.5, 4.1, 1.1 Hz, 1H), 2.00–1.93 (m, 1H), 1.94–1.83 (m, 2H), 1.70–1.52 (m, 1H), 0.87 (t, *J* = 7.1 Hz, 6H). ¹³C NMR (75 MHz, Benzene-*d*₆): δ = 210.0, 172.4, 165.9, 139.2, 134.5, 61.0, 60.9, 47.1, 45.2, 38.8, 27.4, 22.4, 14.1, 14.1. HRMS: C₁₄H₂₁O₅ [M + H]⁺ calc 269.1384 Da, found 269.1386 Da. IR: 2979, 2935, 1731, 1647, 1446, 1369, 1303, 1251, 1108, 894, 734, 702 cm⁻¹.

diethyl (E)-4-(4-methoxyphenyl)-6-oxocyclooct-1-ene-1,3-dicarboxylate (**14c cis**)

Reagents used according to the general procedure: vinylbicyclic cyclopropane **9c** (35 mg, 0.07 mmol), 1.4 mL of *o*-xylene. Temperature: 100 °C. The cyclooctenone **14c-cis** was isolated as a colourless oil (14.3 mg, 54%) and as a mixture of diastereomers (92 : 7 dr). Sole the major diastereomer has been described.

¹H NMR (400 MHz, Benzene-*d*₆): δ = 7.71 (dd, *J* = 10.8, 1.4 Hz, 1H), 7.05–6.94 (m, 2H), 6.71–6.62 (m, 2H), 4.12–4.02 (m, 2H), 3.81 (dt, *J* = 12.4, 5.3 Hz, 1H), 3.74 (q, *J* = 7.1 Hz, 2H), 3.52 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.25 (s, 3H), 3.06–2.96 (m, 1H), 2.58 (t, *J* = 12.4 Hz, 1H), 2.40–2.34 (m, 2H), 2.16 (dd, *J* = 12.3, 4.7 Hz, 1H), 1.87–1.77 (m, 1H), 0.98 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, Benzene-*d*₆): δ = 210.3, 170.2, 166.4, 159.4, 137.5, 134.1, 131.6, 129.8, 129.8, 114.1, 114.1, 61.1, 60.8, 54.7, 48.3, 47.4, 46.3, 43.2, 23.5, 14.3, 14.1. HRMS: C₂₁H₂₇O₆⁺ [M + H]⁺ calc 375.1802 Da, found 375.1801 Da. IR: 2929, 1733, 1512, 1247, 1191, 1180, 1162, 1105, 1074, 1029, 838, 765 cm⁻¹.

diethyl (3R,5R,E)-5-isopropyl-6-oxocyclooct-1-ene-1,3-dicarboxylate (**15j**)

Reagents used according to the general procedure: vinylbicyclic cyclopropane **9j** (55 mg, 0.13 mmol), 2.6 mL of *o*-xylene. Temperature: 160 °C. The cyclooctenone **15j** was isolated as a colourless oil (28.1 mg, 70%) and as single diastereomer (95 : 5 dr). This compound partially crystallized when stored at - 4 °C for a prolonged period. X-ray data are available for this molecule.^[22]

¹H NMR (400 MHz, Benzene-*d*₆): δ = 7.42 (d, *J* = 8.2 Hz, 1H), 4.01–3.82 (m, 4H), 3.13 (ddd, *J* = 11.9, 8.2, 2.1 Hz, 1H), 2.76 (ddd, *J* = 12.1, 5.4, 2.3 Hz, 1H), 2.66 (td, *J* = 12.3, 11.8, 5.4 Hz, 1H), 2.26 (dd, *J* = 12.9, 5.3 Hz, 1H), 2.23–2.13 (m, 1H), 2.02 (m, 2H), 1.78–1.65 (m, 2H), 0.94–0.83 (m, 6H), 0.73 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (75 MHz, Benzene-*d*₆): δ = 212.9, 172.7, 165.8, 139.8, 134.6, 61.1, 60.9, 56.1, 48.5, 46.0, 32.8, 31.8, 22.1, 20.4, 20.2, 14.1. HRMS: C₁₇H₂₇O₅⁺ [M + H]⁺ calc 311.1853 Da, found 311.1854 Da. IR: 2962, 1733, 1708, 1251, 1189, 1176, 1035, 761 cm⁻¹.

diethyl (3R,5R,E)-5-cyclohexyl-6-oxocyclooct-1-ene-1,3-dicarboxylate (**15k**)

Reagents used according to the general procedure: vinylbicyclic cyclopropane **9k** (52 mg, 0.11 mmol), 2.2 mL of *o*-xylene. Temperature: 160 °C. The cyclooctenone **15k** was isolated as a colourless solid^[22] (34.4 mg, 87%) and as a single diastereomer (95 : 5 dr). X-ray data are available for this molecule.

¹H NMR (300 MHz, Benzene-*d*₆): δ = 7.44 (d, *J* = 8.2 Hz, 1H), 4.02–3.79 (m, 4H), 3.14 (ddd, *J* = 11.9, 8.2, 2.1 Hz, 1H), 2.85–2.61 (m, 2H), 2.35–2.10 (m, 3H), 2.04 (dt, *J* = 13.2, 2.2 Hz, 1H), 1.78–1.30 (m, 10H), 1.00 (m, 2H), 0.89 (m, 6H).

¹³C NMR (75 MHz, Benzene-*d*₆): δ = 213.1, 172.8, 165.8, 139.9, 134.6, 61.1, 60.9, 55.4, 48.7, 46.1, 41.4, 32.1, 30.8, 30.7, 26.8, 26.6, 26.5, 22.2, 14.1, 14.1. HRMS: C₂₀H₃₄NO₅⁺ [M +

NH₄⁺ calc 368.2432 Da, found 368.2430 Da. IR: 2925, 2852, 1733, 1706, 1448, 1369, 1301, 1249, 1184, 1165, 1134, 1095, 1033, 763 cm⁻¹.

CCDC-2219778 to CCDC-2218793 and CCDC-2221202 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.

Acknowledgements

K.M. thanks the French Ministère de l'Enseignement Supérieur et de la Recherche (MESR) for a Ph.D. fellowship. All authors are grateful to Michel Giorgi from Spectropole for X-Ray diffraction. Institutional financial support from Aix-Marseille Université (AMU), the Centre National de la Recherche Scientifique (CNRS), and Centrale Marseille are gratefully acknowledged.

References

- [1] a) N. A. Petasis, M. A. Patane, *Tetrahedron* **1992**, *48*, 5757–5821; b) G. Mehta, V. Singh, *Chem. Rev.* **1999**, *99*, 881–930; c) M. E. Maier, *Angew. Chem. Int. Ed.* **2000**, *39*, 2073–2077; *Angew. Chem.* **2000**, *112*, 2153–2157; d) A. Michaut, J. Rodriguez, *Angew. Chem. Int. Ed.* **2006**, *45*, 5740–5750; *Angew. Chem.* **2006**, *118*, 5870–5881; e) M. Tori, R. Mizutani, *Molecules* **2010**, *15*, 4242–4260; f) E.-J. Hu, L.-X. Li, J.-C. Han, L. Min, C.-C. Li, *Chem. Rev.* **2020**, *120*, 5910–5953; g) S. McN Sieburth, N. T. Cunard, *Tetrahedron* **1966**, *52*, 6251–6282; h) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3008; i) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, 2791–2805; j) Z.-X. Yu, Y. Wang, Y. Wang, *Chem. - Asian J.* **2010**, *5*, 1072–1088; k) L.-N. Wang, Z.-X. Yu, *Youji Huaxue* **2020**, *40*, 3536–3558.
- [2] a) T. Granier, J. A. Bajgrowicz, A. Hanhart, WO Patent 2004/035017 A1, 2004; b) M. C. Wani, H. L. Taylor, M. E. Wall, P. Coggon, A. T. McPhail, *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327; c) R. F. Shang, J. T. Wang, W. Z. Guo, J. P. Liang, *Curr. Top. Med. Chem.* **2013**, *13*, 3013–3025; d) M. Norte, F. Cataldo, M. Castillo, *Tetrahedron Lett.* **1993**, *34*, 5143–5146; e) M. Sultanbaa, S. Surendrakumar, P. Bladon, *Phytochemistry* **1987**, *26*, 799–.
- [3] a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95–102; b) C. Galli, L. Mandolini, *Eur. J. Org. Chem.* **2000**, 3117–3125.
- [4] a) A. K. Clarke, W. P. Unsworth, *Chem. Sci.* **2020**, *11*, 2876–2881; b) J. R. Donald, W. P. Unsworth, *Chem. Eur. J.* **2017**, *23*, 8780–8799; c) B. Biletskyi, P. Colonna, K. Masson, J.-L. Parrain, L. Commeiras, G. Chouraqui, *Chem. Soc. Rev.* **2021**, *50*, 7513–7538; d) D. J. Mack, J. T. Njardarson, *ACS Catal.* **2013**, *3*, 272–286; e) T. Seiser, T. Saget, D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2011**, *50*, 7740–7752; *Angew. Chem.* **2011**, *123*, 7884–7896; f) X. Cai, W. Liang, M. Dai, *Tetrahedron* **2019**, *75*, 193–208; g) P. Natho, L. A. T. Alle, P. J. Parsons, *Tetrahedron Lett.* **2020**, *61*, 151695; h) J. Le Bras, J. Muzart, *Tetrahedron* **2020**, *76*, 130879.
- [5] For recent reviews on the subject, see: a) E. Sansinenea, A. Ortiz, *Eur. J. Org. Chem.* **2022**, e202200210; b) W. Wu, Z. Lin, H. Jiang, *Org. Biomol. Chem.* **2018**, *16*, 7315–7329.
- [6] a) E. Vogel, *Angew. Chem.* **1960**, *72*, 4–26; b) T. Hudlicky, R. Fan, J. W. Reed, K. G. Gadamasetti, *Org. React.* **1992**, *4*, 1–133; c) S. Krüger, T. Gäich, *Beilstein J. Org. Chem.* **2014**, *10*, 163–193; d) H. M. L. Davies, D. G. Stafford, B. D. Doan, J. H. Houser, *J. Am. Chem. Soc.* **1998**, *120*, 3326–3331; e) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061–3071.
- [7] With their 60° bond angles (compared to the classical 109° for typical Csp²–Csp³ bonds), cyclopropane units are small rings with considerable double bond character. Their reactivity can indeed be compared to that of alkenes.
- [8] I. Özkan, M. Zora, *J. Org. Chem.* **2003**, *68*, 9635–9642.
- [9] For seminal report on DACs, see: a) E. Wenkert, M. E. Alonso, B. L. Buck-walter, K. J. Chou, *J. Am. Chem. Soc.* **1977**, *99*, 4778–4782; b) H.-U. Reissig, E. Hirsch, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 813–814; *Angew. Chem.* **1980**, *92*, 839–840.
- [10] For recent reviews on DACs, see: a) H. K. Grover, M. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655–671; b) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; c) T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504–5523; *Angew. Chem.* **2014**, *126*, 5608–5628; d) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051–3060; e) F. De Nanteuil, F. De Simone, R. Frei, F. Benfatii, E. Serrano, J. Waser, *Chem. Commun.* **2014**, *50*, 10912–10928; f) Special issue: “Chemistry of Donor-Acceptor Cyclopropanes and Cyclobutanes”, *Isr. J. Chem.* **2016**, *56*, 367–577; g) F. De Simone, J. Waser, *Synthesis* **2009**, 3353–3374; h) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196; i) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969–2984; j) Z. Wang, *Synlett* **2012**, *23*, 2311–2327; k) F. De Simone, T. Saget, F. Benfatti, S. Alemida, J. Waser, *Chem. Eur. J.* **2011**, *17*, 14527–14538; l) S. Reisman, R. Nani, S. Levin, *Synlett* **2011**, 2437–2442; m) M. Mel'nikov, E. Budylnina, O. Ivanova, I. Trushkov, *Mendeleev Commun.* **2011**, *21*, 293–301; n) M. Campbell, J. Johnson, A. Parsons, P. Pohlhaus, S. Sanders, *J. Org. Chem.* **2010**, *75*, 6317–6325; o) T. Lebold, M. Kerr, *Pure Appl. Chem.* **2012**, *82*, 1797–1812; p) D. Agrawal, V. Yadav, *Chem. Commun.* **2008**,

- 6471–6488; q) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117–3179; r) M. Yu, B. Pagenkopf, *Tetrahedron* **2005**, *61*, 321–347; s) E. M. Budynina, K. L. Ivanov, I. D. Sorokin, M. Ya Melnikov, *Synthesis* **2017**, *49*, 3035–3068; t) K. Ghosh, S. Das, *Org. Biomol. Chem.* **2021**, *19*, 965–982; u) Y. Xia, X. Liu, X. Feng, *Angew. Chem. Int. Ed.* **2021**, *60*, 9192–9204; v) O. A. Ivanova, I. V. Truskhov, *Chem. Rec.* **2019**, *19*, 2189–2208; w) M. C. Martin, R. Shenje, S. France, *Isr. J. Chem.* **2016**, *56*, 499–511; x) H. K. Grover, M. R. Emmett, M. A. Kerr, *Org. Biomol. Chem.* **2015**, *13*, 655–671; y) R. A. Novikov, U. V. Tomilov *Mendeleev Commun.* **2015**, *25*, 1–10; z) K. Ghosh, S. Das, *Org. Biomol. Chem.* **2021**, *19*, 965–982; aa) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804–818; ab) M. J. Di Grandi, *Org. Biomol. Chem.* **2014**, *12*, 5331–5345.
- [11] a) A. Kreft, P. G. Jones, D. B. Werz, *Org. Lett.* **2018**, *20*, 2059–2062; b) K. V. Potapov, D. A. Denisov, V. V. Glushkova, R. A. Novikov, Y. V. Tomilov, *J. Org. Chem.* **2020**, *85*, 15562–15576; c) D. A. Denisov, R. A. Novikov, K. V. Potapov, V. A. Korolev, E. V. Shulishov, Y. V. Tomilov, *ChemistrySelect* **2016**, *1*, 6374–6381.
- [12] a) B. Trost, A. Brandi, *J. Am. Chem. Soc.* **1984**, *106*, 5041–5043; b) B. M. Trost, D. C. Lee, *J. Am. Chem. Soc.* **1988**, *110*, 6556–6558; c) B. M. Trost, D. W. C. Chen, *J. Am. Chem. Soc.* **1996**, *118*, 12541–12554; d) B. M. Trost, P. H. Scudder, *J. Org. Chem.* **1981**, *46*, 506–509; e) S. A. Monti, F. G. Cowherd, T. W. Mc Aninch, *J. Org. Chem.* **1975**, *40*, 858–862. For reviews, see: f) B. M. Trost, *Top. Curr. Chem.* **1986**, *133*, 3–82; g) J. R. Y. Salaün, J. Top, *Curr. Chem.* **1988**, *144*, 1–71.
- [13] For review on vinylcyclopropanes, see: a) J. Wang, A. Blaszczyk, X. Li, W. Tang, *Chem. Rev.* **2021**, *121*, 110–139; b) M. Meazza, H. Guo, R. Rios, *Org. Biomol. Chem.* **2017**, *15*, 2479–2490.
- [14] For a recent example on a vinylogous DAC, see: N. L. Ahlburg, O. Hergert, P. G. Jones, D. B. Werz, *Angew. Chem. Int. Ed.* **2023**, *62*, e202214390.
- [15] The vinylcyclopropane **10a** could easily be prepared from commercially available (1-ethoxycyclopropoxy)trimethylsilane in three steps only: P. A. Wender, A. J. Dyckman, C. O. Husfeld, M. J. C. Scanio, *Org. Lett.* **2000**, *2*, 1609–1611.
- [16] H. M. L. Davies, D. M. Clark, D. B. Allgood, G. R. Eiband, *Tetrahedron* **1987**, *43*, 4265–4270.
- [17] *cis*-relationship confirmed by the numerous X-ray structures obtained for the different bicyclopropanes.
- [18] a) H. M. L. Davies, T. J. Clark, L. A. Church, *Tetrahedron Lett.* **1989**, *30*, 5057–5060; b) K. S. Rathore, S. Katukojvala, *Tetrahedron Lett.* **2014**, *55*, 6370–6372; c) Y.-L. Lin, E. Turos, *J. Organomet. Chem.* **2001**, *630*, 57–66.
- [19] CCDC-2221202 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via <https://www.ccdc.cam.ac.uk/structures/>.
- [20] See Supporting Information for the detailed synthesis of the newly formed diazo compounds **11a** and vinylcyclopropanes **10b–m**.
- [21] The relative stereochemistry of **9m** was unambiguously determined through X-ray structural determination (see the Supporting Information) CCDC-2218784 contains the supplementary crystallographic data for this paper.
- [22] CCDC-2218782 and CCDC-2218781 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via <https://www.ccdc.cam.ac.uk/structures/>.
- [23] The transient *trans*-enol ether in a 1,5- or 1,3-cyclooctadiene has been reported before but as far as our knowledge goes, never in the 1,4 cyclooctadiene case: a) R. C. Gadwood, R. M. Lett, *J. Org. Chem.* **1982**, *47*, 2268–2275; b) B. B. Snider, A. J. Allentoff, *J. Org. Chem.* **1991**, *56*, 321–328; c) N. Arichi, K.-I. Yamada, Y. Yamaoka, K. Takasu, *J. Am. Chem. Soc.* **2015**, *137*, 9579–9582; d) T. Ito, M. Tsutsumi, K.-I. Yamada, H. Takikawa, Y. Yamaoka, K. Takasu, *Angew. Chem. Int. Ed.* **2019**, *58*, 11836–11840; *Angew. Chem.* **2019**, *131*, 11962–11966; e) D. Sondag, L. Maartense, H. de Jong, F. F. J. de Kleijne, K. M. Bongers, D. W. P. M. Löwik, T. J. Boltje, J. Sommerholt, P. B. White, D. Blanco-Aia, F. P. J. T. Rutjes, *Chem. Eur. J.* **2022**, e202203375.
- [24] For detailed computational studies on (*E,Z*)-cycloocta-1,4-diene conformers see: I. Yavari, H. Kabiri-Fard, S. Moradi, *Monatsh. Chem.* **2002**, *133*, 1459–1468.
- [25] CCDC-2218783 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via <https://www.ccdc.cam.ac.uk/structures/>.
- [26] The most reactive dienophile *trans*-cyclooctene is seven orders of magnitude more reactive than *cis*-cyclooctene toward tetrazines: F. Thalhammer, U. Wallfahrer, J. Sauer, *Tetrahedron Lett.* **1990**, *31*, 6851–6854.
- [27] a) P. A. M. Dirac, R. H. Fowler, *Proc. Royal Soc.* **1929**, *123*, 714–733; b) J. C. Slater, *Phys. Rev.* **1951**, *81*, 385–390; c) J. P. Perdew, Y. Wang, *Phys. Rev. B* **1992**, *45*, 13244–13249; d) J. P. Perdew, K. Burke, M. Ernzerhof, *Phys. Rev. Lett.* **1996**, *77*, 3865–3868; e) J. P. Perdew, M. Ernzerhof, K. Burke, *J. Chem. Phys.* **1996**, *105*, 9982–9985; f) S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, *132*, 154104; g) A. Schäfer, H. Horn, R. Ahlrichs, *J. Chem. Phys.* **1992**, *97*, 2571–2277; h) F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, *7*, 3297–3305; i) F. Weigend, *Phys. Chem. Chem. Phys.* **2006**, *8*, 1057–1065.
- [28] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B.* **2009**, *113*, 6378–6396.